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***UNIFIED THEORY OF
HUMAN
AND ANIMALS AGING***

***BIOENERGY CONCEPT
AGING
AS A DISEASE***

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Aging is caused by the main pathogenic factor initiating this disease - oxygen deficiency in organs and tissues. Hypoxia accelerates the degeneration of the weak link - the sensitive nerve endings of the autonomic nervous system. The sequence of events connected by a network of cause-and-effect relationships and representing the pathogenesis of aging disease is considered. The second etiological factor that determines the pathogenesis of aging disease is local hyperoxia of stem cell niches, which leads to accelerated differentiation of stem cells and, as a result, to age-related depletion of their pools. Within the framework of the Concept, the explanation of known significant facts that characterize this disease, but which have not received a clear explanation within the framework of other hypotheses, is considered. Acquisition of disease status by aging makes it possible not only to actively slow down aging, but also to reverse it.

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Алексей Фитин

Unified theory of human and animals aging. Bioenergy concept aging as a disease

1. Part One

One of the principal objects of theoretical research in any department of knowledge is to find the point of view from which the subject appears in its greatest simplicity.

J. W. Gibbs

My Comment to the Epigraph of the Famous Thermodynamicist (Energeticist) Josiah Willard Gibbs

A distinctive feature of biology is the incredible diversity (heterogeneity) of elements and an even greater variety of connections between them. This diversity is manifested at all levels of organization of living things from molecules to social formations.

Obviously, the maximum simplicity of representing such a global phenomenon as aging should not be achieved due to primitive concepts, that is, due to neglect of the complexity of the organism structure.

Obviously, the maximum simplicity of representing such a global phenomenon as aging should not be achieved due to primitive ideas about it, that is, due to neglect of the complexity of its structure. It was energy that turned out to be that golden key, with the help of which I was able to penetrate into the essence of one of the central problems of biology and medicine – aging. Consideration of this complex problem from the standpoint of bioenergetics revealed the very, truly divine simplicity, which made it possible to unravel the complex tangle of numerous facts regarding this phenomenon and predict a number of consequences of energy deficit for the body. I believe that one of the most important results of the bioenergetic approach to aging became the identification of the leading role of the autonomic nervous system in the pathogenesis of this disease.

Science is built up of facts, as a house is built of stones; but an accumulation of facts is no more a science than a heap of stones is a house.

Henri Poincare "Science and Hypothesis", 1902

Introduction. How the Bioenergy Concept of Aging Was Born

In connection with the immense breadth of the topic of aging, which must be presented in the limited space of an analytical review, I will present the Concept practically in a thesis form, linking together the etiology and the main stages of pathogenesis by cause-and-effect relationships. As “test words” in the second part of the review, I will present an explanation within the framework of the Concept of a number of long-known phenomena of aging and the most significant facts characterizing this disease, but which have not received a clear explanation within the framework of other hypotheses.

I will cite only the most important facts necessary for an adequate understanding of the Concept and will try not to overload the text with references to facts widely known to gerontologists and geriatricians. The modern possibilities of the Internet allow readers to quickly find the most recent works available in the open access and concerning any fact mentioned in the review.

There are no new facts concerning aging in this work. The Concept offers a new look at this disease, its etiology and pathogenesis. A patient has a chance to be healed if the pathogenic factor that caused his disease (etiology) and the sequence of events in the mechanism of the development of his disease (pathogenesis) are known.

Treatment of aging, like any other disease, blindly or by symptoms, without knowledge of the etiology and pathogenesis, is not only useless, but also harmful (pathogenic) occupation. Many modern authors have already called aging a disease, and not a process, as has been accepted since the second century AD. However, most of them are limited only by etiology and often scattered elements of pathogenesis, linking them to its terminal stages. We do not know anything about the early stages of the pathogenesis of aging. Most of the clearly formulated aging hypotheses are based on pathogenic factors causing chaos in the metabolism of cells and tissues: – on numerous toxic metabolites of the intestinal bacterial flora [1]; – on highly reactive metabolites – free radicals of oxygen and nitrogen, entering into chemical reactions with biological polymers [2] and on chemically active aldehyde – glucose, which modifies amino groups of proteins, with excessive consumption of sugars. The hypothesis of accumulation of mutations is also based on chaos [3].

All of the above hypotheses, in fact, are one-act (primitively simple) and are suitable for explaining only pathological, but in no way physiological aging. Chemical or physical (energy quanta: electrons, photons, alpha particles) impact of a set of pathogenic factors on a huge list of targets in the human body – enzymes, transmembrane carriers, structural proteins, nucleic acids and phospholipids should lead to an unimaginable variety of effects on everyone levels of the organization.

The first stage of pathogenesis, with a similar beginning of aging, can be designated as “metabolic chaos”, which eventually leads to the second stage – a “black box”, about which, in principle, we do not know anything. And unexpectedly, at the later stages of pathogenesis, the interaction of these two sets – pathogenic factors and targets, leads to a quite definite set of one and a half dozen proliferative-degenerative senile pathologies with quite predictable general unified events of pathogenesis.

Trying to explain this paradoxical phenomenon, I came to the conclusion that the listed pathogenic factors on their own can hardly be the cause of physiological aging.

