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EXPERIMENTAL STUDIES

ENALAPRILAT AS A NEW MEANS OF PREVENTING THE DEVELOPMENT OF RETINOPATHY OF PREMATURITY

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In a rat model of experimental retinopathy of prematurity (ROP), the safety of enalaprilat and its effect on the level of angiotensin-converting enzyme (ACE) and angiotensin-II (AT-II) in the vitreous body and retina were investigated. The study was performed on 136 newborn Wistar rat pups divided into 2 groups: group A — experimental (animals with ROP, n=64) and group B — control (n=72). Each group was further divided into 2 subgroups: A0 and B0 (n=32 and n=36, respectively) — animals that did not receive injections of enalaprilat, and A1 and B1 (n=32 and n=36, respectively) — animals treated with daily intraperitoneal (i.p.) injections of enalaprilat (0.6 mg/kg of body weight). This treatment started on day 2 and lasted either to day 7 or to day 14 in accordance with the therapeutic scheme. Animals were taken out of the experiment on day 7 and day 14. In samples of the vitreous body and retina, the content of ACE and AT-II was determined by enzyme immunoassay. On day 7 in subgroups A1 and B1 the levels of ACE and AT-II in the vitreous did not differ, while on day 14 were lower than in subgroups A0 and B0, respectively. Changes in the parameters studied in the retina were somewhat different from those found in the vitreous body. On the seventh day, the level of ACE in the retina of animals of subgroup B1 did not differ significantly from subgroup B0, and in subgroup A1 it was increased compared to subgroup A0. On day 14, its significant decrease was noted in subgroups A1 and B1 as compared with subgroups A0 and B0. At the same time, the level of AT-II in the retina of rat pups of subgroup B1 was lower than in subgroup B0, both on day 7 and day 14. On day 7, the concentration of AT-II, as well as the concentration of ACE, increased in subgroup A1 as compared to subgroup A0. On day 14, this parameter in subgroup A1 was significantly lower as compared to subgroup A0, but significantly higher than in subgroup B1. It should be noted that i.p. injections of enalaprilat, increased a death rate of animals of both groups. The use of enalaprilat, starting from the preclinical period of the ROP development, led to a decrease in the activity of the renin-angiotensin system (RAS) in ROP animals at the onset of retinopathy in the experimental model used. This opens up prospects for considering enalaprilat as a means of preventing the development of this pathology; however, the recognized high toxicity of the drug requires further studies and correction of the timing of its administration and dosage in order to achieve a balance of efficacy and safety of use in order to prevent the development of ROP in children.

Key words: retinopathy of prematurity; experimental model; prevention; enalaprilat

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INTRODUCTION

Retinopathy of prematurity (ROP) is a leading cause of visual impairment in children worldwide for several decades [1, 2]. In Russia ROP ranks as the 3rd-4th leading cause of visual disability (per 10,000 child population) [3]. It was originally described in the 40s of the last century. Since that time the clinical “portrait” of ROP has changed with the development of ophthalmic and neonatal services: from retrolental fibroplasia to zone I ROP. To date, significant success has been achieved in the monitoring and treatment of “classic forms” of ROP. The main tasks facing researchers and clinicians include the study of pathogenesis, optimization of screening and increase in the frequency of favorable anatomical and functional outcomes of severe forms of ROP that develop in very preterm infants with extremely low birth weight [4-7]. Since these forms of ROP are often resistant to conventional laser coagulation of the retina, the efficacy and safety of anti-VEGF therapy still need further active study. One of the important issues is the search for ways to prevent the development and progression of ROP, which is based on the study of the role of various molecular agents in the induction of abnormal vasoproliferation.

The pathogenetic significance of a wide range of pro- and anti-angiogenic factors in the development of various vasoproliferative ophthalmopathology is the subject of research by scientists around the world. Most of these factors are polyfunctional molecules, the predominant properties of which at a particular moment are determined by the tissue in which they are located, the receptors with which they interact, and interaction with other factors. This interaction has a complex multilevel character and is capable of changing the agent activity vector to the opposite direction.

In the context of problems related to pathological vasoproliferation, the angiogenic properties of the renin-angiotensin system (RAS) attract much attention due to the main function of this system is the regulation of blood pressure and tissue perfusion [8]. There is evidence that its key vasoactive peptide angiotensin II (AT-II) also has a pronounced vasoproliferative activity, which is realized through various mechanisms, including vascular endothelial growth factor (VEGF) mediated [9, 10]. In a series of our experimental and clinical studies, an increased content of AT-II at the local and systemic levels was revealed precisely at the stage of induction of the pathological process [11]. The data obtained formed the basis for the assumption about the possible protective role of drugs that reduce the concentration of AT-II, in particular angiotensin-converting enzyme (ACE) inhibitors, and about the prospects for their use to prevent the development of pathological vasoproliferation in ROP.

