PEPTIDES AND BIOREGULATION

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The expansion of active human life span is one of the most important aims of modern gerontology and prophylactic medicine as a whole. Present-day development of gerontology not only promotes our understanding of the mechanisms of ageing, but also opens new possibilities for the creation of geroprotectors, which are physiologically adequate for humans. Multipronged studies of the mechanisms of effect of peptides showed, that this class of compounds enables the most adequate response to these requirements. Recent genome level studies of peptides activity substantiate the classical data on the normalizing influence of peptides on age-related hormonal-metabolic and immune alterations.

The authors of the article develop a new concept giving a comprehensive view on evolutionary and biological role of peptides in the organism. Peptides exert a wide range of physiological effects, manifested in the regulation of the expression of certain genes and restoration of their structure, these effects being aimed at supporting homeostasis and holding back genetically predetermined ageing.

Preventing premature ageing and age-related pathology for the purpose of expanding life span and preserving active longevity of humans is one of the priority tasks of present-day biology and medicine.

Ageing is characterized by an intricate complex of molecular-genetic and biochemical alterations, which are accompanied by disordered peptidergic system of organism functions regulation. In terms of morpho-functional equivalents ageing may be defined as involution of organs and tissues, first of all of those related to the main regulatory systems - nervous, endocrine and immune. The study of processes underlying age-related involution of organs and tissues revealed a low level of physiologically active peptide substances production in these organs and tissues, which prompted a conclusion on the importance of peptides in the regulation of the mechanisms of ageing. The system of peptides is universal for neuroimmunoendocrine interactions. Alongside with that, peptide regulation of physiological functions of the organism involves tissue specific peptides, which support cellular homeostasis. Peptide bioregulators exist in different cells and tissues, are generated in the process of limited proteolysis, reveal a wide range of biological effects and coordinate the development and functions of multicellular systems. Being parts of a multilevel hierarchy, the mechanisms of peptide regulation of homeostasis perform one common task, consisting in the coordination of biosynthesis in organism cells by affecting gene expression (Khavinson, Malinin, 2005).

Due to the close interconnection of immune functions and ageing, the study and design of medications for correcting stress-induced immune deficiencies and preventing premature ageing are of utmost importance.

Present-day development of medicine is characterized by significant achievements in the design of peptide immunomodulators, in the study of their clinical efficac y and in the substantiation of the expedience of their use in the complex treatment of different diseases and pathologies.

We have proposed a concept of peptide thymomimetic regulation of protective and restorative functions of the organism, based on small peptides, which are involved in the proliferation and differentiation of T-lymphocytes. Our concept enables new approaches to the design of peptide medications revealing thymomimetic and immunomodulating effects. It was revealed, that natural and synthetic peptide thymomimetics play an important role in the regulation of cellular immunity, as well as of inflammatory and regenerative processes. Theoretically and practically important data prompted a conclusion that peptide thymomimetics originate not only from the thymus, but also from other cells, which produce such peptides in the process of limited proteolysis using predecessor proteins (cytokines, growth and thymic factors, immunoglobulins and other proteins) within close proximity of T-lymphocyte receptors. This enables the organism to perform thymomimetic regulation in damaged tissues without direct dependence on thymus functions. This supports the idea of a universal system of bioregulation, which is based on tissue specific oligopeptides, selectively transmitting the information, which is vital for supporting cellular homeostasis, by means of interaction between immune, nervous and other systems cells.

Presently we possess pathophysiological data pointing out the expedience of using peptide thymo-

mimetics as pharmaceuticals in case of thymus dependent immune incompetence and reduced resistance of the organism. The use of peptide medications with thymomimetic and immunomodulating activity for the correction of immune disorders caused by adverse impacts substantiates high clinical and immunologic efficacy of these medications. Peptide medications are useful as a part of a complex of rehabilitation measures after extreme impacts for the prevention of premature ageing, for the improvement of protective functions and adaptive capacities of the human organism.