As for pathological aging, which can be influenced by a huge number of pathogenic factors of a very different nature, even in this case, I doubt that each pathogenic factor that provokes or aggravates pathological aging has its own unique mechanism of action on this disease. I assumed that a huge variety of pathogenic factors of the most diverse nature affects pathological aging through a unified mechanism.

The path to the main and unique pathogenic factor, the same for physiological and pathological aging, which not only initiates, but also prolongs this disease at different stages of pathogenesis, turned out to be quite long and with numerous dead ends.

Analyzing the research results of V. M. Dilman [4] regarding age-related coarsening of the sensitivity of the hypothalamus functions to peripheral regulatory signals of negative feedback (peripheral hormones and key metabolites), accompanied by an increase in the basal level of one of the stress hormones, cortisol, I suggested that in addition to hormonal and metabolic signals that determine this phenomenon, there is a more powerful and significant regulator of the activity of the hypothalamus – the peripheral part of the autonomic nervous system (ANS) – evolutionary metabolic regulation system No. 1, which ensures the rapid adaptation of the body to changing conditions as the environment and the internal environment of the body. I was convinced of this by the results of experiments W. B. Cannon [5] by removing in animals the sympathetic ganglia of the ANS, which provide the neural connection of the brain stem structures with the periphery.

Such an operation did not lead to any significant disturbances in the normal life of animals at rest and under constant environmental conditions. However, such animals lost the ability to quickly adapt and died from insignificant stressful influences. The behavior of the operated animals with a distant peripheral sympathetic nervous system reminded me of the behavior of elderly people. This similarity was expressed in a low threshold of a stress response to what seemed to be the most insignificant, both external and internal influences, manifested in humans in inadequately strong and unreasonable feelings, fears and worries.

This strengthened me in the consciousness that I was on the right track. I became interested in the fine structure of the ANS and the structural features of the neurons of this metabolic regulation system, looking for weak links that could make it the most vulnerable component of the aging mechanism of the body. The success of the search was largely predetermined by my “bioenergetic” past in science [6]. Since then, I have viewed all significant aging events through the prism of bioenergetics.

Such weak links were quickly discovered – incredibly extended processes of pseudo-unipolar neurons, in which a single axon leaves the cell body, splitting into two branches: a long one towards the sense organ and a short one towards the central nervous system, as well as slow and energy-consuming processes of axonal transport over long distances of tens of centimeters, which determines the slow process of their regeneration.

The volume of cytoplasm located in the extended processes of such neurons is hundreds of times greater than the volume of cytoplasm in the body of the neuron, in which the nucleus and the Golgi apparatus are localized, supplying the processes with all the necessary “building materials” for their growth and regeneration due to slow axonal vesicular transport, the speed which is much less than the blood flow velocity. The speed of vesicular transport in the axon reaches 20–50 cm / day, and the blood flow rate is in the range from 0.03 cm / sec in the capillaries to 40 cm / sec in the aorta.

Thus, the rate of vesicular axonal transport of mitochondria and enzymes accumulated in the Golgi apparatus and is 50–70000 times less than the rate of transport of nutrients by the circulatory system. This difference predetermines the limiting stage of the regeneration process of axons damaged in one way or another, which is from 2 to 5 mm per day. I came to the conclusion, that it is the energetics of these unique neurons that can be a limiting factor in their effective work and the regeneration of their offshoots. And since the energetics of a neuron is based on oxidative phosphorylation, I came to the preliminary conclusion that only oxygen can be the initial limiting factor in the work of these unique neurons. Later it turned out that the weakest point of these neurons are the terminal areas of axons farthest from the cell nucleus and from the Golgi apparatus, on which receptors are localized and which are capable of regeneration after physiological degeneration.

1.1 Etiology of Aging

The death of the body is the inevitable outcome of the disease of aging. When assessing the dynamics of aging, two indicators are important – the average indicator and the indicator of the maximum life expectancy.

Searching for the stages of pathogenesis that limit a long and healthy life, I came to the conclusion that the ***indicator of the maximum or species life expectancy is associated with physiological aging (senescence) and depends on the only unique internal pathogenic factor – oxygen deficiency in organs and tissues and is determined by specific (per unit mass of body weight per unit of time) by the rate of formation of carriers of free energy: adenosine triphosphoric acid (ATP), reduced forms of nicotinamide-adenine dinucleotides (NADH, NADPH), reduced forms of flavine-adenine dinucleotide (FAD) and acetyl-coenzyme A (acetyl-CoA).***¹

Indicator of maximum life expectancy has not changed over the centuries and therefore is a species-specific feature. At the same time, the partial pressure of oxygen in different organs and tissues differs significantly, and therefore the levels of hypoxia, normoxia and hyperoxia for each organ and each tissue are unique [7].

Max Rubner first drew attention to the limitation of the maximum life span for the species of warm-blooded animals, while studying the energy characteristics of animals under resting conditions. More on this in the second part of the review.

Specific rates of synthesis of energy carriers, in turn, are determined not only by the partial pressure of oxygen in organs and tissues, but also by the specific content of mitochondria in cells, which catalyze the main process of synthesis of carriers of free energy – oxidative phosphorylation.

In a number of cells (stem, tumor) and tissues (embryonic tissue, fetus and «cambial» tissues of stem cell niches), in which aerobic glycolysis and the pentose phosphate cycle make a significant contribution to the production of free energy carriers, the amount of enzymes of these metabolic pathways present in cells also determines the specific rates of synthesis of free energy carriers.

