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Review Article

Role of Short Peptides in Maintaining Liver Functional Activity

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Abstract

The risk of various gastrointestinal diseases, including liver disease, increases with age. All this necessitates the search for effective and safe hepatoprotectors. The review presents the data of studies of hepatoprotective, immunomodulatory properties of tetrapeptide KEDA (Lys-Glu-Asp-Ala). High efficacy of the short peptide KEDA was shown in models of experimental liver pathology in animals and in vitro studies.

Keywords: *Gastrointestinal Diseases; Liver Disease; Hepatoprotectors; KEDA*

Diseases of the gastrointestinal tract, including liver pathology, are one of the leading causes of disability and mortality, especially in older people. It should be noted that liver diseases are especially severe in elderly patients. It has been established that with age, morphological and functional changes are observed in the liver. Despite a general decrease in organ weight, a relative increase in fat content occurs. Also, there is a deterioration in the trophicity of the organ and a decrease in regional blood circulation due to a decrease in the number of capillaries per unit area of the liver. Moreover, in patients over 60 years of age, the number of vessels is 3 - 4 times less than in middle-aged people. At the same time, an increase in the number of collagen fibers is observed in the walls of the blood vessels of the liver. Age-related involution and liver pathology cause metabolic disturbances in the body, contributing to the accelerated aging [5,6].

Emergence of age-associated diseases forces elderly patients to use additional medications, which cannot but affect the function of the liver. It is known that hepatocyte functioning under conditions of high concentrations of drugs leads to cytotoxic damage to liver cells in more than 25% of all cases. In this case, drugs have an apoptotic effect not only on hepatocytes, but also on endothelial cells of the liver. Selective toxicity of xenobiotics against liver vascular endothelial cells is noted. In addition, with age, as well as with drug intoxication in the vessels of the liver, subendothelial deposition of collagen is often found. Moreover, a violation of the rheological properties of blood leads to thrombus formation, which aggravates liver dysfunction in people of the older age group [6].

Therefore, with age, the risk of developing liver cirrhosis, acute and chronic hepatitis increases, which necessitates the search for effective and safe hepatoprotectors.

In recent years, a promising direction in the pharmacological regulation of the physiological functions of organs and tissues is bioregulatory therapy using peptide drugs. A number of peptides has been found to restore the functional activity of organs and tissues by regulating gene expression. Among them, the most widespread in clinical practice are peptide bioregulators which have been created in Russia at the Military Medical Academy since the 1970s. To date, this scientific direction is actively continuing at the St. Petersburg Institute of Bioregulation and Gerontology under the guidance of prof. Khavinson V.Kh. [2,10].

It is known that low molecular weight substances of a peptide nature are formed in cells. They carry out the intercellular transfer of certain information recorded using a sequence of amino acids and conformational modifications, thereby regulating proliferation, differentiation, apoptosis and intercellular interactions. Peptide bioregulators have a wide spectrum of biological activity, affecting gene expression. By regulating gene expression, peptide bioregulators stimulate protein synthesis in the cells of the body, which helps improve the functional activity of 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 weakened, and the course of reparative processes aimed at restoring cellular homeostasis is enhanced. Therefore, a distinctive feature of bioregulatory therapy is its physiological regulating effect on metabolic processes in the cell, which are known to be interrupted by various diseases and the aging process [14,18,20].

Peptides stimulate protein synthesis in the cells of the body and regulate the functional activity of human organs and systems. Long-term experimental studies have shown that short peptides have high biological activity: they increase the average and maximum life span of animals, reduce the incidence of malignant tumors, help increase telomere length, overcome the Hayflick cell division limit, restore the functional activity of cells of the immune system and the endocrine system [9,10]. Among peptide bioregulators, there is a large number of drugs with an unidentified composition. A significant part of them are extracts from certain tissues and organs. However, in recent years, both physiologists and pharmacologists have become increasingly interested in regulatory peptides obtained synthetically in accordance with the amino acid sequence of natural peptides. The prospects of this direction are obvious: use of substances with an identified structure will make it possible to more accurately study the mechanism of their action and create highly effective drugs based on them [1,4,15].

At the St. Petersburg Institute of Bioregulation and Gerontology, the tetrapeptide KEDA (Lys-Glu-Asp-Ala) was constructed by targeted chemical synthesis [13]. The basis for the design of the peptide was the amino acid analysis of a complex peptide preparation isolated from calf liver tissue.

In the course of the research, the regulatory effect of the KEDA tetrapeptide on histogenesis and liver function was studied and the expediency of using this peptide preparation as a hepatoprotector was substantiated.

First of all, the induction activity of the KEDA tetrapeptide was evaluated. The control peptide was the tetrapeptide AEDG (Ala-Glu-Asp-Gly), which has retinoprotective activity. The ectoderm of the early gastrula of the Xenopus Laevis was used as a test system (a pluripotent tissue capable of a certain differentiation under the influence of one or another inducing agent). These short peptides were studied at different concentrations: 2, 10, 20, 50, 100, 200 ng/ml; each concentration was used on 40 cultures in the study and on 20 cultures as a control. The evaluation of the research results was carried out using morphological and immunohistochemical methods.