One of the widely used ACE inhibitors in clinical practice is enalaprilat, which is a derivative of two amino acids — L-alanine and L-proline. Its effect on the RAS is manifested in an increase in plasma renin activity (due to the elimination of negative feedback in response to renin release) and a decrease in aldosterone secretion. Since ACE is identical to the kininase II enzyme, enalaprilat can also block the destruction of bradykinin, a peptide with a pronounced vasodilating effect, which underlies the active use of enalaprilat for the treatment of primary arterial hypertension of any severity and renovascular hypertension, as well as for the treatment or prevention of heart failure [12-14].

At this stage of the research, the goal of our work was to study the safety of using the ACE inhibitor enalaprilat in a rat model of experimental ROP, as well as its effect on the level of ACE and AT-II in the vitreous body and retina of rat pups with ROP.

MATERIALS AND METHODS

The study was performed on 136 newborn Wistar rat pups. Animals were divided into 2 groups: group A — experimental groups (animals with ROP, n=64) and group B — control group (n=72). The ROP model was developed by us in the course of previous studies [15]: in order to reproduce the pathology, newborn rat pups were placed in an incubator for 14 days together with the female who gave birth to them. Every 12 h, the oxygen concentration in the incubator was changed from 60% to 15% by switching the oxygen concentrator on and off. Rats of the control group from the moment of birth were under conditions with normal oxygen content (21%).

Animals of the experimental and control groups were divided into 2 subgroups: (i) A0 and B0 (n=32 and n=36, respectively): animals that did not receive enalaprilat injections, (ii) A1 and B1 (n=32 and n=36, respectively): animals treated with enalaprilat injections from the second to the seventh or fourteenth days of life (depending on the period of withdrawal from the experiment); enalaprilat (Enap-R, KRKA, Slovenia) was injected intraperitoneally (i.p.) at a dose of 0.6 mg/kg of body weight.

Animals of all subgroups were kept at constant temperature (26°C) and light (12 h day, 12 h night) regimes throughout the experiment.

Animals of all subgroups were taken out of the experiment on the day 7 (half of the total number of animals of each subgroup) and day 14 (the second half of the animals) by cervical dislocation.

All animals underwent binocular enucleation at the indicated time. The eyeball was opened along the limbus, the cornea and lens were removed along with the remnants of the persistent vascular bag and hyaloid artery, and vitreous samples were taken using filter paper strips, which were weighed before and after sampling. The eye cup was then placed in cold saline and the retina was isolated. The components of the vitreous body were eluted with 0.05 M phosphate buffer, pH 7.4 (1:20, by weight), and centrifuged for 10 min at 3000 *g*. The supernatant was collected, frozen, and stored at -70°C until the study.

Each retina was placed in 200 μl of cold lysis buffer (Lysis buffer-3, Cloud-Clone Corp., USA), homogenized using an UP50H ultrasonic homogenizer (Hielsher, Germany) for 15 s (amplitude 122 μm, 125 V/cm^2), centrifuged for 10 min at 3000 *g*, the supernatant was collected, frozen, and stored at -70°C until the study.

In samples of the vitreous body and retina, the content of ACE and AT-II was determined by enzyme immunoassay using ELISA kits for Angiotensin I Converting Enzyme and ELISA kits for Angiotensin-II (Cloud-Clone Corp.). The concentration of total protein was determined by the Lowry method [16]. The optical density of the samples was determined using a multifunctional photometer for microplates Synergy MX (BioTek, USA).

The choice of the particular terms for conducting biochemical studies was due to the primary focus of this part of the work on the prevention of the development of the pathological process, which could be carried out at the preclinical stage of the development of the disease. According to previous studies, peripheral avascular zones of the retina were determined on day 7 of the experiment, both in the experimental and control groups of animals; on day 14 the process of normal retinal vascularization completed in the animals of the control group, while the experimental animals had the initial stage of pathological neoangiogenesis [15].

Statistical processing of the results was carried out using statistical packages Microsoft Excel and Statistica. The significance of differences between groups with a significance level of at least 95% was assessed using the nonparametric Mann-Whitney U-test.

