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EXPERIMENTAL STUDIES ON THE MODEL OF ENCEPHALITIS AND MENINGOENCEPHALITIS

Abstract: *Of greatest importance for the restoration of the functioning of the brain, at present, there is a shift in emphasis towards neuroprotective (preventing the premature apoptosis of neurons) and neurotrophic (promoting the growth of neurons) drugs.*

Key words: *encephalitis, meningoencephalitis, neuro-pathophysiological processes, cerebrolysin.*
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Introduction

The widespread adoption and successful use of these drugs is opposed by a number of factors, such as dogmatic adherence to simplified models for understanding neuropathophysiological processes and simplified interpretation of clinical trial results. However, in addition to these rather trivial factors, there are more objective, scientific factors, namely, the lack of information on the molecular mechanisms of action of modern neurotrophic and neuroprotective drugs. The lack of information on the mechanisms of action is due, in turn, to the incompleteness of data on the composition of medicines.

Materials and Methods

Cerebrolysin (EBEWE, Austria) is one such drug. Cerebrolysin is produced on the basis of an extract from the brain of young pigs. An innovative study of the composition of this drug using protein mass spectrometry showed that cerebrolysin is a concentrate of low molecular weight neurotrophic compounds with a molecular weight not exceeding 6000-7000 Da (Fig. 1).

Sequencing (determination of the amino acid sequence) of the peptides corresponding to peptide light fractions (less than 500 daltons), led to the discovery of a composition cerebrolysin peptides thyrotropin (amino acid sequence of glu-his-pro), glutathione (gly-cys-glu) enkefalinopodobnogo peptide (tyr- gly-gly-phe), as well as a number of dipeptides such as ala-pro, val-glu. The main functions of thyroliberin are to enhance the secretion of thyrotropin by the anterior pituitary gland and to stimulate the secretion of corticotropin. Glutathione is

an antioxidant and the ratio of reduced to oxidized glutathione is one measure of cytotoxicity. The enkephalin-like tetrapeptide can act as an agonist of enkephalin receptors. Dozens of different dipeptides were also found in the light fraction of cerebrolysin (less than 500 Da). These dipeptides include ala-pro, val-glu, ile-gln, ala-gln, etc. The dipeptides in the light fractions of cerebrolysin do not have a specific biological function and arise during the preparation process as a result of nonspecific proteolysis. It is possible that dipeptides in the composition of cerebrolysin, like the amino acids of the drug, stabilize the spatial structure of larger peptides.

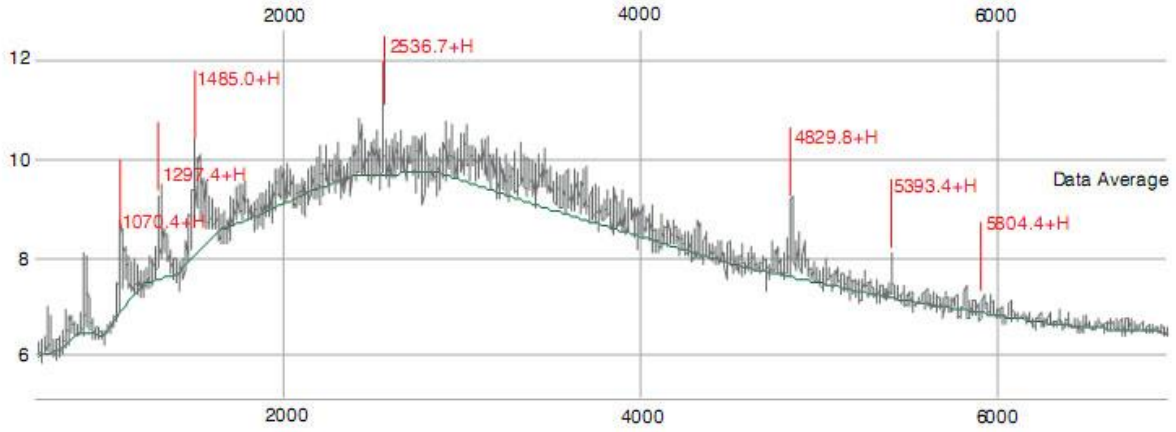

Figure 1. Mass spectrum extract cerebrolysin (peaks up to 6500 Da)

Dipeptides and neuropeptides thyroliberin, glutathione and enkephalin- like peptide are the main components of light peptide fractions (200-500 Da) of cerebrolysin [2]. The light peptide fractions correspond to the aforementioned peptides of 2-4 amino acids in length. These peptides are obviously not the only ones.

Reverse phase nano- LC-MS / MS was performed using an Agilent 1200 nano-flow LC system connected to a CHIP-Q- TOFAgilent Technologies 6520B mass spectrometer. The sample was fractionated using an Agilent Technologies 1200 series chromatograph, through a ZorbaxSBC18 chip, 5 µm, 75mkm x 43 mm. Mobile phase: A - 0.1% formic acid solution + 5% acetonitrile, B - acetonitrile + 0.1% formic acid + 10% deionized water. Application was performed on an Agilent Technologies 12 6 0 CapPump instrument at a flow rate of 4 µL / min. Elution was performed on an Agilent Technologies 12 6 0 NanoPump instrument at a flow rate of 0.6 µL / min. The concentration gradient of solution B - in minutes : 0% - 3 minutes, 60% - 12-18 minutes, 0% - 20 minutes. The solutions were degassed on an Agilent Technologies 1260 µ-degasser. Samples were loaded onto the column using an Agilent Technologies MicroWPS instrument, 2 µL each. The eluted fractions were analyzed by mass spectrometry under the following conditions:

Ionization source: ESI +, drying gas flow: 4 l / min, drying gas temperature: 350 ° C , voltage at the skimmer cone: 65V, at the fragmented 175V, mass range: in MS50 mode - 3000 m / z, in MS / MS mode 50 - 2500 m / z, with voltage on the CAP in the range of 1800-2500V. Ionization method: positive.

