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Effect of long-term constant irradiation on retinal glia

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ABSTRACT

Aim. To study the response of retinal glial cells to constant irradiation of various intensity and to develop a mathematical model allowing to evaluate the dynamics of damage to radial glial cells and predict their photodamage depending on the duration and intensity of irradiation.

Materials and methods. Outbred sexually mature white rats ($n = 50$) weighing 180–200 g were exposed to constant round-the-clock light (200, 3,500 lux, days 1, 2, 7, 14, 30). The control group consisted of 25 non-irradiated animals. Using semi-thin sections stained with toluidine blue, we counted the number of pycnomorphic cells in the radial glial cells. Ultrastructural changes in the glial cells were studied using the JEM-100 CX-II electron microscope.

Results. The study showed that after photodamage, oligodendrocytes and astrocytes were mainly characterized by mitochondrial swelling and expansion of endoplasmic reticulum cisterns. Microglial cells at the late stage of the experiment (day 30) were localized in the inner layers of the retina; their density depended on the intensity of irradiation. The earliest (days 1, 2) changes in the radial glial cells were noted in the subretinal space and were manifested by proliferation of scleral processes and phagocytosis of dead sensorineural cell fragments. The intensification of destructive changes in the radial glial cells led to disturbances in neuron – glia interactions in the retina and a decrease in regeneration of retinal neurons (day 7–14). The developed mathematical model allowed to assess the dynamics of damage to the radial glial cells in the retina and to predict photodamage depending on the duration and intensity of irradiation.

Conclusion. Glial responses in the retina after photodamage depend on the intensity and duration of light exposure. As the duration of irradiation increases, degenerative changes in glial cells intensify and are more pronounced after high (3,500 lux) irradiation intensity.

Keywords: radial glial cells, microglial cells, astrocytes, oligodendrocytes, light, photodamage

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Влияние продолжительного постоянного освещения на глию сетчатки

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РЕЗЮМЕ

Цель. Изучить реакцию глиальной популяции сетчатой оболочки глаза при непрерывном световом облучении различной интенсивности и разработать математическую модель, позволяющую оценить динамику поражения радиальных глиоцитов и прогнозировать их световые поражения во временной и дозовой зависимости.

Материалы и методы. Беспородных половозрелых белых крыс (n = 50) массой 180–200 г подвергали постоянному круглосуточному освещению (200, 3 500 лк, 1-, 2-, 7-, 14-, 30-е сут). В качестве контроля использовали 25 необлученных животных. На полутонких срезах, окрашенных толуидиновым синим, проводили подсчет числа пикноморфных клеток радиальной глии. Ультраструктурные изменения глиоцитов изучали в электронном микроскопе JEM-100 CX-II.

Результаты. Исследование показало, что олигодендроглиоциты и астроциты после фотоповреждения в основном характеризуются набуханием митохондрий, расширением цистерн эндоплазматического ретикулума. Клетки микроглии в поздние сроки эксперимента (30 сут) локализуются во внутренних слоях сетчатки, их плотность зависит от интенсивности облучения. Наиболее ранние (1–2-е сут) изменения радиальных глиоцитов наблюдаются в субретинальном пространстве, выражаясь пролиферацией склеральных отростков и фагоцитозом фрагментов погибших нейросенсорных клеток. Усиление деструктивных изменений клеток радиальной глии приводит к нарушению глионейрональных взаимоотношений в сетчатке и снижению репаративных процессов со стороны нейронов сетчатки (7–14-е сут). Разработанная математическая модель позволяет оценить динамику поражения радиальных глиоцитов сетчатки и прогнозировать световые поражения во временной и дозовой зависимости.

Заключение. Глиальные реакции сетчатой оболочки глаза после фотоповреждения зависят от интенсивности и длительности облучения. По мере увеличения срока облучения в глиоцитах усиливаются дегенеративные изменения, более выражены после высокоинтенсивного (3 500 лк) светового облучения.