RESULTS AND DISCUSSION

The course of enalaprilat administration was accompanied by a high death rate of animals of both groups. Until day 14 of the experiment, only 25-50% of the pups from the experimental group and about 75% of the pups of the control group survived. The most frequent period of death was 4-5 days of life. In subgroups A0 and B0, all animals were alive throughout the experiment.

The ACE Level in the Vitreous Body

On day 7 of the experiment, the ACE level in the vitreous body in animals of subgroup A0 tended to increase as compared to the animals of subgroup B0. On day 14, the increase in the content of ACE in the vitreous body in subgroup A0 reached the level of statistical significance (p=0.0005) (Fig. 1).

The data obtained indicate the involvement of RAS in the pathogenesis of ROP, particularly, in the induction of pathological angiogenesis; this confirms the data obtained in our earlier studies [11].

On day 7 in animals of subgroups A1 and B1, the level of ACE in the vitreous body did not differ from that in animals of subgroups A0 and B0, respectively. On day 14, this parameter in both subgroups of animals treated with enalaprilat (A1 and B1) was significantly lower than in animals of subgroups A0 and B0, respectively (p=0.034 for subgroup A0 and p=0.0014 for subgroup B0) (Fig. 1).

The Level of AT-II in the Vitreous Body

Analysis of the AT-II level in the vitreous body confirmed our earlier data on its potential role in the induction of pathological angiogenesis in ROP [11]. On day 7 its content increased in animals of subgroup A0, as compared to subgroup B0 ($p \leq 0.05$). However, unlike ACE, on day 14 of the experiment, this difference disappeared due to the increase of this parameter in subgroup B0 (Fig. 2).

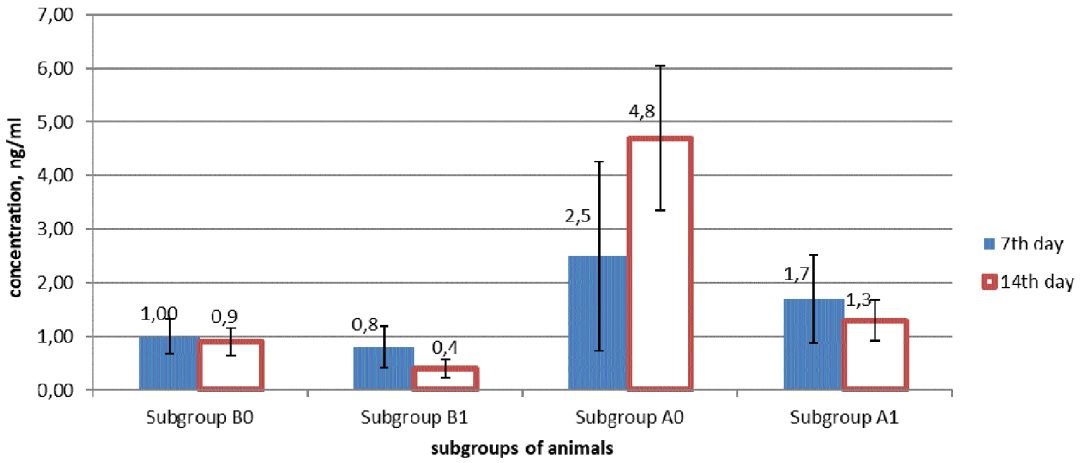

Figure 1. The concentration of ACE in the vitreous body of rat pups (ng/ml).

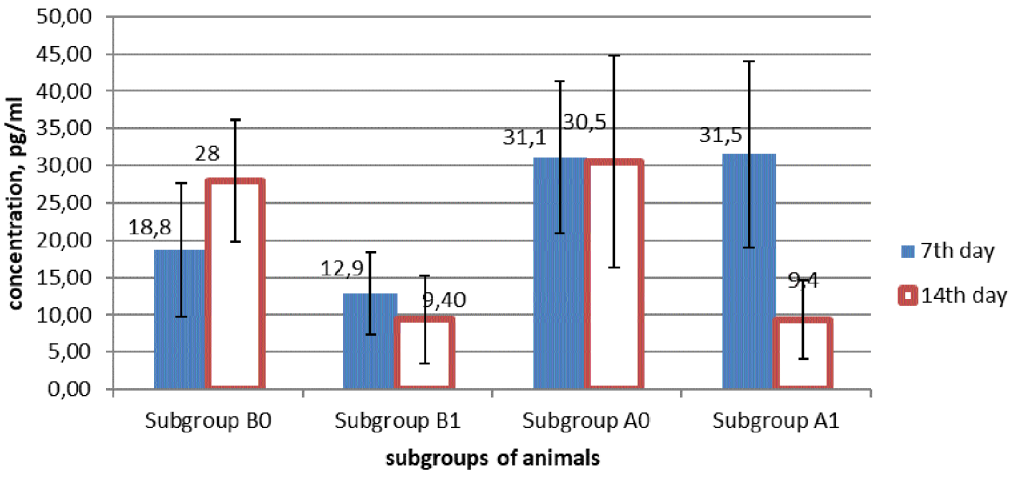

Figure 2. The concentration of AT-II in the vitreous body of rat pups (pg/ml).

