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Mini Review

The Effect of Short Peptides on Increasing the Reserve Capacity of the Human Body

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Abstract

Usage of peptide preparations based on low molecular weight peptides from the thymus and pineal gland contributes to the normalization of neuroimmune-endocrine system function, which is expressed in an increase in the reserve capacity of the human body and an improvement of the quality of life.

***Keywords**: Reserve Capacity; Short Peptides; Stress; Immunity*

The concept of stress was formulated by the famous scientist and physician Hans Selye [8]. The author described stress as a reaction of the body to any external influences. The scientist first proposed the term "adaptation", meaning adjustment of the body to changing conditions in the external environment while maintaining its homeostasis. For a person, preservation of the optimal state of vital functions in new environmental conditions indicates development of adaptation. In violation of adaptation processes and insufficiency of protective and adaptive mechanisms, maladjustment occurs with the development of pathological processes in the body and its accelerated aging [8].

In the theory of the general adaptation syndrome of H. Selye, the state of the endocrine and thymic-lymphatic systems is of the greatest importance. The functioning of these systems is what the failure of adaptation mechanisms with the development of diseases or the increase in the functional reserves of the body with adaptation to a stress factor depends on.

This concept gave Khavinson V.Kh. and Morozov V.G. an opportunity to create drugs based on low molecular weight peptides from thymus and epiphysis back in the 70s of the last century. The introduction of these peptide preparations promotes activation of the endocrine and immune systems' function and increases resistance of the human body to stress. Long-term experimental and clinical studies have shown that the use of peptide preparations based on low-molecular peptides from the thymus and pineal gland contributed to normalization in the work of the neuroimmune-endocrine system of the body, which was expressed by slowing down the aging rate of the human body, increasing its physical performance, and reducing the risk of oncological diseases. Such activation of adaptive capabilities contributed to a significant decrease in mortality among subjects receiving peptide drugs for 15 years [9].

Thus, studies on adaptation are the scientific basis for the primary prevention of not only diseases, but also accelerated aging of the human body, which opens up prospects for managing the adaptation process.

According to numerous studies, under the influence of adverse environmental factors, emotional stress, and development of age-related pathology, the process of self-regulation of the functions of the main body systems is disrupted, correction of which is possible with the help of specific short peptides [2,3,5,7]. In addition, it is known that short peptides are able be resistant to hydrolysis in the gastrointestinal tract and blood, as well as epigenetically regulate gene expression, thereby normalizing metabolism [4,11]. The data of these studies served as the basis for the development of drugs and biologically active food supplements based on short peptides.

Based on the short peptides Ala-Glu-Asp-Gly (AEDG) and Lys-Glu (KE), biologically active food supplements epitalon and vilon were developed. Dipeptide KE (Lys-Glu) is produced and certified as a biologically active food supplement Vilon. Certificate: Certificado De Venda Livre De Suplementos Alimentares Certificate of Free Sale - Food Supplements CVL-SA/811/2021/511 (Italy). Tetrapeptide AEDG (Ala-Glu-Asp-Gly) is produced and certified as a biologically active food supplement EPITALON®. Notified with the Ministero della Salute (Ministry of Health) Italy with the notification number 115680.

Epitalon was developed based on the results of an experimental study of the tetrapeptide Ala-Glu-Asp-Gly. Long-term experimental studies have shown that Ala-Glu-Asp-Gly regulates metabolic processes in cells of the neuroendocrine system, activates antioxidant defense processes, stimulates pineal and extrapineal synthesis of melatonin in the EC cells of the stomach and intestines, leading to optimization of the biorhythms of secretion of cortisol and other hormones [1,5,6].