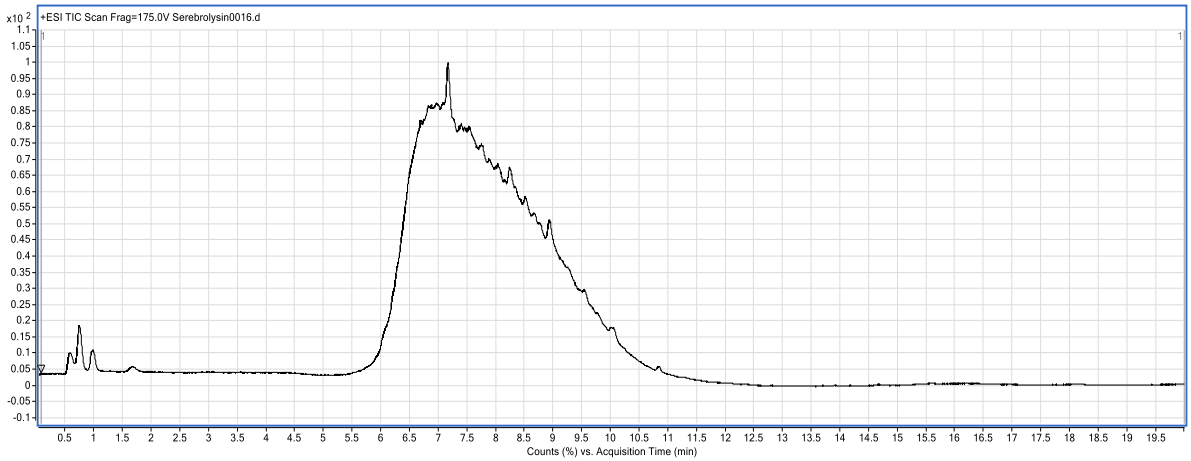

Figure 2. Total ion chromatogram of cerobrolysin

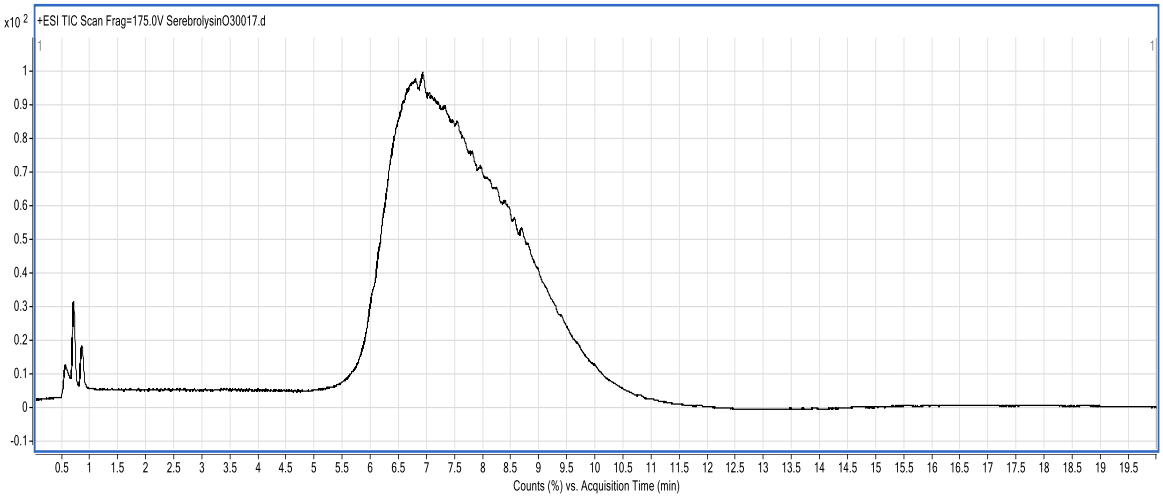

Figure 3. Total ion chromatogram ozonized for 10 minutes Cerobrolysin

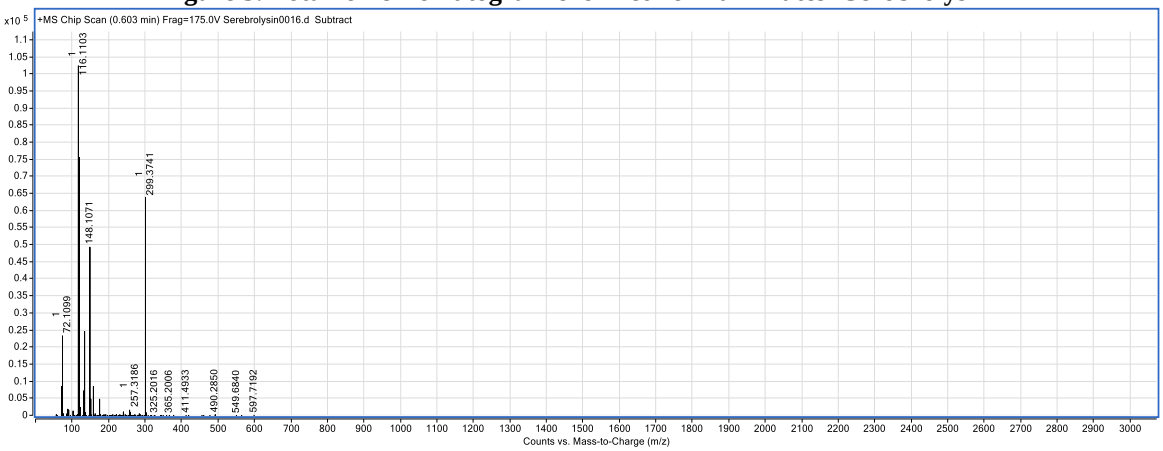

Figure 4.

