Dear friends!

The present article is a continuation in series of publications devoted to scientific achievements in the field of neurobiology and studying our products in order to treat pathologies associated with functional brain disorders.

We invite you to learn about findings into studying the effect of EDR (Pinealon®) and KED (Vezugen®) short peptides in transgenic mouse model of Alzheimer's disease. Results has been published in international journals «Pharmaceuticals» (2021)[1] и «Brain Sciences» (2023)[2].

It should be reminded, that Alzheimer's disease (AD) is one of the most common neurodegenerative disorders that contributes to memory loss in older people. According to the Alzheimer's Association more than 40 millions of people are affected by AD, and the number of patients will more than double by 2050. Modern FDA[3]-approved drugs for AD treatment don't prevent or slow down the neurodegeneration and are characterized by considerable side effects incompatible to normal vital activities of patients. By this reason, development of safe and effective therapeutic agents for AD treatment is a relevant purpose in field of gerontology, neurobiology and molecular medicine.

The EDR (Pinealon®) and KED (Vezugen®) short peptides are promising therapeutic agents for AD treatment in view of the wide range of biologically activities and lack of side effects. These compounds have been effective in patients with brain trauma, cerebral asthenic syndrome, in reduction of memory and attention in older people. It is should be pointed out that the EDR (Pinealon®) and KED (Vezugen®) short peptides are active components of dietary supplements Cerluten® and Ventfort®, respectively.

Loss of neuronal networks underlies the cellular mechanisms of cognitive impairments. It should be reminded, that neuronal connection is provided by

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[1] Khavinson V., Ilina A., Kraskovskaya N., Linkova N., Kolchina N., Mironova E., Erofeev A., Petukhov M. Neuroprotective Effects of Tripeptides—Epigenetic Regulators in Mouse Model of Alzheimer's Disease. Pharmaceuticals. 2021. 14. 515.

[2] Ilina A., Linkova N. A Transgenic 5xFAD-M Line of Mice for Dendritic Spine Morphology Analysis in Alzheimer's Disease. Brain Sciences. 2023. 13. 2. 307.

[3] FDA – Food and Drug Administration

synaptic contact (synapses) mainly represented as a conjunction between two neurons by presynaptic and postsynaptic terminals. The functionally impaired or unstable synaptic contacts were established in the early stage of AD, resulting the decreasing the number of postsynaptic contacts named as dendritic spines. Dendritic spines constitute specific protrusions on neuronal dendrites and play an important role in learning and memory processes. Taking dynamic structure of spines into account, it is therefore likely that changing in spine morphology reflects functional processes in synapses underlies the learning and memory processes. It should be emphasized that the most functionally active spines with large sizes have been named «mushroom spines» and are most exposed by elimination (loss) during neurodegeneration.

The 5xFAD-M transgenic line of mice was developed in the laboratory of molecular neurodegeneration at The Peter the Great St. Petersburg Polytechnic University for investigation into the neuroprotective effects of short peptides in AD *in vivo* and studying the morphological changes in dendritic spines.

The design of investigation was following. Fixed slices of a mouse hippocampus were taken after course injections of peptides. The hippocampus is a brain structure involved in memory processes. The successful development of the transgenic 5xFAD-M line of mice, characterized by the synthesis of green fluorescent protein in the mouse brain, avoided the need for time-consuming immunohistochemically staining of brain slices and, thereby greatly facilitated the visualization of neuronal structures in vivo. Prepared fixed hippocampal slices were directly analyzed by means of confocal microscopy followed by obtaining the microphotographs of neuronal dendrites in mouse hippocampus. Next, morphological analysis of dendritic spines was carried out by specific software, that is studying the shape in order to separate into main types: thin, stubby, mushroom. Shape of spine reflect the functionally state of synaptic contact and neurotransmission as a whole. Decreased synthesis of proteins structurally forming spines and involved in neurotransmission is observed during impaired conduction of nerve impulses against neurodegeneration. As a result, dendritic spines becomes thin

followed by completely disappearing (elimination) that underlies the memory loss. Thus, evaluation of morphological characteristics of spines in 5xFAD-M mice injected by EDR (Pinealon®) and KED (Vezugen®) peptides allowed to analyze the effect of these compounds on functional state of neuronal networks in AD.

The experimental groups were followings: I — control (mice without pathology injected by physiological solution); II — mice of 5xFAD-M transgenic line (AD model) injected by physiological solution; III — 5xFAD-M line of mice injected by EDR (Pinealon®) peptide; IV — 5xFAD-M line of mice injected by KED (Vezugen®) peptide.

It was established that daily intraperitoneal injection of EDR (Pinealon®) and KED (Vezugen®) peptides at the concentration of 400 ug/kg provide statistically significant rising number of mushroom spines by 25% and 27%, respectively, in 5xFAD-M mice from 3 to 5 months of age. Dendritic spine density in neurons of 5xFAD-M mice was increased by 13% and 22% in 5xFAD-M mice injected by EDR and KED, respectively. These findings suggest that EDR (Pinealon®) and KED (Vezugen®) short peptides improve the functionally state of neuronal networks in hippocampus that underlies the neuroprotective effect of these compounds in *in vivo* AD model.

In conclusion, it should be noted that EDR (Pinealon®) and KED (Vezugen®) peptides as active compounds may be recommended to future investigation in order to develop a safe and effective therapeutic agent for the treatment of Alzheimer's disease. Furthermore, Pinealon® and Vezugen® as well as the complex dietary supplements based on cattle vessels (Ventfort®) and brain (Cerluten®) are appropriate to be used in order to prevent age-associated neurodegenerative disorders, including AD. The EDR (Pinealon®) and KED (Vezugen®) peptides are active components of dietary supplements Cerluten® and Ventfort®, respectively.

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