The safety of dietary supplement Ala-Glu-Asp-Gly was confirmed by the results of a study of its general toxic effect. In the study of acute toxicity, it was found that a single administration of Ala-Glu-Asp-Gly solution to animals at a dose exceeding the therapeutic dose recommended for clinical use by 5000 times does not cause toxic reactions. The study of subacute and chronic toxicity of Ala-Glu-Asp-Gly indicates absence of side effects in its long-term use at doses exceeding the therapeutic dose by 100 - 1000 times. When assessing the general condition of animals, morphological and biochemical parameters of peripheral blood, morphological state of internal organs, state of the cardiovascular and respiratory systems, liver and kidney function, no pathological changes were found in the body. Thus, the absence of a general toxic effect indicates the safety of using Ala-Glu-Asp-Gly as a biologically active food supplement in order to maintain the function of the neuroendocrine system.

A clinical study of the effectiveness of the biologically active food supplement Epitalon showed its high efficiency in subjects with conditions caused by chronic stress factors.

The study involved 560 subjects aged 35 to 68 years (260 men and 300 women) with conditions after prolonged exposure to professional or psycho-emotional stress, including those caused by frequent changes in time zones.

Stress is a pathological process, which consists in the formation of a complex of non-specific protective, compensatory and pathological reactions of the body that occur in response to the action of emergency or pathological stimuli that really threaten homeostasis: pain, hypoxia, hunger, psycho-emotional overstrain and other emergency factors that lead to the similar type of changes in the lymphoid tissue, including the thymus gland, blood composition, adrenal glands, leading to a change in the biorhythm of hormone secretion. There are close links between stress and the occurrence of somatic diseases. Modern experimental and clinical data, based on observations of people and animals, confirm the results obtained, at one time, by H. Selye, the classic of the doctrine of stress, and reveal those psychological processes through which emotional reactions to stress can make a person susceptible to diseases [8].

Recently, more and more often in clinical practice, the cause of violations of the biorhythm of hormone synthesis and related disorders of the autonomic nervous system (insomnia, emotional lability, apathy, etc.) is jet lag syndrome, a mismatch of the human biorhythm with the daily rhythm, due to frequent changes in time zones.

The subjects were randomly divided into two groups: main and control. The surveyed main group (270 people) received dietary supplement Epitalon 1 capsule per day during meals for 20 days. The control group included 290 subjects with similar conditions who received a placebo according to a similar schedule. Informed consent was signed with each participant of the study in accordance with protocol No. 7 dated March 5, 2018, approved by the ethical committee of the St. Petersburg Institute of Bioregulation and Gerontology.

All subjects were under professional or psycho-emotional stress for a long time, including 142 people were subject to jet lag syndrome, 430 people were under professional stress caused by extreme psycho-emotional stress at work, lack of rest during long time. The subjects complained of an asthenic condition: general weakness, loss of appetite, headaches, sleep disturbance, increased irritability, apathy, emotional lability, fatigue, decreased performance, memory and attention loss, dizziness, increased sweating, changes in blood pressure.

The effectiveness of the dietary supplement Epitalon was assessed subjectively, by studying the dynamics of the complaints of the subjects, and by objective indicators, including the determination of the content of cortisol, adrenocorticotropic hormone (ACTH) and melatonin in the blood serum. The content of melatonin in the blood was measured twice: in the morning at 9:00 and in the evening at 21:00.

It was established that the use of Epitalon contributed to the improvement of the general condition of patients in the study group. The subjects who received Epitalon noted an improvement in all subjective indicators, as can be seen from the data presented in table 1.

Indicator	Control n = 290 abs./%		Main n = 270 abs./%	
	Before placebo	After placebo	Before using the peptide	After using the peptide
Apathy	275/94,8	262/90,3	259/95,9	135/ 50,0*#
Emotional lability	282/97,2	288/99,3	265/98,1	100/37,0*#
Sleep disturbance	195/67,2	211/72,7	182/67,4	87/32,2*#
Rapid fatigability	286/98,6	284/97,3	268/99,2	110/40,7*#
Decreased performance	280/96,5	271/93,4	267/98,8	107/39,6*#
Decreased concentration	199/68,6	202/69,6	175/64,8	88/32,5*#

Table 1*: Influence of Epitalon on the dynamics of subjective indicators in patients subject to prolonged exposure to professional, psycho-emotional stress or jet lag syndrome.*

**p < 0.05 compared with the primary indicator; #p < 0.05 compared with the corresponding indicator in the subjects of the control group.*

From the data in table 1, it follows that the use of Epitalon in patients subject to prolonged exposure to professional or psycho-emotional stress, including those caused by frequent changes in time zones, showed an improvement in subjective indicators that significantly differed from those before the use of dietary supplements and from those in patients in the control group.

