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Research Article

Prospects for the Use of Dipeptide in Patients with Chronic Atrophic Gastritis

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Abstract

Conducted numerous experimental studies prove that the dipeptide (Lys-Glu) significantly enhances the proliferative activity of T-lymphocytes, accelerating their differentiation and migration rate, as well as the proliferative potential of stem cells of the stomach and intestines. In our opinion, this particular biological activity of the dipeptide contributes to the stimulation of the restoration of the structural and functional organization of the gastric mucosa, which leads to an improvement in the clinical picture. In this regard, the biologically active food supplement Vilon can be recommended as a maintenance immunomodulatory therapy in patients with chronic atrophic gastritis.

Keywords: *Helicobacter pylori (HP); Dipeptide; Chronic Atrophic Gastritis*

Introduction

Chronic gastritis is a disease characterized by the presence of inflammatory and degenerative processes in the gastric mucosa. A decrease in the mass of functionally active glandular tissue of the stomach leads to the development of atrophic gastritis with, as a rule, reduced secretion of hydrochloric acid. In addition, according to a number of authors, a decrease in the acid-forming function of the stomach serves as a trigger for development of pathogenic microflora, in particular, *Helicobacter pylori* (HP) with subsequent aggravation of the pathological process - occurrence of a stomach ulcer with the possibility of its malignancy [13,20]. However, even successful eradication of the microorganism does not always contribute to complete restoration of acid production in the stomach, especially in the case of severe atrophic changes in the gastric mucosa [12,15,16].

Thus, restoration of the atrophied mucosa and indirect improvement of the acid-forming function of the stomach is an important component in the treatment of patients with chronic *H. pylori*-associated atrophic gastritis, as well as a method for early prevention of carcinogenesis.

In recent years, a promising direction in the pharmacological regulation of the physiological functions of organs and tissues is bioregulatory therapy using peptide preparations. There are a number of such peptides that, by regulating gene expression, restore the functional activity of organs and tissues. Among them, the most widely used in clinical practice are peptide bioregulators created in Russia since the 1970s at the Military Medical Academy. To date, further study of these peptide bioregulators is being actively continued at the St. Peters-

burg Institute of Bioregulation and Gerontology under the guidance of prof. Khavinson V.Kh., as well as in leading scientific universities in Europe and America [1,2,9,18].

It is known that low molecular weight substances of a peptide nature are formed in cells, which carry out the transfer between cells of certain information recorded using an amino acid sequence and conformational modifications, thereby regulating proliferation, differentiation, apoptosis and intercellular interactions. Peptide bioregulators have a wide range of biological activity, affecting gene expression. By regulating gene expression, peptide bioregulators stimulate protein synthesis in body cells, which improves the functional activity of human organs and systems. Thus, as a result of regulatory processes, despite the action of pathogenetic factors, DNA damage, mutations and pathological transformations are prevented or attenuated, and the course of reparative processes aimed at restoring cellular homeostasis is enhanced. Therefore, a distinctive feature of bioregulatory therapy is its physiological regulatory effect on metabolic processes in the cell, which are known to be disrupted in various diseases and during aging [6,7,19].

Dipeptide KE (Lys-Glu) has an immunomodulatory, geroprotective, regenerative, oncostatic effect, stimulates the functional activity of fibroblasts. KE is a peptide thymomimetic, which is present in the structure of thymalin. At the molecular-cellular level, the main immunomodulatory effects of KE are the stimulation of thymocyte differentiation into T-lymphocytes, stem cells differentiation into precursors of T- and B-lymphocytes, activation of the immune response of T-lymphocytes and macrophages, activation of the proliferation of T-, B-lymphocytes and macrophages, as well as a decrease in the level of their apoptosis during natural and accelerated aging of the immune system [3,10,14,17]. The geroprotective effect of the KE peptide is expressed in an increase in the proportion of euchromatin and telomere length in blood lymphocytes of people of different ages, an increase in the life expectancy of animals [8]. The oncostatic effects of the KE peptide include a decrease in the number of lymphoma and hepatoma cells in culture, a decrease in the expression of the HER2/neu gene and the diameter of tumors in transgenic mice with mammary adenocarcinoma [1]. The KE peptide is able to penetrate the cell membrane into the nucleus and regulate gene expression [4,5]. KE regulates the synthesis of certain proteins. Using physicochemical methods and bioinformatics, a model of the interaction of this dipeptide with the promoter zone of genes with the participation of hydrogen bonds was created [11].

Purpose of the Study

The purpose of this study was to evaluate the effectiveness of the dipeptide in restoring the acid-forming function in the stomach according to daily pH-metry in patients with chronic H. pylori-associated atrophic gastritis.

Materials and Methods

A single-center, open, prospective, randomized, placebo-controlled study included patients treated at the St. Petersburg Medical Center of the Institute of Bioregulation and Gerontology with a clinical diagnosis of chronic atrophic gastritis (K 29.4). Patients were randomized using the envelope method.

The inclusion criteria for the study were the presence of chronic atrophic gastritis, confirmed by endoscopic examination, as well as pH-metry data on the presence of a hypoacid state (pH over 5.0). The exclusion criteria from the study were the presence of the following signs: exacerbation of any somatic, including infectious, diseases that can affect the course of the disease; patients taking corticosteroids; the presence of hepatic, renal, cardiovascular, adrenocortical insufficiency, tuberculosis in the active stage, hepatitis, HIV infection, oncological diseases and mental disorders; pregnant and lactating women; patients for whom, in the judgment of their physician, any of the procedures in the protocol may pose a risk that outweighs the potential benefit of participating in the study. Participants' participation in the study was voluntary and was confirmed by signature in the informed consent form.