The importance of the physiological role of peptides in the regulation of ageing confirms the expedience of study and design of peptide geroprotectors. Design of effective geroprotectors becomes more and more important due to the widening range of adverse impacts on the human organism and premature development of age-related pathology. Adaptive transformations under the impact of premature ageing factors take place against the background of age-related alterations in neurohumoral regulation and the decline of tissue specific proteins synthesis. This ultimately infringes the reserve capacities of the organism, accumulates catabolism products, promotes destructive processes, disorders cell functions and entails the development of diseases. In spite of an existing range of theories on ageing, there is a logical interconnection between the effects of all known factors, which successively launch the genetic program of cell degeneration. The leading role in this case belongs to the changing expression of different genes, regulating cell proliferation, differentiation and death.

It is noteworthy, that among all known peptide geroprotectors dipeptide carnosine (_-Ala-His), which was the first endogen peptide substance to be discovered, plays a special role. Geroprotective activity of carnosine is related mainly to the antioxidant activity of this peptide substance.

The study of structural and functional features of peptides is fundamentally important for the understanding of the mechanisms of their geroprotective effect. Several peptide substances with geroprotective properties were synthesized after the analysis of amino acid composition of natural polypeptides. Comparative study of the biological activity of polypeptides and synthetic peptides showed a range of similar effects on different organs and tissues of the organism in the norm and in pathology (Khavinson, 2002).

Geroprotective activity of both polypeptide and synthetic peptide medications is related to their impact on the mechanisms of antioxidant protection and hormonal regulation. The administration of thymus and pineal gland peptides to mice and rats of different lines caused a reliable increase in the mean lifespan by 30-40% and suppressed the growth of spontaneous, induced and transplanted tumors in animals with respect to the control (Anisimov, Khavinson, 2003). The animals showed restored levels of melatonin and antioxidant enzymes, as well as normalized components of mitochondrian respiratory chain. The administration of pineal gland peptides to old monkeys reliably restored the level of melatonin, cortisol and glucose in the blood up to the level of young animals.

Small peptides stimulate the processes of tissue regeneration, restore cellular metabolism in the lymphocytes, macrophages and fibroblasts, normalize vascular permeability, activate neoangiogenesis, reduce inflammatory reactions and accelerate the healing of wounds.

Peptides, which are generated from proteins in the process of digestion, are much faster transported by intestinal regulatory systems. This substantiates the nutritional value of biologically active peptides, which are received with food, as well as their ability to coordinate the functioning of organism regulatory systems. It was shown, that small peptides exert a regulatory effect on the activity of gastrointestinal tract enzymes in ageing. The studies of small peptides effect on the activity of old rats' digestive enzymes pointed out, that the improvement of small intestine enzyme system functions after the administration of peptides contributes to a better assimilation of food, as well to the normalization of digestive functions in ageing.

Data received in genome level studies of peptides supplement our knowledge of the normalizing effect of peptides on age-related hormonal-metabolic and immune alterations (Khavinson, Malinin, 2005).

Experimental studies of small peptides confirmed the hypothesis stating that geroprotective effects of these substances are largely related to the regulation of gene expression and biosynthesis processes, which become disordered with age. It was found, that peptides Thymogen (Glu-Trp), Vilon (Lys-Glu), Epitalon (Ala-Glu-Asp-Gly), Cortagen (Ala-Glu-Asp-Pro), Livagen (Lys-Glu-Asp-Ala) and Prostamax (Lys-Glu-Asp-Pro) restore DNA structure and reduce the occurrence of chromosome aberrations in case of irradiation, chemical impacts and hypokinesia. The introduction of peptides into the culture of older humans' lymphocytes entailed the decondensation of densely packed chromatin fibrils, which correlates with the restored expression of genes, which were repressed by the condensation of euchromatin zones in ageing.

