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Studies of underlying molecular mechanisms of retinitis pigmentosa in experimental model and clinics

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The article concerns the analysis of underlying molecular mechanisms of retinitis pigmentosa on the experimental model of the rabbits and on the patients diagnosed with this pathology. The studies were conducted on Chinchilla male rabbits having body mass of 2.2-2.6 kg. Serum was obtained from the patients with retinitis pigmentosa. Retinitis pigmentosa was modelled in the rabbits through i.v. administration of monoiodacetic acid (MIAA; grave degree, 26 mg/kg of body mass). With the application of indirect ELISA-test the levels of serotonin-modulating anticonsolidation protein (SMAP; Mekhtiev, 2000) in the hypothalamus, heat shock protein 70 kDa (HSP70) and rhodopsin in the retina and natural anti-SMAP autoantibodies in the serum of the patients were measured. The data were analysed on Student's t-criterion. Significant downregulation of rhodopsin ($p<0.001$) and upregulation of HSP70 ($p<0.001$) in the retina, as well as upregulation of SMAP ($p<0.01$) in the hypothalamus of the MIAA-administered rabbits were noticed. Intra-vitreal administration of SMAP to the MIAA-administered rabbits resulted in a significant upregulation of rhodopsin ($p<0.001$) and HSP70 ($p<0.001$) in the retina. Noticeable downregulation of the titres of natural autoimmune anti-SMAP antibodies in the serum of the diagnosed patients with retinitis pigmentosa relatively to healthy persons of the same age ($p<0.01$) was revealed. Molecular mechanisms underlying hypothalamic trophic regulatory effects on retina receptor cells through retrograde and anterograde axonal transports are considered.

Keywords: *Retinitis pigmentosa, rabbits, serotonin-modulating anticonsolidation protein (SMAP), rhodopsin, heat-shock protein 70, anti-SMAP antibodies, retina, hypothalamus, natural anti-SMAP autoantibodies.*

INTRODUCTION

Retinitis pigmentosa is a severe and to-date incurable form of ophthalmological pathology, manifesting by a damage of receptor apparatus of the retina along with loss of visual function. Although most of researchers relate etiology of retinitis pigmentosa to inborn mutations of the receptor cells (Diager et al., 2013; Xiao et al., 2019), others relate it to disturbances of normal interaction of hypothalamus with the retina and to decline of hypohalamic trophic support of the cellular elements of the retina (Katsnelson, 1958). This idea was partially proven by the studies of Prof. Gadjieva with her colleagues on a model of retinitis pigmentosa on the rabbits, wherein pulse stimulation of ventromedial nucleus of hypothalamus promoted quick recovery of the amplitudes of electroretinogram (ERG) (Agayev et al., 2004). The results mentioned indicate an existence of a significant trophic influence of the hypothalamic nuclei onto maintenance of the retina functions. Earlier in the Academician Abdulla Garayev Institute of Physiology, NAS of Azerbaijan serotonin-modulating anticonsolidation protein (SMAP), being in linear relation with serotonin and realizing its functions on subcellular level, was purified from the rat brain (Mekhtiev, 2000). On the vertebrates it was shown that SMAP possesses anti-mutagenic and anti-toxic activities in response to adverse factors of chemical and bacteriological origin (Allahverdiyeva et al., 2019). Proceeding from the above said, the goal of

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the present study was analysis of molecular pathogenetic and reparatory mechanisms of the retina and hypothalamus under conditions of experimental dystrophy of receptor apparatus of the retina on the rabbits, as well as on the patients diagnosed of retinitis pigmentosa.

MATERIALS AND METHODS

Biochemical methods. SMAP was purified from the cow brains. The main stages of purification were: (1) precipitation of proteins from the brain extract in 40% ammonium sulphate; (2) gel-chromatography on the column of Sephadex G-150. Process of picking up the immune positive protein fractions after each stage was conducted under control of indirect ELISA-test (Catty, 1989; Mekhtiev, 2000).

