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Molecular-Physiological Aspects of Peptide Regulation of the Function of the Retina in Retinitis Pigmentosa

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Abstract—Peptide bioregulators promote restoration of the physiological activity of the retina in retinitis pigmentosa in older adults and in animal models. The molecular mechanism of the physiological activity of peptides is associated with their ability to epigenetically regulate the synthesis of protein markers of the differentiation of retinal neurons and pigment epithelium.

Keywords: peptides, retinitis pigmentosa, epigenetic regulation, cell differentiation
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Visual system plays a key role in obtaining information about the environment. Monitoring the state of visual functions as well as improving and maintaining the functionality of the organ of vision are important tasks of modern ophthalmology.

Retinitis pigmentosa (RP) is ranked first among the inherited retinal diseases and cause blindness with a primary lesion of the pigment epithelium and photoreceptors [1]. This is due to this disease being widespread (the incidence in the population is 1 per 3000 subjects; there are approximately 1.5 million patients in the world) and the lack of effective methods for its treatment. A characteristic feature of RP is an insidious onset of the disease [2]. It is difficult to diagnose RP in the early stages and treat it.

Physiologically, RP manifests itself in the reduction of the functions of rods and concentric narrowing of the field of view [3]. Degenerating outer segments of the rods are removed and digested by the pigment epithelium, which leads to strong pigmentation. The diagnosis of RP is based on the characteristic ophthalmoscopic picture (pigment deposition in the form of "bone bodies," a decrease in the number and thinning of blood vessels, and waxy pallor of the optic nerve), functional symptoms (increased light sensitivity thresholds and concentric narrowing of the field of views), and electroretinography data, which quantitatively characterize the function of photoreceptors and retinal pigment epithelial cells.

Today, various approaches with the application of advances in molecular biology are used to restore the visual function. For example, J. Elliot et al. propose a method to restore the functional activity of retinal neurons by cell replacement therapy with the use of neural stem cells [4]. They found that the expression of the *ikaros* gene is verified in the early neuronal progenitors capable of differentiating into seven types of retinal cells. However, this experimental development has not yet been used in clinical practice. Other studies have also described the possibility of using pluripotent cells to treat retinal pathologies. However, all these works are devoted only to experiments with laboratory animals. The therapeutic effect of pluripotent cells is studied in animals with inherited retinal pathology [5–8].

In addition, it is known that the progression of RP can be slowed by using antioxidants—vitamins *A* and *E*; however, these agents can only be used as auxiliary retinoprotective drugs and, according to some authors, are ineffective [9].

Thus, the use of pluripotent neural precursors is currently studied only in vitro and in animal models and is not used in clinical practice for the treatment of RP, and antioxidants can play only a secondary role in the treatment of RP.

However, a new group of drugs, peptide bioregulators, is successfully applied in clinical practice [10–12], among which the peptides exhibiting tissue-specific activity are most interesting [13–15]. The key peptide bioregulator in ophthalmology permitted for medical use by the Ministry of Health of the Russian Federation is retinalamine [16]. Twenty years of experience in the use of retinalamine isolated from the retina of animals with retinal diseases of different etiologies have showed a high clinical efficacy of this drug [17]. It was found that retinalamine improves the functional interaction between the pigment epithelium and the outer segments of photoreceptors, the

Table 1. Dynamics of the results of statistical computer perimetry in patients of the control group and the main group with 3 retinitis pigmentosa (RP) [16]

Characteristic of the field of view	Number of test objects in the field of view (%)								
	before treatment			after treatment			3 months after treatment		
	RP stage			RP stage			RP stage		
	III	IV	V	III	IV	V	III	IV	V
Control group									
Norm	37.6	8.3	1.6	38.9	8.0	1.7	34.2	8.5	1.5
Relative scotomata	28.2	7.5	3.1	23.7	7.9	2.9	30.7	2.3	1.1
Absolute scotomata	34.2	84.2	95.3	37.4	84.1	95.4	35.1	89.2	97.4
Main group									
Norm	35.4	8.5	1.1	43.3	11.1	2.1	46.1	13.8	2.6
Relative scotomata	28.1	11.1	2.1	30.3	14.8	3.7	31.2	15.8	4.8
Absolute scotomata	36.5	80.4	96.8	26.3	74.1	94.1	22.7	70.4	92.6

Table 2. Effect of the tetrapeptide on the bioelectrical activity (total activity of waves *A*, *B*, and *C* of the electroretinogram, mV) of the retina of Campbell rats