Probably, in subgroup B0 animals maturation is accompanied by expected consumption of ACE for the physiological production of AT-II; this explains the obtained dynamics of the parameters studied. In subgroup A0, by the time of onset of pathological vascularization development, regulatory mechanisms are impaired and the key RAS reaction (synthesis of AT-II with the help of ACE) begins to function under conditions of peak concentrations of its components. In this context, it seems promising to study the content of other RAS components to assess the level of imbalance of all its components.

On day 7 of the experiment, the level of AT-II in the vitreous body in animals of subgroups A1 and B1 basically did not differ from the level in animals of subgroups A0 and B0, respectively, while on day 14 of the experiment, this parameter decreased in subgroups A1 and B1 as compared with subgroups A0 and B0, respectively (p=0.011 for subgroups B0 and B1, p=0.0054 for subgroups A0 and A1) (Fig. 2).

Thus, the data obtained indicate that the systemic use of the ACE inhibitor leads to a blockade of the increase of the ACE level and to a significant decrease in AT-II in the vitreous body of animals with ROP by the critical time for the development of retinopathy, the time of the onset of pathological neovascularization. This may indicate the presence of the effect of "accumulation" of the activity of the drug and makes it relevant to study its effect at later time intervals.

The Level of ACE in the Retina

On day 7 of the experiment, the level of ACE in the retina of rat pups of subgroups A0 and B0 did not differ significantly. On day 14, in animals of subgroup B0, there was a tendency to its increase, while in subgroup A0, there was a downward trend, which made the difference between the groups statistically significant by this time interval (p=0.0016) (Fig. 3).

On day 7, the ACE level in the retina of animals of subgroup B1 did not differ significantly from subgroup B0, and in subgroup A1 it tended to increase as compared the subgroup A0. On day 14, its level in animals of subgroups A1 and B1 significantly decreased as compared with animals of subgroups A0 and B0, respectively (p=0.0014 for subgroups B0 and B1, p=0.031 for subgroups A0 and A1) (Fig. 3).

The Level of AT-II in the Retina

The level of AT-II in the retina of animals of subgroup A0 was significantly higher than in animals of subgroup B0 both on day 7 (p=0.008) and on day 14 (p=0.004). This confirms the results of our previous study (Fig. 4).

In the retina of animals of subgroup B1, there was a tendency to decrease in the level of AT-II compared to subgroup B0 observed both on day 7 and day 14. In animals of subgroup A1 on day 7, the concentration of AT-II, as well as the concentration of ACE, was increased as compared to animals of subgroup A0 (p=0.008). On day 14, in animals of subgroup A1, this parameter was significantly lower than in animals of subgroup A0 (p=0.046) and significantly higher than in animals of subgroup B1 (p=0.004) (Fig. 4).

The discorrelation of the level and dynamics of parameters found in the vitreous body and retina of animals can be explained by the fact that a significant source of various RAS factors in the vitreous body is the systemic blood flow: they enter the vitreal cavity from the hyaloid artery functioning at a given time in the development of animals. The local RAS functions in the retina and the synthesis of its components occurs independently.

Analysis of the level of the studied parameters in the retina of animals treated with enalaprilat injections requires a very cautious approach, since the activity of the drug may be limited due to the presence of the blood-retinal barrier. Although the blood-retinal barrier demonstrates its inferiority and failure during the ROP development [17], however, the degree of its permeability for each specific molecule at each specific period of development certainly requires further investigation.