In order to pursue changes of retinitis pigmentosa under the studied preparations, the method of measurement of rhodopsin in the retina by indirect ELISA-test was elaborated. Retinas were removed surgically from 35 cow eyes, water-soluble proteins were extracted and 1.8 mg of rhodopsin were purified through centrifugation in sucrose density gradient (Ohguro et al., 1995) and used for production of anti-rhodopsin immunoglobulins. All operations on purification of rhodopsin were realized in the darkened room, elucidated by lantern (25 W) with red filter.

Anti-SMAP and anti-rhodopsin immunoglobulins were produced through 5-6-month immunezation of the rabbits by sub-cutaneous administration of 300 μg of the purified correspondent protein per animal, in mixture with complete Freund adjuvant (Sigma, Germany).

Measurements of the levels of rhodopsin and HSP70 in the retina and SMAP – in hypothalamus of the rabbits of the intact, control and experimental groups were carried out by indirect ELISA-test (Catty, 1989) on polysterene plates (Sigma, Germany). The animals had been anesthetized and sacrificed, and the retinas and hypothalamus were removed at the end of experiments and frozen under a temperature of -70°C. Prior to the beginning ELISA-test, the water-soluble proteins were extracted from the studied samples. The results of the reaction were registered in the photometer for the ELISA-test "Spectra Max 250" (Molecular Devices Co., USA) on the wavelength 492 nm.

Anti-SMAP polyclonal antibodies were purified from the solution of anti-SMAP immunoglobulins through a technique of immune-affinity chromategraphy performed on the column of CNBr-Sepharose (Sigma, Germany) with covalently immobilized SMAP (Osterman, 1985). In a single cycle up to 12 mg antibodies were eluted from the affinity column.

Physiological methods. The studies were undertaken on Chinchilla male rabbits of 2.2-2.6 kg body mass kept in the vivarium conditions. All experiments on administration of the preparations to the animals were conducted in daytime, between 13.00 h and 16.00 h. Retinitis pigmentosa was formed through single administration of MIAA in 2 ml of a sterile saline into the ear edge vein of the anesthetized rabbits at a dose of 26 mg/kg of body mass (grave degree) with needles of size 21 during 3 min (Agayev et al., 2004). Retina was removed from the rabbit's eyes in the darkened room, illuminated with lantern (25 W) with red filter.

As corpus vitreous of the eye is poorly washed with biological liquids and does not have blood supply, excluding spreading preparations from one eye into another one, the studies were realized on both eyes.

The main series of the studies were conducted over the following scheme. In the 1st series of studies the rabbits (n=4) were i.v. administered with MIAA and after 12 days the anaesthetized animals were sacrificed and the retinas from the both eyes (8 eyes) and hypothalamus were removed and water-soluble proteins were extracted; with application of the indirect ELISA-test in the retina the levels of rhodopsin and HSP70, while in hypothalamus the level of SMAP was measured.

In the 2nd series of studies 3 groups of animals were formed: 1) intact group (n=4; 8 eyes); 2) control group (n=4; 8 eyes) and 3) experimental group (n=4; 8 eyes). In the control group of animals MIAA was i.v. administered and after 22 days they were anaesthetized and sacrificed and retina was removed. In the animals of the experimental group retinitis pigmentosa was formed and after 15 days they were administered with 150 μL of SMAP at a concentration of 1.5 mg/mL in the sterile saline into the corpus vitreous of both eyes through the pars plana during 2 min. 7 days from administration of SMAP (22nd day after administration of MIAA) the anaesthetized rabbits were

sacrificed, the retinas were removed from both eyes, water-soluble proteins were extracted and the level of HSP70 was determined in the retina of the rabbits of all groups.

In the 3rd series 3 groups of animals were formed: 1) intact group (n=4; 8 eyes); 2) control group (n=4; 8 eyes) – i.v. administration of MIAA plus intravitreal administration of inactivated SMAP; and 3) experimental group (n=4; 8 eyes) – i.v. administration of MIAA plus intravitreal administration of SMAP. The preparations were administered in an amount of 150 μL at a concentration 1.5 mg/mL in a sterile saline in 2 min on the 5th day after administration of MIAA and after 7 days the anaesthetized animals were sacrificed and levels of rhodopsin and HSP were evaluated in the protein extract of the retina.

