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Chapter 4

SEARCH FOR NEW THEORIES OF ETIOPATHOGENESIS OF PRIMARY OPEN ANGLE GLAUCOMA: FEATURES OF LEVEL OF INTRAOCULAR PRESSURE AND NUMBER OF RETINAL GANGLION CELLS IN CONDITIONS OF GENETIC DEFECT OF DIFFERENT SUBTYPES OF A1-ADRENORECEPTORS

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ABSTRACT

The search for new information on the etiopathogenesis of primary open angle glaucoma (POAG) is relevant to the whole world, because population aging affects all countries.

The first part of the research executed with the organizational and financial support of the German Academic Exchange Service (DAAD) and the Ministry of Education and Science of the Russian Federation within the program of the academic exchange for a subject 'Fundamental ophthalmology: a role of sympathetic nervous system in a pathogenesis of primary open angle glaucoma' (the agreement with the researcher No. 91578056) is presented in the Chapter.

The features of intraocular pressure (IOP) and number of retinal ganglion cells (RGC) of 36 laboratory mice older than one year six months having a genetic defect of one of the subtypes of α1-adrenoreceptors (α1a, α1b, α1d) were studied. The control group was formed of ten intact laboratory mice of the same age.

Modern method of a dot contact measurement of IOP level of laboratory animals was applied (ICare-TonoLab-Tonometer). Also an immune-fluorescent method was used for differential visualization of cells in retinal wholemount preparations using the Brn3a marker allowing RGC to be counted.

For the first time, regular features of the level of IOP and the number of RGC in mice with genetic defects of one of the subtypes of the α1-adrenoreceptors (α1a, α1b, α1d) were discovered.

The received results demonstrate the specificity of the role of α1a-, α1b-, α1d-adrenoreceptors in a process of maintaining of normal IOP. In addition, the results provide evidence of the specific contributions of the α1a-, α1b- and α1d-subtypes of adrenoreceptors in the process forming the anatomical-topographic features of the retina.

Thus, the above suggests that ADRA-1A-line mice can be considered as a likely experimental model for studying the etiopathogenesis of primary open angle glaucoma.

Keywords: glaucoma, POAG, etiology, pathogenesis, theory of development, IOP, RGC, Brn3a marker, α1-adrenoreceptors

INTRODUCTION

It is known that the humoral system of the body has a significant effect on the morphofunctional state of the eye [1, 2, 3, 4, 5, 6], including the intraocular pressure (IOP) regulation [7, 8]. The important influence of the autonomic nervous system on maintaining a normal IOP level and maintaining the visual analyzer functions (visual acuity, color perception, visual field, stereoscopic vision, etc.), for example, in patients with primary open-angle glaucoma (POAG), has been proven [9, 10, 11]. The eye tissues sensitivity to trophic nervous influences is confirmed, among other things, by the expression of adrenergic receptors in them [12, 13, 14, 15, 16, 17, 18]. The role of alpha-1-adrenergic receptors in the regulation of a number of physiological processes has been repeatedly described – the nervous system functioning (for example, synaptic plasticity modulation) [19], blood and intraocular pressure, arterioles spasm, decreased vascular wall permeability, the pupil constriction, the eye hemodynamics regulation, IOP circadian rhythms and etc [20, 21, 22, 23, 24, 25, 26, 27, 28, 29]. Practicing ophthalmic surgeons have noted [30, 31, 32] that it is in patients with POAG during surgical removal of nuclear-type cataracts that it is most difficult to achieve the required drug-induced pupil dilation using adrenomimetics (‘pupil rigidity,’ ‘iris flopy’ syndrome), which may indicate a low functional activity of α-1-adrenergic receptors of the iris. Similar intraoperative difficulties have also been noted in patients who took an α-1-adrenergic receptor antagonist for a long time to treat, for example, prostate adenoma [16, 30, 31, 32, 33]. Such state-of-the-art antiglaucoma drugs as selective α-adrenoreceptor agonists with confirmed efficacy unfortunately produce actions at the early stages of formation of POAG, which may be associated with the gradual loss of sensitivity of eye tissues to sympathetic influences [1]. However, until now, the selective effect of individual α-1-adrenergic receptors subtypes on IOP and on the anatomical-topographic characteristics of the retina has not been studied, which can help in studying the nervous trophism role in the ophthalmotonus regulation, especially if we take into account that IOP fluctuations during the day are controlled by the suprachiasmatic nucleus

of the hypothalamus, which modulates activity of the sympathetic and parasympathetic innervation of the eye [34], responsible for the aqueous humor production and its outflow [7, 14, 35]. Also this is important for investigating the role of the neural trophics of the visual analyzer. This is particularly relevant in view of the known fact that about 25% of retinal ganglion cells die by the time stage I of POAG has formed [36, 37].

The aim of the present work was to conduct a comparative study of the intraocular pressure and the number of retinal ganglion cells in mice with genetic defects to different α-1-adrenoreceptor subtypes.

