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ORIGINAL ARTICLE

Peptides of pineal gland and thymus prolong human life

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Abstract

OBJECTIVES AND DESIGN. Researchers of the St. Petersburg Institute of Bioregulation and Gerontology of the North-Western Branch of the Russian Academy of Medical Sciences and the Institute of Gerontology of the Ukrainian Academy of Medical Sciences (Kiev) clinically assessed the geroprotective effects of thymic (Thymalin) and pineal (Epithalamin) peptide bioregulators in 266 elderly and older persons during 6–8 years. The bioregulators were applied for the first 2–3 years of observation.

RESULTS. The obtained results convincingly showed the ability of the bioregulators to normalize the basic functions of the human organism, i.e. to improve the indices of cardiovascular, endocrine, immune and nervous systems, homeostasis and metabolism. Homeostasis restoration was accompanied by a 2.0–2.4-fold decrease in acute respiratory disease incidence, reduced incidence of the clinical manifestations of ischemic heart disease, hypertension disease, deforming osteoarthrosis and osteoporosis as compared to the control. Such a significant improvement in the health state of the peptide-treated patients correlated with decreased mortality rate during observation: 2.0–2.1-fold in the Thymalin-treated group; 1.6–1.8-fold in the Epithalamin-treated group; 2.5-fold in the patients treated with Thymalin plus Epithalamin as compared to the control. A separate group of patients was treated with Thymalin in combination with Epithalamin annually for 6 years and their mortality rate decreased 4.1 times as compared to the control.

CONCLUSIONS. The obtained data confirmed the high geroprotective efficacy of Thymalin and Epithalamin and the expediency of their application in medicine and social care for health maintenance and age-related pathology prevention in persons over 60 to prolong their active longevity.

Introduction

The state of closely interacting neuroendocrine and immune systems, along with genetic predispositions, plays an important role among life span determining factors [1, 2, 3].

It is known that thymus, pineal gland, cerebral cortex, retina, vessels and other organs and tissues undergo hypoplasia and, in some cases, partial atrophy with age [1, 4, 5]. Age-related involutionary changes in organs and tissues lead to their functional decline manifested at the cellular level in disturbed synthesis of specific proteins. A significant decrease in the intracellular synthesis of a number of regulatory peptides and reduced sensitivity of target cells to them has been found. It is accompanied by the disturbed activity of all peptide regulation chains and by the gradual functional deterioration of an aging organism [1, 6, 7, 8].

Physiologically active peptides from thymus and pineal gland have been isolated according to a special technology to correct disorders provoked by age-related thymic and pineal involution. These peptides served the basis for creating pharmaceuticals Thymalin and Epithalamin [9, 10, 11]. Numerous investigations conducted over 1971–2001 on various strains of mice, rats and *Drosophila melanogaster* have demonstrated that the application of these bioregulators significantly prolonged life span and inhibited the development of age-related disorders in the animals and flies [12, 13, 14, 15].

Thymalin and Epithalamin are obtained from natural raw material of animal origin, which can cause the risk of contamination with prions, infectious agents, protooncogens or nucleic acids. In this connection, it is important to accentuate that the technology of manufacturing Thymalin and Epithalamin operates special extraction and purification methods, which result in the complete degradation of macromolecular proteins and other agents but secure the preservation of peptides with molecular weight under 10 kDa in the substance used in Thymalin and Epithalamin production. Such measures provide maximal protection of the bioregulators from the presence of infectious agents and a number of other potentially hazardous substances. Investigation of Thymalin and Epithalamin composition by the methods of electrophoresis in polyacrylamide gel, histochemistry, immunoblotting and electron microscopy has demonstrated the absence of prions, protooncogens and viruses, thus excluding contamination risk and securing complete safety of the pharmaceuticals. It is also noteworthy that clinical trials of Thymalin and Epithalamin and their application for 25 years in patients of different age groups have not exposed any allergizing or other side effects, which confirms the safety of using these bioregulators in medical practice.