In the 4th series of studies 3 groups of animals were formed: 1) 1st control group (n=4; 8 eyes); 2) 2nd control group (n=4; 8 eyes); 3) experimental group (n=4; 8 eyes). The animals of both control, as well as experimental groups were i.v. administered with MIAA and after 15 days the rabbit non-immune γ-globulins or anti-SMAP polyclonal antibodies were administered into the corpus vitreous of the animals of the 2nd control and experimental groups, correspondently. The preparations were administered in an amount of 200 μL at a concentration of 1.8 mg/mL, in a sterile saline, slowly, during 2 min. 7 days later, the rabbits were sacrificed, the retinas were removed from the both eyes, water-soluble proteins were extracted and the levels of rhodopsin and HSP70 were determined.

In the 5th series of studies the rabbits (n=3) were immunized with SMAP as described above for 3 months. Blood samples were taken from the rabbits and the level of anti-SMAP immunoglobulins was evaluated by the indirect ELISA-test. The anaesthetized animals were sacrificed, eyes were removed, water-soluble proteins were extracted and the levels of HSP70 and rhodopsin were measured in the retina.

In the 6th series of studies in the observed patients retinitis pigmentosa was diagnosed in the clinics of Academician Zarifa Aliyeva National Center of Ophthalmology by recording ERG in response to light flashes presented to the patients' eyes with a frequency of 0.2 Hz, duration of 5 sec and duration of a single stimulus 200 msec. From patients (n=9) and healthy volunteers (n=9) blood samples were taken from the vein, serum was saved, diluted 100 times and used as the first antibodies in the indirect ELISA-test in order to determine the level of natural anti-SMAP antibodies (Poletayev, 1995).

The averages of the levels of the studied antigens in the hypothalamus and retina of both eyes of the rabbits as well as the levels of natural anti-SMAP autoantibodies in the serum of patients were calculated within each group and analyzed on Student's t-criterion.

The work is complied with the ARVO statement on the use of animals in scientific research.

RESULTS

In the 1st series of studies the animals were administered with MIAA and 12 days later sacrificed and retinas from both eyes and hypothalamus were removed. Evaluation of the level of rhodopsin and HSP70 in the retina revealed noticeable downregulation of rhodopsin and upregulation of HSP70. In particular, if the level of rhodopsin in the intact animals (n=4; 8 eyes) made 0.275±0.011 optic units, in the animals of the experimental group (n=4; 8 eyes) its level was 0.207±0.007 optic units ($p<0.001$; Fig. 1). In this case, the level of HSP70 in the retina of the intact animals made 0.094±0.004 optic units, while in the animals of the experimental group its level made 0.14±0.007 optic units ($p<0.001$; Fig. 1). Moreover, upregulation of SMAP was revealed in the hypothalamus in the animals of the experimental groups. Particularly, the level of SMAP in the animals with retinitis pigmentosa made 0.298±0.009 optic units, whereas in the intact animals its level was 0.24±0.01 optic units ($p<0.01$; Fig. 1).

In the 2nd series of studies for the purpose of clarifying, if SMAP actually upregulates synthesis of HSP70, the study of the effect of SMAP on the level of HSP70 in the retina of the rabbits with this pathology was undertaken. 7 days after intravitreal administration of SMAP (150 μL, 1.5 mg/ml, in 2 min) sharp upregulation (23 times) of HSP70 in the animals of the experimental group relatively to the control animals (received MIAA) was revealed. Particularly, if the level of HSP70 in the retina of the intact animals (n=4; 8 eyes)

made 0.367±0.04 optic units, in the control animals (n=4; 8 eyes) – 0,039±0.001 optic units (p<0.001), in the animals of the experimental group (n=4; 8 eyes) its level made 0.902±0.042 optic units (p<0.001; Fig. 2).