METHODS

Studies were performed from November 10, 2015 to January 10, 2016 on 36 male laboratory mice (experimental group) aged 18-23 months with genetic defects in one of the following three α-1-adrenoreceptor subtypes: α1a (15 mice), α1b (11 mice), and α1d (10 mice). All laboratory mouse strains studied (ADRA-1A, ADRA-1B, and ADRA-1D) were provided by Gutenberg University (Mainz, Germany) within the framework of grant-supported scientific research. The control group consisted of 10 intact laboratory mice (C57Bl/6NTac) of the same age and sex.

Specific Detection of the Intraocular Pressure (IOP)

All animals of the control and experimental groups were kept in the same conditions of natural illumination of the vivarium: 107±14 lux – in the morning hours (08:00-09:00) and 71±12 lux – in the evening (16:00-17:00), the level of which was controlled using a photoelectric light meter twice a day before starting the IOP measurements. Studying IOP fluctuations in the laboratory animals in the morning and evening hours was carried out using the intermittent daily tonometry technique, recommended for outpatient conditions and early diagnosis of glaucoma and assuming IOP measurement twice a day at the beginning and end of an outpatient appointment (in the morning at 8-9 hours and in the evening at

17-18 hours) [9, 38, 39]. The vivarium natural illumination level was determined by weather conditions – cloudy weather, typical for late autumn and winter. In addition, the maximum possible illumination stability of the animal cells in the morning and evening hours was achieved by placing them remote from the window at a distance twice the vertical size of the window. The daily changes dynamics in the natural light level at sunrise and sunset during the entire calendar period selected for the study corresponds to the time of IOP measurement in the above morning and evening hours, for example, on November 10, 2015: sunrise at 07:31, sunset at 16:50-17:25; December 10, 2015: sunrise at 08:14, sunset at 16:25-17:03; January 10, 2016: sunrise 08:23, sunset 16:46-17:23 (Europe/Berlin local winter time). Taking into account the recommendations for intermittent daily tonometry and the periods of daily changes in natural light (sunrise, sunset), the periods of IOP measurement of laboratory animals in the morning (08:00-09:00) and evening (16:00-17:00) hours were determined.

Tonometry was performed using the ICare-TonoLab-Tonometer. This device is specially designed for high-speed dot measurement of IOP in laboratory mice and does not require preliminary local anesthesia of the eye, because dot contact tonometry is based on the disposable probe effect on the cornea, minimal in terms of area and force, the low weight and effect rate of which form a mechanical impulse that does not change the cornea shape, which avoids irritating effects on the cornea (forward and backward movement of this probe is current in the inductor of the named device). In order to maximally comply with the above-described time parameters for measuring IOP in the morning and evening hours, the study of animals from the control group and the ADRA-1A group was carried out on odd days; from groups ADRA-1B and ADRA-1D – on even days (IOP of each animal was measured at least 10 times).

Experiments were performed only on the right eye, as three cases of injury to the left eyeball were noted among animals of the line ADRA-1D experimental animals included in the study, these injuries being caused by other animals of the same strain kept in the same cage and associated with their marked aggressive behavior.

Specific Detection of the Retinal Ganglion Cells (RGC)

A standard protocol for immunofluorescent differential visualization of retinal cells using the Brn3A marker was used (Santa Cruz Biotechnology, Germany); this is a nuclear protein and endogenous marker for retinal ganglion cells (RGC). Enucleation of the study eye was performed immediately after harvesting of mice from the experiment by carbon dioxide gas inhalation, after which the enucleated eyeball was placed in 4% formaldehyde (Sigma, Germany) for 30 min at room temperature, which was followed by washing with phosphate-buffered saline (PBS solution, Invitrogen, Germany) and preparation of retinal wholemount preparations with four incisions of the peripheral part at 3, 6, 9, and 12 o'clock (Figure 1).

Retinal preparations were placed in an eppendorf with the internal (vitreal) surface uppermost, washed 2 × 10 min with PBS solution supplemented with 0.5% Triton X-100 at room temperature and frozen in PBS solution supplemented with 0.5% Triton X-100 at –70°C for 15 min. Retinal preparations were kept at room temperature to thaw, and washed 2 × 10 min with PBS solution containing 0.5% Triton X-100. Retinal preparations were incubated with primary antibodies diluted 1:750 (sterile PBS solution, 2% Triton X-100, Brn3a antibody, 2% normal donkey serum, Santa Cruz Biotechnology, Germany) for 2 h at room temperature and overnight at +4°C. Retinal preparations were then washed with PBS solution containing 2% Triton X-100 at room temperature for 5 min and 4 × 10 min with PBS solution containing 0.5% Triton X-100. Retinal preparations were incubated with secondary antibodies diluted 1:500 (sterile PBS solution containing 2% Triton X-100, Alexa fluor-568 solution, Invitrogen, Germany) for 2 h at room temperature, washed with PBS solution containing 2% Triton X-100 for 5 min at room temperature and a further 4 × 10 min with PBS solution containing 0.5% Triton X-100, placed on slides and, after application of 1 drop of DAPI-chromogen (4,'6'-diamino-2-phenylindole – a universal nuclear stain emitting blue fluorescence in the area of cellular DNA) (Sigma, Germany), protected with a cover slip.