Ключевые слова: радиальная глия, микроглиоциты, астроциты, олигодендроглиоциты, свет, фотоповреждение

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

In the age of scientific and technological progress, people are constantly subjected to long-term exposure to numerous lighting devices, such as LED lamps, TV screens, computer displays, digital tablets, and smartphones [1–4]. Fluorescent lamps are widely used in industries and public institutions [5–7]. Replacing incandescent lamps with more economical energy-saving ones raises concerns about their safety for

human health and potential risks to the retina due to their specific spectral and energy characteristics [8–10]. LED lamps are generally characterized by intense blue light emission, which can damage structural components of the retina under both low-intensity lighting and extreme experimental conditions [1–3, 9–14].

The glial population of the retina is rather diverse. Astrocytes are located along blood vessels, oligodendrocytes are between the nerve fibers, and microglia are in the inner plexiform layer and ganglionic layer. Despite the fact that these cells do not participate directly in the process of light perception, they participate in metabolism and phagocytosis [15–17]. Radial glial cells play an important role in maintaining homeostasis and ensure protection of sensorineural cells. In case of their massive death, hypertrophy of glial cells occurs; they proliferate, migrate to the center of damage, and fill the site of injury with their processes, forming glial scars, which leads to reconstruction of the retina at a later stage of degeneration [18–22]. The available literature provides very little information on the quantitative assessment of changes in retinal glial cells in response to photodamage.

The aim of the study was to investigate the response of retinal glial cells to constant irradiation of various intensity and to develop a mathematical model allowing to evaluate the dynamics of damage to radial glial cells and predict their photodamage depending on the duration and intensity of irradiation.

MATERIALS AND METHODS

The study was performed on 75 outbred sexually mature white rats weighing 180–200 g, obtained from vivariums of Siberian State Medical University and the Goldberg Research Institute of Pharmacology and Regenerative Medicine of Tomsk NRMC. The animals were kept in a laboratory vivarium under fixed artificial light conditions (25 lux, 12:12 light – dark cycle) in accordance with the requirements of the Russian Construction Rules and Regulations II-A.9-71 to the standards of artificial lighting of rooms. In the first and second series of experiments, the animals (n = 50) were exposed to constant round-the-clock illumination (200, 3,500 lux; day 1, 2, 7, 14, 30). The control group consisted of 25 rats that were not exposed to constant round-the-clock illumination and were kept under similar conditions as experimental ones. Each experimental group contained five animals. The illumination equipment consisted of rectangular reflectors with embedded LB-40 cool white fluorescent lamps providing even illumination from five sides. The experiments were carried out in compliance with the rules adopted by the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986) and the rules of good laboratory practice (Order of the Ministry of Healthcare of the Russian Federation No. 267 of 19.06.2003).

The animals were decapitated immediately after the end of exposure to light. The central sections of the posterior segment of the eye and the optic nerves were fixed in 2.5% glutaraldehyde in the cacodylate buffer (pH 7.4) and postfixed in a 1% osmium tetroxide solution and embedded in epoxy resin. Semi-thin sections were stained with toluidine blue. After that, the number of pycnomorphic radial glial cells of the retina was counted (200 cells per 15 fields of vision from 5 sections in each animal) at 10 × 90 magnification. Ultrastructural changes in the glial cells of the retina were studied using the JEM-100 CX-II electron microscope using ultra-thin sections contrasted with uranyl acetate and lead citrate.

Statistical data was processed using the nonparametric Mann – Whitney test in the Statistica 6.0 software program. The results of the study were presented as $M \pm m$, where M is the mean, and m is the standard error of the mean. The differences were considered significant at $p < 0.05$. Based on the results obtained in the experiment, using the methods implemented in the mathCAD software environment (interpolation, regression, approximation), a mathematical model was built that makes it possible to estimate changes in the light-induced damage to radial glial cells in the retina.