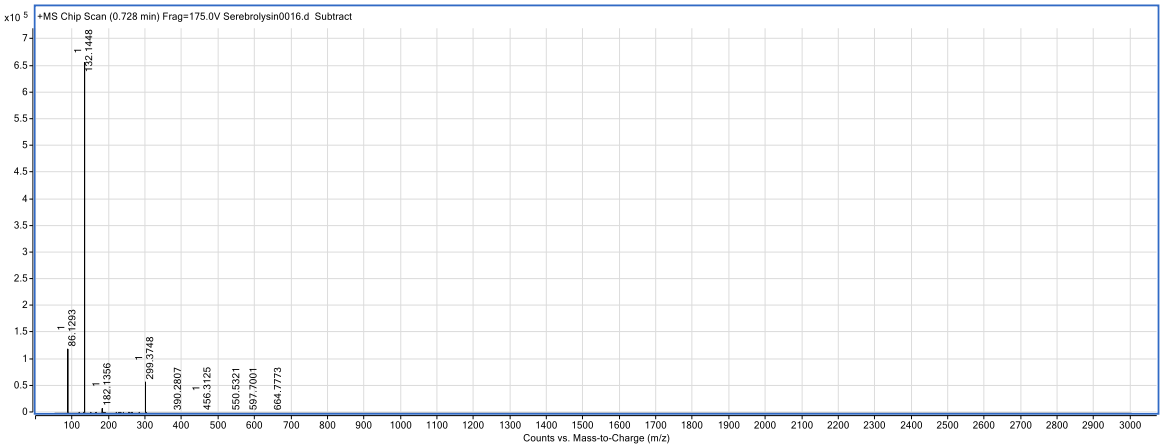

Figure 5. Mass spectrum 2

As can be seen from Figs. 2 and 3. And the subsequent mass spectra in the first three peaks of the mass spectra show that the composition of cerebrolysin contains amino acids: the first peak is alanine, phenylalanine and aspartic acid, the second peak is serine, methionine and treptophan, the third peak is lysine ... After ozonation, the amount of amino acids in the second peak increases significantly, mainly the amount of methionine

Further, in the bumpy area of the total ion chromatogram, the peptide components of the cerebrolysin preparation are eluted, which are presented in the following mass spectra. These components are dipeptides and neyropeptidytiroliberin, glutathione and en u

efalinopodobny peptide - the major component of lung peptide fractions (200-500 Da) Cerebrolysin. The light peptide fractions correspond to the aforementioned peptides of 2-4 amino acids in length. Also, in the composition of cerebrolysin, larger peptides with a molecular weight of 1000 to 4000 Da were found.

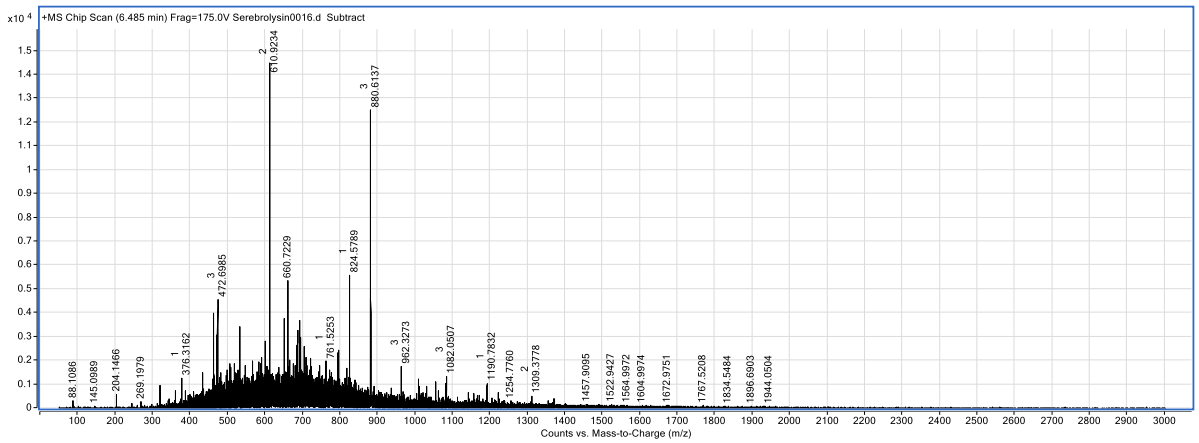

Figure 6.

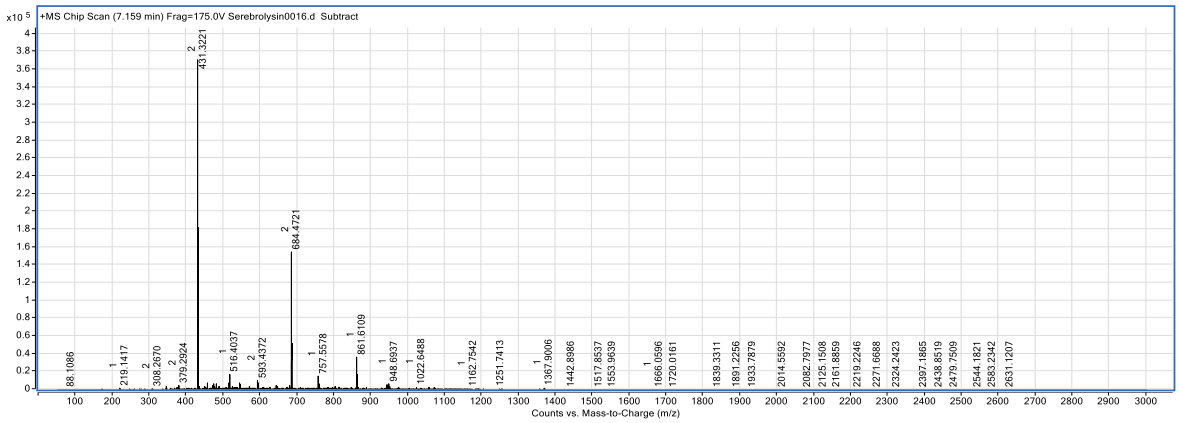

Figure 7.