Ready retinal preparations were studied with an MX51 microscope (Olympus, Germany) in 16 fields (magnification ×40) using an observation zones scheme and counting (Figure 1). Mean total number of retinal cells were determined and the number of cell nuclei visualized with a DAPI-filter in the observation areas were counted; mean number of retinal ganglion cells (RGC) were counted in terms of the number of cell nuclei visualized using a TRITC-filter in the same 16 observation zones [40, 41].

Data were analyzed statistically in Statistica 6.0 to compute the mean number of cells in microscope fields and their standard errors. Significant differences between mean number of retinal cells for each line of animals were identified using Student's test. Laboratory studies were carried out in compliance with the principles of the Helsinki Declaration of the World Medical Association and the Principles of Good Laboratory Practice (Russian state standard GOST R 53434-2009).

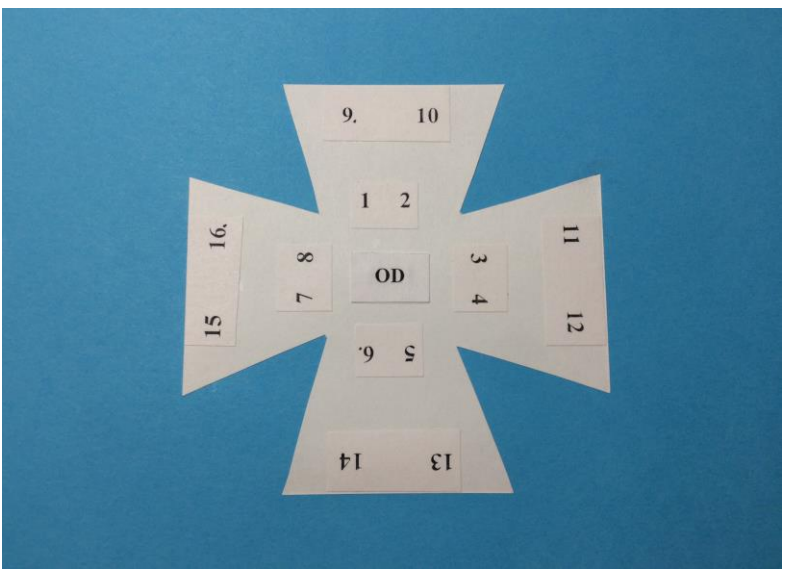

Figure 1. Diagram showing the positions of observation zones and counting of cell nuclei in retinal wholemount preparations in mice: 1–8) observation and counting zones in the central part of the retina; 9–16) observation and counting zones in the peripheral part of the retina; OD – optic disk.

RESULTS

Intraocular Pressure (IOP)

The applied method of measuring IOP made it possible to establish the following features in mice with a genetic defect of one of the alpha-1-adrenergic receptors subtypes (Table 1).

It was found that the IOP of all the studied control and experimental groups of mice was higher in the evening than in the morning.

IOP of intact mice of the control group (line C57Bl/6NTac) in the morning hours was 05.81 ± 0.28 mm Hg, in the evening hours – 08.64 ± 0.37 mm Hg.

In the experimental group of mice with a genetic defect in α-1a-, α-1b- and α-1d-subtypes of adrenoreceptors (lines ADRA-1A, ADRA-1B and ADRA-1D), morning IOP was equal to: 06.88 ± 1,02 mm Hg, 09.98 ± 0.42 mm Hg and 10.18 ± 0.29 mm Hg.

The studied mice with a genetic defect in one of the adrenergic receptor subtypes (ADRA-1A, ADRA-1B, and ADRA-1D mice lines) had higher IOP values in the evening hours, which amounted to 17.58 ± 1.82 mm Hg, 10,25 ± 0.52 mm Hg. and 11.89 ± 0.31 mm Hg, respectively.

Table 1. Features of intraocular pressure (IOP) in the mouse lines studied (C57Bl/6NTac, ADRA-1A, ADRA-1B, ADRA-1D) ($x \pm s_x$)

Laboratory mice line	**Intraocular pressure (IOP), mm Hg**		**Absolute ranges of morning and evening IOP, mm Hg**
	Morning hours (08:00 – 09:00)	Evening hours (16:00 – 17:00)	
C57Bl/6NTac	05.81 ± 0.28	08.64 ± 0.37	3.48
ADRA-1A	06.88 ± 1.02*	17.58 ± 1.82*	13.54
ADRA-1B	09.98 ± 0.42*	10.25 ± 0.52*	1.21
ADRA-1D	10.18 ± 0.29*	11.89 ± 0.31*	2.3

* Significant differences between the intraocular pressure of the mouse line C57Bl/6NTac and the intraocular pressure of the mouse lines ADRA-1, $p < 0.05$.

