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V. L. Povh, N. V. Zaichko, A. V. Melnyk, O. A. Khodakivskiy
M. PYROHOV VINNYTSIA NATIONAL MEDICAL UNIVERSITY

ASSOCIATION OF NEURORETINA DESTRUCTION MARKERS WITH RETINAL LEVEL OF HYDROGEN SULFIDE IN TRAUMATIC INJURY OF THE VISUAL ANALYZER

Introduction. *Glutamate exitotoxicity plays a leading role in damaging of the visual analyzer of traumatic genesis. As it was shown recently, hydrogen sulfide (H_2S) system is involved in the regulation of neurotransmission, ophthalmotonus and retinal injury, but its role in the pathogenesis of post-traumatic injury of the visual analyzer has not been clarified.*

The aim of the study *– to evaluate the association of neuroretinal destruction markers with retinal level of hydrogen sulfide in experimental traumatic injury of the visual analyzer.*

Research Methods. *Experiments were carried out on 24 male rabbits weighing 3.0–3.9 kg. Traumatic injury of visual analyzer in rabbits was caused by the action of carbon dioxide stream under pressure on the cornea of the eye. The levels of H_2S, glutamate, cytometric markers of apoptosis in the retina, and the levels of neuron specific enolase (NSE) and S100 protein in the blood serum were determined.*

Results and Discussion. *Traumatic injury of the visual analyzer in the rabbits was characterized by increase levels of NSE neuronal markers and S100 protein in serum, and increase in glutamate level and the number of cells in the SUB-G0G1 phase (apoptotic marker) in the retina during 24 hours, followed by the escalation of neuroretinodestruction signs in 7 days. After 24 hours after the injury, increase of H_2S level (2-times) was observed in retina, but in 7 days its level was significantly decreased (4-times). Formation of H_2S deficiency in retina was associated with aggravation of glutamate excitotoxicity and neuroretinal destruction signs.*

Conclusions. *Thus, H_2S system is involved in the mechanisms of retina injury in case of contusive eye trauma. H_2S level correction in the retina may be a promising strategy in traumatic injury to the visual analyzer and this direction is appropriate for further study.*

KEY WORDS: **visual analyzer; contusion; hydrogen sulfide; neuroretinal destruction.**

INTRODUCTION. Various injury of the visual analyzer is a significant medical and social problem due to the increasing prevalence and complexity of treatment [1]. In particular, in the United States annually, about 2.5 million people receive traumatic eye injury with subsequent blindness [2]. Traumatic injury of the visual analyzer is accompanied by the development of retina ganglion cells destruction, which is the main cause of visual impairment. Among the molecular mechanisms of retinal injury the following can be distinguished: glutamate exitotoxicity, inflammation, oxidative and nitrosative stress, apoptosis and endoplasmic reticulum stress [3, 4]. It has been shown recently that hydrogen sulfide system (H_2S) is involved in the regulation of neurotransmission, ophthalmotonus and retinal injury [5]. In the retina production of H_2S from L-cysteine occurs involving cystationine β-synthase, cystationione γ-lyase, and 3-mercaptopyruvate sulfurtransferase [5, 6]. The role of H_2S system in visual analyzer injury pathogenesis is still controversial. Thus, *in vivo* experiments, in the ischemic injury of retina there was increase in H_2S production and of cystathionine-β-synthase expression [7], and in glaucoma there was decrease in H_2S level and H_2S-synthesizing enzymes expression, respectively [6]. Neuroretinoprotective effect of H_2S donor (NaHS) in glaucoma has been experimentally confirmed [6]. Therefore, the study of the role of H_2S system in traumatic injury to the visual analyzer is expedient.

The aim of the study – to evaluate the association of neuroretinal destruction markers with retinal level of hydrogen sulfide in experimental traumatic injury of the visual analyzer.

RESEARCH METHODS. Experiments were carried out on 24 Chinchilla male rabbits weighing

3.0–3.9 kg. The animals were kept in the standard conditions of vivarium of VNMU, water and food was received ad libitum, and were divided into groups of 6 animals in each. During the work with the animals, bioethical norms were observed in accordance with the First National Congress of Bioethics of Ukraine (Kyiv, 2001), the provisions of the "European Convention on the Protection of Vertebrate Animals" (Strasbourg, 1986), the Law of Ukraine No. 3447-IV dated February 21, 2006 "On the Protection of Animals from ill-treatment" as certified by VNMU Bioethics Commission (protocol No. 8 dated 09.10.2016). All traumatic manipulations and euthanasia of animals were performed under propofol anesthesia (60 mg/kg intraperitoneally).

