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Medicinal Peptide Drugs: A Promising Direction in Modern Pharmacology

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Studies of the role of peptides in the regulation of basic bodily functions occupy a leading place not only in fundamental research, but also in clinical research [6,10,15-17]. Although the first drugs of a peptide nature were created in the middle of the last century, it was only in the last decades that the pharmaceutical industry began to actively engage in the creation of drugs based on peptides. Natural origin, high efficiency, the possibility of usage in small doses, and most importantly virtually no side effects, formed the basis for the increased interest of modern pharmacology in peptide drugs [12,13,30,32].

As mentioned above, the first peptide drugs appeared on the European pharmaceutical market in the middle of the last century. However, they were few in number. The leading creators of medicinal peptides were Austria, Switzerland and Russia.

Among Austrian peptide preparations, the two most famous are Cerebrolysin® (EVER Neuro Pharma GmbH) and Actovegin® (TAKEDA AUSTRIA, GmbH).

Cerebrolysin® is isolated from the brain of pigs and contains low molecular weight biologically active neuropeptides that penetrate the blood-brain barrier and regulate the functions of brain neurons. The drug normalizes metabolism; has an organ-specific effect on brain cells under conditions of hypoxia and ischemia and improves intracellular protein synthesis in the brain during aging. Cerebrolysin® is a nootropic drug which has a normalizing effect in cases of impairment of cognitive functions, and improves the processes of memorization [11].

Actovegin®, in contrast to Cerebrolysin®, is a protein-free polypeptide extract from the blood of calves. Actovegin® stimulates energy processes in cells, increases the uptake of glucose and oxygen by tissues, and improves blood circulation and tissue regeneration [9].

Close in pharmacological action to Actovegin is the drug Solcoseryl® (LEGACY PHARMACEUTICALS SWITZERLAND, GmbH), produced in Switzerland. The drug is a deproteinized dialysate from the blood of calves and contains a wide range of low molecular weight components with a molecular weight of up to 10 kDa (including glycoproteins, nucleosides and nucleotides, amino acids, oligopeptides). Solcoseryl® stimulates tissue regeneration, improves oxygen and glucose transport to cells, increases ATP synthesis by cells, stimulates fibroblast proliferation and collagen synthesis in the vascular endothelium [29].

Raveron® (Robapharm, Switzerland) is a standardized polypeptide extract from the prostate gland of cattle. Raveron® has a normalizing effect on the function of the prostate gland, improves urodynamics and stimulates the smooth muscles of the bladder in various pathologies of the genitourinary system [8].

Another Swiss-made bovine tissue extract is Thymostimulin® (TP-1 Serono). The drug is an extract containing a complex of thymus polypeptides. Thymostimulin® promotes an increase in the number and activity of T-lymphocytes in conditions of their deficiency (primary and secondary immunodeficiency) [7,14].

A significant contribution to the study of the action mechanism of peptides was made by studies carried out at the Kirov Military Medical Academy and St. Petersburg Institute of Bioregulation and Gerontology (Russia), where various peptides involved in maintaining the structural and functional homeostasis of cell populations and regulation of aging were extracted, and then synthesized and studied [16,19,25,33]. It is known that the aging process is characterized by a complex of molecular-genetic and biochemical changes, accompanied by disorganization of the peptidergic system of body function regulation and aging mechanisms. The study of the processes of age-related involution in organs and tissues of the body revealed a decrease in the production of physiologically active substances of a peptide nature and the intensity of protein synthesis in them, which made it possible to draw a conclusion about the important role of peptides in the regulation of aging processes [3,4,5,20,21].

The first peptide bioregulators were created by V. Morozov and V. Khavinson in the early 70s of the last century. The basis for the creation of these extracts was the concept of Selye's general adaptation syndrome: during the stage of anxiety after exposure to stress, the functions of the thymus and pineal gland are suppressed. As is known, it is the pineal gland and thymus that have the main regulating effect on the work of the neuroimmunoendocrine system and, as a consequence, the aging processes of the human body. The stage of resistance following the stage of anxiety normally develops on day 4 - 5 and is characterized by the restoration of these organs. However, with various disorders this stage can slow down, which potentially leads to the emergence of various diseases, including those contributing to the accelerated aging of the body. Considering these fundamental physiological prerequisites, scientists decided to create preparations from the thymus and pineal gland to stimulate the stage of resistance [12,16,31].