It is necessary to pay attention to the value fluctuations between the absolute IOP values recorded during the study (the highest in the evening and the lowest in the morning) in various conditions of the functioning of the sympathetic division of the autonomic nervous system. The named IOP fluctuations were 3.48 mm Hg in the control group, as well as 13.54 mm Hg in ADRA-1A mice, 1.21 mm Hg (line ADRA-1B) and 2.3 mm Hg (line ADRA-1D).

Retinal Ganglion Cells (RGC)

Differential visualization of retinal cells allowing them to be counted provided the first measurements of their quantitative characteristics for each line of male mice (C57Bl/6NTac, ADRA-1A, ADRA-1B, and ADRA-1D) aged 18–23 months.

In the control group, consisting of C57Bl/6NTac mice, the total mean number of retinal cells was 248.3 ± 6.41 cells/field (c/f) (Figure 2). The total number of retinal cells in experimental knockout mice of line ADRA-1A (Figure 4), ADRA-1B, and ADRA-1D had very close values: 249.8 ± 1.21, 248.62 ± 8.22, and 246.5 ± 9.88 c/f, respectively (Table 2).

Specific detection of retinal ganglion cells (RGC) showed that number in the control and experimental knockout groups differed. The mean count in the retinas of C57Bl/6NTac mice was 107.23 ± 2.69 c/f (Figure 3). The retinas of mice with genetic defects of one α-1-adrenoreceptor subtype (experimental knockout mice of line ADRA-1A (Figure 5), ADRA-1B, and ADRA-1D) had mean RGC counts of 95.8 ± 0.12, 116.45 ± 7.29, and 112.55 ± 4.47 c/f, respectively.

Furthermore, the percentage ratios of RGC to the total number of retinal cells were also different in each line. The mean proportion of RGC in C57Bl/6NTac mice was 43.19 ± 0.64%. Relative RGC contents typical of the retinas of mice with genetic defects of single α-1-adrenoreceptor subtypes (lines ADRA-1A, ADRA-1B, and ADRA-1D) were 38.34 ± 0.64%, 46.68 ± 1.76%, and 45.71 ± 1.14%, respectively.

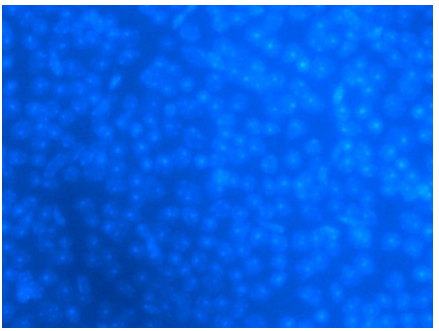

Figure 2. Cell nuclei in the retina in a C57Bl/6NTac mouse (retinal wholemount preparation, zone 5). Brn3a-immunofluorescent staining. DAPI-filter. Olympus MX51. Magnification ×600.

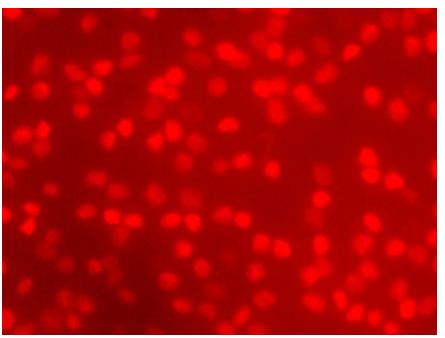

Figure 3. Brn3a-positive retinal ganglion cells in a C57Bl/6NTac mouse (retinal wholemount preparation, zone 5). Brn3a-immunofluorescent staining. TRITC-filter. Olympus MX51. Magnification ×600.

Table 2. Quantitative characteristics of retinal cells in the mouse lines studied (C57Bl/6NTac, ADRA-1A, ADRA-1B, ADRA-1D) ($x \pm s_x$)

Laboratory mice line	**Total number of retinal cells per field**	**Number of retinal ganglion cells (RGC)**	
		Mean number of RGC per field	Relative content of RGC among total retinal cells, %
C57Bl/6NTac	248,30 ± 6,41	107,23 ± 2,69*	43,19 ± 0,64
ADRA-1A	249,80 ± 1,21	95,80 ± 0,12*	38,34 ± 0,64
ADRA-1B	248,62 ± 8,22	116,45 ± 7,29*	46,68 ± 1,76
ADRA-1D	246,50 ± 9,88	112,55 ± 4,47*	45,71 ± 1,14

* Significant differences between the total number of retinal cells and the number of retinal ganglion cells per field, $p < 0.05$.