Thus, the indicator of the maximum or species life expectancy of organisms is determined by the specific rates of synthesis of free energy carriers (per gram of tissues and organs per unit of time): ATP, NADH, NADPH, FMN, FADH₂, Acetyl-CoA.

The parameter limiting the indicator of the maximum life span of a species, according to my proposed bioenergetic Concept of aging, is the specific rate (per kilogram of body weight) of the formation of carriers of free energy, which depends on the content in cells and activity of mitochondria that carry out oxidative phosphorylation of ADP and reduction of NAD⁺.

The indicator of the average life expectancy is associated with pathological or premature aging, and just like the indicator of the maximum life expectancy depends on the oxygen concentration in organs and tissues, but, at the same time, it is determined not by the rates of formation of carriers of free energy, but the rates of their expenditure.

Pathological aging is accelerated by the influence of numerous factors of a biological, chemical and physical nature, which is realized through a unified process of consumption of deficient oxygen or free energy, both on the work of the body's safety systems (detoxification systems; immunity systems; stress response systems and supply systems a high level of selectivity of enzymes of matrix synthesis of DNA, RNA and protein, as well as a system for correcting errors made by these enzymes), as well as to overcome metabolic chaos in the form of diseases caused by infections, poisoning, distress and mutations, if the power of energy dependent security systems the body was not enough.

All expenditure of free energy by the body can be divided into two categories. The first is associated with the expenditure of free energy to maintain the basic vital functions, without which

¹ Free energy or Gibbs-Helmholtz energy – part of the internal energy of molecules that can be converted into work during reactions.

life is impossible, and which includes the costs of growth, development, reproduction, functioning, adaptation to small changes in the surrounding and internal environment of the body (costs for the constantly ongoing process of changing enzymatic patterns in cells and for the response to eustress), on maintaining body temperature and creating physiological endogenous reserves of nutrients for the smooth functioning of the body. The listed costs of energy are in a competitive relationship.

For example, the more free energy is spent on adaptation or on reproduction, the less it remains for other functions and the lower the indicator of the maximum life span of the species (see the example of the Shrew in the second part of the review). Another example – long-lived mutants of roundworms – soil nematodes *Caenorhabditis elegans* for the age-1 or daf-23 gene, encoding the catalytic subunit of phosphatidylinositol-3-kinase, localized in the signal transduction chain from the insulin-like growth factor, were characterized by either complete sterility, or fewer offspring and a high level of embryonic mortality.

I hope that the high energy consumption of the above basic vital functions is obvious to the reader, perhaps, except for the cost of adaptation. In this regard, I will briefly dwell on the mechanism of one of the most energy-consuming life processes – the adaptation of an organism to changes in its internal environment. The process of adaptation underlies the pathogenesis of aging as the longest chronic disease. This is not about the global (strategic) and slow process of adaptation of organisms to environmental conditions for many generations, which underlies the evolution of species and affects the changes in genes, but about the constantly going "every minute" adaptation of the organism to the continuous changes of the organism itself, manifested at the epigenetic level, without changing the genes themselves.

Such operational adaptation is expressed both in a change in the activity of enzymes due to a change in their content in cells, and in a change in their lists (patterns). It is impossible to constantly keep in the cells of this or that organ or tissue the entire set of necessary enzymes for all occasions. A large number of enzymes are classified as inducible and their amount in a cell can vary significantly depending on the situation. The relatively short half-life of many enzymes – from several tens of minutes to a day, indicates both the high rate of change of enzymatic "communities" (patterns) of the cell, and the significant expenditure of free energy, which goes both for synthesis and for degradation proteins. When I first drew attention to the high rate of protein turnover in the cell, I could not understand for a long time the reason for the high degree of cell wastefulness in terms of the expenditure of always deficient free energy.

Indeed, the ribosomal synthesis of only one peptide bond at a cost of 2 kcal/mol is accompanied by the consumption of four high-energy compounds (ATP, pyrophosphate and 2 GTP), with a total cost of 30 kcal/mol. In addition, the intracellular transport of protein to its workplace and folding of the protein into the working conformation also requires considerable additional energy consumption. The highest energy cost is characteristic of proteins delivered by energy-dependent vesicular transport over huge distances from the body of neurons along axons.

Only now, considering the energy costs underlying the life of cells and the organism as a whole, I realized the high cost of adaptation to the changing conditions of the internal environment of the organism. An example is the activation of the synthesis of a large list of enzymes under hypoxic conditions. For example, hypoxia of cell culture of cytotoxic T lymphocytes leads to an increase in the number of more than 7600 proteins [8]. Considering the huge variety of cells involved in the response to hypoxia, a large amount of the body's energy expenditures for adaptation to hypoxia should be assumed.

In my opinion, it is hypoxia that is the most common cause of changes in cell enzymatic patterns. A feature of hypoxia as a leading pathogenic factor is the high frequency of its manifestation in certain local volumes of organs and tissues. With age, the frequency of episodes of local hypoxia, their duration and depth increase, and, therefore, the expenditure of free energy both for adaptation and for exiting the adapted state and return to normoxia, also accompanied by a change in enzymatic patterns, increases.

The constant implementation of such cycles, initiated by episodes of local or general hypoxia, makes the adaptation process the most energy-consuming process that accelerates aging.