The first drug from this group in was Thymalin®, created in 1982 and manufactured by Samson-Med LLC (St. Petersburg, Russia), registration certificate 82/1108/8. Thymalin® is a complex of peptides with a molecular weight of up to 10 kDa, isolated from the thymus of cattle. Long-term experimental and clinical studies have shown that the drug restores impaired immunity, regulates the number and ratio of T- and B-lymphocytes and their subpopulations, stimulates cellular immunity reactions, enhances phagocytosis, stimulates the processes of regeneration and hematopoiesis in the event of their suppression and also improves the course of processes cell metabolism [26]. The introduction of the drug helps to increase life expectancy and reduce the incidence of tumors in animals [1,16]. Also, the introduction of Thymalin® leads to the normalization of the immune system function and an increase in the quality of life in people of the older age group. In addition, the results of recent studies have shown that the use of Thymalin in the treatment of patients suffering from COVID-19 contributes to the normalization of cytokine synthesis, has an anti-inflammatory effect, prevents development of disseminated intravascular coagulation, acute respiratory distress syndrome and multiple organ failure [17].

The next drug was Epithalamin®, which was created in 1990 and is produced by Samson-Med LLC (St. Petersburg, Russia), registration certificate 90/250/6. The drug is isolated from the pineal gland of the brain of cattle and is a complex of peptides with a molecular weight of up to 10 kDa. Long-term experimental and clinical studies have shown that the drug normalizes the functions of the anterior pituitary gland, the concentration of gonadotropic hormones in the blood, the secretion of melatonin, and increases the sensitivity of the hypothalamus to endogenous hormonal influences. Administration of the drug to animals led to an increase in the average life span, a decrease in the incidence of tumors, and the restoration of the cyclic activity of the ovaries in old animals. Epithalamin® increased the body's resistance to stress, and normalized carbohydrate metabolism [2,16].

As is known, a decrease in the melatonin-producing function of the pineal gland is one of the characteristic manifestations of physiological aging. Disruption in melatonin production increases with accelerated aging and age-dependent pathologies: coronary heart dis-

ease, arterial hypertension, Alzheimer's disease, non-insulin-dependent diabetes mellitus. The use of Epithalamin® in elderly patients promoted the restoration of a reduced level of melatonin, improved functions of the immune, endocrine, cardiovascular, antioxidant systems, and brain functions [23].

At the same time, the data of studies on the effectiveness of long-term peptide preparation use of the pineal gland and thymus in elderly patients against the background of age-related diseases, as well as signs of accelerated aging of the body, are of considerable interest. For this purpose, several clinical studies of the geroprotective action of peptide bioregulators have been carried out.

Evaluation of the long-term results in these patients with a 15-year follow-up is certainly of interest [28].

According to O. Korkushko., *et al*. (2011), 79 patients took part in a long-term study. At the beginning of the study, the patients were between 60 and 69 years old. The main selection criteria were: 1) presence of ischemic heart disease (CHD) with stable exertional angina of the 2nd functional class, 2) presence of accelerated aging in the cardiovascular system, 3) low level of melatonin in the blood plasma (below 40 ng/L at 3 AM). Participation of subjects in the study was voluntary and was confirmed by signature in the informed consent form.

All patients were randomized into two groups that did not differ significantly in baseline parameters (age, number of men and women, functional age (FA) of the cardiovascular system, exercise tolerance, severity of the disease, etc). Patients of both groups (study and control) received the same basic treatment for the underlying disease (IHD) for 15 years of observation.

Against the background of basic therapy, patients of the 1st study group (39 persons) received epithalamin. The peptide drug was administered according to the following pattern: 10 mg in 2 ml of physiological solution intramuscularly, once every 3 days, 5 injections per course, 6 month intervals between courses. The course dose of epithalamin was 50 mg. The drug was administered in the morning, since previous experimental and clinical studies have shown that morning injections of epithalamin lead to the maximum increase in melatonin synthesis at night.

Before the start of the clinical study, as well as during the subsequent period of observation, twice a year, all participants (control and study groups) underwent a medical examination. The effectiveness of treatment in both groups was assessed by changes in the following indicators: functional age of the cardiovascular system, degree of aging of the cardiovascular system, physical activity threshold, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), fasting glucose concentration and 2 hour glucose tolerance test, and plasma melatonin concentration.

To assess the significance of differences between the control group and the group using epithalamin, calculations were presented using the statistical tests χ^2, χ^2 with Yates' correction, correction for likelihood and Fisher's exact test. The level of significance varied within the limits of $P < 0.05$ for all the studied criteria. For statistical processing, the method of constructing life tables, survival curves and Kaplan-Meier estimates was also used. The significance of the revealed differences was assessed using the statistical tests Breslow (generalized Wilcoxon) and Log Rank (Mantel-Cox).