RESULTS

In the astrocytes accompanying blood vessels, the structure of the glial and fibrillary apparatus is preserved in the early stages (day 1–2) after light exposure (200, 3,500 lux), but the swelling of cisterns in cytoplasmic reticulum and mitochondria is observed. With prolonged light exposure (7–30 days, 200, 3,500 lux), most retinal astrocytes do not differ in the structure from the control ones, but the nuclei in some of them are characterized by pyknotic changes. Oligodendrocytes are located between the nerve fibers of the optic nerve, forming myelin sheaths to the axial cylinders. After exposure to low-intensity light (200, 1–30 days), focal demyelination followed by myelin phagocytosis by glial elements is observed. After

1–2 days of exposure to high-intensity light (3,500 lux), some of the organelles swell in oligodendrocytes. With prolonged (7–30 days) light exposure (200, 3,500 lux), the myelin sheath stratifies in some areas or around the entire perimeter of the nerve fiber. The processes of oligodendrocytes lying near the foci of demyelination are characterized by a decrease in the electron density and an increase in the number of fragments of phagocytized membrane myelin sheaths of various sizes and shapes.

After 30 days of light exposure (200, 3,500 lux), in the inner nuclear layer, we observed cells with an irregular (scalloped) shape of the nucleus, with high electron density of the karyoplasm and uniform distribution of chromatin. Their cytoplasm contained numerous vacuoles and lysosomes of different sizes. Based on the structure, we attributed these cells to microglia. It should be noted that their number was greater under high-intensity light exposure.

The nucleated parts of radial glial cells are located in the inner nuclear layer, and their processes penetrate the layers of the retina in different directions and form the outer and inner boundary membranes. After 1–2 days of low-intensity light exposure, numerous vacuoles and swollen mitochondria are observed in the cytoplasm of the apical regions of radial glial cells. The processes of glial cells grow through the outer boundary membrane into the subretinal space; these glial processes contain parts of the outer and inner segments of the sensorineural cells (Fig. 1). The bodies of radial glial cells containing nuclei with condensed chromatin and numerous free ribosomes in the cytoplasm are between the neurons of the inner nuclear layer, at the border with the plexiform layers (Fig. 2).

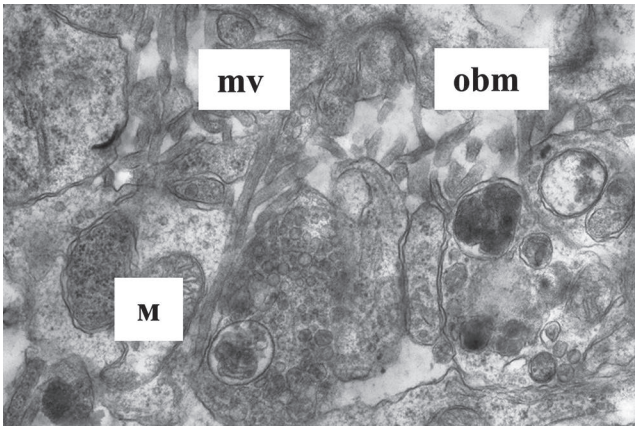

Fig. 1. Ingrowth of glial microvilli in the subretinal space and destruction of mitochondria in the inner segments of retinal sensorineural cells after light irradiation (200 lux, day 1). ×14,000. OBM – outer boundary membrane, MV – microvilli, M – mitochondria

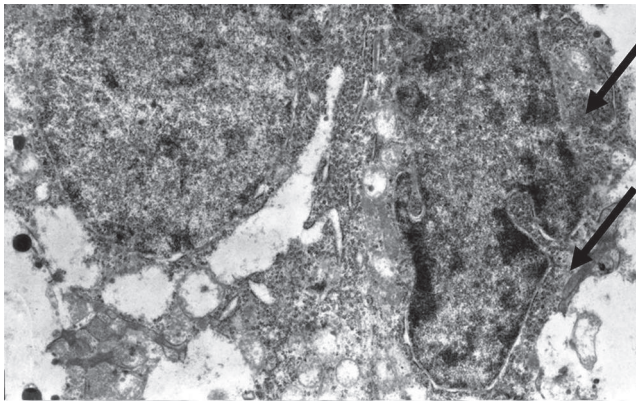

Fig. 2. An increase in the degree of chromatin condensation in the nucleus and an increase in the number of free ribosomes in the cytoplasm of a radial glial cell (arrows) after day 1 of exposure to low-intensity (200 lux, 1 day) light. ×5,800

After 1–2 days of exposure to high-intensity light, the number of radial glial cells with degenerative changes increases (Fig. 3). These cells show a decrease in the electron density and vacuolization of the scleral process cytoplasm and pyknosis of the nucleus. It is worth noting that these cells often lie on the border of the inner nuclear and plexiform layers. The structure of vitreal processes is without any changes.