After ozonation, some changes were found in the peptide spectrum of the preparation, which can be observed in the total ion chromatogram . For example, the entire bumpy part of the chromatogram is mixed forward, which means that the hydrophobicity of the constituent molecules of the drug is accommodated. The peak disappears with a retention time of 7.16 minutes. The intensity of the remaining peaks decreases.

Due to the displacement of the tuberous part in the chromatogram, a peak with a retention time of 6.8 minutes appears in the place of the disappeared peak with a retention time of 7.2 min.

The mass spectra of the altered components show:

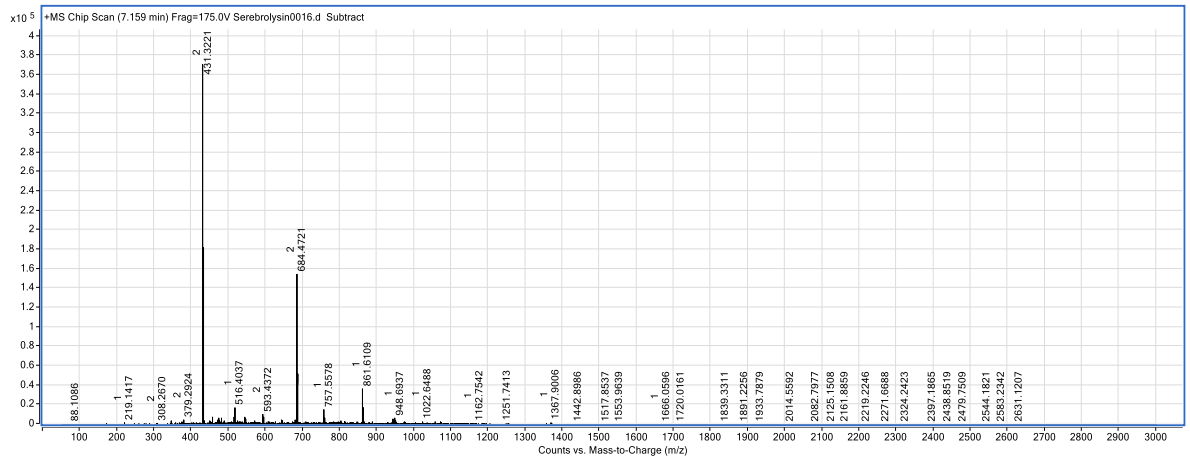

Figure 8.

Two peptides with a molecular weight of 431.32 * 2 = **862.64 DA** and 684.47 * 2 = **1368.94 DA**

After ozonation in the mass spectra of the changed components, the following is observed:

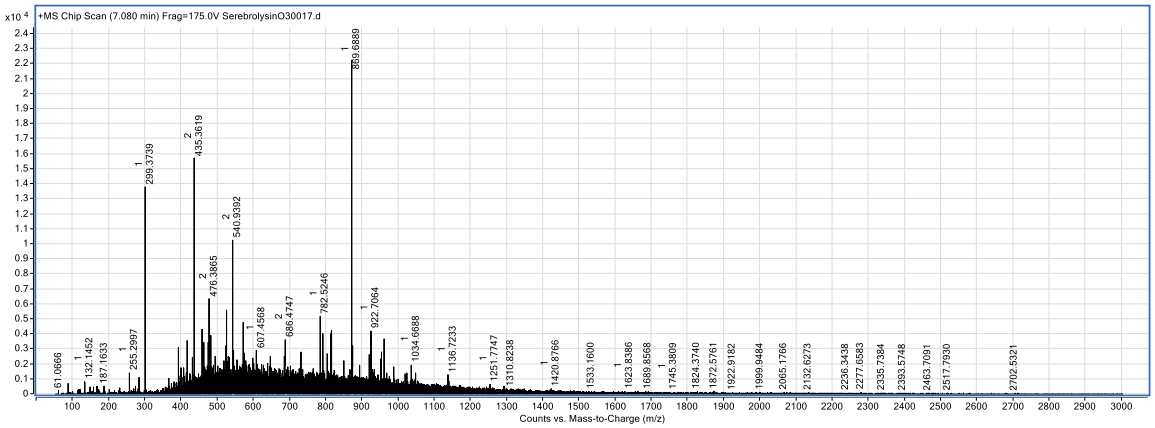

Figure 9.

Four peptides with molecular weights 435.36 * 2 = **780.72 Da,** 476.38 * 2 = **952.76 Da,** 540.93 * 2 = **1081.88 Da** and **869.69 Da**

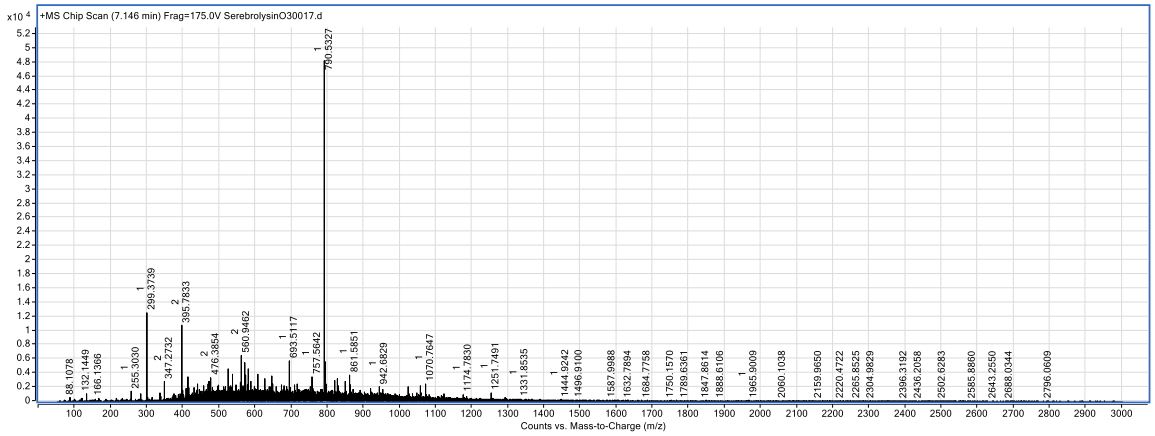

Figure 10.