Given the importance of the scientific data obtained, we present the original of some reports of a clinical study published in several scientific Russian monographs [22,27].

According to O. Korkushko., *et al*. the initial examination in all patients of the control and main groups before the start of the study revealed accelerated aging of the cardiovascular system with an initial significant decrease in the night-time plasma melatonin level, which indicated functional insufficiency of the pineal gland. The introduction of a peptide preparation of epithalamin in patients of group 1 led to a significant 2-fold increase in the night-time level of melatonin in the blood plasma and the restoration of the circadian rhythm of the

melatonin-forming function of the pineal gland. These favorable changes were observed after 1 course and persisted during long-term use of epithalamin. At the same time, no changes in the circadian rhythm of the plasma melatonin concentration were observed in the control group.

As noted above, before the use of epithalamin, the functional age of the cardiovascular system in elderly patients significantly exceeded the calendar age (CA) (by 10 years or more), which indicates accelerated aging of the cardiovascular system. After 3 years, the functional age of the cardiovascular system in the group of people receiving epithalamin did not change significantly from the initial one (Table 1) and therefore the degree of aging of the cardiovascular system (the difference between functional and calendar age) decreased by 3.6 ± 1,7 years ($p < 0.05$). At the same time, the functional age of patients in the control group who did not receive epithalamin and the degree of aging of the cardiovascular system during the same period increased by 4.5 ± 2.2 years ($p < 0.05$), which indicates accelerated aging process of the cardio-vascular system.

13 years after the start of the study, the functional age of the cardiovascular system in patients of both groups was re-determined. It turned out that the degree of aging of the cardiovascular system in patients of the main group was significantly lower than in patients who had not previously received the peptide preparation of the pineal gland. These results undoubtedly indicate the geroprotective effect of the peptide preparation of the pineal gland in people with accelerated aging of the cardiovascular system (Table 1).

Indicators	Study period	Main group (basic therapy and epithalamin)	Control group (basic therapy)
Calendar age, years	Initial	64,5 ± 0,9	65,1 ± 1,1
	In 3 Years	67,6 ± 1,0*	68,3 ± 1,0*
	In 13 Years	76,4 ± 1,2*	77,8 ± 1,1*
CVS's functional age, years	Initial	89,1 ± 1,7	86,2 ± 1,8
	In 3 Years	88,7 ± 1,8	93,9 ± 1,9**
	In 13 Years	96,2 ± 2,0*	102,2 ± 2,1**
Degree of CVS's aging (FA - CA), years	Initial	+ 24,6 ± 1,3	+ 21,1 ± 1,5
	In 3 Years	+ 21,0 ± 1,7*	+ 25,6 ± 1,9**
	In 13 Years	+ 19,8 ± 1,9*	+ 24,4 ± 1,7**

Table 1: *Indicators of functional age and the degree of aging of the cardiovascular system [28].*

**: p < 0,05 compared to the indicator in the initial examination.*

***: p < 0,05 compared to the indicator in the main group.*

It should also be noted that there are favorable changes in physical performance during the course and long-term use of epithalamin. For instance, the physical activity threshold, even after 1 course of epithalamin administration, increased in 58% of patients by 21% on average, while in the group of patients who did not receive epithalamin, an increase in working capacity was noted only in 7% of the examined. Physical performance continued to be significantly maintained at a higher level during long-term use of epithalamin, while in the control group during this period it significantly decreased.

With prolonged use of the peptide geroprotector in elderly patients, favorable changes in the parameters of carbohydrate and lipid metabolism were noted. If before the start of epithalamin administration, 56% of the examined had impaired glucose tolerance (glucose level in the 2 hour glucose tolerance test was over 7.8 mmol/l), then by the end of the examination only 24% of patients had impaired glucose tolerance. In the control group, the frequency of this disorder of carbohydrate metabolism remained practically unchanged.

Along with the normalization of glucose tolerance, long-term use of epithalamin resulted in favorable changes in the lipid spectrum of blood serum. There was a gradual decrease in total cholesterol and low-density lipoprotein cholesterol levels. In the control group patients who did not receive the peptide geroprotector, the levels of TC and LDL cholesterol during the observation period, on the contrary, significantly increased.

