

Biochemical Changes in Retinal Tissue During Vitreoretinal Pathology

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Abstract

We have investigated the mechanism of the protective effect of Plaferon LB, a synthesized preparation from the amniotic membrane of human placenta, on the retinal tissue in the experimental model of the proliferative vitreoretinopathy (PVR). On the basis of ESR spectroscopic studies it became clear that the lowering of the level of the regenerated NAD.H, decrease of the intensity of the synthesis of macroergic combinations, the inactivation of the Superoxide-Dismutase had taken place; ischemia, oxidative stress and the intensification of NO synthesis had developed in the experimental model of PVR. In the model of PVR Dexazon partially provides the protection of the integrity of the retinal tissue cellular structures and helps diminish oxidizing processes in it. However, it is unable to normalize the intensity of the nitric oxide synthesis; the latter may be due to its inhibiting effect only on the post translation intensity of forming iNOS. Therefore Dexazon does not provide the limitation of the ADP ribolizing activity of the surplus NO, and consequently cannot restore the content of the regenerated NAD.H in the retina cells. Unlike Dexazon, Plaferon LB, due to its inhibiting activity on the NMDA receptors, limits the intensity of forming both the generators of the active forms of oxygen and the nitric oxide, and in this way helps diminish the intensity of the oxidative stress, preserve the physiological concentrations of NO, protects the cells from the intense utilizing of NAD, and apoptosis, induced by inflammatory processes.

Key words: *proliferative vitreoretinopathy, nitric oxide, dexazon, plaferon LB*

Introductions

Numerous researches have evidenced the important role of nitric oxide (NO) in the physiological processes of the organ of vision (Goldstein et al., 1996). NO in the retina tissue is exposed mainly in the amacrine and ganglionic cells, in the inner nuclear layer as well as in the outer and inner plexiform layers (Huang et al., 1993; Yamamoto et al., 1993). Some authors advance their opinion that in the photoreceptors NO obtains the modulation effect on the transduction of visual perceptions due to change of conduction in the ionic canals (Goldstein et al., 1996). In the amacrine cells production of NO can be connected with activation of the soluble guanylatcyclase (Koistinaho et al., 1993). Nitric oxide mainly synthesized by the

neuronal-NO-synthase (nNOS) takes active part in regulation of retinal vessels tension (Faraci & Breese, 1993). NO produced by the inducible-NO-synthase (iNOS) obtains the immunomodulating effect in the Muller's glial cells and, thus, provides protection of the retina against various microorganisms (Goldstein et al., 1996).

However, stimulation of NMDA-receptors by the surplus quantity of glutamates as well as increase in the level of cytokines and toxic free radicals in the retina tissue resulted from the crippling of the hemato-ophthalmic barrier at the experimental PVR causes activation of the neuronal and induced NO-synthases (nNOS, iNOS) and the increased generation of nitric oxide (Cotinet et al., 1997; Osborne et al., 1999; Muller & Koch, 1998; Bonne

et al., 1998), activation of the reaction cascade including activation of the arachidonic acid cycle, intensification of the peroxide oxidation of lipids (POL) and, finally, destruction of the retina cells with development of the persistent transgression of its functions.

Recently, the different data on the successful use of the amniotic membranes in the keratoplasty have been accumulated (Pires et al., 2000; Prabhasawat et al., 1997).

In this connection our attention has been attracted by preparation Plaferon LB synthesized from the amniotic membrane of the human placenta with the application of the original method developed under the direction of Prof. V. Bakhutashvili at the Institute of Medical Biotechnology of the Academy of Sciences of Georgia.

It is a well-known fact that Plaferon LB is characterized with the antiphlogistic and immunomodulating effect (Bakhutashvili et al., 1995; Chikovani, 1997; Gulordava, 1994; Javakhishvili et al., 1999; Chikovani et al., 1999). Taking into consideration the progress achieved in the sphere of applying amniotic membranes in the ceratoplasty we have assumed that Plaferon LB in virtue of the above listed aspects of its effect due to the properties of its natural protein-peptide components can be applied in the treatment of various ischemic diseases of the retina.