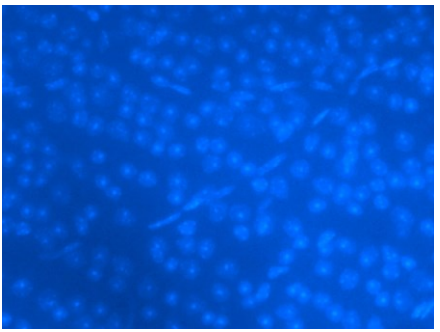

Figure 4. Cell nuclei in the retina in a ADRA-1A mouse (retinal wholemount preparation, zone 5). Brn3a-immunofluorescent staining. DAPI-filter. Olympus MX51. Magnification ×600.

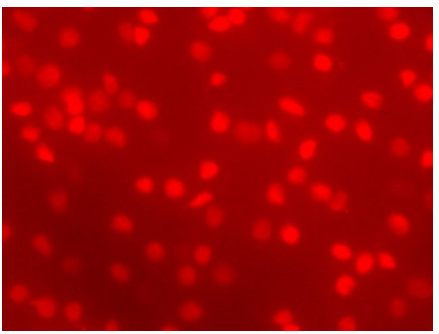

Figure 5. Brn3a-positive retinal ganglion cells in a ADRA-1A mouse (retinal wholemount preparation, zone 5). Brn3a-immunofluorescent staining. TRITC-filter. Olympus MX51. Magnification ×600.

DISCUSSION

Intraocular Pressure (IOP)

The higher IOP level described by this study in all studied control and experimental groups of mice in the evening and lower in the morning does not contradict the results of other studies of IOP in animals with a nocturnal lifestyle, indicating a significant increase in their IOP at 24:00, less pronounced an increase in IOP at 15:00 compared with a lower IOP in the morning [17]. In addition, the presence of a daily fluctuations rhythm

in human IOP (adjusted for the nocturnal lifestyle of the studied animals) was established, consisting in an increase in IOP in the morning hours and a decrease in the evening and night [42, 43, 44, 45, 46], which allows us to note the general IOP dependence on tone of different parts of the autonomic nervous system of the organism [7].

Retinal Ganglion Cells (RGC)

Analysis of the present results showed that the retina in ADRA-1A mice had the smallest and the retina of ADRA-1B mice the largest number of RGC among the lines tested. It is important to consider this result alongside those of previous studies in the same experimental animal lines [20, 23, 24, 25, 29, 45], establishing that mice with genetic defects of single α-1-adrenoreceptor subtypes are characterized by higher intraocular pressure (IOP) than intact mice. The most marked daily variations in IOP were seen in ADRA-A1 mice. This creates conditions for marked instability in the hydro- and hemodynamics of the eye, especially in the head of the optic nerve; impairments to the trophic of the optic nerve and retina are initiated, with reperfusion injury to the tissues and death of retinal ganglion cells [36, 37, 47, 48] – this damage was more marked when the drop in IOP was maximal [37, 43, 46]. The results presented here help to refine our understanding of the mechanisms of impairment to the autoregulation of ocular blood flow and ophthalmic tone by analysis of other previous studies [44, 46]. It is important to note the fact that the greatest range of daily variation in IOP, characteristic of marked instability of hydrodynamics in the eyeball, has previously been reported in ADRA-1A mice [45], which in the present study showed the greatest reduction in the number of RGC. The smallest range of daily oscillation in IOP, typical of relatively stable ocular hydrodynamics, was seen in animals of lines ADRA-1B [45], which in the present study were characterized by the greatest level of preservation of the number of RGC.

Increases in IOP are among the key factors in the pathogenesis of glaucoma. Most patients with POAG show elevated IOP in the morning

[43, 46, 49, 50], when there is rhythmic alternation of the functional activity of the compartments of the autonomic nervous system of the organism [51, 52]. The consequence of this is that patients are advised to modify their lifestyles – by getting up early in the morning. The reducing the predominance of parasympathetic effects, this decreases the harmful action of high IOP on the head of the optic nerve in the low arterial blood pressure conditions of the morning hours typical of patients with POAG [43, 44, 46, 50]. At the same time, it is known that POAG is more often formed in patients with a predominance of parasympathetic effects of the autonomic nervous system [6, 7, 9, 10], which are characterized by bradycardia, hypokinetic type of hemodynamics, red dermographism, Horner's syndrome, etc. An available marker of this imbalance is, for example, age-related nuclear cataract [7, 53]. In addition to increased IOP, glaucoma is characterized by pronounced instability of hydro- and hemodynamic parameters of the eye, which leads to progressive loss of vision due to the retinal ganglion cells death and associated visual field defects [54, 55, 56].

Furthermore, increased IOP produces a reflex constriction of the intraocular arteries (the vascular Kalf reflex), distortion of which in conditions of an imbalance in the autonomic nervous system, for example in the presence of defects in adrenoreceptor subtypes, can be very important in the pathogenesis of POAG.

Considering the nonidentical roles of different α-1-adrenoreceptor subtypes in controlling the hydro- and hemodynamics of the eye and blood pressure in producing the conditions for reperfusion damage of eye tissues and progression of glaucoma, further study of the features of blood pressure and perfusional intraocular pressure in mice with these genetic defects is needed [10, 35, 57, 58].