Such operational adaptation of the organism to changes in its internal environment occurs not only at the intracellular level, but also at the level of changes in the ratio of cells, one or another specialization. When it is necessary to survive, the body “puts under the knife” even the cells and tissues that are important for it, using them as a full-fledged, operative endogenous nutrition, completely restoring them in conditions of rest, sleep or anabiosis. Thus, deficient oxygen and free energy are also spent on changes in the cellular composition of the body in the process of adaptation.

In this brief review, I will not consider the expenditure of energy for the work of adaptive mechanisms for the consumption of deficient oxygen at the physiological level, which consists in the redistribution of blood between organs and tissues.

In general terms, adaptation is a positive phenomenon, without which life is impossible. But, adaptation is an energy-consuming process. The pathogenic nature of the operational adaptation constantly going on in the body in the cycle: is due to the large additional costs of energy and, accordingly, oxygen, thereby aggravating hypoxia.



Unlike the operational adaptation to hypoxia that is constantly going on in the body, long-term adaptation to oxygen deficiency, especially from the very beginning of ontogenesis, has an absolutely positive character, which manifests itself in longevity. In the second part of the review, two examples of longevity due to constant hypoxia are considered – the example of the naked mole rat and the example of mountain dwellers.

One of the first results of the constantly occurring adaptive reactions of the body are structural changes accumulating with age in cells, tissues and organs. Signs of aging begin to appear on the connective tissue formations. The system for maintaining homeostasis prevents the accumulation of changes in actively functioning components of cells, and therefore such pathological changes occur and accumulate over time in changes in structural components that are less susceptible to the influence of homeostatic mechanisms. We are talking about changing the content of each of these components or about changing their localization both inside and outside the cells.

I will list a number of examples of structural age-related changes: – replacement of noble cellular elements with connective tissue (according to I. I. Mechnikov); – additional age-dependent collagen deposits around most cells in compactly organized tissues and in the basement membranes of organs; – connective tissue cords in tissues, which are the remnants of remnants of small blood vessels, without endothelial cells and without SMC media of vessels; – deposition of lipofuscin and tau protein inside neurons; – deposition of beta-amyloid in the intercellular space; – pathological slowly metabolized fatty deposits on the organs of the chest and abdominal cavities; – «sliding» of fatty deposits in the lower part of the facial part of the skull under the influence of gravity; deposits of kidney stones and gallbladder; deposition of arteriosclerotic plaques on the walls of blood vessels.

Cells of actively functioning tissues can maintain homeostasis, including due to the surrounding connective tissues, dumping metabolic waste and excess metabolites into them (for example, lactate from cells living on glycolysis). The formation of blood clots in the capillaries of the circulatory system is also a possible result of such local discharge. Structural changes can be accompanied by the loss

of components, a striking example of which is osteoporosis, accompanied by the loss of the mineral component of bone tissue, mainly due to its rare use.

Thus, senile changes, which we judge about aging, are manifested primarily at the level of structural (morphological and anatomical) changes: – changes in the skeleton; changes in the connective tissue basis of organs; – an increase in the number of elements of extracellular connective tissue and its subsequent ossification. Ultimately, all slowly metabolized waste of cell life first enters the extracellular fluid and then into the blood before being excreted in the urine.

Structural pathological changes in cells, tissues and organs act as secondary pathogenic factors, entailing malfunctions of functional elements.

The second category of free energy expenditures includes the costs of operating security systems and overcoming metabolic chaos in the form of diseases, which I wrote about above. The more energy is spent on the operation of security systems and on overcoming metabolic chaos, the less it remains for vital functions and the lower the average life expectancy. One of the results of metabolic chaos, manifested in the form of inflammation that accompanies many diseases, is an increase in body temperature, indicating a decrease in the efficiency of bioenergetic mechanisms.

Spending funds (energy) on conditioning the environment, that is, removing from habitat pathogenic microorganisms, toxic substances and reducing the levels of negative physical (radiation) and mental influences, humanity thereby provides the economy of free energy by organisms, which they spend on combating various pathogenic factors and metabolic chaos, thereby reducing the rate of pathological aging and increasing life expectancy.

The sharp increase in the average life expectancy in the twentieth century was provided by the work of infectious disease specialists, hygienists, parasitologists and epidemiologists, who defeated most of the infections. In the second half of the twentieth century, ecologists, clinical epidemiologists, toxicologists and technologists did it, overcoming the negative consequences of the first technical revolutions associated with chemical and physical pollution of the environment.

Hypoxia, reducing the activity of the main source of free energy – the mitochondrial system of oxidative phosphorylation, leads to a decrease in both phosphate and redox potential of cells. The unique property of hypoxia as the main pathogenic factor causing aging is the presence of numerous enhancers of its action. First, a decrease in oxygen concentration leads to a decrease in the rate of free energy production in the cell, the main mass carriers of which are ATP, NADH, NADPH and gradients of hydrogen, sodium, potassium and chlorine ions on cell membranes.

Cells contain more than 500 NADH- and NADPH-dependent enzymes (dehydrogenases), which, due to the free energy of oxidation of pyridine nucleotides, direct cell metabolism. Also in cells there are more than 200 ATP hydrolases that catalyze reactions that require the supply of free energy for their course. In the plasma membranes of various cells, there are energy-dependent translocases, which, due to the energy of the sodium cation gradient, provide the transport of a large list of metabolites into the cell against their concentration gradients.