CONCLUSIONS

The involvement of RAS components in the pathogenesis of various diseases, not directly related to the regulation of vascular tone but related to the polyfunctionality of its components, particularly, AT-II, made it relevant to study the effects of pharmacological agents that affect RAS activity and their applicability for the treatment and prevention of these pathological conditions. In the context of ROP, ACE inhibitors and AT1 receptor blockers significantly reduced VEGF-A expression during disease progression [9, 18]. Using an experimental model of ROP, it has been shown that under conditions of intravitreal administration of the AT1 receptor antagonist valsartan, there was a significantly higher survival rate of retinal astrocytes, improved revascularization of the retina, and suppression of preretinal neovascularization. This led to the conclusion that AT1 receptor blockers have a protective effect on glial cells and blood vessels in experimental ROP [19].

In our study, the use of enalaprilat, starting from the preclinical period of the ROP development, led to a decrease in RAS activity in rat pups with ROP at the critical period of retinopathy development (the onset of the disease in the experimental model used). This opens up broad prospects for considering it as a means of preventing the development of this disease.

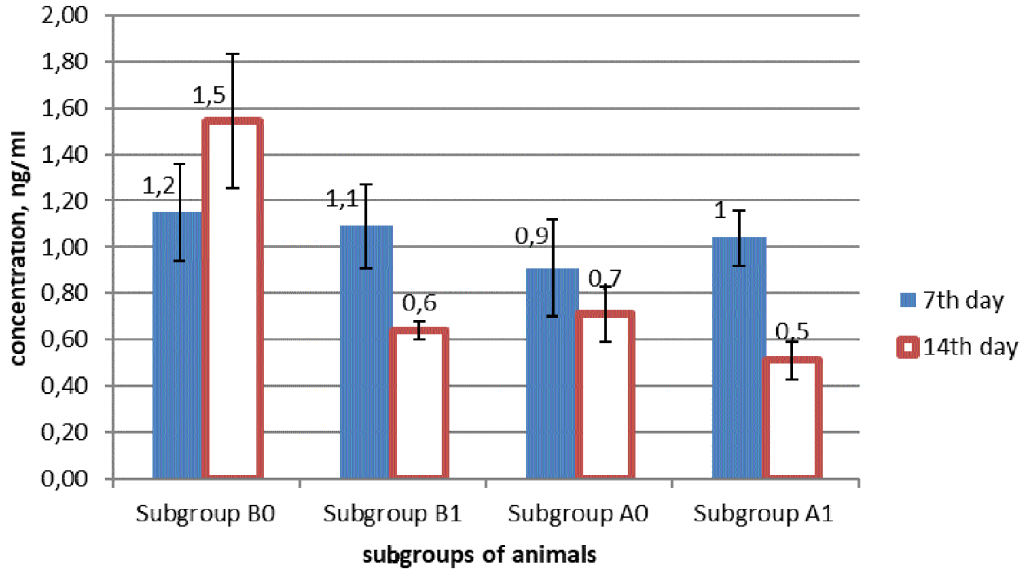

Figure 3. The concentration of ACE in the retina of rat pups (ng/mg of protein).

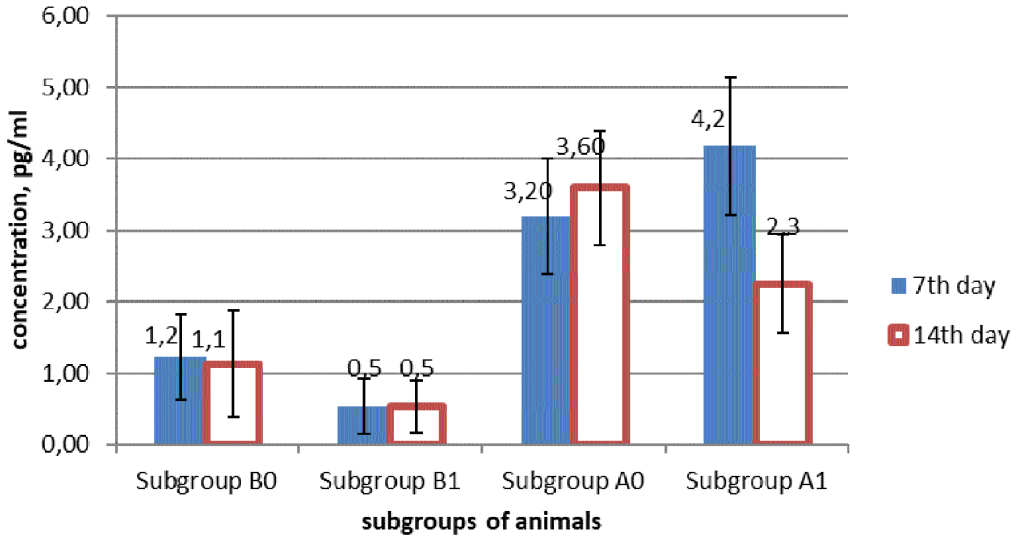

Figure 4. The concentration of AT-II in the retina of rat pups (pg/mg of protein).