Group	Time of observation, days						
	23	35	41	53	65	71	81
Control	90.5 ± 11.2	80.6 ± 9.2	38.4 ± 7.4	0	0	0	0
Experiment	94.5 ± 12.1	106.6 ± 13.3*	107.1 ± 12.8*	91.4 ± 11.7	68.3 ± 9.5	54.1 ± 8.4	21.6 ± 5.8

* Differences from the control values were significant at $p < 0.05$ [21, 22].

regulation of metabolism, the activation of antioxidant protection, and restoration of the light sensitivity of the retina. Long-term studies in RP patients with the use of retinalamine showed its high efficiency: clinical improvement was observed in 90% of cases [16]. Application of retinalamine caused a significant increase in visual function (change in the visual acuity and expanding the boundaries of the field of view), improved the results of electrophysiological studies and the somatic status, and normalized the antiradical activity of blood in all patients (Table 1). The administration of RP patients with retinalamine showed no adverse reactions, complications, of drug dependence, even in persons with severe allergy [18]

The study of induction of the pluripotent ectodermal cells of an early *Xenopus laevis* gastrula with retinalamine showed that retinalamin exhibits a neural induction activity. The treatment of the ectoderm with the drug triggers neural differentiation, including the retina and pigment epithelium [19].

On the basis of amino acid analysis of retinalamine, the tetrapeptide *Ala-Glu-Asp-Gly* was synthesized, which exhibits pronounced geroprotective and antioxidant activity and regulates cell metabolism in the retina [20]. The improvement of the clinical course of RP by the retinal peptide was substantiated by the experimental data.

In the previous studies, we investigated the effect of the tetrapeptide on the development of RP in Campbell rats—pale-hooded pink-eyed rats homozygous for hereditary retinal dystrophy, with disturbance of the specific phagocytic function of the retinal pigment epithelium. The effect of the tetrapeptide on the PR development in the animals was assessed by electrophysiological and histological methods. Electroretinography is the leading method for the assessment of the functional state of the retina, which makes it possible not only to identify the dystrophic changes in the retina but also to diagnose the biochemical and functional abnormalities that precede the clinical manifestations of the disease.

In the control group of rats with hereditary RP, a sharp decline in the bioelectric activity from day 23 to 35 was observed; on day 53, the electroretinogram (ERG) could not be recorded in any animal. The treatment with the tetrapeptide led to an increase in the amplitude of the ERG in the experimental group of rats, which was retained at a relatively high level on days 23–41 and began to slowly decline only starting from day 41. Thus, on day 41, the amplitude of the

ERG in the experimental group exceeded that in the control group by a factor of 2.8 (Table 2).

A comparative study of the histological preparations of the retina of experimental and control rats showed better preservation of morphological structures under the treatment with the tetrapeptide: all layers had more distinct boundaries, whereas the retinal layers in the control group were narrowed. On day 41, destruction of layers was observed in the control rats, whereas the morphological pattern in the experimental group remained preserved. After day 71, partial destruction of layers in the experimental group was observed, whereas the layer of photoreceptors was preserved and remained intensely stained. After day 81, despite the destructive changes, some functional elements of the retina remained preserved. Thus, the tetrapeptide extended twice the period during which the morphological structure of the rats' retina was retained.

Next, we studied the effect of the tetrapeptide on the cell culture of the retina and pigment epithelium of rats. The peptide at concentrations of 2, 10, 20, 50, 100, and 200 ng/mL was added to the cell culture twice a week for one month. The mitogenic activity of the tetrapeptide in the cell culture was determined by spectrophotometric determination of living cells in suspension.

It was found that the pigment epithelium cells proliferated more actively than the retinal cells. The results of the first week of cultivation showed that the highest mitogenic activity in the retinal cell cultures was observed at a tetrapeptide concentration of 10 and 100 ng/mL; in the pigment epithelium cell culture, at 10 and 20 ng/mL. After 3 weeks of cultivation, the most active proliferation was observed at concentrations of 2 and 10 ng/mL [23].

The above data testify to the ability of the tetrapeptide to activate proliferation in cell cultures of the retina and pigment epithelium.