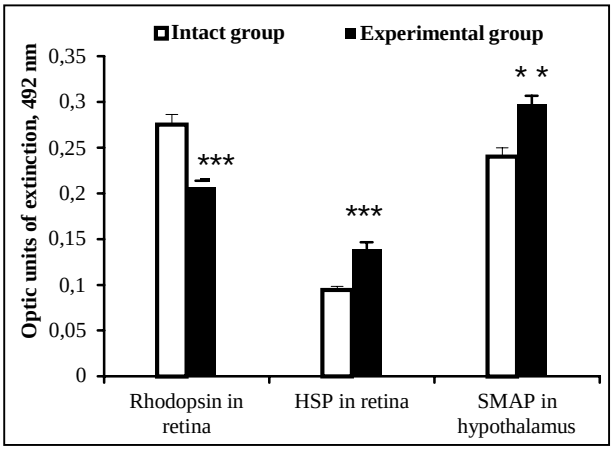

Figure 1. Effects of i.v. administration of MIAA on the levels of rhodopsin and HSP70 in the retina, and on the level of SMAP in the hypothalamus of the rabbits (n=4, 8 eyes).* - p<0.01; *** - p<0.001.

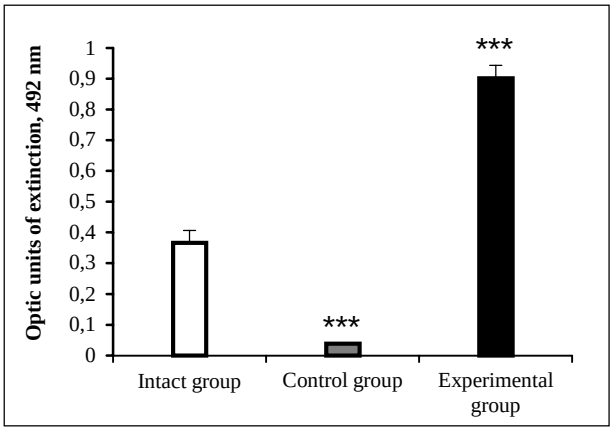

Figure 2. Effect of intra-vitreal administration of SMAP 15 days after i.v. administration of MIAA on the level of HSP70 in the retinas of the rabbits (n=4, 8 eyes). *** - p<0.001.

Hence, if under MIAA the level of HSP70 in the retina downregulated drastically, then under administration of SMAP the level of HSP70 on the animals with retinitis pigmetosa not only overcame the controls, but significantly exceeded the level of the intact animals (p<0.001).

In the 3rd series of studies on 5th day after i.v. administration of MIAA the animals were administered intra-vitreally with active SMAP or heat-inactivated SMAP. After 7 days since administration of SMAP (150 μL, 1.5 mg/mL, in 2 min) noticeable upregulation of rhodopsin in the retina was revealed. In particular, in the intact animals (n=4; 8 eyes) the level of rhodopsin in the retina made 0.187±0.005 optic units, in the animals of the control group (n=4; 8 eyes; inactivated SMAP) - 0.13±0.008 optic units (p<0.001), while in the animals of the experimental group (SMAP; n=4; 8 eyes) – 0,193±0.011 optic units (p<0.001; Fig. 3A). Moreover, the level of HSP70 in the retinas of the intact animals made 0.085±0.004 optic units, while in the control animals – 0.102±0.004 optic units (p<0.05), and in the animals of the experimental group – 0.123±0.005 optic units (p<0.001; Fig. 3B).

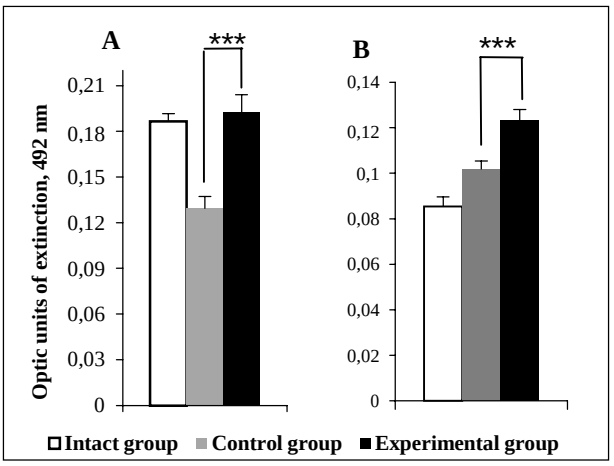

Figure 3. (A) Effect of intra-vitreal administration of SMAP 5 days after i.v. administration of MIAA on the level of rhodopsin in the retinas of the rabbits (n=4, 8 eyes). ***- p<0.001. **(B)** Effect of intra-vitreal administration of SMAP 5 days after i.v. administration of MIAA on the level of HSP70 in the retinas of the rabbits (n=4, 8 eyes). * - p<0.05; *** - p<0.001.