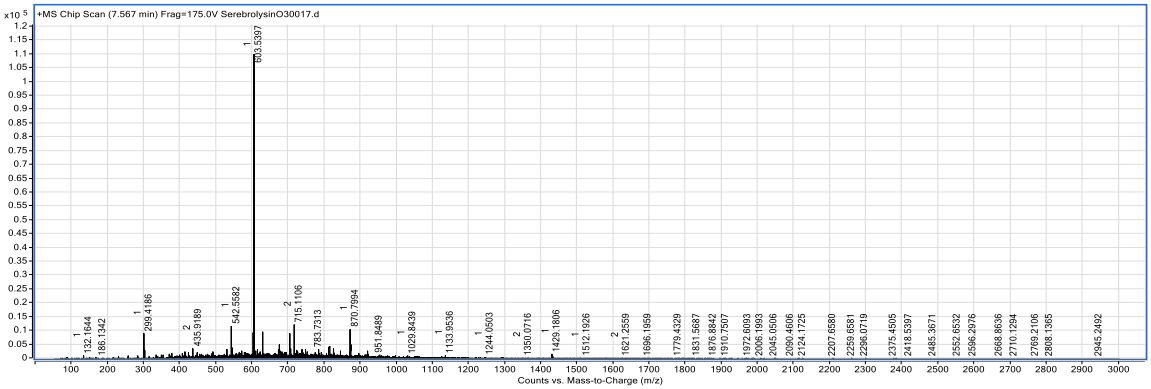

Figure 11.

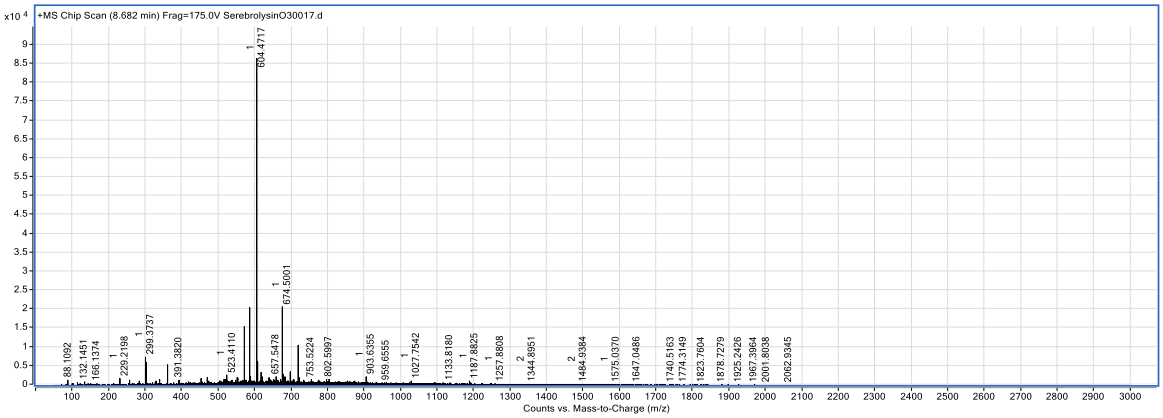

Figure 12.

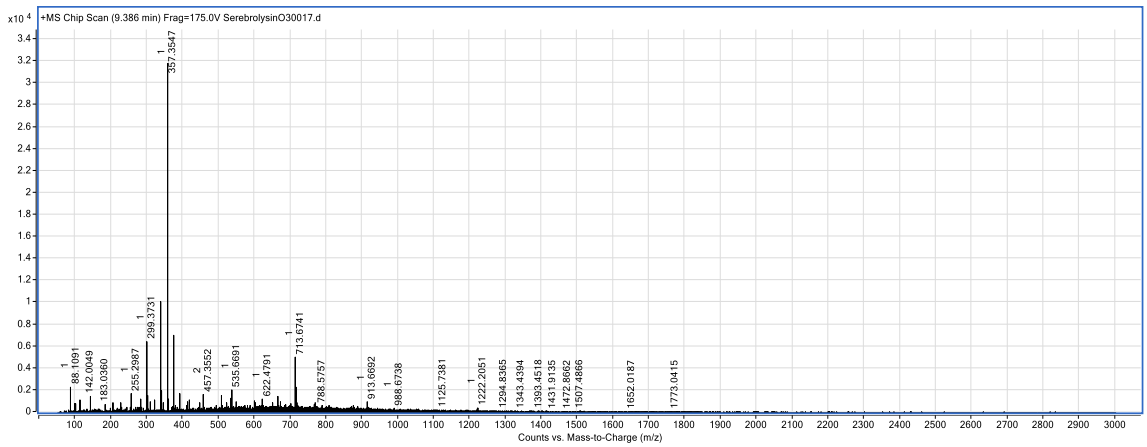

Figure 13.

Serebrolysin8 min O3

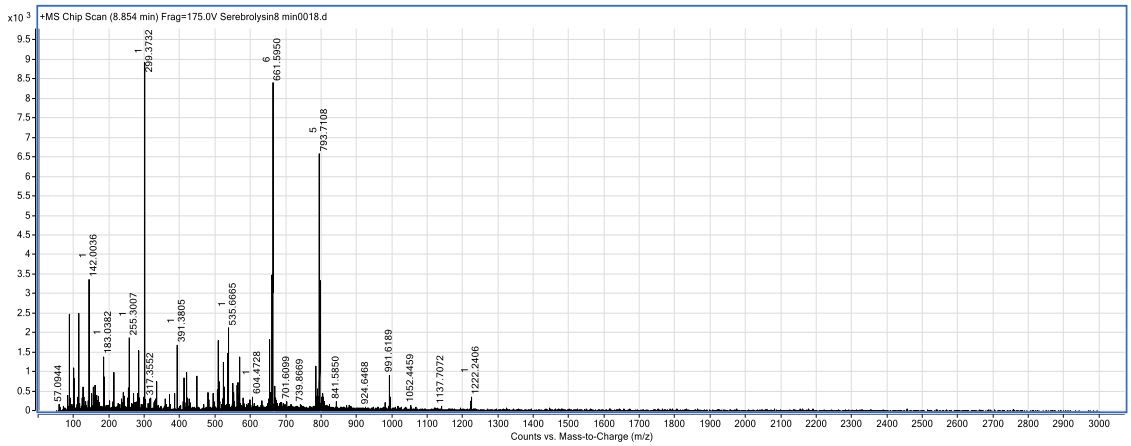

Figure 14.