Thymalin is a polypeptide complex extracted from the thymus. It is approved for medical application as an immunomodulator by USSR Ministry of Health Order No. 1008 of 10.11.1982 (Registration No. 82.1008.8). In experimental studies the bioregulator has been proven capable of promoting a significant decrease in neoplasm incidence both in intact animals and after the impact of ionizing radiation or carcinogens [16, 17]. Thymalin has been also found to produce a pronounced anti-atherosclerotic effect in rabbits with experimental hyperlipidemia [18].

The results of a Thymalin clinical trial in 7 patients after thymectomy for benign thymus tumors appeared extremely significant for this research. In 6–18 months after the surgery these patients developed immune deficiency with considerably decreased quantitative and functional indices of T immunity system and phagocytosis processes, increased incidence of acute respiratory infections, recurrent pneumonia, furunculosis, suppressed regeneration processes, weakened muscular tone and the signs of accelerated aging (graying hair, decreased skin elasticity, increased fat gain, disturbed functions of endocrine glands etc.). After Thymalin application all the patients showed a pronounced improvement in their health state and disappearance of most of the above complications and symptoms of immune deficiency. The attained clinical immunological remission was preserved for 6–8 months. However, further the signs of immune deficiency in these patients developed again and therefore repeated Thymalin courses were prescribed [18]. It was also relevant that some of these patients had been taking Thymalin for 15–20 years. The results of this unique clinical trial demonstrated that immune deficiency states after thymus removal were accompanied by expressed accelerated aging and that regular Thymalin courses once every 6 months helped to diminish these signs of age-related disorders.

The clinical screening of persons aged 70–88 years (with acquired somatic diseases or infectious processes in remission) exposed a decrease in the functional indices of T immunity system and changes in the spectrum of lactate dehydrogenase (LDG) isoenzymes in lymphocytes. This pointed at intensified anaerobic glycolysis (metabolism typical of poorly differentiated cells), increased B lymphocyte level and blood immunoglobulins of all classes (especially, IgA). Besides, these persons had higher blood levels of glucose, cholesterol, urea nitrogen and alkaline phosphatase (AP), as well as hypercoagulation and inhibited fibrinolysis. Thymalin therapy resulted in the restoration of most of the initially disturbed indices, thus confirming its distinct homeostatic effect in elderly and older persons. This effect was manifested in normalized immunity, metabolism and intracellular biochemical processes, as well as in the intensified expression of differentiation antigens of blood lymphocytes [19, 20, 21, 22].

As a rule, Thymalin in a complex treatment (with radio- and chemotherapy) of patients with lymphogranulomatosis, tumors of the mammary gland, *corpus uteri*, lungs, stomach and other organs prevented leukopenia and immune functional decline, thus reducing the incidence of various complications, facilitating postoperative wound healing and prolonging the patients' lives [10, 11, 20]. Consequently, the results of applying Thymalin in elderly and older persons, as well as in can-

cer and thymectomy patients confirmed good prospects of its use as a geroprotective agent.

Epithalamin is a polypeptide complex extracted from the pineal gland. It is approved for medical application as a regulator of the neuroendocrine system by USSR Ministry of Health Order No. 250 of 19.06.1990 (Registration No. 90.250.1). Epithalamin regulates metabolic processes in the pineal gland, enhances hypothalamic sensitivity to endogenous impacts, normalizes the functions of pituitary anterior lobe and hormone content in the blood. In experiments Epithalamin significantly increased mean life span (up to 41%) and reduced the incidence of spontaneous, as well as radiation- and carcinogen-induced tumors in animals (2.6–3.4 times) [17, 17, 23, 24]. The administration of Epithalamin intensified the neurosecretory activity of cells in the paraventricular and supraoptic nuclei of the hypothalamus, normalized reproductive functions in senescent animals, significantly increased anti-oxidation defense and normalized melatonin blood level in animals of different species [25,26, 27]. Epithalamin application in senescent (20–26 y. o.) monkeys enabled the complete normalization of initially disturbed melatonin and glucose levels, as well as the restoration of tissue sensitivity to insulin and of cortisol secretion circadian rhythm. Thus, long-term comprehensive animal studies of Epithalamin demonstrated its unique geroprotective activity [28].