CONCLUSION

Thus, the study revealed the features of the intraocular pressure and quantitative differences of retinal ganglion cells in mice with a genetic

defect in one of the α-1-adrenergic receptors (α-1a-, α-1b-, α-1d-) subtypes, which allowed us to draw the following conclusions:

1) in the morning hours, the IOP values of intact C57Bl/6NTac mice are lower than in mice with the studied genetic defects (lines ADRA-1A, ADRA-1B, ADRA-1D);
2) in the evening hours, mice with a defect in one of the α-1-adrenergic receptor subtypes have a higher IOP than intact C57Bl/6NTac mice;
3) among the mice with the aforementioned genetic defects, the lowest morning IOP and the highest evening IOP are found in ADRA-1A mice, which creates conditions for pronounced eye hydrodynamics instability in mice of this line;
4) the retina in ADRA-1A mice had the smallest number of RGC (95.8 ± 0.12 c/f) compared with C57Bl/6NTac mice, ADRA-1B, and ADRA-1D (107.23 ± 2.69, 116.45 ± 7.29, and 112.55 ± 4.47 c/f, respectively);
5) the retina in ADRA-1B mice had the largest number of RGC (116.45 ± 7.29 c/f) compared with mice of the C57Bl/6NTac, ADRA-1A, and ADRA-1D mice (107.23 ± 2.69, 95.8 ± 0.12 and 112.55 ± 4.47 c/f, respectively);
6) the total number of retinal cells in C57Bl/6NTac mice (248.3 ± 6.41 c/f) and mice with genetic defects of lines ADRA-1A, ADRA-1B, and ADRA-1D (249.8 ± 1.21, 248.62 ± 8.22, and 246.5 ± 9.88 c/f, respectively) were similar.

The results obtained confirm the importance of the modulating effects of the autonomic nervous system and indicate the specific contribution of α-1a, α-1b, and α-1d subtypes of alpha-1-adrenergic receptors in the normal intraocular pressure maintenance and the number of retinal ganglion cells.

The aforementioned allows us to advance in the search for a new etiopathogenesis theories of primary open-angle glaucoma and suggest: an organism having a genetic defect of the α-1a-adrenoreceptors has a

genetically determined predisposition to a higher risk of the increased intraocular pressure, instability of the eye hydrodynamics and a more pronounced loss of the retinal ganglion cells.

Therefore, such an organism can be considered as the most likely model for the formation of primary open-angle glaucoma.

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AUTHORS’ CONTRIBUTIONS

Study concept and design: N.V.K.; collection and processing of specimens: N.V.K.; statistical processing of data: N.V.K., E.I.K.; data analysis and interpretation: N.V.K.; writing of text N.V.K., E.I.K.

Conflicts of Interests

The authors have no conflicts of interests.

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Korsakova Evgeniia Igorevna – Student of the Faculty of General Medicine of the Pirogov Medical University.

BIOGRAPHICAL SKETCH

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Education:

2013-current	Professor, Dr. Med. at the Department of ophthalmology and otolaryngology, Chuvash State University, Cheboksary, Russia
2015-2016	Scientific academic exchange for Professors (program of German Academic Exchange Service - DAAD, Bonn, Germany) The research project 'Fundamental ophthalmology: a role of sympathetic nervous system in a pathogenesis of primary open angle glaucoma,' Department for Ophthalmopharmacology and Physiology, Department of Ophthalmology, University Medical Center of J. Gutenberg University of Mainz, Mainz, Germany
2011	MD Thesis 'Nervous factor's influence on kind's formation of human age cataract,' Moscow People Friendship University, Moscow, Russia MD Diploma
2009-2011	Clinical internship in speciality 'Ophthalmology,' 'The S. Fyodorov Eye Microsurgery Federal State Institution,' Moscow, Russia
2007-2013	Senior lecturer at the rate of eye illnesses of the chair of hospital surgery, Chuvash State University, Cheboksary, Russia

2006-current	Ophthalmologist of Cheboksary Branch of 'The S. Fyodorov Eye Microsurgery Federal State Institution,' Cheboksary, Russia
2007	The Higher qualifying category on a speciality 'Ophthalmology,' Ministry of Health of the Chuvash Republic, Cheboksary, Russia
2004	PhD Thesis 'The morphofunctional characteristic of structures of lens containing a histamine, in norm and experiment,' Mordovian State University, Saransk, Russia PhD Diploma
2003-2007	Assistant of chair in hospital surgery at the rate of eye illnesses of the Chuvash State University, Cheboksary, Russia
1997-2006	Ophthalmologist at the City Hospital, Cheboksary, Russia
1996-1997	Clinical internship in speciality 'Ophthalmology,' Republic Clinical Ophthalmology Hospital, Cheboksary, Russia
1990-1996	Medical Faculty of the Chuvash State University, Cheboksary, Russia High school diploma
1980-1990	Comperehensive Secondary School No 10, city of Obninsk, Kaluga region, Russia Secondary school diploma

Research and Professional Experience:

Preventive and predictive ophthalmology: research of fundamental mechanisms pathogenesis with the development of technologies in decreasing losses from the socially significant age diseases of a vision organ.