A peptide was found in the mass spectrum of the ozonized sample: 793.7 * 5 = 3968.5 DA

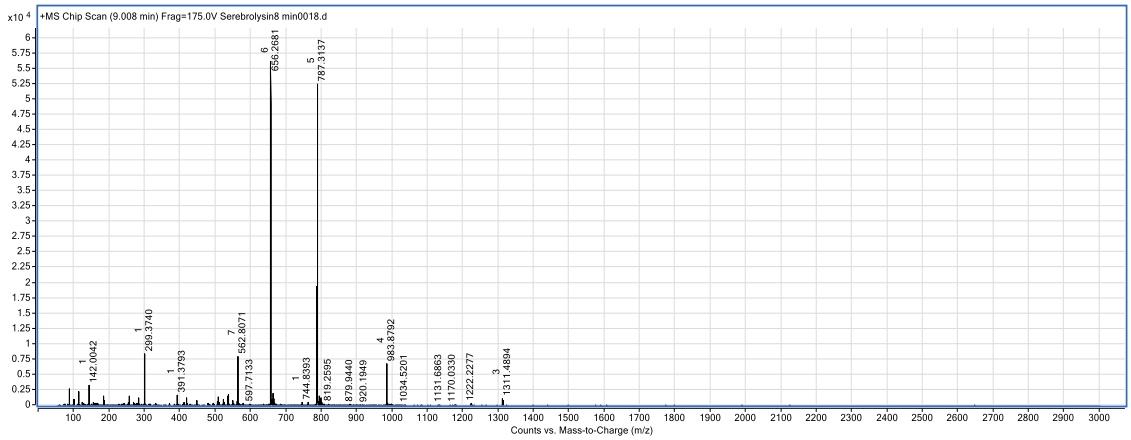

Figure 15.

The mass spectrum of the ozonized sample contains peptides: 787.3 * 5 = 3936.5 DA

Before ozonation Cerebrolesin peak at 11 min

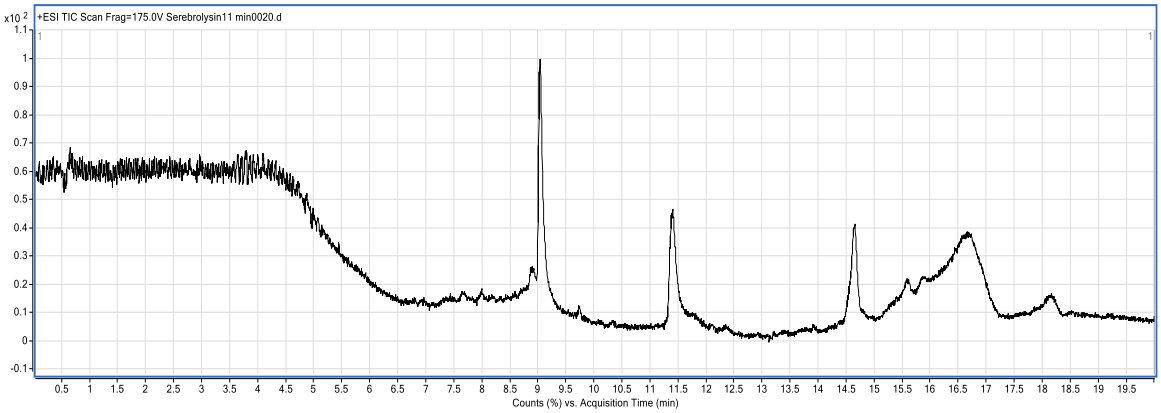

Figure 16.

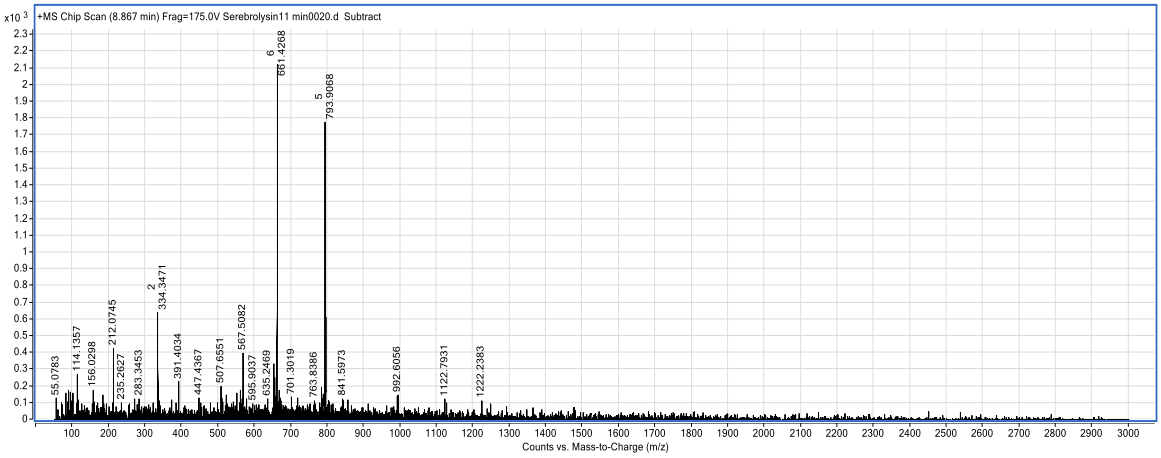

Figure 17.