Total anti-oxidation and anti-radical activity is known to go down in aging persons setting off an imbalance between different pro- and anti-oxidation indices. The application of Epithalamin in elderly and older persons promoted the complete normalization of anti-oxidation indices (increased total anti-oxidation and anti-radical activity of blood serum, reduced content of peroxide lipid oxidation products, intensified activity of superoxide dismutase and glutathione peroxidase) [10, 11, 29, 30].

The results of studying melatonin exchange in aspirin asthma patients (accompanied by considerably decreased melatonin synthesis) are of great theoretic and practical relevance. The administration of Epithalamin in aspirin asthma patients increased the initially lowered urine excretion of basic melatonin metabolite – 6-sulfatoxymelatonin, which reflected the intensification of melatonin synthesis in the organism [8]. Simultaneously, cellular and humoral immunity indices in these patients were normalized. After the bioregulation therapy a remission period of 4 to 6 months was attained, during which the patients had practically no acute respiratory diseases.

The results of assessing Epithalamin efficacy in patients with non-insulin dependent diabetes mellitus (NIDDM) appeared extremely important and interesting. Epithalamin therapy in NIDDM patients exerted a prolonged normalizing effect upon their carbohydrate metabolism. The hypoglycemic effect of the bioregulator was conditioned by amplified stimulated secretion of insulin combined with increased sensitivity of tissues to insulin [10, 19, 20]. Epithalamin brought down the level of low and very low density lipoproteins and raised the content of high density lipoproteins in the blood serum of NIMMD patients promoting a decrease in the atherogenicity of lipid fractions. Such an improvement was preserved for 3 months after the end of the therapy course. In NIMMD patients with hypertension disease Epithalamin promoted a decrease in arterial blood pressure and restoration of myocardial functions. The hemodynamic basis for Epithalamin hypotensive activity consisted in its ability to lower peripheral vascular resistance, which to a great extent was conditioned by the reduction of basal hyperinsulinemia. In elderly NIDDM patients with purulent-inflammatory diseases Epithalamin also compensated for carbohydrate metabolism disorders and restored immune functions, which resulted in the activation of tissue repair processes and in the significant acceleration of post-operative wound healing [31].

The studies of Epithalamin effectiveness in patients with asthenia syndrome entailed by long-term exposure to extreme conditions demonstrated a nearly complete elimination of major asthenia symptoms (vertigo, ear noise, general weakness, increased fatigability, disturbed sleep and headaches) in 1 month after a course of Epithalamin [10].

The application of Epithalamin in women with vegetative dyshormonal myocardial degeneration was rather effective. Its positive effect was manifested in significant clinical improvement, normalized ECG, enhanced tolerance to physical loads and normalized blood content of follicle-stimulating hormone [19, 20, 22].

Since Epithalamin normalized endocrine and immune functions and produced an anti-tumor effect, it was studied in cancer patients, mostly, with hormone-dependent forms (tumors of the mammary gland, *corpus uteri*, uterine cervix, ovaries and other localizations). Its application in cancer patients restored the disturbed indices of cellular immunity and phagocytosis and distinctly decreased the incidence of recurrences and metastasis as compared to the control. The efficacy of Epithalamin in patients treated with 2–3 courses once every 4–6 months annually for 10–20 years was especially remarkable [10, 20].

The use of Epithalamin in a complex treatment for mammary cancer significantly increased the incidence of partial or complete tumor regression, decreased leukopenia incidence and expressiveness, normalized immune functions and prolonged the patients' lives [8, 31].

Thus, the briefly described results of comprehensive experimental and clinical trials of Thymalin and Epithalamin allowed positioning them as potential geroprotectors. However, special investigations assessing their influence on the main systems, functions and human life span were necessary to confirm their geroprotective effectiveness. Certainly, this purpose could hardly be attained completely, yet a preliminary evaluation appeared possible.

In the view of the above, Thymalin and Epithalamin were clinically studied for their geroprotective efficacy at two gerontological research centers in Russia and

the Ukraine, which disposed of due conditions, sufficient expertise and many years' experience.