We also studied the effect of the tetrapeptide on the differentiation of the pluripotent ectodermal tissue of an early *Xenopus laevis* gastrula. The tetrapeptide stimulated differentiation of pluripotent cells to the nervous tissue and epidermis. At doses of 10, 50 and 100 ng/mL, the tetrapeptide had the same effect, stimulating the differentiation of approximately 14% of the pluripotent cells to epithelial and neural tissues. Thus, the ability of the synthetic tetrapeptide to stimulate the differentiation of pluripotent tissue can underlie its tissue-specific geroprotective effect [24].

The authors of other studies also reported the effect of various signaling molecules on neuronal differentiation in organotypic cultures of human and animal retina [25]. It was established that the addition to the culture medium of the brain-derived neurotrophic factor (*BDNF*) at a concentration of 100 ng/mL promoted the induction of expression of glia markers (glial fibrillary acidic protein (*GFAP*)) and mature neurons (3-1P-tubulin). Probably, the tetrapeptide stimulates the differentiation of retinal neurons in a similar manner to *BDNF* [26, 27].

Table 3. Mechanism of retinal cell differentiation [29]

Type of retinal cells	Transcription factors			
Bipolar cells	*Chx10* → *Vsx1*			
Horizontal cells	*Pax6* →			*Prox1*
Amacrine cells		*Math1* →	→	
Ganglion cells		*Math5*	*Brn3*	*BarH*

Further studies were performed to study the effect of the tetrapeptide on the markers of differentiation of retinal and pigment epithelial cells.

Organotypic retinal cultures were divided into three groups: control (with the addition of saline) and two experimental (supplemented with the control dipeptide at a concentration of 0.05 ng/mL and with the tetrapeptide at a concentration of 0.05 ng/mL).

The cultures were stained immunocytochemically using the monoclonal antibodies to the markers *Pax6, Brn3, Prox1, Vsx1, mChx10, Math1, Math5*, and *TTP* (1 : 50, Dako), which are the key factors of retinal cell differentiation [28]. The transcription factors *Chx10* and *Vsx1* were selected as markers of initial and terminal differentiation of retinal bipolar cells; *Pax6*, as a marker of differentiation of multipotent retina progenitors; *Math5* and *Brn3*, as markers of differentiation of ganglion cells; *Math1*, as a marker of differentiation of retinal horizontal cells; *Prox1*, as a marker of mature amacrine and horizontal cells; and *TTR*, as a marker of differentiation of retinal pigment epithelium (Table 3).

The results of immunocytochemical staining were evaluated in a morphometric study.

The tetrapeptide had a stimulatory effect on the expression of the studied markers of differentiation of retinal neurons and pigment epithelium.

The area of expression of the marker of initial differentiation of bipolar cells *Chx10* in group 2 significantly increased relative to the control (from 0 to $0.02 \pm 0.007\%$, $p < 0.005$), and the optical density increased from 0 (group 1) to 0.31 ± 0.05 arb. units. In group 3, the area of expression of *Chx10* increased from $0.05 \pm 0.01\%$, and the optical density also increased to 0.66 ± 0.02 arb. units (Table 4).

The area of expression of the *Vsx1* marker in group 2 increased by 82% compared to the control, whereas the optical density did not change significantly. In

Table 4. Effect of the tetrapeptide on the area and optical density of expression of differentiation markers of retinal cells

Group	*Chx10*	*Vsx1*	*Pax6*	*Math1*	*Math5*	*Brn3*	*Prox1*	*TTR*
				Expression area, %				
Control (group 1)	0	0.011 ± ± 0.003	0.026 ± ± 0.009	0.014 ± ± 0.005	0.025 ± ± 0.007	0.02 ± ± 0.008	0.027 ± ± 0.008	0.019 ± ± 0.007
Group 2	0.02 ± ± 0.007*	0.02 ± ± 0.006	0.026 ± ± 0.003	0.02 ± ± 0.004	0.016 ± ± 0.004	0.04 ± ± 0.01*	0.024 ± ± 0.005	0.021 ± ± 0.006
Group 3	0.05 ± ± 0.01*	0.043 ± ± 0.02*	0.058 ± ± 0.011*	0.044 ± ± 0.009*	0.04 ± ± 0.007*	0.07 ± ± 0.02*	0.08 ± ± 0.009*	0.04 ± ± 0.01*
				Optical density, arb. units				
Control (group 1)	0	0.56 ± ± 0.16	0.62 ± ± 0.05	0.42 ± ± 0.14	0.54 ± ± 0.05	0.83 ± ± 0.005	0.65 ± ± 0.03	0.44 ± ± 0.09
Group 2	0.31 ± ± 0.05*	0.62 ± ± 0.02	0.87 ± ± 0.03*	0.8 ± ± 0.04*	0.54 ± ± 0.1	0.75 ± ± 0.04	0.73 ± ± 0.12	0.39 ± ± 0.03
Group 3	0.66 ± ± 0.02*	0.79 ± ± 0.05*	0.87 ± ± 0.07*	0.63 ± ± 0.04*	0.77 ± ± 0.03*	0.59 ± ± 0.03	0.76 ± ± 0.05*	0.59 ± ± 0.02*