The mass spectrum of the unozonized sample contains peptides: 793.9 * 5 = 3969.5 Da

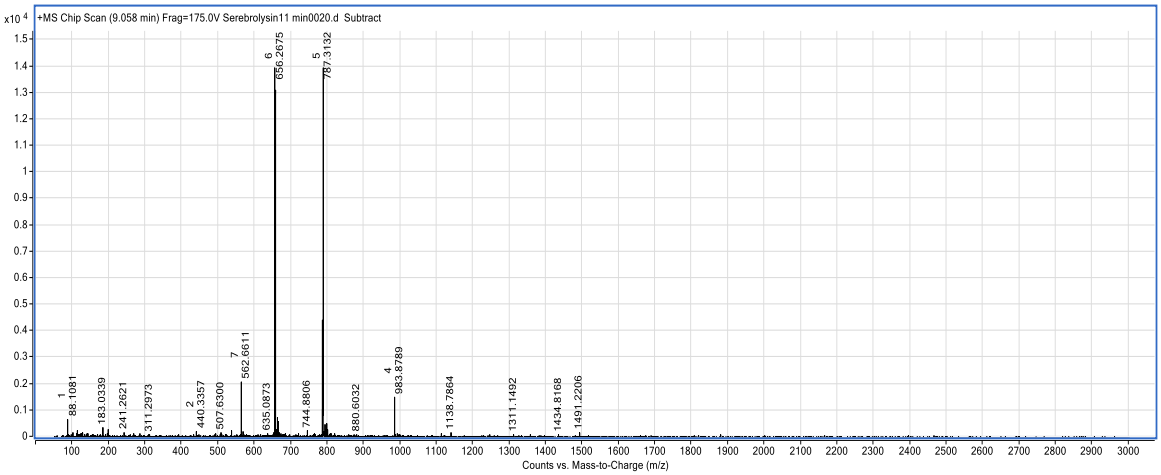

Figure 18.

The mass spectrum of the unozonized sample contains peptides: 787.3 * 5 = 3936.5 Yes

Thus, ozonation e drug Cerebrolysin led to structural changes in the spectrum of the peptide drug, as evidenced by the change time output column of the peptides with molecular weights of 3969.5 and 3936,5Da Yes, due to a change in the secondary structure of polypeptides. Thus, 89% seizing w flushes the quality of the drug, reduces the complications of 77%, increases the scale of use, enhanced effect of the drug in small doses.

The experimental animals were divided into groups II. In the I group was carried out with administration of conventional treatments intravenously ozonation the Cerebrolysinum well, and I I group was the control (uninfected rats). Treatment in groups was carried out for 20 days.

Traditional therapy in combination with ozonized cerebrolysin promotes an earlier positive clinical and morphological picture on the 20th day in the cerebral cortex and glia. During this period, there are single vascular and perivascular cellular infiltrates of hematogenous and local origin. In the nervous tissue, pericellular edema is sporadic and small in size. In the vasculature, the lumen of the blood vessels is slightly dilated. The lumen of some blood vessels is filled with blood corpuscles; diapedetic hemorrhages are noted around them. After traditional therapy, the number of vessels in which there is desquamation of the wall endothelium decreased in the morphological picture. Against the background of ozonated cerebrolysin is observed proliferation in structures of crust and glia. Intravenously introduced 0.02ml ozonized cerebrolysin on the weight of the rats of 180 to 200 grams.

In the clinic, against the background of the use of ozonized cerebrolysin in experimental animals, a more accelerated and qualitative recovery of neurological defects occurred (the rats became active

and the phenomena of paralysis of the limbs decreased noticeably faster, the self-defense reflexes were more pronounced.

On the 30th day of administration of ozonized cerebrolysin, plethora was even observed in the vessels of the ependyma. The sizes of the cytoplasm of astrocytes are the same, no nucleoli are found anywhere. The processes of astrocytes are the same size everywhere. Mononuclear phagocytic macrophages are rare.

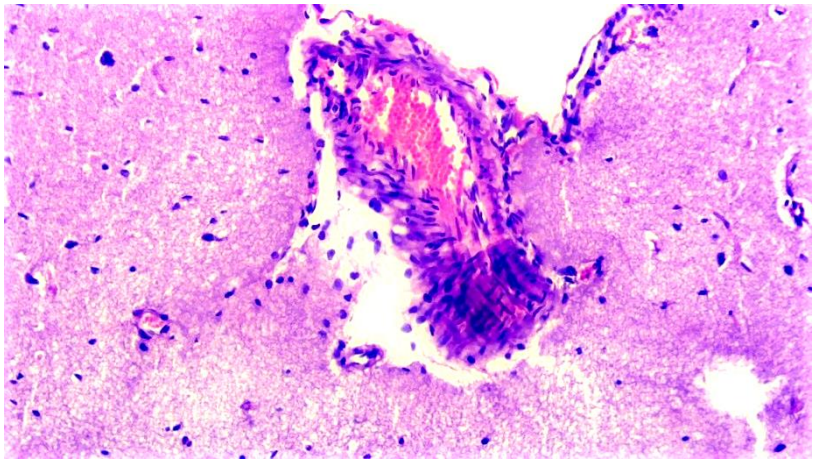

Figure 19. On the 30th day after the start of treatment. The blood vessels of the brain are filled with blood, macrophage-mononuclear cells and a slight edema of the brain tissue are visible. Coloring: hematoxylin-eosin. X: about 10, rev. 20 (magnification - 200 times).

Edematous loosening is less pronounced and affects only individual vessels of the brain.