Contusion of the eye in rabbits was caused by the action of carbon dioxide under pressure, which was created by a single blank shot of a pneumatic pistol close to the center of the cornea of the eye [8]. After 24 hours and 7 days after the pathology modeling, enucleation was performed, the eyeballs were washed with 1.15 % KCl (4-8 °C) cooled solution, conjunctiva and muscles were eliminated, the anterior part of the eye and the lens were removed, the rest was screwed in, so that the eye bottom can be seen and the parts of the retina were removed. To determine H_2S content, the retina was perfused with a cold 1.15 % KCl solution, homogenized for 1–2 min. in a cooled medium of 0.01 M NaOH in the ratio of 1:5 (mass / volume) at 3000 rpm (Teflon-glass). To 1 ml of homogenate 250 µl of 50 % CCl_3COOH was added, centrifuged at 3000 rpm for 15 min, supernatant was taken. Content of H_2S was determined by reaction with N, N-dimethyl-p-phenylenediamine sulfate [9]. Content of glutamate was determined by thin-layer chromatography [10]. Protein content in retinal homogenates was determined by the microbiuretic method [11]. DNA content in reticulum cells nuclei of rabbits was determined by flow cytometry using the multifunctional "Partec PAS" cytometer (Partec, Germany). Retinal cell nucleus suspensions were obtained using kits for nuclear DNA analysis CyStain DNA Step 1 and CyStain DNA Step 2 (Partec, Germany). The activity of apoptosis was estimated by the number of cells in SUB-G0G1 phase (with signs of DNA fragmentation). In the blood serum, the content of neuron specific enolase (NSE, EC 4.2.1.11) was determined by "NSE ELISA KIT" (DAI, USA) and S100 protein by "S100 ELISA KIT" (Fujirebio Diagnostics Inc., Sweden).

Statistical analysis was carried out using statistical software MS Excel, SPSS22 for Windows, "STATISTICA 6.0". The Student's t-test and the Mann-Whitney U criterion were used to detect differences between groups. A value of $p<0.05$ was considered to indicate a statistically significantly difference.

RESULTS AND DISCUSSION. Direct external injury of the eyeball caused by high-speed impact is usually accompanied by violations of hemodynamics and hydrodynamics of eye, hemorrhages, massive alteration and necrobiotic changes in eye tissues, development of neuroretinopathy in post-traumatic period. The study of biochemical markers of neuroretinodestruction – levels of NSE and protein S100 in animals with traumatic injury to the visual analyzer showed their significant increase in the acute and subacute post-contusion period (Fig. 1). 24 hours after eye contusion in experimental rabbits, NSE level (marker of membrane integrity of neurons) was significantly 43.4 times higher than in intact animals ($p<0.001$). In acute post-contusion period, similar increase in NSE level in-

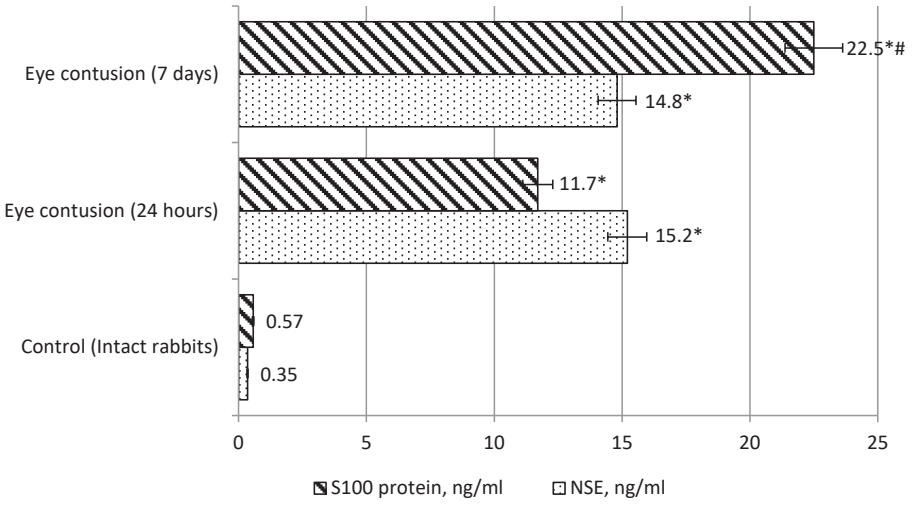

Fig. 1. Level of neuronspecific enolase and S100 protein in rabbits' serum with model eye contusion (n=8, M±m). The reliability of the differences relatively to the group of intact rabbits – * ($p<0.001$); relatively to the group with eye contusion 24 hours – # ($p<0.05$).

dicates the development of significant degeneration of neurons in ganglionic layers of retina (neuronecrosis). On the 7th day after the eye injury, NSE level was 42.3 times higher than in intact animals ($p<0.001$), which may indicate persistence of intense necrobiotic processes in neuronal cellular elements of retina and optic nerve. Traumatic injury to the visual analyzer was characterized by a significant increase of S100 protein level in the blood serum in the acute period (20.5 times), with subsequent significant increase on the 7th day of the post-contusion period – 38.8 times relatively to the intact animals and 1,92 times relatively the state on the first day. Such dynamics of S100 protein indicates the activation of neuroglial cells initially in response to irreversible primary alteration with further progression of proliferative processes in retina against the backdrop of secondary alteration, hemodynamic and hydrodynamic disturbances.