While apathy, fatigue, decreased performance were noted during the initial examination in all patients of both groups, then after the correction with Epitalon dietary supplements, these complaints decreased in half of the cases in patients of the main group. While in the control group, there were no significant changes, in addition, complaints of emotional lability and decreased concentration even increased. It should be noted that the regulation of the function of the neuroendocrine system with the help of Epitalon contributed to the restoration of sleep in more than half of the subjects. No significant changes were registered in the control group.

As can be seen from the data in table 1, upon re-examination, all subjective indicators in patients of the main group significantly differed from those in patients in the control group: the complaints of patients, characterizing the state after prolonged exposure to stress factors, had a positive trend, only in the surveyed main group.

During the initial study of the level of melatonin in the blood of patients of both groups, it was found that the level of melatonin in the morning (9:00) was reduced by 1.3 times, the level of melatonin in the evening (21:00) was reduced by 2.3 times compared to the lower limit normal values (Table 2). After using Epitalon, a significant increase in the level of melatonin in the morning (up to 18.2 ± 1.4 pg/ml) and in the evening (up to 72.3 ± 3.6 pg/ml) to the lower limit of the reference values was observed, while in the subjects in the control group, the levels of melatonin in the morning and evening increased slightly and did not reach the lower limit of the norm.

Indicator	Norm	Before placebo	After placebo	Before using the peptide	After using the peptide
Melatonin in blood serum in the morning, (pg/ml)	8,0 - 20,0	6,3 ± 0,9	7,8 ± 1,1	6,9 ± 1,1	18,2 ± 1,4*#
Melatonin in blood serum in the evening, (pg/ml)	70 - 150	31,4 ± 1,2	37,2 ± 1,9	35,1 ± 1,3	72,3 ± 3,6*#

***Table 2**: Effect of Epitalon on blood melatonin levels in patients subject to prolonged exposure to professional, psycho-emotional stress or jet lag syndrome.*

**p < 0.05 - significant compared with the primary indicator; #p < 0.05 - significant compared with the indicators in the control group*.

The use of Epitalon in patients subject to prolonged exposure to professional or psycho-emotional stress contributed to the stabilization of the hormonal status, which indicates the leveling of maladjustment disorders and catabolic reactions (Table 3).

Indicator	Norm	Before placebo	After placebo	Before using the peptide	After using the peptide
Cortisol (nmol/l)	250 - 750	232,7 ± 20,1	236,4 ± 19,6	239,1 ± 18,9	386,7 ± 18,4*#
ACTH (pg/ml)	10 - 80	10,9 ± 0,9	11,2 ± 1,0	12,6 ± 1,0	31,4 ± 1,0*#

***Table 3**: The effect of Epitalon on the level of cortisol and adrenocorticotropic hormone in the blood plasma of patients subject to prolonged exposure to professional, psycho-emotional stress or jet lag syndrome.*

**p < 0.05 - significant compared with the primary indicator; #p < 0.05 - significant compared with the indicators in the control group.*

The content of cortisol and adrenocorticotropic hormone (ACTH) before the start of the examination was noted to be at the lower limit of the norm, which indicated the depletion of the reserves of the adrenal cortex. After complex treatment with the use of Epitalon, the level of cortisol and ACTH in the blood plasma returned to normal and was detected in the middle range of reference values for these indicators, which is extremely important for optimizing the body's response to stress factors. These changes correlated with improvement in subjective measures. Attention must be drawn to the absence of positive dynamics in the content of cortisol and ACTH in the blood of the subjects in the control group.