The administration of small peptides to mice altered the profile of gene expression in animal myocardium and brain. Transgenic mice treated with peptides showed a 2-4-fold suppression of HER-2/neu mammary gland cancer gene expression, which correlated with reduced adenocarcinoma size. The influence of peptides on IL-2 and c-fos genes expression provides for oncomodifying and stress protective properties of these substances. Treatment of human fibroblasts with Epitalon peptide induced the telomerase activity and caused the increase in the mean length of telomeres by 2.5 times as compared to the control. This increased the number of cell divi-

sions by 42.5%, i.e. enabled the overcoming of Hayflick's limit.

The study of peptides effect on the expression of different genes and DNA synthesis in different experimental models prompted an assumption that small peptides serve as activators and agonists for transcriptional factors. Complementary site-specific binding of a peptide in the DNA major groove is a primary start signal for the binding of the transcriptional factor with the promoter (Khavinson et al., 2005). Experiments revealed the formation of a complex involving a tetrapeptide and DNA double helix. Peptide binding with the double helix is accompanied by a hyperchrome effect, which points out the local splitting of double helix strands entailing the launch of protein synthesis in the cells.

Studies of molecular-genetic mechanisms of peptides effect enabled a new concept, which reflects the evolutionary-biological role of peptides in the organism in most details. Peptides and the DNA are two classes of biopolymers, which carry information and exchange it at the moment of gene transcription initiation. The interaction between peptides and DNA restores the expression and structure of genes. This provides for genetic stability and normalization of age-related metabolic disorders, prevents age-related pathology and expands the lifespan up to the specific limit (Khavinson, Malinin, 2005). Peptides may be also regarded as informational regulators of genetic stability. Hence the stabilization of main physiological functions and the deceleration of organism ageing. This finding is even more important with respect to the determining role of the genetic apparatus in the mechanisms of individual development and the occurrence of many diseases. It is noteworthy, that regulatory peptides are a new generation of medications producing a corrective physiological effect without any side effects.

The creation of peptide-based medications enabled the development and introduction to clinical practice of bioregulation therapy - a new technology of correcting the genetic predisposition of the organism to age-related pathologies and of restoring cell functions, which become infringed with age. This technology is based on the complex administration of peptide regulators of genetic stability and cellular metabolism for prophylactic and therapeutic purposes. Peptides normalize main physiological functions, enhance adaptive capacities and decelerate the process of organism ageing. The administration of thymus and pineal gland peptides to old and very old patients restored the level of melatonin, as well as the indices of antioxidant, immune, endocrine and cardiovascular systems and brain functions. Thus death rate in this group of patients was reduced by 2 times during 8-12 years of the study.

Thus, ageing is an evolutionarily determined biological process of age-related alteration of the expression and structure of genes. As a consequence, the synthesis of regulatory tissue specific peptides in different organs and tissues is infringed, causing structural and functional alterations and diseases. Small peptides are a new group of cellular transmitters playing an important role in the regulation of histogenesis, regeneration, immunity and inflammation. Further studies of mechanisms underlying the activity of small peptides opens new prospects for the concept of peptide regulation of ageing, as well as for the design of effective geroprotectors.

REFERENCES

1) Anisimov V.N., Khavinson V.Kh. Small peptide-associated modulation of aging and longevity // Modulating aging and longevity. - Kluwer Academic Publishers (Printed in Great Britain) - S.I.S. Rattan (ed.), 2003. - P. 279-301.

2) Khavinson V.Kh. Peptides and ageing. - Neuroendocrinology Letters. - Special Issue, 2002. - 144 p.

3) Khavinson V.Kh., Malinin V.V. Gerontological aspects of genome peptide regulation. - Basel: Karger, 2005. - 104 p.

4) Khavinson V., Shataeva L., Chernova A. DNA double-helix binds regulatory peptides similarly to transcription factors // Neuroendocrinology Lett. - 2005. - V. 26, N. 3. - P. 237-241.