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Peptide Bioregulators: A New Class of Geroprotectors. Message 1: Results of Experimental Studies

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Abstract—This review summarizes the results of long-term research of authors who studied the mechanisms of aging and the effectiveness of peptide bioregulators in preventing age-related diseases in laboratory animals. The data on evaluating the peptide effects produced using the advanced techniques in research institutes in Russia and abroad are presented. The most attention is focused on the ability of peptide bioregulators to increase the life span and inhibit the carcinogenesis in animals.

Key words: peptides, bioregulators, cytomedines, cytogens, geroprotective effect, carcinogenesis, aging
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Experimental studies that have been performed at Kirov Military Medical Academy since 1973 provided the basis for the new scientific concept of peptide bioregulation, which was formulated by V. G. Morozov and V. Kh. Khavinson in 1983 [39, 40]. It was revealed that cells produce low-molecular-weight compounds of a peptide nature, which provide the intercellular transfer of certain information encoded in the amino acid sequence and conformational modifications, thus regulating proliferation, differentiation, and intercellular interactions. These substances were isolated from various tissues and called peptide bioregulators, or cytomedines (from Greek "kitos" for "cell" and Latin "mediator," meaning "transmitter"). The main function of cytomedines is the normalizing effect on tissues of the organ; they were derived from and also substitute or complement biologically active substances secreted by this morphological structure [24, 27, 28, 39, 69].

Peptide bioregulators were initially isolated from the pineal gland, thymus, and hypothalamus [36, 37]. In addition to their influence on CNS, these compounds provided protective function for the organism and reproductive organs. Then, peptide bioregulators were isolated from the vessel wall [6, 30], bone marrow [6, 38, 54], various parts of the CNS [12, 20, 35], the retina and lens [41, 66, 69], all endocrine glands [12, 20, 27, 35], the placenta and its membranes [28], heart [27, 28, 49], various regions of gastrointestinal tract [27], kidneys, liver, lungs and bronchi mucous membrane [28], cartilage, bone, periosteal coverage [41], bladder [41], parodontium, submandibular and parotid glands [27], erythrocytes [28], leukocytes [27, 38], thrombocytes [28], blood plasma [26, 27], lymph [27], etc.

It was revealed that peptide bioregulators participate in the regulation of gene expression and protein synthesis. This fact is in accordance with the concept of the regulation of cascade peptide of physiological functions of the organism formulated by I. P. Ashmarin [17, 18]. Regulatory processes result in the prevention or suppression of DNA damage, mutations and pathological transformations and stimulation of reparation, which is aimed at restoring cellular homeostasis despite the action of pathogenetic factors [55].

In 1999, V. Kh. Khavinson suggested the method of creating peptide bioregulators synthesized based on the analysis of the amino acid composition of peptide extracts isolated from animal tissues and consisted of two to four amino acids [68]. Synthesized short peptides were shown to possess properties of natural peptide bioregulators [24, 25, 43, 61, 85, 88]. Moreover, short peptides have an effect in considerably lower concentrations than peptide extracts.

The study of short peptides with the determined structure allowed us to not only study the mechanism of their action, but also to create a new class of peptide bioregulators termed cytogens. Short peptides are able to interact with DNA regions and thus affect the genome condition and consequently the synthesis of certain proteins, including those that control the physiological functions of the organism [72, 85, 88].

It has been shown that many natural and synthetic peptide bioregulators possess marked geroprotective and antitumor activity [2–8, 10–13, 23, 48, 53, 54, 61, 64, 70–72, 78, 85, 88, 90], as well as promote the resistance of the organism to stress [31, 48].

In this review, we will consider the properties of the most-studied natural and synthetic peptide bioregula-

tors. All experiments on animals were performed in accordance with the World Medical Association Declaration of Helsinki from 1964 with the changes from 1975, 1983, 1989, and 2000.

Thymalin

In 1974, V. G. Morozov and V. Kh. Khavinson developed the method of isolating low-molecular-weight peptides from calf thymus, which resulted in the creation of the first drug from the class of peptide bioregulators called "thymalin" (registration number 82/1108/8, USSR Ministry of Health Order No. 1108 from November 10, 1982) [44]. The first observations showed that thymalin stimulated the expression of receptors on T- and in to a lesser extent on B-lymphocytes in in vitro experiments. The effect of thymalin was the most pronounced in cases when lymphocytes of the secondary immunodeficiency patients were used in experiments [22, 42].