Material and methods

Researchers of the St. Petersburg Institute of Bioregulation and Gerontology of the North-Western Branch of the Russian Academy of Medical Sciences started clinical trials of Thymalin and Epithalamin in 1996. The main group included 94 women aged 66–94 years who lived at the War Veterans Home located at the most ecologically friendly district of St. Petersburg. They were provided with comfortable living conditions (separate apartments, strict regimen, continuous medical follow-up and anytime medical service, regular nutrition). The majority of the veterans used to be professionally engaged in intellectual activities (top and linear management), had good living conditions, constant medical and sanatorium treatment, sufficient nutrition, which let them preserve a rather good state of health and workability by the moment of their admission to the War Veterans Home. The selection of women-patients only was explained by their predominance among the population over 60 and by the peculiarities of women's endocrine system, since previous investigations of this system had confirmed a significant influence of Thymalin and, especially, Epithalamin, upon women's hormonal level.

The most typical age-related pathologies in this group of patients included ischemic heart disease (IHD) (stress stenocardia of functional classes I–III), hypertension disease (Stage II) and deforming osteoarthrosis. The following parameters were examined to assess the condition of the main bodily systems: 17 immune indices (leukocytes, lymphocytes, $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, $CD20^+$, $CD56^+$, reaction of leukocyte migration inhibition with Concanavalin A (RLMI with Con A), IgM, IgG, IgA, circulating immune complexes (CIC), phagocytic numbers); 8 endocrine indices (blood levels of adenocorticotropic (ACTH), thyroid-stimulating (TSH), luteinizing (LH), follicle-stimulating (FSH) and somatotropic (STH) hormones, insulin, cortisol and estradiol); 19 metabolic indices (cholesterol, triglycerides, glucose, urea, creatinine, total bilirubin, total protein, albumins, globulins, albumins/globulins, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), lactate dehydrogenase (LDH), γ-glutamyl aminotransferase (GGT), potassium, phosphor, iron). Homeostasis stability coefficient (HSC) was used as the integral parameter for evaluating the studied systems. HSC was calculated by the formula:

$$HSC = \frac{\text{number of indices corresponding the norm}}{\text{number of the studied indices}} \times 100\%$$

where 100% HSC corresponded to the norm.

After a complex screening of the patients they were divided into 4 groups by the method of stratification randomization [32]. The patients of Group I (control) received placebo, the patients of Group II were treated with Thymalin, Group III – with Epithalamin, Group IV – with Thymalin in a complex with Epithalamin. All the agents were injected intramuscularly daily at 10 mg for 10 days (at 100 mg per course). The trial was double blind. The bioregulators were applied in combination with a standard therapy for corresponding indications. The patients were examined again in 10 days after the therapy completion and then in 4 months. The therapy with Thymalin and Epithalamin was repeated in one year (1997). Consequently, the patients underwent 2 courses of bioregulators over 2 years.

A separate group included 10 women and 10 men treated with Thymalin and Epithalamin simultaneously at 10 mg each for 10 days annually for 6 years (1996–2001).

Researchers of the Institute of Gerontology of the Ukrainian Academy of Medical Sciences (Kiev) started clinical studies on the efficacy of Thymalin and Epithalamin in 1992 [33]. The trials included 152 persons (71 men and 81 women) who were under continuous observation at the Institute outpatient department. The observed group consisted chiefly of patients with IHD resulting from the accelerated development of age-related changes in cardiovascular system and entire organism. The patients had no concomitant nervous, endocrine or respiratory diseases. Along with IHD patients, this group of persons with accelerated aging included 68 subjects without any organic pathology.

All the patients were divided into 3 groups by stratification randomization. The patients of Group I (control) received placebo; patients of Group II were administered with Thymalin; patients of Group III – with Epithalamin. Each agent was intramuscularly injected in 5 consecutive doses at 10 mg per day at the intervals of 2–3 days (50 mg per course). An interval between the courses equaled 5–6 months. The patients were treated for 3 years (6 bioregulation courses in all). As a rule, the patients did not take any strong medications during the period of screening and therapy with the bioregulators. Thymalin and Epithalamin efficacy was assessed by the dynamics of indices of the patients' subjective health state, functional age of physiological systems, physical and mental workability, immunity, bone tissue condition, liver detoxication ability, blood lipid spectrum, tolerance to carbohydrates, oxygen tissue exchange, vegetative regulation and the functional state of endocrine glands [34].