The most important results were obtained at the end of a 15-year follow-up for two groups of patients. The data obtained indicated a statistically significant decrease in mortality in patients who received epithalamin, compared with the control group, where only basic therapy was used.

By the end of the 15-year follow-up, according to Korkushko., *et al*. 16 of 40 patients in the control group (40%) and 26 of 39 patients who had previously received epithalamin (66.7%) were alive. The construction of Kaplan-Meier life tables and survival curves made it possible to establish a statistically significant reduction in the risk of death in the group of patients treated with the peptide geroprotector compared with the control group.

Among the deceased in the group of patients receiving epithalamin, myocardial infarction and stroke were the cause of death for 6 out of 13 people (46.2%), while in the control group it was for 20 out of 24 people (83.3%). Consequently, long-term administration of the peptide preparation of the pineal gland significantly reduced the number of deaths associated with cardiovascular pathology. The data obtained indicate a favorable effect of epithalamin on the long-term results of treatment in elderly patients with ischemic heart disease and accelerated aging of the cardiovascular system.

Thus, as a result of the 15-year observation of two groups of elderly patients with accelerated aging of CVS, it was found that long-term use of the peptide geroprotector from the pineal gland reduces the rate of aging of CVS, prevents an age-dependent decrease in physical performance, and has a normalizing effect on the daily rhythm of melatonin production, carbohydrate and lipid exchange. The geroprotective effect of the peptide preparation of the pineal gland is also evidenced by a significant decrease in mortality in the group of patients who received epithalamin against the background of basic therapy.

The results of another long six-year clinical study are worth mentioning [23,27]. It was attended by 42 people aged 69 - 94 years. All patients were randomized into two groups that did not differ significantly at baseline. The main group (20 people) during the entire observation period received courses of peptide drugs: epithalamin and thymalin. The use of bioregulators was carried out against the background of standard treatment, which was prescribed in accordance with the diagnosis. Patients of the control group (22 people) received standard treatment in accordance with the diagnosis.

The observation results showed that with the combined use of bioregulators in patients of both sexes for 6 years, a significant clinical effect was noted. This was expressed in a decrease in the incidence of acute respiratory infections, coronary artery disease, hypertension and deforming arthrosis compared with the baseline values of these in patients ($p < 0.05$). In the study, the differences in mortality rates between the control and study groups were presented as a percentage. By recalculating the data into absolute values, statistically significant differences were also obtained (according to Fisher's test), which are shown in table 2. Thus, a statistically significant decrease in mortality was obtained in all patients when taking peptide drugs compared with the control group.

Indicators	Control group (basic therapy)	Main group (basic therapy and peptide bioregulators)
Number of patients	22	20
Mortality, %	81,8%	20,0%**
Mortality, absolute numbers	18	4###

Table 2: *Effect of medicinal peptide bioregulators thymalin and epithalamin on the mortality rate of patients [23].*

*Differences are statistically significant when **p < 0,001 according to Student's t-test. Differences are statistically significant according to Fisher's test ###p = 0,001.*

Thus, the long-term study and use of peptide preparations of the pineal gland and thymus showed their high efficiency in older patients (over 60 years old). As a result of 15-year and 6-year clinical observation of two groups of elderly patients with accelerated aging of CVS, it was found that long-term use of peptide geroprotectors from the pineal gland and thymus reduces the rate of aging of CVS, prevents age-dependent decrease in physical performance, has a normalizing effect on the daily rhythm of melatonin production, carbohydrate and lipid metabolism, and reduces the risk of acute respiratory diseases. The geroprotective effect of drugs from the pineal gland and thymus is also evidenced by a significant decrease in mortality in the group of patients who received these peptides against the background of basic therapy. The undoubted advantage of this group of peptide bioregulators-geroprotectors is also absence of any side reactions.

It should be noted that in international clinical practice there are no such long-term clinical studies of peptide drugs. Therefore, the results of the geroprotective action of peptide bioregulators, presented in this review, undoubtedly open up great prospects in the field of peptide pharmacology.

Approval of Ethnic Committee

Following standard pre-clinic and clinical studies, peptide bioregulators were approved for medical application by the USSR Ministry of Health (later on Russian Ministry of Health), whose competence covered observation of ethic norms in studying new medicine:

1. Thymalin - USSR Ministry of Health Instruction # 1008 of 10.11.1982 (Reg. # 82.1008.8).
2. Epithalamin - USSR Ministry of Health Instruction # 250 of 19.06.1990 (Reg. # 90.250.6).

In this review, undoubtedly open up great prospects in the field of peptide pharmacology.

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