The injection of thymalin in guinea pigs stimulated both lymphoid and epithelial components of thymus. Furthermore, the structure of the thymus changed due to the proliferation and differentiation of lymphoid elements and an increase in the number of mature lymphocytes in it [62, 63]. The injection of thymalin in rats decreased the titer of complement but increased serum bactericidal activity and β-lysins content. In this case, the number of karyocytes in the thymus decreased, but the total number of leukocytes in blood and karyocytes in the spleen increased. Consequently, thymalin activated the cell population of lymphoid organs and stimulated the migration of lymphoid cells [19, 36, 42]. The injection of thymalin in thymectomized animals restored the number of T-cells in the blood, spleen, and lymph glands [19, 37, 42, 62, 63]. The injection of thymalin in thymus-deprived mice decreased the rejection terms of the allogenic graft and evened them with values characteristic of the control animals [51].

Administration of thymalin caused increase in number of T-lymphocytes in blood and thymus of guinea pigs with radiation induced immunodeficiency. Activation of proliferation and differentiation of thymocytes and regeneration of thymic histoarchitecture were also observed in this case. Thymalin enhanced both colony-forming and cluster-forming abilities of granulomonopoietic precursors, which is indicative of its stimulating effect on the proliferation and differentiation of bone-marrow stem cells [50].

Thymalin had moderate anticoagulant effect and suppressed fibrinolysis in vitro. The preparation modulated gemostatic reactions that reset blood coagulability and fibrinolysis in in vivo experiments [27–29].

The administration of thymalin by irradiated mice and rats for 10 days every month caused a double decrease in number of malignant neoplasms. The use of thymalin resulted in 3.5-fold decrease in number of tumors in mice undergone fractionated irradiation. Tumor frequency in female rats injected with 7,12-dimethylbenz[a]anthracene and thymalin decreased by 24%; the analogous value for mammary adenocarcinoma frequency was 3.8 times [58]. The cases of leukemia were not fixed in the group of mice given thymalin, while in the control group, it was observed in 13.4% of cases. The frequency of spontaneous tumors in SHR line mice given thymalin since the age of 4 months decreased by up to 40% compared to 55% in the control group. The frequency of spontaneous tumors and mammary adenocarcinoma in C3H/Sn female mice given thymalin for their entire lives since the age of 3.5 months decreased by 2.8 and 2.6 times, respectively [4–6, 10, 45, 58].

The latent stage of tumor growth increased by 1.5–2.5 months in rats that had undergone treatment with N-nitrosoethylurea in antenatal life and had been given thymalin for their entire lives since the age of 2.5 months. In this case, the frequency of tumors in spinal medulla decreased by one-third [58].

It was revealed that thymalin increased the content of cAMP and decreased the level of cGMP in T-lymphocyte precursors and thymocytes. At the same time, spleen cells treated with thymalin showed an increase in cGMP concentration, which was accompanied by enhanced proliferative activity of splenocytes [33]. The injection of thymalin into rats and rabbits with an experimental model of hyperlipidemia and atherosclerosis resulted in a decrease in the cholesterol level in the blood, liver, and aorta; atherosclerotic changes in the aorta were far less pronounced than in the control group [43].

It is evident that thymalin's ability to decrease the frequency of tumors and atherosclerosis and also increase the lifespan of experimental animals allows classifying it as a geroprotector.

Thymogen

It was revealed that extracts isolated from the calf thymus contain peptides with molecular weights of less than 1000 Da. One of these substances turned out to be a dipeptide, Glu-Trp, which was called "thymogen" [41, 92]. This peptide was isolated from thymalin, then synthesized and is now used in medicine and veterinary (registration number 90/250/1, USSR Ministry of Health Order No. 250 from June 19, 1990).

Thymogen enhanced lymphocyte transformation and regulated the level of proinflammatory cytokines IL-1α, IL-8 and TNF-α in in vitro experiments [43].

The administration of thymogen for 30 days resulted in an increase in the number of lymphocytes in control animals. Thymogen caused a marked increase in the number of T-lymphocytes in thymus-deprived animals. The doses of thymogen were 100–1000 times less than the doses of thymalin [75]. The comparative study of the effect of immunomodulating peptide drugs, i.e., thymalin and thymogen, on the immune response in rats immunized with sheep eryth-

rocytes revealed that thymogen had a more pronounced effect. Thymogen caused an increase in the amount of spleen antibody-producing cells with an increased concentration of cyclic nucleotides. Lymphocyte transformation under the action of phytohemagglutinin was more intensive in these rats. Thymogen restored T- and B-systems of immunity in animals with experimental immunodeficiencies.