Thus, under intra-vitreal administration of SMAP on the 5th day after injection of MIAA group simultaneous upregulations of rhodopsin and HSP70 in the retinas of the animals of the experimental were noted.

The goal of the 4th series of studies included analysis of the effect of polyclonal antibodies-mediated blockade of SMAP on the level of rhodopsin in the retina of the rabbits with prior induced

retinitis pigmentosa. It was found that intra-vitreal administration of the anti-SMAP antibodies (200 μL, 1.8 mg/mL, during 2 min) to the rabbits with retinitis pigmentosa resulted in considerable upregulation of the level of rhodopsin and HSP70 relatively to their values in the animals of the 1st (MIAA) and 2nd (MIAA plus non-immune γ-globulins) control groups. Particularly, in the animals of the 1st control group (n=4; 8 eyes) the level of rhodopsin made 0.182±0.012 optic units, in the 2nd control group (n=4; 8 eyes) – 0.184±0.009 optic units, whereas in the animals of the experimental group (n=4; 8 eyes) its level was 0.242±0.012 optic units ($p<0.01$ on Student's t-criterion; Fig. 4). Correspondently, in the animals of the 1st control group the level of HSP70 made 0.082±0.012 optic units, in the 2nd control group – 0.109±0.004 optic units, while in the animals of the experimental group its level was 0.158±0.01 optic units ($p<0.001$; Fig. 5).

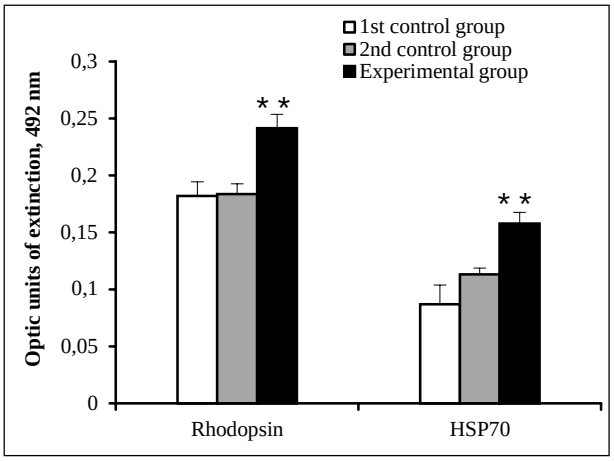

Figure 4. Effect of intra-vitreal administration of anti-SMAP antibodies after i.v. administration of MIAA on the levels of rhodopsin and HSP70 in the retinas of the rabbits (n=4, 8 eyes). ** - $p<0.01$.

In the 5th series of studies the effect of the anti-SMAP autoantibodies on the level of HSP70 and rhodopsin in the retina of the rabbits was studied. As a result of immunization with SMAP, the anti-SMAP antibodies of high titer were produced in the rabbits' organisms and they realized blocking effect on the activity of SMAP in all tissues. In the retina of the immunized rabbits significant upregulation of HSP70 relatively to the intact animals was revealed. Notably, in the intact animals (n=3; 6 eyes) the level of HSP70 in the retina made 0.087±0.01 optic units, as a result of immunization its level was upregulated to 0.176±0.01 optic units ($p<0.001$; Fig. 6). In addition, in the retinas of the SMAP-immunized animals upregulation of rhodopsin was noticed: 0.186±0.005 and 0.213±0.004 optic units in the intact and immunized animals, correspondently ($p<0.01$).

In the 6th series of studies the levels of natural anti-SMAP autoantibodies in the blood serum of the patients with retinitis pigmentosa were evaluated. The blood serum was used as the first antibodies in the indirect ELISA-test. Natural autoantibodies to all antigens are revealed normally in the healthy organism of the animals and humans (Avrameas, 1991; Poletayev, 1995; Lacroix-Desmazes et al., 1998). Hence, on basis of the revealed titers of the natural autoantibodies to certain antigens, one can make a conclusion concerning the levels of these antigens in the tissues.