However, the high toxicity of enalaprilat recognized in this study indicates that this drug suppresses not only pathological neovascularization during the ROP development, but can also have a negative effect on the normal growth of blood vessels in other immature organs of newborn rat pups, and obviously, cause significant, incompatible with life hemodynamic changes.

In this regard, we plan to continue this work and optimize the timing of drug administration and its dosage in order to achieve a balance between the effectiveness and safety of its use in order to prevent the development of ROP in children.

COMPLIANCE WITH ETHICAL STANDARDS

The study was carried out in accordance with GOST 53434-2009 dated 02.12.2009 "Principles of Good Laboratory Practice GLP", by the Decree of the Chief State Physician of the Russian Federation no. 51 dated August 29, 2014 "On approval of SP 2.2.1.3218-14 "Sanitary and epidemiological requirements for the device, equipment, and the maintenance of experimental biological clinics (vivariums)"", Federal Law no. 61-FZ of April 12, 2010 "On the circulation of medicines". The study protocol was approved by the local ethical committee.

FUNDING

The study was performed without external funding.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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ЭНАЛАПРИЛАТ КАК НОВОЕ СРЕДСТВО ПРОФИЛАКТИКИ РАЗВИТИЯ РЕТИНОПАТИИ НЕДОНОШЕННЫХ

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На крысиной модели экспериментальной ретинопатии недоношенных (ЭРН) изучена безопасность применения эналаприлата и его влияние на уровень ангиотензин-превращающего фермента (АПФ) и ангиотензина-II (АТ-II) в стекловидном теле и сетчатке. Исследование выполнено на 136 новорожденных крысятах породы Wistar, разделённых на 2 группы: группа А — опытная (животные с ЭРН, n=64) и группа Б — контрольная (n=72). Каждая из указанных групп была разделена на 2 подгруппы: А0 и Б0 (n=32 и n=36 соответственно) — животные, не получавшие инъекции эналаприлата, и А1 и Б1 (n=32 и n=36 соответственно) — животные, которым со вторых по седьмые или четырнадцатые сутки жизни (в зависимости от сроков выведения из эксперимента) ежедневно интраперитонеально вводили эналаприлат (0,6 мг/кг веса). Животных выводили из эксперимента на седьмые и четырнадцатые сутки. В образцах стекловидного тела и сетчатки определяли содержание АПФ и АТ-II методом иммуноферментного анализа. На седьмые сутки в подгруппах А1 и Б1 уровни АПФ и АТ-II в стекловидном теле не отличались, а на четырнадцатые сутки были ниже, чем в подгруппах А0 и Б0 соответственно. Динамика показателей в сетчатке несколько отличалась от динамики показателей в стекловидном теле. На седьмые сутки уровень АПФ в сетчатке животных подгруппы Б1 существенно не отличался от подгруппы Б0, а в подгруппе А1 был повышен по сравнению с подгруппой А0. На четырнадцатые сутки было отмечено его значимое снижение в подгруппах А1 и Б1 по сравнению с подгруппами А0 и Б0. В то же время уровень АТ-II в сетчатке крысят подгруппы Б1 и на седьмые, и на четырнадцатые сутки был ниже, чем в подгруппе Б0. В подгруппе А1 на седьмые сутки концентрация АТ-II, также как и концентрация АПФ, была повышена по сравнению с подгруппой А0. На четырнадцатые сутки в подгруппе А1 данный показатель был достоверно ниже по сравнению с подгруппой А0, но достоверно выше, чем в подгруппе Б1. Важно отметить, что на фоне интраперитонеальных инъекций эналаприлата была отмечена высокая гибель животных обеих групп. Применение эналаприлата, начиная с доклинического срока развития ЭРН, приводит к снижению активности ренин-ангиотензиновой системы (РАС) у животных с ЭРН на сроке дебюта ретинопатии в используемой экспериментальной модели. Это открывает перспективы для рассмотрения его в качестве средства профилактики развития данной патологии, однако выявленная высокая токсичность препарата требует продолжения работы и проведения коррекции сроков его введения и дозировки для достижения баланса эффективности и безопасности применения с целью профилактики развития ретинопатии у детей.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: ретинопатия недоношенных; экспериментальная модель; профилактика; эналаприлат

Финансирование. Исследование проведено без использования источников внешнего финансирования.

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