The active transmembrane Ca^{2+} exchange and redistribution of intracellular concentrations of cAMP and cGMP are responsible for the molecular mechanism of the preparation. Changes in DNA replication, transcription, and reparation that induce gene expression with the subsequent proliferation and differentiation of certain lymphocyte populations occur as a result [43].

In guinea pigs infected with pseudotuberculosis, the 6–15-day administration of thymogen resulted in the restoration of the cell content of immunity organs and the functional activity of lymphocytes and neutrophiles. In the height of disease injection of the preparation decreased dissemination of causative agent by five times in the liver and mesenteric lymph nodes and by ten times in the spleen and enhanced production of specific agglutinins [64]. The administration of thymogen for 1 year suppressed radionuclides that induced carcinogenesis in rats; the frequency of all tumors decreased by 3.3 times, while the frequency of mammary adenocarcinoma decreased by 6 times. Moreover, the lifespans of animals increased by 14% [58].

The shown data are apparently indicative of the geroprotective effect of thymogen.

After that, the Lys-Glu dipeptide was synthesized and called "vilon" [68]. The injection of vilon into animals in concentrations of 10 ng/L to 100 μg/L caused an increase in the intracellular Ca^{2+} level in thymocytes and macrophages, which is one of the mechanisms of cell activation. It was revealed that vilon stimulated the synthesis of IL-2 mRNA in mouse spleen lymphocytes after 5 h of incubation [43]. Vilon significantly increased the receptor expression in T- and B-lymphocytes of secondary immunodeficiency patients, as well as stimulated the production of IL-1α, IL-1β, IL-8, and TNF-α in in vitro experiments. At the same time, vilon diminished IL-8 production in astrocyte culture but increased the synthesis of IN-g in lymphocytes [43]. In thymocytes and epithelial cells, vilon stimulated the expression of argyrophilic proteins in nucleolar organizer regions (NOR), which are responsible for the synthesis, assembly, and transport of ribosomes into the cytoplasm, in such a way as to determine the intensity of protein synthesis that occurs in these structures. The addition of vilon into culture medium resulted in the transformation of the lymphocyte into blast proliferating cells, which is connected with the enhanced functional activity of NOR and ribosome genes localized there and, consequently, with an increase in the speed of ribosome RNA synthesis [70, 75]. Moreover, vilon caused the activation of genes repressed due to the heterochromatization of euchromatic regions of chromosomes that is observed at aging. The administration of vilon increased the viability of rats irradiated with a dose of 6 Gy promoted the restoration of the thymus and spleen, as well as stimulated the reparative processes in the irradiated organism [43, 72]. The injection of vilon in a dose of 0.01 μg/kg for 6 days in mice of the CBA line was accompanied by the increase in the T-lymphocyte content in spleen. Furthermore, vilon enhanced the spontaneous and induced ability of macrophages to restore chemotactic and phagocytic abilities of neutrophiles [43].

Vilon, thymalin, and thymogen possess marked nootropic effects. It was shown that thymalin enhanced development and memorizing of active avoidance; thymogen promoted locomotor and passive avoidance; and vilon stimulated passive and active avoidance [64]. The administration of vilon promoted an increase in the number of lymphocytes in peripheral blood, enhance of activity of acid phosphatase in histiocytes (in proliferation phase) in rabbits with septic wounds of soft tissues. Fast cleansing from necrotizing tissues and enhanced epithelialization of wounds were simultaneously observed [64]. Vilon addition after partial hepatectomy stimulated hepatic regeneration that was seen in enhanced mitotic activity of hepatocytes.

The injection of vilon promoted the activation of regenerative processes in sublethally irradiated animals. In this case, the differentiation for the cortex and marrow was clearly seen in thymic lobules. The proliferative activity in lymphoid follicles and extramedullary hemapoiesis zones increased by 1.6 and 4 times, respectively, in the spleens of rats given vilon. Furthermore, the population density of Ig-containing cells increased by 1.7-fold. Moreover, hyperplasia of thymic mast cells was observed under the action of vilon. It is possible that vilon activates the proliferative activity of marrow stem cells (precursors of T-lymphocytes and mast cells) that survived after γ-irradiation [43].

The administration of vilon by 5-day-long courses over the entire lifespan beginning from the age of 6 months promoted an increase in the maximum lifespan and decreased the frequency of spontaneous tumors by 1.5 times in CBA mice. Vilon caused a 2.5-fold decrease in pulmonic adenoma in mice. It also decreased the frequency of mammary adenocarcinomas in them. The number of mice that reached the age of 23 months was 2.6 times greater in the group given vilon compared to the control group. Furthermore, the maximum lifespan under the action of vilon increased by nearly 2 months compared to the control group [56, 57, 64, 72, 79]. It is evident that vilon is a geroprotector, as well as thymalin and thymogen.