The list of grants, the work over which is carried out as the head of the scientific project:

1. The scientific project on a subject 'Fundamental ophthalmology: a role of sympathetic nervous system in a pathogenesis of primary open angle glaucoma.' The grantor – German Academic Exchange Service (DAAD, Bonn, Germany), J. Gutenberg University of Mainz (Mainz, Germany, 2015-2016);

2. The scientific project on a subject: ‘Development innovative and pathogenetic reasonable methods of forecasting, prevention and treatment of a secondary cataract of the person.’ The grantor – the Ministry of Education and Science of the Russian Federation, the Federal target program ‘Scientific and the Research and Educational Personnel of Innovative Russia’ (Moscow, 2012-2013);
3. The scientific project of the Winner in the 3rd All-Russian scientific conference of young scientists in the nomination ‘Fundamental Problems of Ophthalmology’ on the subject: ‘The immunohistochemical status of lens cells at the different types of an age-related cataract of the person.’ The grantor – ‘The S. Fyodorov Eye Microsurgery Federal State Institution,’ (Moscow, 2009-2011).

Professional Appointments:

- Member Russian Society of Ophthalmologists (2008-current);
- Member of the Russian Academy of Natural Sciences (2012-current);
- Reviewer of ‘Russian Annals of Ophthalmology / Vestnik Oftal`mologii’ (2016-current);
- Reviewer of ‘American Journal of Clinical and Experimental Medicine’ (2016-current);
- Reviewer of ‘Journal Gerontology & Geriatrics studies’ (2016-current);
- Reviewer of scientific journal ‘International Journal of Immunology’ (2017-current);
- Editorial Board of ‘International Journal of Ophthalmology & Visual Science’ (2017-current).

Honors:

- Report about results of research project 'Fundamental Ophthalmology: Role of the sympathetic nervous system in the pathogenesis of primary open-angle glaucoma' was approved (January 31, 2016) by J. Gutenberg University of Mainz (Mainz, Germany) and German Academic Exchange Service DAAD (Bonn, Germany) – Agreement with the researcher No. 91578056.
- On May 29, 2014 as a result of the I All-Russian Competition 'The Best Young Scientist of the Year' Professor Korsakova N. V. was awarded the honorary title of laureate in the nomination 'The best young Doctor of Science – 2013' (medical sciences).
- For the cycle of monographs on ophthalmology published by the Russian and foreign publishing houses, Dr. Med. Korsakova N. V. in 2012 was awarded the State Award of the Chuvash Republic and an honorary title 'The Winner of the State Award of Chuvash Republic in the Field of Natural Sciences in Ophthalmology.'
- For the contribution in inventions' development by the decision of the Presidium of Russian Academy of Natural Sciences 27.09.2012 Korsakova N. V. were awarded by 'The Medal after name of Alfred Nobel.'
- Report by Korsakova N. V. on a theme: 'The Immunohistochemical cell's status of a lens at different kinds of an age-related human's cataract,' presented at III All-Russia's scientific conference of young scientists with participation of foreign experts ('The S. Fyodorov Eye Microsurgery Federal State Institution,' Moscow – 2008), became the Winner and was awarded the First Award in a nomination 'Fundamental problems of ophthalmology.'

Publications:

Proceedings (printed): 109 scientific publications (93 in the central Russian press and 16 articles in the central foreign publishing houses), 5 monography (2 of them were published in 2010 and 2012 in English language by 'Nova Science Publishers' publishing house, NY, USA and 1 monography was published in 2018 in English language by publishing house 'AvidScience,' India-Germany).

List of Publications from the Last 3 Years:

1. Korsakova, NV. Features of blood pressure in mice with a genetic defect of different subtypes of alfa-1-adrenoreceptors in morning clocks. *Russian Annals of Ophthalmology*, 2020, 136(5), 103-8. In Russ. doi:10.17116/oftalma2020136051103.
2. Korsakova, NV. The prymary open-angle glaucoma: modern theory of development (literature review). *Advances in Gerontology*, 2018, 31(1), 95-102. In Russ.
3. Korsakova, NV. Numbers of Retinal Ganglion Cells in Mice with Genetic Defects in Different A1 Adrenoreceptor Subtypes. *Neuroscience and Behavioral Physiology*, 2019, 49(8), 1027-31. doi:10.1007/s11055-019-00833-w.
4. Korsakova, NV. Ophthalmologic State of Patients with Different Types of Secondary Cataract. *International Journal of Biomedical Engineering and Clinical Science*, 2018, 4(1), 21-4. doi:10.11648/j.ijbecs.20180401.14.
5. Korsakova, NV. New Fluorescent-Histochemical and Immuno-Histochemical Aspects of Secondary Cataract Pathogenesis in Humans. *International Journal of Immunology*, 2017, 5(5), 80-7. doi:10.11648/j.iji.20170505.11.
6. Korsakova, NV. Intraocular pressure in mice with genetic defects of different α1 adrenoreceptor subtypes in the morning and evening hours. *Ros. Fiziol. Zh*, 2017, 103(5), 562-9. In Russ.