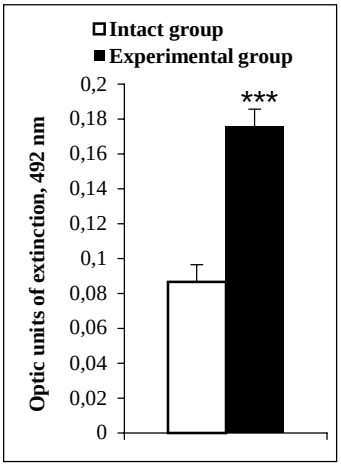

Figure 5. Effect of anti-SMAP autoantibodies (4-month immunization with SMAP) on the level of HSP70 in the retinas of the rabbits (n=3, 6 eyes). ** - $p<0.01$

In each of 9 patients, retinitis pigmentosa was diagnosed in clinical conditions by recording ERG. As a result, ERG was not recorded in any of 9 examined patients that indicates to a serious impairment of the receptor apparatus of the retina, i.e. retinitis pigmentosa.

The conducted studies revealed that in the blood serum of the patients with diagnosis of retinitis pigmentosa the level of natural anti-SMAP autoantibodies was significantly lower than in the healthy persons of the same age. Particularly, if the level of

natural anti-SMAP autoantibodies in the blood serum of the healthy persons (n=9) made 0.106±0.008 optic units, in the patients (n=9) their level made 0.076±0.004 optic units ($p<0.01$ on Student's t-criterion; Fig. 6).

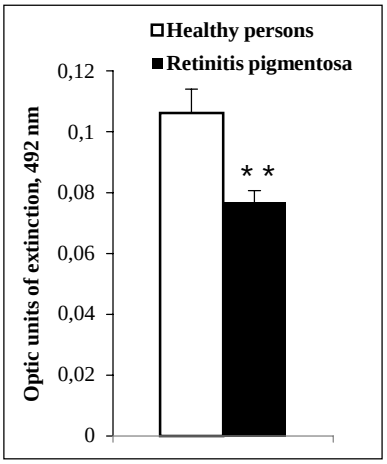

Figure 6. Changes of the level of natural anti-SMAP autoantibodies in the serum of the patients with diagnosed retinitis pigmentosa (n=9).
** - $p<0.01$.

On these grounds one can make a conclusion on downregulation of SMAP in the hypothalamus and retina of the patients with retinitis pigmentosa.

DISCUSSION

Finalizing the results of the conducted seven series of studies on the model of grave form of retinitis pigmentosa, the following conclusions might be made. Modeling grave form of retinitis pigmentosa on the rabbits through i.v. administration of MIAA at a high dose induces noticeable changes in a character of functioning of the receptor apparatus of the retina. In this case, sharp decline in the amplitudes of total ERG and downregulation of rhodopsin are noticed. In addition, in the formation of retinitis pigmentosa a number of molecular changes in the retina, apparently, underlying initiation and realization of regulatory processes both in the retina itself and outside it, in particular, in hypothalamus, are observed. Particularly, along with downergulation of rhodopsin, upregulation of HSP70 in the retina and upregulation of SMAP in the hypothalamus are revealed.

Sequence and cause and effect relations of these molecular events become apparent when we consider the results of other series of the studies as well. In particular, in the 3rd series of studies intra-vitreal administration of SMAP induces 23-fold upregulation of HSP70 in the retina that indicates to a capacity of SMAP in inducing powerful synthesis of this chaperon protein. Conversely, simultaneous upregulations of HSP70 and rhodopsin in the retina of the animals with grave form of retinitis pigmentosa under intra-vitreal administration of SMAP give grounds to making a conclusion that the nuclei of hypothalamus realize trophic regulation of the receptor apparatus of the retina, in particular, maintaining rhodopsin in a functionally active conformation through keeping baseline activity of serotonergic system in the hypothalamus, inducing in downstream way synthesis of HSP70 in the retina. Increase of the amplitude of total ERG under intra-ventricular administration of SMAP to the rabbits with retinitis pigmentosa supports the conclusion in regards to the trophic effects of SMAP toward the rhodopsin.