Epithalamin

A polypeptide complex isolated from the pineal gland, called "epithalamin" (registration number 90/250/6, USSR Ministry of Health Order No. 250 from June 19, 1990) is able to decrease the threshold of hypothalamic estrogen sensitivity and restore regular estrous cycles in old rats with constant estrous [12, 14]. The administration of epithalamin provided the restoration of the immune status in old animals. Moreover, epithalamin injections into mice immunized by sheep erythrocytes resulted in an increase in the amount of spleen antibody-producing cells and enhanced the titer of hemagglutinins and hemolysines in blood. Epithalamin caused a significant increase in the viability of CC57Br/Mv mice infected by *Salmonella tiphimurium* and enhanced the activity of phagocytic activity and the extension of the engraftment rate [48].

Rats without pineal glands demonstrated a disorder in the proliferation of granulocytes and macrophages. In the case of epithalamin administration, these processes were restored up to the normal condition. Epithalamin enhanced the concentration of thymic factors that promote the growth and maturation of T-lymphocyte populations in plasma of young mice. An analogous but less marked reaction was observed in old mice, which also had an increased number of antibody-producing cells in spleen.

The rapid maturation of cortex lymphocytes, hyperplasia, and medullar differentiation of thymic epithelial cells were observed in AKR mice given epithalamin for a long time. The tumor frequency in female rats injected with epithalamin since the age of 15 months decreased by 1.6 times. The analogous value for malignant tumors was 2.7 times. The course of the administration of epithalamin (5 days per month) by female mice since the age of 3.5 months resulted in a 2.1-fold diminution of frequency of all tumors and 2.9-fold decrease in frequency of mammary adenocarcinoma [3, 6–8, 11, 70]. The most efficient malignant tumor suppression was observed in mice simultaneously administering epithalamin and thymalin.

Daily epithalamin injections in the dose of 2 mg per a mouse caused suppression of growth of transplantable breast cancer (PCM strain) by 76–88%, cervical cancer by 55–87%, hepatoma 22a by 31–51%. At the same time the preparation increased the average lifespan of mice with intramuscularly inoculated lymphocytic leukemia by 31–67% but did not affect the viability of mice with intraperitoneally transplanted L-1210 leukemia, the growth of sarcoma-180 and Harding–Passey melanoma, or the development of the ascitic strain of Ehrlich carcinoma, although it did prevent the metastasis of cancer cells [48]. Epithalamin significantly enhanced the antineoplastic effect of cyclophosphan dermoid cervical cancer in mice.

Epithalamin injections in C3HA mice with subcutaneously transplanted hepatic carcinoma (hepatoma 22a) starting from the eighth day for 9 days caused an approximately fourfold decrease in tumor size compared to the control group. Moreover, tumor tissue in the experimental group of mice had large necrotic regions with only islets of cancer cells among them; among the latter, cells with dark nuclei and pronounced dystrophic changes prevailed. There was large unicellular sclerosis among the islets of remaining tumor cells that was not noted in control animals. Consequently, epithalamin caused not only the suppression of growth in the transplanted hepatic tumor, but also its destruction accompanied by cell death and their substitution by the connective tissue in mice [34].

Epithalamin suppressed the metastasis of Pliss lymphosarcoma and Lewis lung carcinoma [7]. It also had a strong antileukemic effect, i.e., suppressed neurosecretion, which was accompanied by a decrease in the level of somatotropic hormone [34].

Epithalamin inhibited radiation carcinogenesis by decreasing the number of tumors by 2.7 times [11]. Daily epithalamin consumption significantly inhibited blastomatous growth induced by 7,12-dimethylbenz[a]anthracene in female mice. The control group had adenocarcinoma in 81.1% of cases, while this value was only 25.7% for the experimental group. Moreover, multiple adenocarcinoma formation decreased by four times [8]. Epithalamin suppressed carcinogenesis induced by single, full-body X-irradiation. In this case, the frequency of malignant tumors (mammary adenocarcinoma, tumor of uterus, ovaries, thyroid gland, etc.) generally decreased by 2.7 times. Transplacental carcinogenesis was suppressed under the action of epithalamin; the frequencies of tumors in bone marrow, kidneys and peripheral nerves decreased by 28, 25, and 15%, respectively [20].