* Differences from the control values were significant at $p < 0.05$.

group 3, the area of expression increased 3.9 times compared to the control group, whereas the optical density increased by 41% (Table 4).

The area of expression of the marker of *Pax6* progenitors under the influence of the dipeptide (group 2) did not change significantly, whereas under the influence of the tetrapeptide (group 3) it increased by a factor of 2.2. In groups 2 and 3, the optical density of expression increased significantly (by 40%) relative to control (Table 4).

In group 2, the area of expression of *Math1* and *Math5* markers did not change compared to the control; the optical density of *Math1* increased by 91%, whereas that of *Math5* remained at the same level. In group 3, the area of expression of *Math1* and *Math5* increased 3.1 times and by 60% compared to the control group, and the optical density of expression increased by 50 and 43%, respectively (Table 4).

The area of expression of the differentiation marker of ganglion cells *Brn3* in groups 2 and 3 increased 2 and 3.5 times, respectively, compared to the control, whereas the optical density of expression in both groups did not change significantly (Table 4).

The area and optical density of expression of the *Prox1* marker increased significantly only in group 3: under the influence of the tetrapeptide, the area and optical density of expression increased 3 times and by 17%, respectively, compared to the control group (Table 4).

The area and optical density of expression of the marker of retinal pigment epithelial cells *TTR* in group 3 increased 2.1 times and by 34%, respectively, compared to control. In group 2, these parameters did not change significantly (Table 4).

In addition, it was found that the tetrapeptide epithalon enters the cytoplasm, nucleus, and nucleolus and regulates gene methylation and endonuclease activity [30–32]. Based on these data, it was assumed that the tetrapeptide can bind to the DNA.

In order to confirm this assumption, we constructed a model of interaction of the tetrapeptide with the promoter region of the genes that regulate retinal cell differentiation.

The most energetically favorable conformation of the tetrapeptide *Ala-Glu-Asp-Gly* was preselected by the molecular dynamics method, which makes it possible to reproduce the motion of individual molecules in a given time interval. The main results were obtained in the force field MM^{+}. In each mode, approximately 100 preselected conformations of peptides were analyzed, and then the optimal energy of the rotamers was selected.

We also performed computer simulation of the interaction between the tetrapeptide *Ala-Glu-Asp-Gly* and DNA sequence containing the putative binding site *ATTTC*. Calculations for complexes were performed in the AMBER99 force field. The energy of binding of the peptide to DNA (kcal/mol) was calculated as the difference between the energies of individual DNA molecules, the peptide, and the peptide–DNA complex. It was found that the tetrapeptide interacts with the major groove of the DNA double

helix. Apparently, epithalon interacts with the 5'-*ATTTC*-3' sequence and the complementary 5'-*GAAAT*-3' sequence via van der Waals forces, electrostatic interactions, and hydrogen bonding between the functional groups of both molecules [33]. The *ATTTC* sequence, which is complementary to the tetrapeptide, was found in the promoter region of *Vsx1, Shx10, Pax6, Brn3, Math1, Prox1*, and *TTR* genes.

The results of this study indicate that the tetrapeptide epithalon stimulates the expression of differentiation markers of the retina and pigment epithelium cells by binding to the promoter areas of genes, which leads to the restoration of the inner nuclear layer and the pigment epithelium.

Thus, the physiological effect of peptide bioregulators consists in tits ability to restore the functional activity of the retina in patients with RP and in animal models of this disease. Their mechanism of action is associated with the regulation of the expression of signaling molecules—retinal cell differentiation markers.

Taking into account the fact that no effective method to treat RP has been found to date, the possibility to apply cellular technologies (transplantation of retinal pluripotent cells with their subsequent differentiation) in the RP therapy is studied only in vitro and in animals, and that antioxidant drugs only decelerate the progression of RP, peptide bioregulators, in our opinion, are sufficiently effective, clinically tested drugs with a studied mechanism of action.

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