Antibodies-mediated blockade of SMAP activity, administered locally, into the corpus vitreous of the eyes of the animals with previously formed retinitis pigmentosa, induces noticeable upregulation of HSP70 and rhodopsin in the retina. These data indicate that anti-SMAP antibodies are captured by the retina cells from the corpus vitreous and, apparently, through anterograde axonal transport are delivered to the hypothalamic nuclei, wherein through antigen-antibody reaction they block the molecules of SMAP. In the literature there are data on the existence of direct retino-hypothalamic pathways capable of trophic regulation of receptor cells of the retina (Reuss, Fuchs, 2000; Trachtman, 2010). On the basis of the principle of negative biofeedback, compensatory synthesis of SMAP is initiated and its molecules through retrograde axonal transport are delivered from the hypothalamus to the retinal cells, wherein they launch mighty synthesis of HSP70. HSP70, due to their chaperon nature (Daugaard et al., 2007; Qu et al., 2015), recover normal conformation of the rhodopsin, disturbed by high dose of MIAA. Moreover, systemic blockade of SMAP with auto-antibodies, produced as a result of im-

munization of the rabbits, probably, through the mentioned above mechanism leads to significant upregulation of HSP70 and rhodopsin in the retina. Perhaps, this mechanism underlies getting the information about the functional status of receptor molecules of the retina by the engaged hypothalamic nuclei, and further adequate tuning on the system of its regulatory and synthetic activity in order to maintain receptor molecules in active conformational state occurs.

The revealed declined titer of natural anti-SMAP autoantibodies in the patients with retinitis pigmentosa, reflecting, correspondently, downregulation of SMAP in the organism's tissues, as well as the results of other series of the studies, conducted on the rabbits, provide grounds to put forward a conjecture that formation of this retinal pathology in the patients might be launched by insufficient synthesis of SMAP in the hypothalamic nuclei and poor realization of trophic support of the receptor apparatus of the retina.

This idea, in particular, is supported indirectly by the results of the 1st and 2nd series of studies, which revealed downregulation of amplitude of ERG and rhodopsin level in the retinas of the animals with retinitis pigmentosa and following spontaneous recovery of normal amplitude of ERG with time course.

In addition, possible existence of the described mechanism of retinitis pigmentosa as well indicates to compensatory upregulation of SMAP in the hypothalamus on the background of retinitis pigmentosa in the 2nd series of studies, as well as the results of the 1st and 4th series of the studies, wherein administration of SMAP, correspondently, into the brain lateral ventricle and corpus vitreous of the animals, significantly alleviated the manifestations of retinitis pigmentosa and promoted recovery of the disturbed functions of the retina (upregulation of declined amplitude of ERG and rhodopsin level).

Hence, the consideration of the results in a whole provides grounds to support the idea, proposed earlier by other authors, concerning mechanism of development of retinitis pigmentosa, related to impairment of trophic support of the retina, realized permanently by the hypothalamic nuclei.

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Eksperimental modeldə və klinikada torlu qişanın piqmentli distrofiyasının əsasında duran mexanizmlərin tədqiqi