In connection with this, the object of the given work is investigation of mechanisms of the protective effect of Plaferon LB on the retina tissue in the experimental model of proliferative vitreoretinopathy (PVR).

Material and methods

36 Chinchilla rabbits of 2-2.5 kg weight were administered.

Modeling of experimental PVR. Modeling of PVR was executed by intravitreal injection of 3 units (IU) of preparation Lidase and human thrombocytes in amount of 10 m (6 rabbits -I group). As a control the eyes of intact animals (6 rabbits-II group) were used. The animals of III group (12 rabbits) directly after modeling of PVR were once intravitreally injected Plaferon LB in dose of 4 microgram. The animals of IV group (12 rabbits) directly after modeling were once intravitreally injected Dexazon in dose of 3 mg.

ESR spectroscopic studies. The retina tissue of the experimental eyes of rabbits was taken on the 10th and 30th day after the beginning of examination, placed in the polyethylene tubules of 0.5 cm diameter and 2cm length and frozen in the liquid nitrogen (-196 °C) for the ESR spectroscopic studies. The spectra of retina tissue were registered at the radiospectrometer RE 1307 (Russia) in the quartz Dewar vessel at the liquid nitrogen temperature. The intensity of generation of nitrogen oxide was studied with the low-temperature equipment for ESR spectroscopy with the use of spin-trap of NO-natrium diethyldithiocarbamate

Results

Effect of Dexazon and Plaferon LB on the content of nitric oxide in the retina tissue in the experimental PVR.

The results of investigation are given in Table 1. As it is evident from the Table, in the control group in the retina tissue the registered ESR signal of the spin-tagged nitric oxide was of small intensity. In 10 days after modeling of the experimental PVR the intensity of ESR signal of nitric oxide increased by 16 % and on the 30th day the intensity made 193 % as compared with the control.

	Control	PVR		PVR+Dexazon		PVR+ Plaferon LB	
		10 th day	30 th day	10th day	30 th day	10 th day	30 th day
NO	8.0±0.5	9.3±0.5	15.5±1.2	8.0±0.4	15.0±1.2	8.0±0.5	9.0±0.8

Tab.1 *Change of intensity of ESR Signal of the Spin-Tagged Nitric Oxide in the Retina Tissue in the Experimental Model PVR and against the Background of Effect of Dexazon and Plaferon LB*

		n	Free radicals g=2.00		FeS	Mn ²⁺	Fe ²⁺
			I	ΔH (Gs)			
Control		6	6.5±0.3	8.6±0.5	5.2±0.3	2.6±0.8	5.6±1.0
PVR	10 th day	6	17.1±1.0	7.5±0.5	3.2±0.8	5.5±0.7	5.5±1.0
	30 th day	6	18.0±1.2	7.5±6.6	1.5±1.0	17.6±1.8	14.0±2.0
PVR+Dexazon	10 th day	6	9.0±0.5	8.6±0.8	3.6± 0.5	5.6±0.5	5.8±1.2
	30 th day	6	12.5±0.6	8.0±0.4	2.0±1.2	6.0±0.5	5.8±1.2
PVR+Paferon LB	10 th day	6	8.6±0.5	8.5±0.7	4.5±0.5	2.3±0.5	5.0±0.8
	30 th day	6	8.8±0.5	8.5±0.6	4.0±0.8	2.4±0.5	4.5±0.5

Tab.2 *Change of Metabolic Paramagnetic Centres of the Retina Tissue in the Experimental PVR, Effect of Dexazon and Plaferon LB*

Under the influence of Dexazon the content of nitric oxide in the retina tissue reduced up to the control value on the 10th day of PVR, but, then continued to grow and on the 30th day reached the value exceeding the control value by 87 %.