It was revealed that animals with transplanted tumors that had undergone treatment with a carcinogenic agent had significantly lower sensitivity to estrogens. It is possible that epithalamin injections restore endocrine regulation, which is accompanied by the growth suppression of hormone-dependant tumors [48]. Furthermore, epithalamin promotes the restoration of a normal level of p53, which enables the suppression of tumor growth [70].

It is known that the lack of a pineal gland causes a decrease in the lifespan of experimental animals. Epithalamin administration (five times per week for 20 months) by female rats since the age of 3.5 months extended their lifespan by 25%. The continuous injection of epithalamin in C3H/Sn mice began at the age of 3.5 months and promoted an increase in the average lifespan by 40%. In this case, the maximum lifespan increased by 3.5 months, i.e., up to the top species limit [6].

In female rats, aging is accompanied by an increase in the sensitivity threshold of the hypothalamic-pituitary complex that regulates the secretion of gonadot-

ropin to the inhibiting action of estrogens, followed by the termination of reproductive function. When old female rats were given epithalamin, their sensitivity threshold of hypothalamic-pituitary system to estrogen inhibition decreased and regular estrous cycles were restored [14]. Furthermore, almost 40% of female rats at the age of 16–18 months had estrous dysfunction. This deviance was observed 5.5 times less frequently in animals injected with epithalamin from the age of 3.5 months. Some of the rats that were kept together with males got pregnant. This fact was not observed in the control group [64].

Epithalamin injections caused an increase in the blood concentration of luteinizing hormone and testosterone in old male rats. These data are indicative of the normalizing effect of pineal gland polypeptides on the reproductive function of old animals [7, 89].

The use of epithalamin significantly (by 17%) increased the average lifespan and decreased the age rate by 2.12 times in female *Drosophila melanogaster* of the VES line. Moreover, epithalamin caused a marked diminution in the concentration of conjugated hydroperoxides and ketodienes in female fly tissues. This effect ameliorated sex differences in the lipid peroxide content, the level of which was far higher in female flies than in males in the control group [65, 75, 90]. The administration of epithalamin enhanced the activity of the enzymes responsible for energetic processes in CNS (succinate, α-ketoglutarate, and pyruvate dehydrogenases) in the control animals.

It was shown that rats that lacked pineal glands had damage to certain types of learning, an increased number of trial movements, and a longer search time for the necessary object 10–30 days after operation. These changes were totally removed under the action of epithalamin. The effect of epithalamin was accompanied by the enhanced formation of conditioned visual detection (39% in average) due to faster adaptation. Moreover, epithalamin promoted learning motivation, and increased the percentage of correct responses in fear conditioning. Consequently, epithalamin stimulates motivation mechanisms of learning [28]. The administration of epithalamin decreased the rhythmic depression index and extended forced swimming time in rats [28]. The intravenous introduction of the preparation caused a sedative effect in dogs. The sleepy state lasted for 2–3 h [28].

The introduction of epithalamin for 10 days activated the neurosecretory elements in paraventricular and supraoptic hypothalamic nuclei and increased the accumulation of neurosecretion in neurohypophysis [73]. The stimulation of pinealocytes was observed in rat pineal glands after the injection of epithalamin [73]. The single or daily morning epithalamin administration for 5 days caused an increase in the concentrations of serotonin, N-acetylserotonin, and melatonin in the pineal gland at nighttime in young rats [23].

The 5-day-long introduction of epithalamin into young rats resulted in an increase in the triiodothyronine level and decrease in thyroxin concentration in blood. In old rats epithalamin reduced concentrations of both hormones. An increase in the level of corticosterone and aldosterone in the blood and a decrease in the concentration of the adrenocorticotropic hormone were noted in male rats 1 h after the injection of epithalamin. The 5-day-long introduction of epithalamin to old CBA/Ca rats caused a decrease in the level of corticosterone in the blood, which was accompanied by the restoration of the sensitivity of the pituitary–hypothalamic system to corticosteroids [49]. The administration of epithalamin for 3 weeks caused a decrease in the blood concentrations of insulin and triglycerides and an increase in the glucose tolerance in rabbits.

It was revealed that epithalamin directly affects the pancreatic insular area. The introduction of epithalamin caused increase in carbohydrate tolerance after glucose loading and lowering of the basal insulin level. In this case, the stimulation of basal and reactive insulinemia was observed during the first week, while the insulin level decreased in the course of peripheral glucose disposal in 3 weeks [28].

Epithalamin caused an increase in the number of T-lymphocytes and antibody-producing cells in the spleen; stimulated an immune response; increased the titer of hemagglutinins and hemolysines; significantly reduced disseminated intravascular coagulation; and normalized the functions of cardiovascular system and kidneys in wound- and burn-shocked rats and dogs, which was accompanied by the increased viability of animals. The activation of the pituitary–adrenal system plays an important role in antishock action of epithalamin; a decrease in cAMP and an increase in cGMP concentrations underlie it on the cellular level [49, 64].