Results and discussion

The results of the screening conducted at the St. Petersburg Institute of Bioregulation and Gerontology of the Russian Academy of Medical Sciences demonstrated that the elderly and older women had increased blood levels of B lymphocytes ($CD20^+$), IgA, IgG and CIC and decreased indices of NK cells ($CD\ 56^+$), RLMI with Con A and phagocytic reactions. They also had increased content of cortisol, TSH and insulin and reduced blood levels of ACTH, estradiol and LH. The raised levels of cholesterol, triglycerides, uric acid, urea, creatinine, AP, LDH and GGT along with a blood phosphor decrease were registered. Thymalin application in

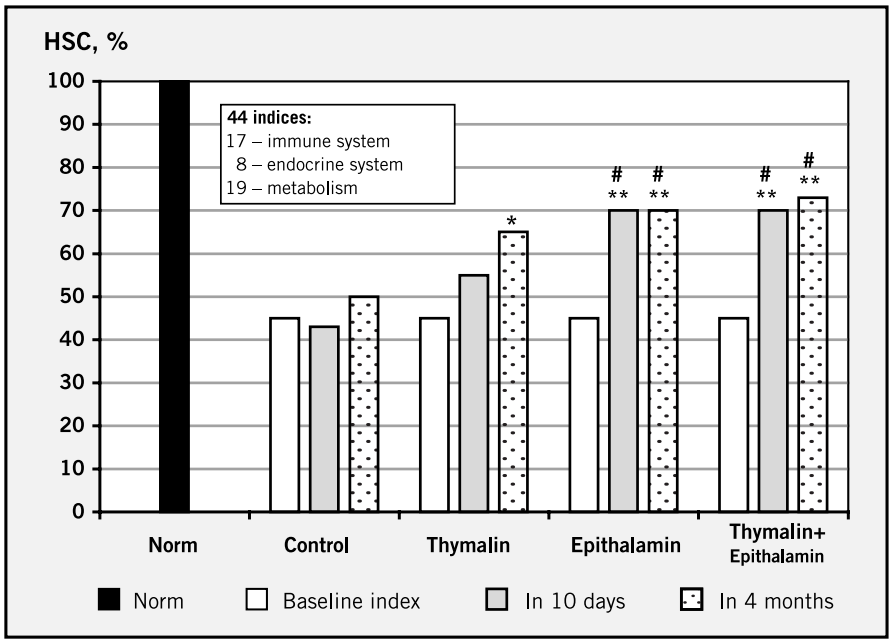

Figure 1. Effect of Thymalin and Epithalamin on the state of immune, endocrine systems and metabolism. * – P<0.01; ** – P<0.001, as compared to the baseline level for this group; # – P<0.001, as compared to the analogous index for the control group.

$$HSC = \frac{\text{number of indices corresponding the norm}}{\text{number of the studied indices}} \times 100\%$$

Group II normalized RLMI with Con A, CIC, NK cells and phagocytic reactions. Epithalamin in Group III normalized the same immune indices, as well as ACTH, TSH, cortisol and insulin. The levels of cholesterol, uric acid, AP, GGT, and LDH came back to norm in 10 days and remained stable for a long time but for cholesterol level. Thymalin in combination with Epithalamin in Group IV normalized the same immune indices, ACTH, TSH and insulin. The indices of cholesterol, uric acid, AP, GGT and LDH were normalized in 10 days and remained stable for a long time but for LDH.

The comparative complex assessment of the peptide bioregulators effects on immune, endocrine systems and metabolism is displayed in Figure 1. The Figure shows that HSC in the control group remained almost unchanged throughout the investigation.