Secondly, a decrease in the partial pressure of oxygen in organs and tissues leads to a decrease in the enzymatic activity of a number of oxidases. With a decrease in the activity of even one of the oxidases, important metabolic consequences arise in almost all organs and tissues.

A decrease in the activity of such a huge amount of enzymes under conditions of hypoxia leads to the most catastrophic consequences for cells, causing their death and death of the body.

At the physiological level, with aging, there is also a decrease in the production capacity of carriers of free energy due to a decrease in the supply of oxygen to organs and tissues, due to a decrease in the functions of the respiratory and cardiovascular systems.

The situation is aggravated by the fact that the carriers of free energy and their derivatives (cyclic AMP, cyclic GMP, GTP, CoA, FAD, NAD⁺) are key regulators of metabolism and cells and the body as a whole.

A decrease in the concentration of ATP and NAD(P)H leads to a decrease in the concentration, including nucleotides – substrates for the synthesis of nucleic acids (RNA and DNA): GTP, CTP, UTP, deoxy-ATP, deoxy-GTP, deoxy-CTP and deoxy-TTP.

There is no more toxic and operatively acting pathogenic factor than oxygen deficiency in the body due to the presence of such a large number of enhancers and distributors of its pathogenic effect on cell metabolism.

The whole history of oxygen life takes place under the sign of the economical consumption of always scarce oxygen, at all levels of the organization.

An important mechanism for this saving is the creation of oxygen reserves, especially in intensively functioning tissues and organs. The central nervous system, which is the most powerful and most intensive consumer of oxygen (per gram of mass per unit of time) as the main energy carrier, uses glucose, a semi-oxidized product containing its own oxygen. Glial cells that perform auxiliary functions contain glycogen, which also allows them to conserve oxygen, which is necessary for the functioning of neurons. I will dwell on other mechanisms for saving oxygen later.

I will list some of the main primary consequences of hypoxia for cells and the body as a whole.

1. Activation of an energy-dependent, regulated process of programmed cell death – apoptosis, which is safe for the surrounding tissues and for the organism as a whole, as a result of external influences. Apoptosis is not self-destruction of a cell, but it killing by external factors, in the extreme case, apoptosis can be considered as forcing cells to commit suicide by external factors: – the main physiological – cortisol (circadian rhythm), which with age increasingly becomes pathological (age-dependent growth basal level of cortisol and distress), and the main pathological one – hypoxia.

There is not enough oxygen for the simultaneous work of all cells of the body, it is necessary to save the “most valuable” ones, getting rid of ineffective cells for the survival of the body under hypoxic conditions, and also get rid of cells that may be restored from stem cells. Cascade mechanisms of the sequential elimination of cell components in a certain order require the expenditure of free energy in the form of ATP hydrolysis (for example, ubiquitin).

1.1. Activation of the production of free oxygen radicals by the respiratory chain of dying mitochondria. Free radicals of oxygen (* OH) and nitrogen (* NO), possessing high values of the oxidative potential, as well as ATP and NAD(P)H are mass carriers of free energy and are involved in the normal energy metabolism of cells. Free oxygen radicals generated by dying mitochondria are products of cell apoptosis, but not vice versa, as is often found in the literature.

It is the oxygen deficiency that leads to a network of events ending in apoptosis: – slowing down of the transport of electrons along the respiratory chain; – a decrease in the electrochemical potential difference of hydrogen ions on the inner mitochondrial membrane; – swelling of mitochondria with disruption of the integrity of the outer mitochondrial membrane; – exit from the intermembrane space into the cytoplasm of cytochrome C, which leads to disconnection from the respiratory chain of cytochrome oxidase and to the termination of direct transfer of electrons to oxygen (disconnection of cytochrome oxidase from the respiratory chain is an elegant evolutionary device that excludes the possibility of senseless and therefore harmful “eating” oxygen that is already deficient under conditions of hypoxia); – activation of the reverse transfer of electrons (against the redox potential of the electron carriers of the respiratory chain) entering the respiratory chain from dehydrogenases of the second conjugation point; – increasing the concentration of the reaction product of one-electron reduction of Coenzyme Q; – chemical reaction of oxygen with the Coenzyme Q radical, leading to an increase in the concentration of free oxygen radicals.

1.2. The main results of the impact of free oxygen radicals generated by dying mitochondria. The most important result of the action of free oxygen radicals is the chemical modification of mitochondrial DNA, which is surrounded on all sides by outgrowths of the inner membrane (cristae), in which the enzymes of the respiratory chain are localized. The number of DNA copies

in mitochondria reaches 10, and the number of mitochondrial DNA copies per cell is several tens of thousands due to the large number of mitochondria in it.

The main function of free oxygen radicals generated by the respiratory chain of mitochondria of cells that have entered apoptosis, which is positive for the body, is the covalent modification of mitochondrial DNA and mitochondrial enzymes of its duplication. The meaning of these processes is the inactivation or neutralization of mitochondrial DNA, which is in origin and structure (without introns and without histones) bacterial DNA, capable of integrating into cellular DNA and thereby facilitating cell transformation [20].