Thus, the results of the studies showed that the use of dietary supplement Epitalon contributed to the improvement of the neuroendocrine system of the body, which explains the improvement in the general condition of patients in the main group. Against the background of the use of dietary supplement Epitalon, there was a decrease in complaints about sleep disturbance, headaches, dizziness, apathy, weakness, fatigue, reduced performance, emotional lability, decreased memory and attention, increased sweating, decreased appetite.

In the process of using Epitalon, side effects, complications and drug dependence were not identified.

The results of a clinical study of the dietary supplement Epitalon allow us to conclude that the dietary supplement Epitalon Ala-Glu-Asp-Gly has a regulatory effect on the neuroendocrine system, which allows us to recommend its use in people subject to prolonged exposure to professional or psycho-emotional stress, including jet-lag syndrome due to frequent change of time zones.

Vilon Lys-Glu (KE) was developed based on the results of an experimental study of the dipeptide Lys-Glu (KE). Long-term experimental studies have shown that peptides have a tissue-specific effect. According to experimental studies, Lys-Glu (KE) dipeptide regulates metabolic processes in cells of the immune system, improves cellular and tissue homeostasis in cells of the immune system, restores impaired immunological reactivity, activates antioxidant defense processes, stimulates tissue regeneration processes in case of their inhibition. These properties of Lys-Glu (KE) dipeptide are the mechanism of its immunomodulatory and anti-stress action [3,5,6].

The safety of the dipeptide Lys-Glu (KE) was confirmed by the results of a study of its general toxic effect. In the study of acute toxicity, it was found that a single injection of Lys-Glu (KE) dipeptide solution to animals at a dose exceeding the therapeutic dose recommended for clinical use by 5000 times does not cause toxic reactions. The study of subacute and chronic toxicity of the dipeptide Lys-Glu (KE) indicates the absence of side effects in its long-term use at doses exceeding the therapeutic dose by 100 - 1000 times. When assessing the general condition of animals, morphological and biochemical parameters of peripheral blood, the morphological state of internal organs, the state of the cardiovascular and respiratory systems, liver and kidney function, no pathological changes in the body were found. Thus, the absence of a general toxic effect indicates the safety of using Lys-Glu (KE) dipeptide as a biologically active food supplement in order to maintain the function of the immune system.

A clinical study of the effectiveness of the biologically active food supplement Vilon showed its high efficiency in complex restoration of the functions of the immune system in pathological conditions of various origins, including acceleration of tissue regeneration after various injuries, when exposed to extreme environmental factors, as well as maintaining the functions of the immune system in elderly and senile patients [10].

The study involved 520 people aged 43 to 76 years (268 men and 252 women) in the period of convalescence after acute respiratory, bacterial or viral diseases.

It is known that various factors of physical, chemical and biological nature, depending on the duration or intensity of their impact on the human body, can lead to depletion of adaptive and compensatory mechanisms and cause profound disturbances in various parts of the immune system.

Pathological disorders in the immune system contribute, as a rule, to a protracted course of the underlying disease with a tendency to relapse, a decrease in the body's resistance to infection and development of severe complications.

The subjects were randomly divided into two groups: main and control. The surveyed main group (276 people) received dietary supplement Vilon 1 capsule per day during meals for 20 days. The control group included 244 people with similar conditions who received placebo in a similar way. Informed consent was signed with each participant of the study in accordance with protocol No. 2 dated January 24, 2018, approved by the ethical committee of the St. Petersburg Institute of Bioregulation and Gerontology.