Under the influence of Plaferon LB the intensity of ESR signal of the spin-tagged of nitric oxide has not been changed as compared with the control values during the total period of studies.

Effect of Dexazon and Plaferon LB on the metabolic paramagnetic centers of the retina tissue in the experimental PVR.

Table 2 shows the changes of metabolic paramagnetic centers of the retina tissue in the experimental PVR and effect of Dexazon and Plaferon LB.

In the ESR spectrum of the intact retina there are registered the signals from the free radical centers (g=2.00), ferrum-sulfur centers (g=1.94), Mn²⁺-containing complexes (g1=2.14) and ferrous iron ions Fe²⁺ (g=2.35) of low intensity.

In the PVR model the intensity of free radical signal in the ESR spectrum of the retina sharply increases and makes up 260 % as compared with the control values. At the same time the half width of the free radical (DH) signal decreases by 13 % as compared with the control. The intensity of ESR signal of the ferrum-sulfur centers of rabbits with the experimental PVR decreases by 49 %

on the 10th day and by 72 % on the 30th day as compared with the control.

With development of the experimental PVR in ESR spectrum of the retina the intensity of signal of Mn²⁺-containing complexes and iron ions Fe²⁺ sharply increases. On the 30th day of observation the intensity of the said signals exceed the control values 6.8- and 2.5-times accordingly.

Dexazon in the experimental PVR model on the 30th day of observation promotes decrease in the intensity of free radicals signal by 40 % as compared with the model. The intensity of ESR, signals of Mn²⁺-containing complexes and iron ions Fe²⁺ also decreases (Table 2). However, in this group of animals no changes in the intensity of signals of FeS as compared with PVR group have been revealed. The intensity of this signal against the background of Dexazon stays low and makes up 70 % (on the 10th day) and 40% (on the 30th day) as compared with the control values.

In the group of animals injected with Plaferon LB the intensity of the free radicals signal exceeds the control values by 30 % only, and its half width (DH) coincides with the latter. The intensity of ESR signals of FeS centers in this group of animals is below the control level by 14 % only and the indices of signals of Mn²⁺-containing complexes and iron ions Fe²⁺ do not differ from the control values.

The clinical symptomatology in the laboratory animals was assessed by classification Fastenberg et al. [1]

In PVR model on the 4-10th day without treatment there was observed the expressed dilatation of vessels of conjunctiva and iris, rigidity of pupil; in the front chamber the dredge of cellular elements was observed. In the cavity of vitreous humor there were revealed ophthalmoscopically the floating turbidity and fixed bars. On the 18-21st day there were revealed the coarse preretina membranes with the events of local traction amotio retinae. By the 30th day in the majority of animals the total traction amotio retinae developed.

Against the background of treatment with the steroid preparations in the PVR model there was noted the moderate reaction from the side of the front eye section, in particular, the moderate afferent defect of pupil and moderate vasodilatation of vessels of the iris and conjunctiva.

By the end of the third week in the vitreous humor there were revealed the preretina membranes (in some cases with the events of neovascularization). After 1 month in the majority of animals the local amotio retinae and sometimes the total amotio retinae were observed. The events of irritation of the front eye section against the background of treatment with preparation were slightly observed; in the isolated instances in the front chamber the dredge of cellular elements was observed. The alterations from the side of the back eye section were also expressed slightly in kind of development of the turbidity of the vitreous humor at the initial stages of the inflammation and proliferation (4-10 day) with their further resolution by the end of the third week. Only in the isolated instances on the retina surface the tender epiretina membranes with the isolated focuses of the local traction of the retina were developed.

Discussion of Results

The significant increase in the intensity of ESR signal of Mn²⁺-containing complexes and iron ions Fe²⁺ revealed by us with the means of ESR spectroscopic studies in the retina tissue spectrum, evidences the crippling of the membrane structures and destruction of the retina cells in the experimental model PVR.