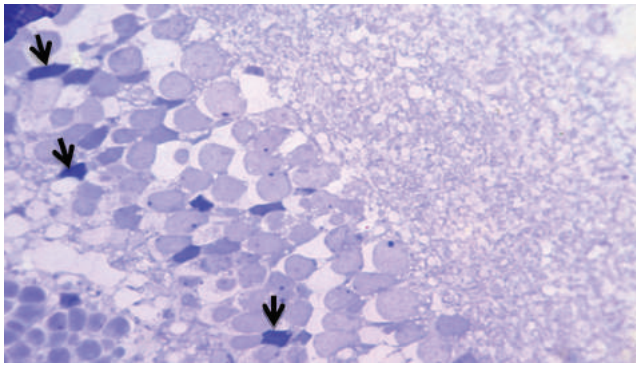

Fig. 3. Pyknosis of radial glial cells (arrows) after light exposure (3,500 lux, 2 days). ×900

After 7–14 days of low-intensity light exposure, sensorineural cells with degenerative changes appear, with fragmentation of most external and internal segments and pyknosis of the nucleus. The apical processes of glial cells surrounding the altered cells are dramatically hypertrophied and contain an increased number of membrane complexes and myelin-like bodies, as well as swollen mitochondria lacking cristae and containing fine granular material.

After 7 days of exposure to high-intensity light, multilayer glial plates appear in place of dead

sensorineural cells, surrounding their preserved nuclei and being in contact with bipolar neurons (Fig. 4). There are glial cells with hypertrophy of the vitreal processes containing swollen mitochondria, expanded cisterns of the endoplasmic reticulum, and numerous osmiophilic granules. After 14 days of exposure to high-intensity light, in the foci of massive death of sensorineural cells in the cytoplasm of the scleral processes in most glial cells, we observed a decrease in electron density, membrane complexes, and an increase in the number of vacuoles with osmiophilic material. Most of the nucleated parts of glial cells in the inner nuclear layer have normal structure.

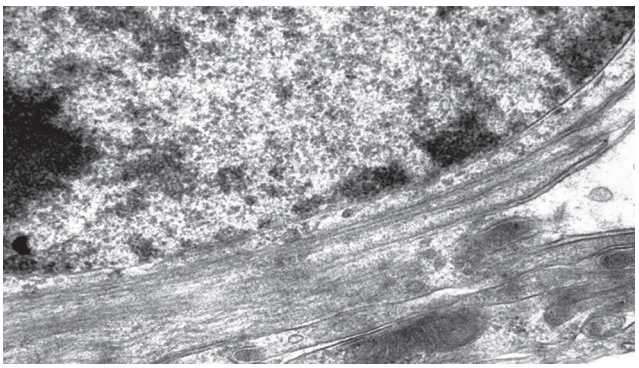

Fig. 4. Multilayer glial plates surrounding the nucleus of a sensorineural cell after 7 days of exposure to light (3,500 lux). ×15,000

After 30 days of light exposure (200 lux), proliferation of the radial glial scleral processes and vacuolization of glioplasm are observed in the outer nuclear layer, with phagocytosis of sensorineural cell nuclei with degenerative changes. After the same duration of high-intensity light exposure, severely hypertrophic processes of radial glial cells containing numerous large vacuoles and membrane complexes are observed in place of the practically absent outer nuclear layer.