Analysis of the results obtained showed that peptide bioregulators have inductive activity. In pluripotent tissue, under the influence of the control peptide AEDG, tissue differentiation occurred, corresponding to the tissues from which the drug was isolated, that is, neural differentiation was triggered, while the tetrapeptide KEDA (Lys-Glu-Asp-Ala) triggered differentiation of mesodermal tissues. Thus, if earlier it had been known about the tissue specificity of peptides at the level of differentiated cell cultures, then work with pluripotent tissues showed the ability of short peptides, consisting of only a few amino acids, to trigger tissue differentiation in normal developing embryonic tissue, which opens up a completely new direction in pharmacology [8,12,16].

Further studies have shown that the KEDA peptide is practically not hydrolyzed by peptide hydrolases of the small intestine, entering first into the blood plasma, and then into various tissues and organs. This is explained primarily by the fact that the regulatory systems of the intestine carry out the transport of peptides formed during digestion from proteins much faster than the absorption of a mixture of free amino acids, to which the body did not adapt during evolution. The small intestine has di- and tripeptide transporters providing absorption of short peptides [3,19]. It is known that the rate of transport of some dipeptides exceeds the rate of transfer of those amino acids of which they are composed. Peptidases of the brush border of enterocytes break down a significant part (about 40 - 60%) of short

peptides only into di- and tripeptides. Then, from the intestine, short peptides are distributed with blood flow to various organs and tissues, penetrate through the cytoplasmic membrane into the nucleus and nucleolus of cells, where they can bind to DNA and epigenetically regulate gene expression. The DNA-peptide interaction is probably the oldest in evolution. This may explain the high biological activity of short peptides, their complete harmlessness, and their successful use as substances with significant physiological effects.

The safety of KEDA (Lys-Glu-Asp-Ala) has been 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 a KEDA (Lys-Glu-Asp-Ala) solution to animals at a dose 5000 times higher than the dose recommended for clinical use does not cause toxic reactions. The study of the subacute and chronic toxicity of the tetropeptide indicated the absence of side effects during its long-term use in doses exceeding the therapeutic one by 100 - 1000 times. When assessing the general state 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, pathological changes in the body were not found.

Like all peptides developed at the St. Petersburg Institute of Bioregulation and Gerontology under the guidance of prof. Khavinson V., KEDA peptide regulates gene expression. This tetrapeptide caused the activation of ribosomal genes and decondensation of heterochromatin in chromosomes 1, 9 and 16 in the cells of elderly people [11,20].

The tissue-specific activity of KEDA (Lys-Glu-Asp-Ala) was revealed during research aimed at studying the effect of the tetrapeptide on the growth of the explant during the cultivation of liver fragments from old rats. The growth rate of explants was assessed by the value of the area index, which is calculated as the ratio of the area of the entire explant, including the peripheral growth zone, to the initial area of the fragment of the explanted tissue (i.e. the area of the central zone). The values of the area index were expressed as a percentage; the area index in the control was taken as 100%. The results of the study indicated a pronounced stimulating effect of the tetrapeptide on liver tissue explants from old animals. So, under the action of the KEDA peptide, the explant area index increased by 15 - 16%, while the control peptide did not give an increase in the explant area index [9,13].

Numerous further studies have proven the hepatoprotective activity of the tetrapeptide. The KEDA peptide in animals with acute experimental toxic hepatitis had a protective and therapeutic effect. At the same time, the content of total bilirubin and cholesterol, ALT and AST normalized, a stimulating effect on tissue repair was evident, destructive dystrophic processes in the liver stroma decreased and the number of cells containing glycogen normalized [13].

In vitro, the tetrapeptide reduced the activity of glycyl-1 leucine dipeptidase in the small intestine by 50%. After oral administration of the tetrapeptide for 2 weeks, the activity of digestive enzymes decreases in young rats, and increases in old ones. It should be noted that the activity of enzymes in old rats after the use of the KEDA peptide in most cases approached the corresponding indicator in the control group [17].

It would seem that the hepatoprotective activity of the tetrapeptide is partly related to its ability to regulate the function of the immune system. In experiments *in vitro,* the KEDA peptide, upon incubation with a suspension of leukocytes, increased the number of lymphocytes carrying markers CD3+, CD4+, CD8+, and decreased the number of CD22+ cells. The KEDA peptide increased the phagocytic activity of neutrophils in healthy people and patients with viral hepatitis A [7].

The KEDA peptide, regardless of the dose, inhibited the activation of complement by the classical pathway in healthy people in *in vitro* experiments. In patients with viral hepatitis A in the same study, the KEDA peptide at a dose of 40 μg/ml activated, and at a dose of 60 - 160 μg/ml inhibited the stimulation of complement along the classical pathway, without affecting the alternative pathway of the complement system activation [17].

The results of further studies showed that the tetrapeptide KEDA, in addition to immunomodulatory, has antioxidant activity. In addition, this peptide influenced the rheological properties of blood, slowing down its clotting and inhibiting fibrinolysis. Moreover, the revealed effects were present to a greater extent in the blood plasma of patients with viral hepatitis A [7].

Thus, the short peptide KEDA in *in vitro* and *in vivo* experiments has pronounced immunoprotective, antioxidant and hepatoprotective properties, contributing to the restoration of liver function on the molecular and cellular level.

Conclusion

Further studies of the hepatoprotective properties of KEDA (Lys-Glu-Asp-Ala) will make it possible to create a safe drug with high hepatoprotective activity on its basis.

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