This does not mean that the appearance of free oxygen radicals (like many other, especially chemically active metabolites) in the wrong place and/or in unusually high concentrations exceeding the capabilities of antioxidant protection does not harm the cell and the body as a whole. This situation, apparently, is realized under conditions of intense radiation exposure.

The function of free oxygen radicals generated by NADPH oxidase of the plasma membrane of immunocompetent cells is also similar, the activity of which increases when they interact with bacteria and viruses. The meaning of the generation of free oxygen radicals, and in this case, lies in the covalent modification of foreign DNA. To destroy a bacterium or cell means, first of all, to damage its DNA.

The pathogenic function of an excess of antioxidants consumed by humans is to reduce the rate of mitochondrial DNA detoxification by free oxygen radicals, which, apparently, leads to an increase in the likelihood of oncological diseases [10].

1.3. Safety of free oxygen radicals generated by the mitochondria of a dying cell for neighboring cells. Due to the high chemical reactivity of free oxygen radicals and due to the small distances of their free path, neighboring cells with intact mitochondria are probably not susceptible to the pathogenic effects of these radicals.

First, in order to leave the mitochondria of a dying cell and get into a neighboring healthy cell, free radicals need to overcome many membranes with built-in densely packed proteins that contain a large number of potential targets for free radicals (unsaturated bonds in lipids and proteins; strong and numerous reducing agents in the form of natural antioxidants – vitamins, glutathione and thiol groups of proteins; as well as enzymes – catalase, peroxidase and superoxide dismutase, which neutralize radicals.

Secondly, even single free radicals that have reached the mitochondria of a neighboring healthy cell are able to engage in the normal functioning of their respiratory chains due to a chemical reaction with Coenzyme Q, a 50-fold excess of which in relation to other electron carriers (cytochromes, ferredoxins and dehydrogenases) is present in the inner membrane of mitochondria and diffuses freely in the membrane.

2. Activation of the disordered process of cell death – necrosis under conditions of deep or prolonged hypoxia, harmful to the surrounding tissues and to the organism as a whole. Disruption of apoptosis into necrosis is caused by a deficiency of oxygen and, consequently, a deficiency of free energy in the form of ATP and NAD(P)H, which are necessary to bring the energy-dependent process – apoptosis to the logical end.

3. Inflammation and autoimmune diseases. One of the last substrates inaccessible to proteases involved in apoptosis are transmembrane proteins of the plasma membrane. These proteins are present in apoptotic bodies, the end products of apoptosis, which are successfully captured by cells and digested by lysosomal enzymes of cells of the immune system. Interruption of this sequence of events under hypoxic conditions leads to the appearance of transmembrane proteins in the blood and to inflammation. The production of antibodies simultaneously against the external and intracellular epitopes of such proteins is likely to lead to autoimmune diseases accompanied by inflammation.

Some of these proteins may play the role of anchoring, that is, devices for mechanically fixing the contacts of a neuron and its extended processes with neighboring cells that have similar proteins

in their membranes, the external water-soluble fragments of which form strong isological dimers with similar fragments of proteins of neighboring cells. After the death of a neuron and the triggering of a specific protease that cleaves off the outer fragments of these proteins, the latter form a densely packed and poorly metabolized conglomerate – beta-amyloid, which accumulates in the tissues of an aging organism.

The transmembrane precursor protein of beta amyloid could play the role of anchor fasteners only if its intracellular part was associated with the polymeric proteins of the cytoskeleton. A candidate for such a polymeric microtubule-forming protein is tubulin. Simultaneously with the appearance of extracellular deposits of amyloid beta during degeneration of neurons and their processes, intracellular deposition of aggregates of tau protein associated with microtubules is recorded. The simultaneous appearance of intracellular and extracellular protein aggregates during neuronal degeneration may be the result of the degradation of a single system that fixes extended nerve processes as they pass through tissues.

4. Selective and reversible inhibition of the metabolism of a number of body cells under hypoxic conditions – mechanisms of oxygen saving (AMP-dependent protein kinase; ATP-dependent potassium channels; reversible inhibition of mitochondrial respiration by * NO radical, with the formation of nitrosylated hemes of cytochromes of the respiratory chain, not conducted by apoptosis). More on this in the second part of the review.

5. Cell poisoning due to a decrease in the activity of energy-dependent reactions for their detoxification and detoxification of the body as a whole: – a decrease in the activity of cytochrome P450 (NADPH-dependent), which carries out oxidative hydroxylation of xenobiotics – a reaction that stands at the beginning of numerous pathways of cell detoxification; – a decrease in the activity of the cell membrane glycoprotein Gp170 – ATP hydrolase, which energy-dependently removes organic pathogens of small molecular weight from the cell; – a decrease in the detoxification function of mitochondria, due to their death, due to the concentration in the mitochondria of a number of organs (liver), toxic metabolites and xenobiotics due to the energy of the difference in the electrochemical potential of the hydrogen ion on the inner mitochondrial membrane, followed by the fusion of mitochondria with lysosomes in the process of autophagy. Mitochondria, which occupy up to 30 % of the cell volume, are the most powerful detoxification systems that cleanse the cytoplasm from a large list of pathogenic factors of chemical and biological nature, thereby preventing chemical modification of various cytoplasmic enzymes by xenobiotics, thereby reducing the likelihood of metabolic chaos.