Thymalin application resulted in an HSC increase up to 64% in 4 months. Epithalamin promoted a significant HSC increase up to 70% already in 10 days, which was preserved even in 4 months. The complex application of the two bioregulators was also very effective providing an HSC increase by 73% in 4 months. The incidence of acute respiratory diseases and recourses to doctors for the clinical manifestations of IHD, hypertension and deforming osteoarthrosis requiring additional pharmacological correction was analyzed in 4 months before and after applying the bioregulators to evaluate their effect on the patients' clinical state (*Table 1*). A 2.0–2.3-fold decrease in acute respiratory incidence among the patients treated with Thymalin only and with Thymalin plus Epithalamin appeared typical. The application of Epithalamin reduced IHD clinical manifestations twice. A similar effect was observed in the patients administered with Thymalin plus Epithalamin. Epithalamin, as well as the combination of both bioregulators, significantly relieved the

Table 1. Morbidity of the patients before and after applying Thymalin and Epithalamin

Diseases	Morbidity before and after applying the bioregulators (number of recourses to doctors)			
	Control before/after	**Thymalin** before/after	**Epithalamin** before/after	**Thymalin + Epithalamin** before/after
Acute respiratory diseases	0.50/0.58	0.58/0.25*#	0.54/0.31	0.62/0.31*
Ischemic heart disease	1.58/1.67	1.33/1.08	1.54/0.77*#	1.40/0.85*#
Hypertension disease	1.25/1.25	1.33/1.17	1.30/0.77*	1.23/0.77*
Deforming osteoartrosis	2.17/2.08	2.17/1.50*#	1.85/1.31*#	1.92/1.31*#

* – P<0.05, as compared to the baseline level;
# – P<0.05, as compared to the analogous index for the control group.

Table 2. Effect of Thymalin and Epithalamin on the patients' mortality rate.

INDEX	CONTROL	GROUP			
		Thymalin	Epithalamin	Thymalin + Epithalamin	Thymalin + Epithalamin
		< < < < < < <	Applied for 2 years	> > > > > > > >	Applied for 6 years
Number of patients	22	24	24	24	20
Baseline age, y. o.	80.2±1.6	80.6±2.5	81.5±2.1	82.1±2.3	79.4±1.8
Age limits, y. o.	70–87	66–93	67–91	67–94	72–91
Mortality rate, % (observed for 6 years)	81.8	41.7*	45.8*	33.3**	20.0**

* – P<0.03, ** – P<0.001, as compared to the control index.

Table 3. Incidence of subjective symptoms exposure in the patients before and after applying Thymalin and Epithalamin, % [33, 34]

Symptoms	Thymalin		Epithalamin	
	Baseline level	After prolonged application	Baseline level	After prolonged application
General weakness	90	38*	92	54*
Decreased physical workability	96	48*	100	54*
Fatigability at a physical load	92	30*	100	50*
Declined interest to life	60	40*	64	36*
Lowered spirits	80	39*	76	38*
Deteriorated memory for current events	75	58	70	38*
Impaired sleep	68	60	76	32*
Decreased appetite	58	27*	52	32
Heartache on exertion	45	30	48	38

* – P<0.05, as compared to the baseline level.

Table 4. Incidence and duration of acute respiratory cases in the patients treated with Thymalin and Epithalamin [33, 34]

INDEX	GROUP	Incidence and duration of acute respiratory cases	
		During 1 year before the application onset	During the 3rd year of the application
Number of acute respiratory cases	**Control**	1.9±0.2	1.8±0.2
	Thymalin	2.2±0.2	0.9±0.2*
	Epithalamin	1.9±0.2	1.6±0.2
Duration of a single acute respiratory case, days	**Control**	5.3±0.9	5.6±0.8
	Thymalin	7.3±1.1	5.4±0.8*
	Epithalamin	6.6±0.9	6.0±0.7

* – P<0.05, as compared to the corresponding baseline index.

Table 5. Results of applying Thymalin and Epithalamin in premature aging [33, 34]

INDEX	GROUP		
	Control	Thymalin	Epithalamin
Number of patients	48	58	46
Baseline age, y. o.	69.3±2.2	70.2±1.3	70.1±1.4
Number of patients with improved subjective state of health,%	12	74*	65*
Number of patients with increased maximal oxygen intake on exertion,%	7	53*	58*
Number of patients with normalized carbohydrate metabolism,%	14	46*	71*
Number of patients with normalized liver detoxication function,%	16	75*	28
Number of patients with increased bone tissue density,%	8	73*	83*
Mortality rate, % (observed for 8 years)	13.6	6.6*	8.5*

* – P<0.05, as compared to the control index.

manifestations of hypertension. Both bioregulators also proved their efficacy in case of deforming osteoarthrosis.