It is well known that Fe²⁺ and Mn²⁺ ions are the powerful promoters of the free radical oxidation; therefore, their occurrence in the retina tissue in PVR promotes intensification of POL processes (Rice-Evans et al., 1985). One of the sources of growth of Mn²⁺ ions may be also the inactivated mitochondrion Super Oxide Disputasa (SOD) that in its turn makes for development of the oxidizing stress in the organ of vision.

The sharp diminution of intensity of signals of FeS centers in PVR evidences the regeneration of NAD.H dehydrogenase and in its turn, appears to be the reason for insufficiency of the macroergic compounds, catabolism of purines, activation of xanthinoxidase, metabolism of free fatty acids and arachidonic acid, the increased production of oxygenic free radicals (H₂O₂, O₂⁻) (Phillis, 1994).

The sharp increase in the intensity of the free radical signal of ESR in the retina tissue in the experimental model PVR may be caused by the oxidation of pigment retinal in the conditions of the oxidizing stress.

As it is well known, the retina tissue contains a great quantity of glutamate-related NMDA receptors, which in the regular conditions take part in transmission of the light signal in NO-related photoreceptor cells (Nawy & Jahrt, 1990). However, stimulation of NMDA-receptors by the surplus quantity of glutamate as it is observed during the ischemia of retina (Lipton & Rosenberg, 1994) and seems to develop in the conditions of experimental model PVR, can promote activation of the reaction cascade, including the increase in the calcium concentration, activation of neuronal-NO-synthase (nNOS), generation of NO, activation of guanylat-cyclase, intensification cGMF synthesis, processes POL and, finally, leads to development of the stable damages and malfunction of retina.

It is like so that in the pathogenesis of PVR along with the neuronal NOS there takes part also the induced-NO-synthase (iNOS) revealed in the glial Muller's cells and exuded by neutrophils and macrophages which penetrate into the retina due to the crippling of the hemato-ophthalmic barrier occurring in PVR.

The physiological activity of NO rather depends on the redox state of the ambient tissue. Provided that the neuroprotector qualities of nitrozonium (NO⁺) ensure inhibition of the increased neurotoxicity of NMDA receptors (Lipton et al., 1993), NO in the conditions of the oxidizing stress and surplus of super oxide radicals (O₂⁻) is transformed into the cytotoxic peroxynitrite (ONOO⁻) and hydroxyl radical (O⁻H) that ensures activation of processes POL with formation of free fatty acids which, in its turn, promotes the further intensification of the free radical oxidation.

Therefore, the sharp increase in the intensity of signals ESR of the free radicals, spin-tagged NO and Fe²⁺ and Mn²⁺ ions, and diminishing of intensity of ESR signal of ferrum-sulfur (FeS) centers in the retina tissue revealed by us, evidences decrease in the level of the restored NAD.H, diminishing of the intensity of synthesis of the macroergic compounds, inactivation of SOD, development of ischemia, oxidizing stress and intensification of NO synthesis in the experimental

model PVR. Inactivation of SOD and increased production of the free radicals of oxygen prevents development of the neuroprotector effect of NO and promotes the further intensifying of ischemia in the retina tissue.

Thus, NO plays the important role in the pathogenesis of the experimental PVR that is mediated by the interaction of nitric oxide with the stimulating amino acid receptors and by its important role in intensification of the free radical processes.

Therefore, modulation of NO concentration plays the significant role in the therapy of retina ischemia. The protective effect of inhibitors NOS in the damage of retina with the bright light and in the retinal ischemia model in rats is described by a number of authors (Goureau et al., 1993; Geyer et al., 1995). Huang et al. (1993, 1994), Nelson et al. (1995) have described the successful application of the selective inhibitors of the neuronal NOS in treatment of the cerebral ischemia.

As results from our researches, Dexazon in PVR model partially provides protection of the integrity of the retina tissue cellular structures and helps diminishing the oxidizing processes in it. The latter is confirmed by the significant decrease in the intensity of signal of the oxidized retinal on the 10th and on the 30th day of development of the experimental PVR.