The introduction of epithalamin into lactating rats and goats caused a significant increase in the secreted milk and enhanced concentrations of lactose, whey proteins, and casein. The effect was most pronounced in the middle of the lactating period [28].

It was shown that aging is accompanied by a marked change in the activity of free radical reactions in the animal organism. The administration of epithalamin caused a 3.4-fold suppression of the intensity of chemiluminescence and LP in blood serum, which was seen in the pronounced diminution of diene conjugates (4.1 times). In this case, the content of Schiff bases decreased insignificantly (by 14.4%). The introduction of epithalamin provided a reliable 35% increase in the total antioxidant status of the blood serum of male rat and 19.7% increase in the SOD activity [67, 77].

Epithalamin is one of the most efficient geroprotectors, which significantly increases the lifespan of control animals in various pathological conditions [9].

An Ala-Glu-Asp-Gly tetrapeptide was synthesized based on the amino acid composition of epithalamine

and named "epithalon" [55, 86]. It possesses properties similar to those of epithalamin. Both epithalon and epithalamin stimulated the growth of explants of subcortical brain structures in vitro and acted as a neuroendocrine system bioregulator in vivo. Mice of the CBA and SHR lines given epithalon had shorter estrous cycles, lower somatic temperatures, and decreased spontaneous carcinogenesis; however, their body weight and average and maximum lifespan increased [80, 81]. The introduction of epithalon to old female monkeys (20–26 years) for 10 days at 9 p.m. caused a threefold increase in the level of melatonin, which was two times less than in young animals (6–8 years) in the control. Moreover, their level of melatonin surpassed that in young animals. This effect was accompanied by the restoration of the circadian rhythm of cortisol in the blood. This reaction was not observed in young monkeys given epithalon, which is indicative of the geroprotective activity of the peptide [23, 70, 83].

The decrease in stress induced enhanced expression of C-fos was observed in neurosecretory hypothalamic nucleus (PVH). The injection of epithalon caused an increase in the C-fos concentration in pinealocytes under the conditions of chronic stress. Consequently, epithalon takes part in the activation of pinealocytes under extreme conditions [70].

Epithalon decreased the frequency of rarely discharging pinealocytes (0.05–0.01 cps) with irregular activity by 35–40% and the frequency of frequently discharging pinealocytes (2.0–0.4 cps) with regular activity by 25% [47]. The intranasal introduction of epithalon decreased the discharging frequency of all types of pinealocytes by 30%.

V. N. Anisimov et al. [13, 15] made subcutaneous injections of epithalon to female transgenic FVB mice bearing the *HER-2/neu* breast cancer gene (1 μg per mouse; 5 days per month since the age of 2 months). The peptide suppressed neoplasia. The maximum size of mammary adenocarcinoma in mice given epithalon was 33% less than in the control group. Moreover, *HER-2/neu* mRNA expression in mammary adenocarcinoma in mice given epithalon was 3.7 times lower than in the control group. The suppression of breast carcinogenesis in transgenic mice may be caused by the inhibition of *HER-2/neu* expression under the action of epithalon [82].

I. A. Vinogradova et al. revealed that introduction of epithalon to rats during the day had a normalizing effect on the majority of parameters in animals kept under conditions of constant and natural lighting regimes and inhibited aging and age-specific abnormalities, including tumors, as well as increased the lifespan [21].

V. Kh. Khavinson et al. showed that the addition of epithalon into human lung fibroblast cultures and incubation for 30 min at 30°C induced telomerase expression, telomerase activity and promoted telomere elongation by 2.4 times [61, 70]. Activation of the gene expression was accompanied by the increase in number of cell divisions by 42.5%. Consequently, epithalon promotes the lifespan of diploid human cells because the Hayflick limit is surpassed [70, 88].

The introduction of epithalon to rats of the Campbell line with inherited retinitis pigmentosa extended the functional activity of retina. This effect may be achieved due to epithalon's ability to bind to either a certain DNA region or protein transcriptional factors [66].

S. V. Anisimov et al. studied the expression of 15247 gene clones in mouse hearts using microarray technology and revealed that epithalon increased the expression of 194 clones (maximum by 6.61 times) and decreased the expression of 48 clones (maximum by 2.71 times) [15, 16]. These data indicate that epithalon has a specific effect on gene expression.