The effectiveness of the use of dietary supplements for food Vilon was evaluated by the dynamics of complaints of the subjects and by a number of objective indicators: general clinical examination of blood and urine, immunological examination of peripheral blood (the count of T- and B-lymphocytes was determined by immunofluorescence with monoclonal antibodies obtained against the differentiation antigens of lymphocytes CD3, CD4, CD8, CD20, the content of immunoglobulins of various classes - by Mancini radial immunodiffusion

in gel, functional activity of T-lymphocytes - by leukocyte migration inhibition (LMI) assay with ConA). The subjects complained of an asthenic condition: general weakness, loss of appetite, headaches, sleep disturbance, irritability, apathy, emotional lability, fatigue, reduced performance.

The conducted studies have shown that the majority of subjects who are in the period of convalescence, regardless of the etiology of the disease (viral as a complication after influenza, acute respiratory infections or pneumococcal), have disorders in the immune status, manifested in a decrease in the number of CD3+, CD4+ cells with a slight increase in the number of lymphocytes with the CD8+ phenotype, which indicates a decrease in the level of immunoreactivity (CD4+/CD8+). The results of LMI assay with ConA characterize a decrease in the functional activity of T-lymphocytes (mainly CD8+, i.e. T-suppressors/killers). The content of CD20+ cells, representing a subpopulation of B-lymphocytes, did not significantly differ from normal values, but, at the same time, an increase in the amount of immunoglobulins M and G in the blood serum was observed (Table 4).

Indicator	Norm	Before placebo	After placebo	Before using the peptide	After using the peptide
Leukocytes, $\times 10^9$/l	4 - 9	4,3 ± 0,1	4,8 ± 0,1	4,6 ± 0,6	6,5 ± 0,2*
Lymphocytes, %	23 - 45	33,2 ± 1,7	31,4 ± 1,6	30,4 ± 1,6	34,6 ± 2,0
$\times 10^9$/l	1,2 - 2,4	1,44 ± 0,01	1,49 ± 0,01	1,36 ± 0,02	1,58 ± 0,01
IgM, (g/l)	0,65 - 1,65	1,79 ± 0,02	1,65 ± 0,02	1,68 ± 0,03	1,58 ± 0,02
IgG, (g/l)	7,5 - 16,0	18,6 ± 0,6	17,9 ± 0,5	16,7 ± 1,0	17,2 ± 0,7
IgA, (g/l)	1,7 - 2,5	1,8 ± 0,09	2,0 ± 0,09	2,0 ± 0,08	1,9 ± 0,09
$CD3^+$, %	60 - 89	48,3 ± 1,8	50,3 ± 1,5	52,4 ± 1,7	61,6 ± 1,6*
$\times 10^9$/l	0,88 -2,4	1,25 ± 0,04	1,35 ± 0,04	1,49 ± 0,01	1,95 ± 0,04*
$CD4^+$, %	31 - 46	23,7 ± 1,6	25,7 ± 1,8	27,4 ± 1,9	33,2 ± 1,6*
$\times 10^9$/l	0,57 - 1,1	0,42 ± 0,01	0,37 ± 0,02	0,52 ± 0,03	0,59 ± 0,02*
$CD8^+$, %	21-41	29,1 ± 1,8	30,4 ± 1,5	32,1 ± 1,9	27,3 ± 1,5
$\times 10^9$/l	0,4 - 0,75	0,48 ± 0,02	0,49 ± 0,02	0,42 ± 0,05	0,45 ± 0,02
$CD4^+/CD8^+$	0,9 - 1,8	0,8 ± 0,02	0,8 ± 0,05	0,9 ± 0,01	1,2 ± 0,02
$CD20^+$, %	15 - 30	14,1 ± 0,3	14,2 ± 0,2	13,9 ± 0,4	15,0 ± 0,3
$\times 10^9$/l	0,4 -0,7	0,33 ± 0,01	0,35 ± 0,02	0,31 ± 0,03	0,34 ± 0,03
LMI, %	40 - 75	89,4 ± 3,6	86,6 ± 3,0	84,2 ± 3,9	76,1 ± 3,1*

***Table 4**: Influence of Vilon on indicators of cellular and humoral immunity*

** p<0.05 - significant compared with the index before treatment.*

It should be noted that for patients of this age, the lower limits of physiological fluctuations in the quantitative indicators of the CD3+ and CD4+ cell content are typical; it may indicate the depletion of their immune system. As a rule, persons with a secondary immunodeficiency state had a pronounced asthenic syndrome and significant changes in the cardiovascular system.