The limiting effect of Dexazon on the intensity of the nitric oxide synthesis is revealed only in the beginning of development of PVR (the 10th day) (on the 30th day ESR signal of the spin-tagged NO sharply increased) that may be due to its inhibiting effect on the post-translation intensity of forming iNOS (Nathan & Xie, 1994). Therefore, Dexazon does not provide limitation of the ADP ribozolizing activity of the surplus NO and, hence, is not able to restore the content of the regenerated NAD.H in the retina cells.

Unlike Dexazon Plaferon LB limits the intensity of forming both the generators of the active forms of oxygen and the nitric oxide (see Tables 1,2), and thus, promotes diminishing the intensity of the oxidizing stress, preservation of physiological concentrations of NO, increase in the content of the regenerated equivalents of NAD.H and creates conditions for manifestation of the compensatory physiological functions of the nitric oxide, reduction of intensity of the ischemia in the retina tissue and provides protection of cells from damage and restoration of its functions.

It is well known that increase in NO synthesis as a result of activation of NMDA glutamate receptor takes place in the ischemia and traumatic injuries of the nerve cells of eye (White et al, 2000). Glutamate-induced synthesis of NO plays the leading role in development of apoptosis of nerve cells mediated by intensification of the oxidizing stress and formation of raptures in DNA (Pieper et al., 1999). As a result of activation of the NO-related poly-ADF ribose of polymerase breakdown of NAD takes place. This effect has been studied in the present research.

In the studies of Bakhutashvili et al, 1996 there was proved that Plaferon LB obtains NMDA-blocking qualities. Inhibition of NMDA-receptor and the neuronal NO-synthase related to it diminishes the intensity of forming NO.

By way of blocking the NMDA-glutamate receptor, the preparation Plaferon LB diminishes the intensity of forming NO and, thus, protects the cells from the intensive utilization of NAD and, consequently, from the apoptosis induced by the inflammatory processes. Application of the homemade preparation Plaferon LB revealed its considerable positive effect on the course of inflammatory process in the eye-taking place in the experimental process PVR.

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Биохимические изменения в ткани сетчатки во время витреоретинальной патологии

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Р Е З Ю М Е

Изучен механизм защитного действия синтезированного из амниотической оболочки плаценты человека препарата плаферон ЛБ на ткань сетчатки в экспериментальной модели пролиферативной витреоретинопатии (ПВР). На основании проведенных ЭПР спектроскопических исследований выявлено, что в экспериментальной модели ПВР имеет место снижение уровня восстановленного NAD.H, интенсивности синтеза макроэргических соединений, инактивация СОД, развитие ишемии, окислительного стресса и интенсификация синтеза оксида азота (NO). Дексазон в модели ПВР частично обеспечивает защиту целостности клеточных структур ткани сетчатки и способствует уменьшению окислительных процессов в ней, однако не способен нормализовать интенсивность синтеза NO, что может быть обусловлено его ингибирующим эффектом лишь на посттрансляционную интенсивность образования iNOS. Поэтому дексазон не обеспечивает ограничение АДР-рибозилирующей активности избыточного NO и, следовательно, не может восстанавливать содержание восстановленного NAD.H в клетках сетчатки. В отличие от дексазона, плаферон ЛБ в силу своей ингибирующей активности на NMDA-рецепторы ограничивает интенсивность образования как генераторов активных форм кислорода, так и NO и, тем самым, способствует снижению интенсивности окислительного стресса, сохранению физиологических концентраций NO, предохраняет клетки от интенсивной утилизации NAD и апоптоза, индуцируемого воспалительными процессами. Использование препарата плаферон ЛБ выявило его значительный положительный эффект на течение воспалительного процесса в глазу, имеющего место в экспериментальной модели ПВР.

Ключевые слова: *пролиферативная витреоретинопатия, окись азота, дексазон, плаферон ЛВ*