Cortexin

The peptide complex isolated from grey substance was named "cortexin" (registration number 99/136/14; Ministry of Health of the Russian Federation Order No. 136 from April 19, 1999). The majority of peptides found in cortexin had the molecular weight of less than 10000 Da [28, 46]. Cortexin affected the functions of neurons and glia [28]. The administration of cortexin for 8 days increased the level of circulating antibodies, as well as direct and indirect antibody-producing cells, but did not influence the level of hemagglutinins in mice. Moreover, cortexin enhanced the expression of receptors in the T- and B-lymphocytes of healthy people and secondary immunodeficiency patients [46]. In the direct test, it was shown that cortexin enhanced lymphocyte migration inhibition by 2.5 times. The preparation did not possess antigenic specificity, did not cause leukocyte sensibilization, and did not promote secretion of cytokines enhancing lymphocyte migration inhibition. Furthermore, the intensity of oxygen-dependent reactions in human leukocytes increased by twofold under the action of cortexin [28].

The average cytochemical coefficient that characterizes the content of lysosomal cationic proteins in neutrophils significantly decreased in the presence of cortexin. This effect maybe connected with the exocytosis of the above-mentioned substances from a phagocyte. The phagocytic coefficient, phagocytic index, and stage of phagocytosis completion markedly increased under the action of cortexin [28, 46].

Cortexin took part in the regulation of neuromediator metabolism and acted as a natural antioxidant by regulating lipid peroxidation. The activation of serotonergic system under the action of cortexin in the model of foot shock stress is indicative of the brain protective and antistress activity of the preparation. This activity is exhibited during the normalization of neuron metabolism and restoration of adaptive capacity of brain. The preparation had marked antihypoxic action by starting the regulatory cascades that

enhanced the resistance of the organism and increased the brain's sensitivity to endogenous peptides. Cortexin reduced the level of TNF-α, which inhibited the autoimmune aggression towards neurons [46].

Cortexin extended the main parameters of thromboelastogram, decreased clot elasticity, enhanced blood and plasma coagulation, and significantly suppressed fibrinolysis in in vivo experiments, which is connected with the presence of a wide range protease inhibitors that possess the ability to block trypsin and plasmin [28].

The regulation of physiological functions by cortexin is caused by its effect on adenylate cyclase with the subsequent reduction of the cAMP level and normalization of cell metabolism [46].

Cortexin had therapeutic effect that surpasses the effect of cerebrolysin in rats with severe brain injury. The restoration of CNS functions was accelerated in the early posttraumatic period; it manifests as better learning ability in animals, as well as the normalization of muscle tone and motion coordination. These data indicate that cortexin stimulates reparative processes in brain [46].

Cortexin promoted the arrest of experimental withdrawal syndrome in rats, which was accompanied by an improvement in the animals' condition, the restoration of normal behavior, the stabilization of sleep–wake rhythm, and the normalization of the appetite. Consequently, cortexin removed the asthenic effect and improved psychical adaptation in animals with alcohol withdrawal syndrome [46].

The anticarcinogenic effect of cortexin was also shown. Transplacental introduction of N-nitrosoethylurea to rats caused tumors in the brain, spinal cord, peripheral nervous system, and kidneys. Cortexin administration significantly decreased the frequency and multiplicity of tumors, which may be connected with the normalization of the differentiation and proliferation of neuroglia [20], as well as the effect on immunity and complement system [27, 28]. All of these facts indicate that cortexin can be classified as a geroprotector.

An Ala-Glu-Asp-Pro tetrapeptide that possesses many properties of cortexin was synthesized based on the cortexin amino acid composition and named "cortagen." Thus, cortagen caused the differentiation of more than 45% of pluripotent tissue into the epidermis [55]. The use of cortagen in the case of cerebral ischemia promoted the fast restoration of distorted individual behavior of rats with various hypoxia resistances, prevented from excess activation of LP and decrease in the activity of antioxidant systems in brain. Due to these facts, cortexin and cortagen can be used to enhance the efficiency of neuroprotective therapy of chronic cerebral ischemia [25]. The introduction of cortagen, as well as cortexin, during 7 days of the postischemic period prevented the loss of certain behavioral patterns and promoted the restoration of individual behavior in animals with high and low hypoxia resistance. The administration of cortagen did not affect the concentrations of histamine and serotonin, but increased the blood concentrations of adrenalin and 5-hydroxyindoleacetic acid (5-HIAA) with a simultaneous decrease in the concentrations of dopamine and noradrenalin in young rats. Unlike young rats, cortagen did not change the content of noradrenalin and 5-HIAA in blood, but rather stimulated an increase in the adrenalin concentration.