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Bu məqalə ada dovşanlarında və torlu qişanın piqmentli distrofiyası diaqnozu müəyyən olunan xəstələrdə torlu qişanın piqmentli distrofiyasının molekulyar patogenetik mexanizmlərinin öyrənilməsinə həsr olunmuşdur.. Tədqiqatlar vivarium şəraitində saxlanilan 2,2-2,7 kq çəkisi Şinşilla cinsi olan erkək ada dovşanın üzərində aparılmışdır. Tədqiqatlarda torlu qişanın piqmentli distrofiyası olan xəstənin damarından götürülmüş qan nümunələri istifadə olunurdu. Torlu qişanın piqmentli distrofiyasini yaratmaq üçün dovşanların damarına monoyodosirkə turşusu (MYST, distrofiyanın ağır dərəcəsi, 1 kq heyvan kütləsinə 26 mq MYST) yeridilmişdir. Dolayı immuno-enzim analiz üsulu ilə hipotalamusda SMAZ-ın (Мехтиев, 2000), torlu qişada isə - rodopsin və 70 kDa molekulyar kütləsi olan istilik şoku zülallarının (İŞZ70) səviyyəsi, xəstələrin qan zərdabında - SMAZ-a qarşı təbii autoanticismlər müəyyən edilirdi. Nəticələr Studentin t-kriteriyasi ilə analiz olunmuşdur. MYST yeridilmiş dovşanlarda torlu qişada rodopsinin səviyyəsinin azalması ($p<0,001$), İŞZ70 səviyyəsinin artması ($p<0,001$) və hipotalamusda SMAZ səviyyəsinin artması ($p<0.01$) müşahidə olunmuşdur. Torlu qişanın piqmentli distrofiyası formalaşmış heyvanlarda SMAZ-in intravitreal daxil edilməsi torlu qişada rodopsinin ($p< 0,001$)və İŞZ70-in ($p<0.001$) səviyyələrinin nəzərə çarpan dərəcədə artmasına gətirir. Torlu qişanın piqmentli distrofiya diaqnozlu xəstələrin qan zərdabında SMAZ-a qarşı təbii autoanticisimlərin səviyyəsi sağlam test olunanlardan nəzərə çarpacaq dərəcədə azalmışdır ($p<0,001$). Məqalədə hipotalamusun torlu qişanın reseptor aparatına retroqrad və anteroqrad aksonal nəqliyyat hesabına mövcud olunmuş trofik təsirinin molekulyar mexanizmlərinin analiz olunmuşdur.

Acar sözlər: *Torlu qişanın piqment distrofiyası,dovşanlar, serotonin-modullu antikonsolidasiya olunmuş zülal (SMAZ), rodopsin, SMAZ-a qarşı anticismlər, torlu qişa, hipotalamus, SMAZ-a qarşı təbii autoanticismlər, 70 kDa molekulyar kütləsi olan istilik şoku zülalları*

Исследование подлежащих механизмов пигментной дистрофии сетчатки в экспериментальной модели и клинике

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Статья посвящена изучению подлежащих молекулярных механизмов пигментной дистрофии сетчатки у кроликов и у больных с данным заболеванием. Исследования выполняли на кроликах породы Шиншилла с массой тела 2.2-2.6 кг. Сыворотку получали от больных с пигментной дистрофией сетчатки. Пигментную дистрофию моделировали на кроликах посредством внутривенного введения монойодуксусной кислоты (МЙУК; тяжёлая степень, 26 мг/кг массы тела). Методом непрямого иммуноферментного анализа в гипоталамусе определяли уровень серотонин-модулируемого антиконсолидационного белка (СМАБ, Мехтиев, 2000) и белков теплового шока с мол. массой 70 кДа (БТШ70): в сетчатке – родопсина, а в сыворотке больных – естественных аутоантител к СМАБ. Результаты были проанализированы по t-критерию Стьюдента. Было обнаружено значительное снижение уровня родопсина ($p<0.001$) и повышение уровня БТШ70 ($p<0.001$) в сетчатке так же, как и повышение уровня СМАБ ($p<0.01$) в гипоталамусе у кроликов, которым предварительно вводили МЙУК. Интравитреальное введение СМАБ кроликам с предварительно введённой МЙУК приводило к значительному увеличению уровня родопсина ($p<0.001$) и БТШ70 ($p<0.001$) в сетчатке. В сыворотке больных с диагностированным пигментным ретинитом сетчатки было выявлено заметное снижение титров естественных аутоантител к СМАБ, относительно здоровых лиц того же возраста ($p<0.01$). В статье анализируются молекулярные механизмы, лежащие в основе гипоталамического трофического регуляторного влияния в отношении рецепторных клеток сетчатки посредством ретроградного и антероградного аксонного транспорта.

Ключевые слова: *Пигментная дистрофия сетчатки, кролики, серотонин-модулируемый антиконсолидационный белок (СМАБ), родопсин, белки теплового шока с мол. массой 70 кДа, антитела к СМАБ, сетчатка, гипоталамус, естественные аутоантитела к СМАБ*