The results of the conducted studies indicate that Vilon is an effective tool for correcting secondary immunodeficiencies that develop in response to exposure to extreme factors. The use of Vilon allowed to normalize the affected parameters of the immune system in 86% of cases.

As follows from the data in table 4, the greatest effect from the use of Vilon was noted in relation to subpopulations of T-lymphocytes and their functional activity: there was a significant increase in the content of CD3+- and CD4+-lymphocytes to the level of normal values with their initial significant decrease, normalization of the CD4+/ CD8+, significant decrease in LMI indicator. A less pronounced reaction was observed on the part of the B-system of immunity (CD20+), probably due to its greater conservatism and insufficient duration of the drug intake, although a tendency to an increase in the content of B-lymphocytes up to the lower limit of the norm was noted. Also noteworthy is a significant increase in the content of leukocytes in comparison with the indicator before the use of the peptide: initially this indicator was at the lower limit of the norm, after the course of the drug, the indicator increased to optimal values, which indicates a faster relief of the inflammatory process in the body than in the patients of the control group.

The positive dynamics of laboratory parameters was accompanied by a pronounced improvement in subjective parameters (Table 5): after the course with the use of Vilon, the subjects who had pneumonia noted a significant improvement in their general condition, leveling of the residual effects of bronchial and lung dysfunction (decrease in cough, shortness of breath) and a decrease in the severity of asthenic syndrome, which always accompanies secondary immunodeficiencies caused by an infectious disease. Thus, the obtained results of the study indicate not only the immunomodulatory effect of the drug, but also its ability to accelerate tissue regeneration due to the immunostimulating effect.

Indicator	Control group n = 244 abs./%		Main group n = 276 abs./%	
	Before placebo	After placebo	Before using the peptide	After using the peptide
General weakness	239/97,9	222/90,9	270/97,8	133/48,1*#
Rapid fatigability	220/90,1	200/81,9	263/95,2	110/39,8*#
Decreased performance	216/88,5	193/79,1	247/89,4	107/38,7*#
Decreased concentration	119/48,7	115/47,1	155/56,1	88/31,8*#

Table 5*: The influence of vilon on the dynamics of subjective indicators in subjects during the period of convalescence.*

**p < 0.05 compared with the primary indicator; #p < 0.05 compared with the corresponding indicator in the subjects of the control group.*

Side effects, complications, contraindications, drug dependence when using Vilon during the clinical study were not identified.

Thus, the conducted clinical study showed that Vilon contributes to the normalization of cellular immunity, stimulates the processes of tissue regeneration in case of their inhibition, does not cause side effects, complications and drug dependence. Food supplement Vilon is recommended to be used to accelerate the recovery of the immune system after inflammatory diseases of infectious and non-infectious origin (including after pneumonia of viral and bacterial etiology), it is also recommended for the elderly to maintain the functional activity of the immune system.

Thus, oral use of biologically active food supplements Epitalon and Vilon, created on the basis of short peptides Ala-Glu-Asp-Gly (AEDG) and Lys-Glu (KE), proved to be effective in clinical studies in order to maintain the functional activity of the immune and neuroendocrine systems.

Conclusion

Experimentally and clinically revealed possibility of oral administration of drugs based on short peptides, their stability in the action of enzymes of the gastrointestinal tract and blood plasma, the ability to activate the absorption of various biological substances in the gastrointestinal tract, penetrate into the cytoplasm, nucleus and nucleolus of target cells of various tissues, interact with DNA and epigenetically regulate expression of genes provides an explanation for their high biological activity and successful use as substances that have a physiologically adequate and geroprotective effect.

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