6. A decrease in the phosphate potential of cells under hypoxic conditions leads to qualitative and quantitative changes in the activity of hormonal systems of cascade regulation of metabolism, built on nucleotides and their derivatives (ATP, GTP, AMP, cyclo AMP, cyclo-GMP), as well as on regulatory enzymes: adenylate cyclases, guanylate cyclases and ATP-dependent protein kinases.

7. Qualitative changes in the systems of nervous regulation of metabolism: – decrease in the value of the potential of the cell membrane, leads to the problem of generation and propagation of the action potential; – a decrease in the ratio of guanine nucleotides (GTP / GDP) leads to significant problems in the synaptic transmission of a nerve impulse with the participation of G-proteins, which energetically remove a strongly bound neurotransmitter from the receptor due to the energy of GTP hydrolysis, thereby turning off the signal (solving the problem of the ratio selectivity and efficiency in the mechanism of synaptic signal transmission).

All of the above indicates hypoxia as a leading pathogenic factor in the disease of aging.

1.2. The Pathogenesis of Aging

This section discusses the sequence of events connected by a network of cause-and-effect relationships and representing the pathogenesis of the disease of aging: – hypoxia; – decrease in the rate of formation of free energy carriers (ATP and NAD(P)H); – degeneration of sensitive nerve endings of the ANS; – irreversible activation of the efferent part of the arc of the unconditioned reflex; – depletion and degeneration of the efferent part of the arc of the unconditioned reflex; – switching the regulation of cellular metabolism and adaptation from the ANS to a less efficient and slow-acting endocrine system; – loss of differentiated properties by the cells of the denervated periphery and the acquisition of the properties of undifferentiated cells – the ability to proliferate and migrate.

In local areas of organs, tissues or blood vessels, the listed stages of pathogenesis are at different stages of development, and therefore, in each organ or tissue, all stages of the pathogenesis of aging are simultaneously implemented. The main pathological consequences of each of the listed stages of pathogenesis and their manifestations in proliferative-degenerative diseases of senile age are considered.

Hypoxia initiates two independent primary structural events.

1) Death of free living cells by apoptosis or necrosis (see above). 2) Degeneration and slowing down of regeneration of afferent nerve fibers of the autonomic nervous system (ANS).

The sympathetic division of the ANS is responsible for stimulating the metabolism of activity (catabolism) associated with the fight-or-flight response. The parasympathetic division of the ANS is responsible for stimulating resting metabolism (anabolism): “rest and digestion” and “feeding and reproduction”.

Afferent fibers are not divided into sympathetic and parasympathetic.

Metabolism at rest is less intense than in a state of physical activity, since the main consumer of free energy is skeletal muscles that are inactive at rest.

The state of activity is characterized by sharp ups and downs of metabolic activity, in contrast to the slow monotonic changes in metabolism in a state of rest. It is in connection with these differences that the degeneration of afferent fibers in the first place negatively affects the efficiency of the functioning of the sympathetic rather than the parasympathetic division of the ANS.

The weak link in autonomic regulation is the afferent, sensitive nerve fibers, each of which departs from a small group of cells or from single specialized receptors (bodies). A decrease, for one reason or another, in the number of cells in such a group or in a specialized receptor innervated by a separate axon leads to an increasingly rare use of the nerve fiber and, as a result, to its degeneration.

The most common cause of degeneration of afferent nerve fibers, apparently, is the death of nerve endings under conditions of deep and/or prolonged hypoxia. Nerve endings are the most distant from the neuron body and oxygen deficiency, leading to a deficiency of free energy, should primarily affect the delivery of nutrients and “building materials” necessary to maintain the integrity of nerve endings and for their regeneration, namely in the nerve endings.

Such degeneration of nerve endings belongs to the physiological category, in contrast to pathological degeneration caused by a violation of the integrity of nerve fibers as a result of injury or inflammation.

Afferent nerve fibers carry out negative feedback in the arc of an unconditioned reflex, turning off the activating effect of efferent fibers on innervated cells.

Due to the presence of a second, nonspecific afferent system of the ANS, the afferent innervation performs not only the passive function of switching off (inhibition) of the efferent part of the unconditioned reflex arc, but also an active function – inhibition of the central structures of the ANS. This function is provided by pacemakers in each small group of cells from which a single

nerve fiber originates. Apparently, most of the time, it is the afferent fibers of the ANS that function, supporting with their signaling through the second, nonspecific afferent system, the inhibited state of the cells of the nuclei of the brain stem (including the hypothalamus).

In addition to the specific afferent system, there is a second or nonspecific afferent system. Information from peripheral sensory nerve endings, represented by many types of receptors (baroreceptors, mechanoreceptors, chemoreceptors, thermoreceptors) in this system is depersonalized, coming through collateral connections to the same neurons.

All nerve signals sent to the central nervous system along the sensory pathways of the nonspecific afferent system enter the reticular formation, which takes part in the activation of the cerebral cortex and in the control of the spinal cord. Signals from the periphery keep the reticular formation in a retarded state.

Signals entering the reticular formation from the cerebral cortex, for example, during stress or upon awakening, activate the reticular formation, thereby providing an integral response of the body to stress or to the initiation of wakefulness.

The nonspecific afferent nervous system of the ANS is an important part of the system of regulation of adaptation metabolism, which makes it possible to increase its rate tenfold.

The property of the most vulnerable link of autonomic innervation, afferent nerve fibers “owe” to several features.