7. Korsakova, NV. New Prediction Method of the Certain Type of Secondary Cataract. *International Journal of Ophthalmology & Visual Science*, 2017, 2(4), 120-4. doi:10.11648/j.ijovs.20170204.17.
8. Korsakova, NV. New Fluorescent-Histochemical and Immuno-Histochemical Aspects of Secondary Cataract Pathogenesis in Humans. *International Journal of Photochemistry and Photobiology*, 2017, 2(5), 121-8. doi:10.11648/j.ijpp.20170205.12.

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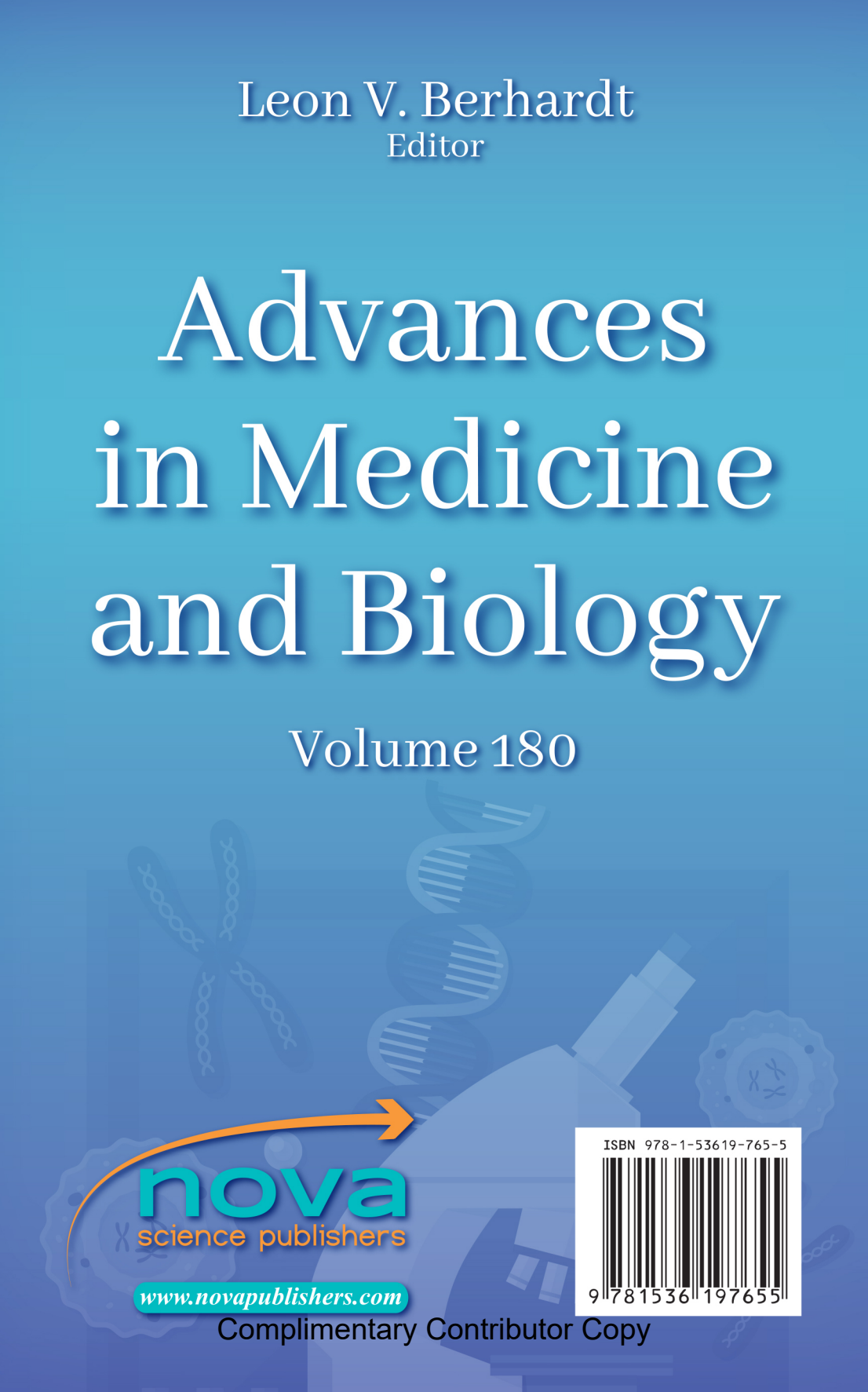

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