The results of analyzing the patients' mortality rate throughout 6 years (1996–2001) were most interesting. As it is shown in Table 2, the application of Thymalin and Epithalamin diminished mortality rate 2 and 1.8 times, correspondingly. Simultaneous application of the two bioregulators decreased mortality 2 times and a half as compared to the control group. The results of applying the peptide bioregulators in patients for 6 years (Table 2) deserved special attention. The rate of their mortality went down 4.1 times as compared to the control group. Consequently, the clinical results demonstrated the obvious geroprotective effectiveness of Thymalin and Epithalamin in elderly and older patients.

The results of applying the bioregulators at the Institute of Gerontology of the Ukrainian Academy of Medical Sciences (Kiev), displayed in Table 3, demonstrated a significant improvement in the patients' health state. Thymalin considerably decreased (2.4 times) the incidence and duration of acute respiratory diseases (Table 4). Immune indices were normalized gradually, as a rule, after several repeated courses, which confirmed the advantage of long-term Thymalin and Epithalamin therapy. The administration of the peptide bioregulators prominently inhibited age-related immune disorders in the subjects with accelerated aging [34]. Their prolonged application decreased the functional age of the central nervous system, which reflected its functional improvement. Thymalin normalized the initially raised blood level of cortisol. This effect remained stable for 3 years of applying the bioregulator. The same result was attained for Epithalamin. A stable decrease in the concentration of cortisol was a favorable factor for IHD patients, since it normalized their lipid metabolism and improved certain immune functions. Prolonged Thymalin therapy promoted the maintenance of testosterone and estradiol concentrations in elderly men and women. Besides, Thymalin significantly increased blood estradiol in women, which was a positive factor facilitating hypolipidemic and osteoprotective effects of the bioregulator. Epithalamin revealed its modulating influence upon the functional state of sexual glands in elderly men and women. The application of Thymalin increased fibrinolysis and reduced the signs of hypercoagulation. The clinical results, exhibited in Table 5, confirmed the obvious geroprotective effects of Thymalin and Epithalamin. The ability of these medications to normalize carbohydrate metabolism (especially, Epithalamin) and liver detoxication function (especially, Thymalin), as well as to intensify bone tissue density appeared extremely important. Thus, the obtained data evidenced the normalizing effect of Thymalin and Epithalamin in various age-related homeostatic disorders in elderly persons with accelerated aging. It was remarkable that the bioregulators were applied for 3 years (1992–1994) with the subsequent observation period of 5 years (1995–1999). The normalization of homeostasis in such patients was accompanied by a mortality decrease during 8 years (1992–1999) – 2.1-fold in case of Thymalin and 1.6-fold – in case of Epithalamin (Table 5).

Conclusion

Consequently, the clinical results of Thymalin and Epithalamin geroprotective activity were obtained at two leading gerontological research centers for the development and study of geroprotectors. The trials included 266 elderly and older patients. The period of observation made 6–8 years, which was sufficient enough to confirm the efficacy of the bioregulators. It was important that the results provided by each of the two institutes revealed a strong similarity despite the absolute independence of the trials. At the same time, these trials added much to each other. Especially important was a nearly similar decrease in the patients' mortality rates during the observation period observed at both gerontological centers, which pointed at the high significance of the findings.

To finish, we would like to emphasize that the results of 30-year long experimental and clinical trials of Thymalin and Epithalamin made it possible to logically ground a conclusion on their high geroprotective effectiveness and the indubitable expedience of their application in medical and social care practice as the means of health maintenance and age-related pathology prevention, thus increasing the span of active life in persons over 60.

Statistics

The results obtained in the above-described clinical trials of peptide bioregulators Thymalin and Epithalamin were assessed by the following methods of statistic analysis: Pearson's (χ^2), Student's (t), and Wilcoxon-Mann-Whitney's (U) criteria, least-squares dimension method (LSD), single-factor dispersion analysis (ANOVA) and Fischer's exact method [35].

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