1) The peripheral part of the afferent system of innervation is a “servant of two states” – the sympathetic and parasympathetic divisions of the ANS, working alternately, and the “master” of the central division of the ANS, participating in the regulation of its work through the second nonspecific afferent system. Afferent connections of the ANS function around the clock, which leads to their primary depletion and degeneration.

One of the most probable mechanisms for the depletion and death of afferent axons is the competition of two energy-consuming processes for a secondary energy source – a gradient of sodium cations on the plasma membrane. One of these processes is represented by the transmission of nerve impulses along an extended axon, and the other is the work of Na^+ -dependent glucose transport into a large volume of the cytoplasm. This is a system with mutual exhaustion, in which each of the processes slows down the other.

2) The presence of unique pseudo-unipolar neurons, when the same neuron provides energy-consuming transport of nutrients and mitochondria over long distances in two different directions, connecting the innervated periphery with neurons of the brain stem or with neurons of the spinal cord.

3) A large network of collaterals that communicate with the neurons of the second afferent system (additional energy costs).

4) A dense network of extended afferent nerve fibers of the ANS, each of which departs from a small group of cells of internal organs or blood vessels (high energy consumption for the operation of the network).

5) A decrease, for one reason or another, in the number of cells in such a small group, connected by electrotonic contacts and innervated by a separate axon, leads to an increasingly rare use of the nerve fiber and, as a result, to its degeneration.

As for the efferent part of the arc of the unconditioned reflex, it is devoid of this “disadvantage”, since its functioning is based on a huge number of neurons and neural networks of the central division of the ANS.

The efferent part of the arc of the unconditioned reflex of the sympathetic division of the ANS also has vulnerable links that contribute to its age-related degeneration.

1) The ganglia of the sympathetic part of the ANS, in which the neurons of the efferent part of the arc of the unconditioned reflex are localized, are supplied with blood (oxygen and nutrients) on a common basis with other cells of the body. while the neurons of the afferent part of the arc, located

in the nerve nodes of the spinal cord and the brain stem, are supplied with oxygen and nutrients in priority, like the neurons of the central nervous system.

2) Degeneration of the afferent part of the arc of the unconditioned reflex, which provides negative feedback between the periphery and the central structures of the ANS located in the parts of the brain stem, leads to irreversible activation of the work of the efferent part of the arc. Long-term non-stop work of neurons of the efferent part of the arc leads to their depletion and death.

However, even before the onset of depletion and subsequent death of neurons in the efferent part of the arc, such irreversible activation of neurons in the sympathetic part of the ANS leads to a number of pathological manifestations. Apparently, it is the long-term functioning of only the efferent part of the autonomic reflex arc, without feedback from the periphery that leads to hyperactivity of the sympathetic nervous system and to the initiation of the development of metabolic syndrome with an increased risk of developing type 2 diabetes, cardiovascular diseases and premature mortality [11].

An obvious additional mechanism for accelerating the pathogenesis of aging at this stage is the wasted oxygen consumption for the excessive and generally not required by the periphery of the activity of the sympathetic nervous system in the absence of a reverse inhibitory afferent connection with the periphery (autocatalytic process). This is one example of the aggravation of hypoxia at one of the stages of the pathogenesis of aging. The second mechanism for the aggravation of hypoxia, initiated by impaired afferent connections, is due to the cessation of the supply of inhibitory signals to the brain stem structures through the neural networks of the second afferent system.

Normally, the second afferent system transmits signals to the structures of the brain stem and, in particular, to the hypothalamus, inhibiting the activity of some of its nuclei. The cessation of this inhibitory activity due to the death of afferent endings, as a result, leads to a gradual release of inhibition and to the activation with age of some nuclei of the hypothalamus. A decrease with age in the intensity of inhibitory signals entering the hypothalamus through this system leads to activation of the endocrine system, designed to replace the regulatory function of the degenerated ANS.

Replacement of the nervous regulation of the periphery with the endocrine one is also realized in additional non-productive oxygen consumption, that is, in an increase in hypoxia. Degeneration of the afferent nerve processes of the sympathetic division of the ANS through the second afferent system activates the production of corticotropin releasing hormone (CRH) by the hypothalamus, which stimulates the synthesis and export of adrenocorticotrophic hormone (ACTH) by the pituitary gland, followed by an increase in the synthesis and export of cortisol by the adrenal glands.

The mechanism of an increase in oxygen deficiency when switching metabolic regulation systems is due to the differences in the regulatory systems of metabolism – the autonomic nervous system (No. 1) and the endocrine system (No. 2). The autonomic nervous system activates metabolism quickly (promptly) and targeted, in those local volumes of organs and tissues, in which there is a need for additional amounts of oxygen and nutrients. Signals about this enter the central control structures of the ANS, located in the brain stem along the afferent nerve connections.

As soon as there is a saturation with oxygen and nutrients of the considered local volume of an organ or tissue, negative feedback turns off the intensive supply of resources. Thus, targeted activation of metabolism for a short period of time means economical consumption of both oxygen and nutrients. A completely different situation with the consumption of oxygen and nutrients is realized in the case of the control of these processes by the endocrine system. At the request from the periphery (through the bloodstream, with a long delay) for an additional supply of oxygen and nutrients, there is a slow increase in the level of hormones in the blood.

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