In medicine, when the number of parameters of the studied trait is small, mathematical models are created for more accurate identification of various algorithms through a system of equations describing the properties of the modeling object under various experimental conditions. In our study, it was necessary to estimate the number of pycnomorphic radial glial cells in the retina taking into account the changes after exposure to light (200, 3,500 lux). Experimental data were taken to solve the problem. As a result of the data analysis, it was found that the number of pycnomorphic radial glial cells in the retina after photodamage is described by the following equation (Fig. 5, Table 1):

$$f(t) = a_0 t^{\frac{100}{J}} + a_1 t^{\frac{200}{J}} + a_2 t^{\frac{300}{J}} + a_3 e^{-t}$$

Fig. 5. The equation describing the number of pycnomorphic radial glial cells of the retina after photodamage: $f(t)$ – number of glial cells with pyknosis; J – surface illumination; a_i – constants obtained in the analysis of experimental data (Table 1); t – experiment duration

Table 1

Constants obtained in the mathematical model			
α_0	α_1	α2	α_3
Light 200 lux			
8.42	2.235	0.146	2.959
Light 3,500 lux			
2.087	0.014	0.034	3.411

Analysis of the data obtained during the modeling shows that under low-intensity (200 lux) light exposure, changes in radial glial cells were characterized by an increase in the number of pycnomorphic glial cells in the early stages of the experiment and a decrease in their number when the duration of light exposure increased. Exposure to high-intensity (3500 lux) light caused similar structural changes in radial glial cells, which were characterized by an increase in the number of dead glial cells when the duration of exposure increased. It should be noted that the obtained mathematical models confirm the experimental data and successfully describe smooth changes in the process.

The analysis of the change pattern regarding the content of pycnomorphic radial glial cells suggests that on day 7 of exposure to low-intensity light (200 lux), this parameter was 1.6 times higher than the control values (3.26 ± 0.23%) (Table 2).

Table 2

The number (%) of radial glial cells in the retina with symptoms of karyopyknosis after exposure to light of varying intensity, %	
Control	3.26 ± 0.23
day 1	
200 lux	3.72 ± 0.54
3,500 lux	2.91 ± 0.72
day 7	
200 lux	5.21 ± 1.08*
3,500 lux	8.15 ± 1.82*
day 14	
200 lux	6.73 ± 1.69*
3,500 lux	6.92 ± 1.28*
day 30	
200 lux	3.41 ± 1.32
3,500 lux	6.03 ± 1.27*

* significant differences compared to the control group, $p < 0.05$

An increase in the exposure period (14, 30 days) led to a decrease in the studied parameter, and on day 30 of the experiment, it did not significantly differ from the control values. After 7 days of exposure to high-intensity light, the content of pycnomorphic radial glial cells was 2.5 times higher than the control values and did not significantly change until day 30 of light exposure. An increase in the studied parameter points out a disruption of the adaptive and compensatory mechanisms and an increase in the destruction processes in the inner layers of the retina.

DISCUSSION

Thus, glial responses in the retina after photodamage depend on the duration and intensity of irradiation and contribute significantly to the damage. The earliest changes are observed in the subretinal space, manifested by proliferation of radial glial cell scleral processes and phagocytosis of fragments of sensorineural cells with degenerative changes. With the destruction of layers formed by sensorineural cells, we observed impaired glutamate metabolism, which regulates synaptic activity in retinal glial cells [23–25].

The intensification of damage in the studied cells leads to disruption of the glioneuronal interactions in the retina and a decrease in reparative processes in retinal neurons [26–29]. In the outer nuclear layer, foci of glial proliferation are detected and multilayer glial membranes surrounding the nuclei of sensorineural cells appear. We did not observe significant ultrastructural changes in the vitreal processes of radial glial cells.

CONCLUSION

The responses of retinal glial cells after photodamage depend on the intensity and duration of irradiation. As the irradiation period increases, degenerative changes in glial cells increase and are more pronounced after exposure to high-intensity (3500 lux) light. The developed mathematical model makes it possible to analyze the dynamics of destructive changes in retinal glial cells and to predict the results of photodamage depending on the duration and intensity of irradiation.

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