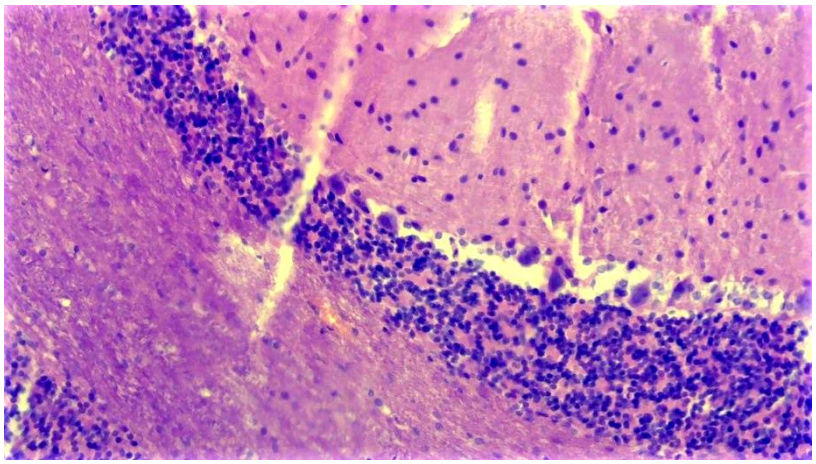

Figure 20. On the 30th day after the start of treatment. Moderate depression and slight loosening of the intercellular stroma of the brain. Coloring: hematoxylin-eosin. X: about 10, rev. 20 (magnification - 200 times).

On the 35th day of treatment with ozonized cerebrolysin, the pericellular edema was insignificantly pronounced. The degree of blood filling of the cerebral vessels in these rats is better than in the groups of animals. where traditional methods of treatment were applied.

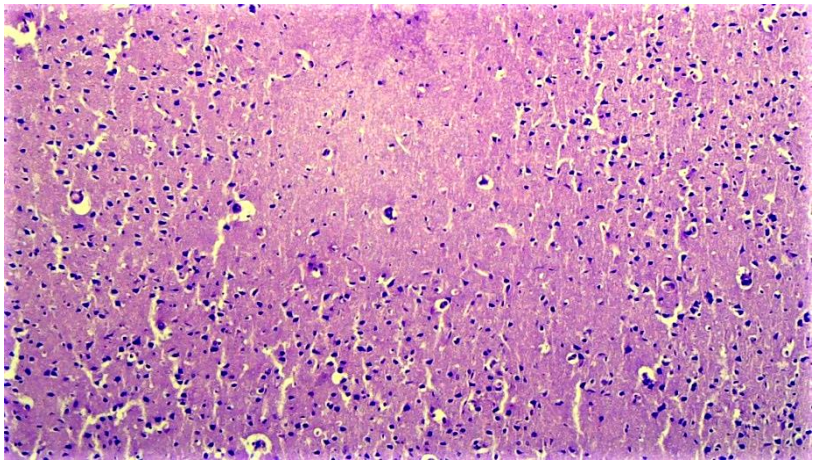

Figure 21. On the 35th day after the start of treatment. Mild pericellular edema of the brain tissue. Coloring: hematoxylin- eosin. X: about 10, rev. 1 0 (magnification - 100 times).

The cells covering the cerebral ventricles are hyperchromically stained, in places two-row, and papillary ramifications are also visible, their vessels are full-blooded, therefore, the nutrition of the cells is satisfactory.

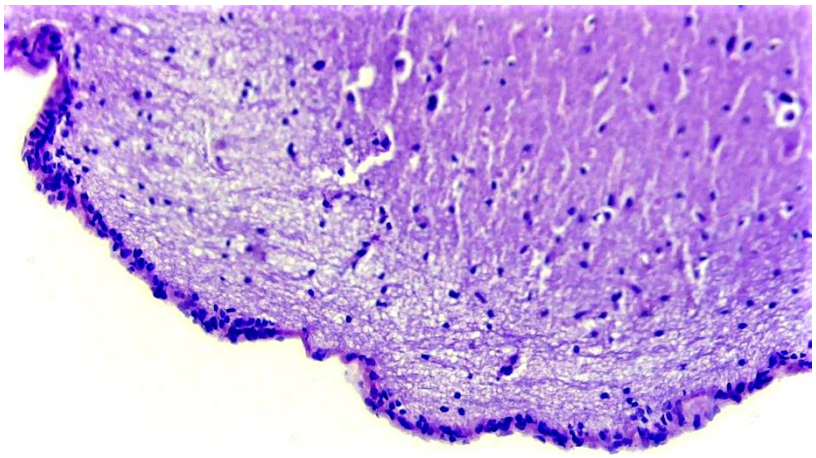

Figure 22. On the 35th day after the start of treatment. In the walls of the lateral ventricle of the brain, ependymocytes are homogeneous. Subepindemic vessels are full-blooded. Coloring: hematoxylin- eosin. X: about 10, rev. 40 (magnification - 400 times).

Conclusion

Thus, summarizing the results obtained, we can conclude that the administration of ozonized cerebrolysin to rats with the consequences of the transferred lesions of the central nervous system after Eph, has a positive effect on the neuroplasticity of the brain structures during treatment. An improvement in cell trophism is noted, which in turn stimulates their compensatory capabilities, an increase in the number of hyperchromic cells and a decrease in the number of hypochromic neurons. In particular, quantitative neuronal rearrangements, changes in neuronal connections, the reaction of glial elements, changes in the structure and function of the neuron, changes in the life support systems of the neuron, including neuroglia and the system of regulation of blood circulation in the brain, were observed.

Mass - spectral analysis of the chromatogram of ozonized cerabrilisin indicate an increase in the effect of the drug in small doses, a decrease in the toxicity of secondary structures secreted by polypeptides, and a decrease in hypoallergenicity.

The therapeutic approach with ozonized cerabralisin, on the model of experimental EF, revealed a positive effect on the neuroplasticity of brain structures, a high level of the regenerative process, including neurogenic and the system of regulation of cerebral circulation. This is confirmed

by the good tolerability of the drug, the positive clinical picture and the macro-micro-morphological picture, especially of the long-term period of the disease.

1

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