Cortagen has a geroprotective effect; it increased the resistance to immobilization stress in young and old rats. Pretreatment with cortagen before hypokinesia or hypoxia substituted stress reaction of young rats for calm activation. At the same time cortagen introduction to old rats before immobilization retained passive resistance by passive activation. Cortagen inhibited the formation of lipid peroxides in young rats. The administration of cortagen increased the activity of SOD and catalase and did not affect LP in old rats [31]. Furthermore, cortagen had sedative and antistress effects that enable the psychoemotional states of the animals to be normalized. These observations reveal that the peptide can be used to treat anxiety and depression, which are often seen in elderly and senile people.

Retinalamin

Retinalamin is a polypeptide complex isolated from animal retina (registration number 99/212/7, Ministry of Health of the Russian Federation Order No. 212 from June 1, 1999). The preparation regulates retinal metabolism, stimulates functions of retinal cells, improves interactions between pigment epithelium and external parts of photoreceptors, enhances the activity of retinal macrophages, and normalizes blood coagulation and fibrinolytic activity [66, 69]. Retinalamin protects vascular endothelium and collagen fibers of perivascular connective tissue and promotes the restoration of the damaged vessel wall [53, 69].

Retinalamin significantly increased receptor expression in T- and B-lymphocytes and also enhanced the phagocytic activity of neutrophiles. Retinalamin had therapeutic action on toxic retinal dystrophy; the decrease of retinal swelling was observed in rabbits given retinalamin by ophthalmoscopy [28]. I. B. Maksimov et al. showed that the use of retinalamin promoted the coating of the epithelium of damaged part of the retina with pigment and prevented further pathologic behavior in cases of experimental laser damage and toxic retinal dystrophy in experimental animals [32]. The preparation also normalized the course of experimental retinal vein thrombosis caused by the injection of thrombin. Treatment with retinalamin markedly reduced the number of hemorrhages and large centers of necrosis and decreased retinal swelling [28].

The addition of retinalamin to pluripotent ectodermal cells of the early gastrula of *Xenopus laevis* caused cell differentiation towards the retina and pigment epithelium. This fact explains the positive clinical effect of retinalamin treatment in patients with retinal degenerative diseases [53, 85] and animals with genetically determined retinitis pigmentosa [91].

Prostatilen

Prostatilen is a polypeptide complex isolated from calf prostate (registration number 92/329/7, Ministry of Health of Russian Federation Order No. 329 from December 17, 1992). The regulating effect of prostatilen on prostatic functions was proved in experimental prostatitis in rabbits. The administration of prostatilen for 5–10 days not only improved the pattern of the disease, but normalized the prostatic function more quickly than the Swiss raveron preparation. In the case of prostatilen, the decrease in the infiltration of interstitial tissue was more pronounced; the signs of improvement in the functional activity of acinic epithelium were clearly seen; venule thrombosis decreased; and the ratio between leukocytes and lipoid bodies was restored in acinic secretion [1]. Furthermore, the action of prostatilen increased the weight of the testes, prostate, and seminal vesicle and improved spermatogenesis parameters in rats with chronic prostatitis. The action of prostatilen resulted in a decrease in the number of tubules with impaired sperm maturation and an increase in the quantity of spermatoblasts in the basal membrane in experimental animals [1].

Prostatilen caused a decrease in bladder capacity and intravesical pressure 5 min after intramuscular administration in rats. This effect eased urination, which started with lesser filling and pressure in the bladder [28].

Prostatilen has a number of unspecific properties common with other peptide bioregulators. The introduction of prostatilen to male rats for 1 week extended the time of blood coagulation and stimulated the antiaggregatory activity of the vessel wall [28, 74]. Prostatilen showed immune protective action; it increased the receptor density in T- and B-lymphocytes primarily in immunodeficient patients. Furthermore, prostatilen enhanced the phagocytic activity of leukocytes and inhibited the complement system [28]. Prostatilen increased the tonus of the vessel and smooth muscles of the bladder, including detrusor [1].

Consequently, prostatilen inhibits prostatic involutive processes that characterize premature aging and promote age-specific prostatic pathology. Thus, it can be classified as a geroprotector.

CONCLUSIONS

This review shows a new class of effective peptide bioregulators that possess a geroprotective effect, which is primarily caused by their ability to regulate gene function. Peptides activate the spare capacity of an organism and provide the optimal conditions for extending lifespan and improving quality of life [7, 59, 60, 70, 76, 84, 85, 87, 88].

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SPELL: 1. peptide, 2. bioregulation