Informed consent was signed with each participant of the study in accordance with protocol No. 9 dated February 1, 2021, approved by the ethical committee of the St. Petersburg Institute of Bioregulation and Gerontology (St. Petersburg, RF).

Dipeptide KE (Lys-Glu) is produced and certified as a biologically active food supplement VILON®. VILON® Capsules are notified with Ministero della Salute Italia- Registro degli integratori alimentari (Ministry of Health Italy- registry of the food supplements) notification number №125865 dated 13.09.2019.

98 patients aged 38 - 74 years (mean age 57.8 ± 0.7) with a diagnosis of chronic atrophic gastritis were observed. Patients were randomly divided into two groups: the first control group of 49 people and the second main group of 49 people. After the randomization procedure before taking the study dipeptide, all patients received standard eradication therapy. Patients of the main group on the background of standard therapy received Vilon dipeptide orally 2 times a day for 30 days. Patients in the control group received placebo according to a similar scheme. All patients before and after therapy underwent daily pH-metry. Daily pH-metry evaluated the minimum pH value, the average pH value, aggressiveness index (AI) and acidity index. Data were compared before and after treatment between groups of patients who received the dipeptide studied and placebo.

Statistical processing of the results was carried out using the SPSS Statistics 17.0 software. Differences between samples were assessed using Student's parametric t-test. The critical level of significance of the null hypothesis (about the absence of significant differences) was taken equal to 0.01 or 0.05. The arithmetic mean ($\bar{X}$) and standard error of the arithmetic mean (SE) were calculated for each sample. The data in the tables are presented as $\bar{X} \pm SE$.

Research Results

In all patients of the main and control groups, the pH-metry data, as well as the results of endoscopy, indicated the presence of a hypoacid state (pH over 5.0) and atrophic changes in the gastric mucosa. In all patients, endoscopy revealed thinning of the gastric mucosa, a decrease in gastric folds and the number of gastric glands. The thinned mucosa visually appeared as grayish-pale areas through which the blood vessels located in the submucosal layer were visible. Therefore, the vascular pattern looked pronounced. This endoscopic picture was revealed in all patients of the control and main groups and indicated the presence of chronic atrophic gastritis in all subjects.

During the initial examination, all patients complained of a decrease or lack of appetite, belching, nausea, bad taste in the mouth, a feeling of heaviness and fullness of the stomach in varying degrees. The severity of these complaints, reflecting the clinical manifestations of chronic atrophic gastritis, was assessed in points (Table 1). The table for each patient was completed twice: before and after taking the dipeptide or placebo.

Intensity	Appetite disorder	Belching	Nausea	Bad taste in the mouth	Feeling of heaviness and fullness in the stomach
Pronounced	3	3	3	3	3
Moderately pronounced	2	2	2	2	2
Mild	1	1	1	1	1
No manifestations	0	0	0	0	0

Table 1: *Assessment of clinical manifestations of chronic atrophic gastritis.*

The use of the dipeptide made it possible to significantly reduce the subjective clinical manifestations of chronic atrophic gastritis in the subjects of the main group compared to patients receiving placebo. As can be seen in table 2, in patients of the main group, the manifestations of almost all complaints significantly decreased. So, 33 subjects (67.3%) noted that their appetite was completely restored and the feeling of nausea disappeared. The feeling of heaviness and fullness of the stomach ceased to bother 27 people (55.1%). In the remaining patients of the main group, complaints became less intense, and the frequency of their manifestations became much less frequent.

Symptoms	Control group		Main group	
	Before treatment	After treatment	Before treatment	After treatment
Appetite disorder	2,40 ± 0,07	2,57 ± 0,08	2,53 ± 0,08	1,11 ± 0,09*
Belching	2,31 ± 0,09	2,21 ± 0,06	2,21 ± 0,08	2,30 ± 0,07
Nausea	1,28 ± 0,09	1,09 ± 0,07	1,41 ± 0,07	0,84 ± 0,09*
Feeling of heaviness and fullness in the stomach	2,46 ± 0,07	2,61 ± 0,04*	2,53 ± 0,09	1,88 ± 0,11*
Bad taste in the mouth	1,98 ± 0,10	1,85 ± 0,09	1,76 ± 0,06	0,78 ± 0,12*

Table 2: *Effect of Vilon dipeptide on the dynamics of clinical signs of chronic atrophic gastritis.*

**P < 0,05 compared to before treatment.*

In the control group, there were no reliable data on a decrease in the intensity or frequency of complaints presented by patients before the study. Also, there were no statistically significant changes in the parameters of gastric pH-metry in the process of taking both placebo and the study drug.

The improvement in the subjective clinical manifestations of chronic atrophic gastritis in subjects who received a course of Vilon (Lys-Glu) can be explained by the regenerating and immunomodulatory activity of this drug. Conducted numerous experimental studies prove that the dipeptide (Lys-Glu) significantly enhances the proliferative activity of T-lymphocytes, accelerating their differentiation and migration rate, as well as the proliferative potential of stem cells of the stomach and intestines. In addition, according to the authors, the positive effect of the dipeptide can be potentiated under the conditions of therapeutic measures aimed at normalizing disturbed hemodynamics and microcirculation, as well as restoring the barrier function of the cells of the stomach and intestines and their ability to detoxify by increasing the intensity of not only proliferative, but also intracellular regeneration [17].

Conclusion

In our opinion, this particular biological activity of the dipeptide contributes to the stimulation of the restoration of the structural and functional organization of the gastric mucosa, which leads to an improvement in the clinical picture. In this regard, the biologically active food supplement Vilon can be recommended as a maintenance immunomodulatory therapy in patients with chronic atrophic gastritis.

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