Pathobiochemical basis of neuronal cells death, including ones in retina, is the phenomenon of glutamate exitotoxicity. Glutamate is a primary retinal neurotransmitter which extracellular accumulation causes hyperactivation of ionotropic glutamate receptors (AMPA and NMDA) with subsequent uncontrolled Ca^{2+} arrival in post-synaptic neurons and initiation of apoptotic cell death. Traumatic injury to the visual analyzer is associated with a significant initial alteration of cellular and subcellular structures, which leads to an increase of extracellular glutamate levels with the development of glutamate exitotoxicity. The results of our studies have shown (Fig. 2) that in acute period (24 hours after contusion), glutamate content in retina of the animal eye increased 2,02 times relatively to intact rabbits ($p<0.001$). 7 days after eye contusion, there was more significant increase in the content of glutamate in retina – 2.42 times in relation to intact animals and 1.2 times in relation to the state 24 hours after the injury.

In traumatic injury of the visual analyzer, death of cellular elements of retina in acute period is mainly realized by necrosis. At the same time, release of proinflammatory and proapoptic mediators from the dead cells induces apoptotic processes in the remained cellular elements. The ratio of necrosis/apoptosis processes is a significant determinant of the traumatic injury of the visual analyzer during the post-contusion period. Cytometric evaluation of apoptotic activity in retina of the eye in rabbits with a model contusion of the eye revealed a significant increase of the pool of cells that were in SUB-G0G1 phase at different times of the experiment (Fig. 3). This rate of DNA fragmentation in experimental animals 24 hours later exceeded that in the intact animals 14.6 times, and on the 7th day – 10 times ($p<0.01$). On the 7th day, the percentage of retinal cells in SUB-G0G1 phase was lower than on the 1st day after eye contusion, but these differences did not reach the limit of reliability.

The level of H_2S in retina of intact rabbits was 3.31 (95 % CI 2.63–4.28) nmol/mg protein. Significant primary injury of retinal neurons was accompanied by increase in H_2S level in retina in 1.88 times 24 hours after the contusive eye injury (Fig. 4). However, on the 7th day, H_2S content decreased in 4.03 times compared to 24 hours state ($p<0.01$). In addition, on the 7th day, H_2S level was 2.14 times lower than in the control. H_2S level in retina inversely correlated with the parameters of neuroretinodestruction – levels of NSE, S100 protein in the blood and the level of glutamate in retina ($r=-0.65$; -0.68; -0.72; $p<0.05$).

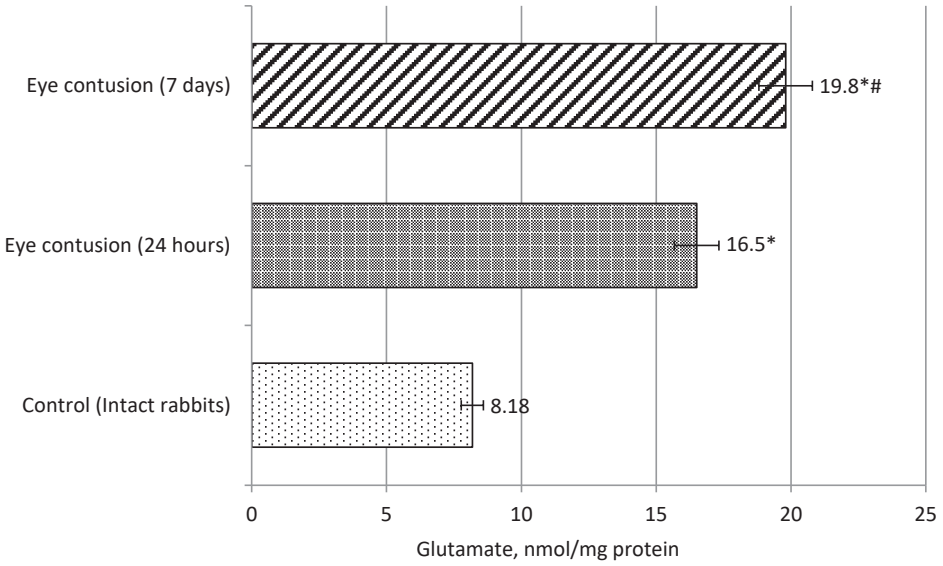

Fig. 2. Level of glutamate in retina of rabbits with model eye contusion (n=6–8, M±m). The reliability of the differences relatively to the group of intact rabbits – * ($p<0.001$); relatively to the group with eye contusion 24 hours – # ($p<0.05$).

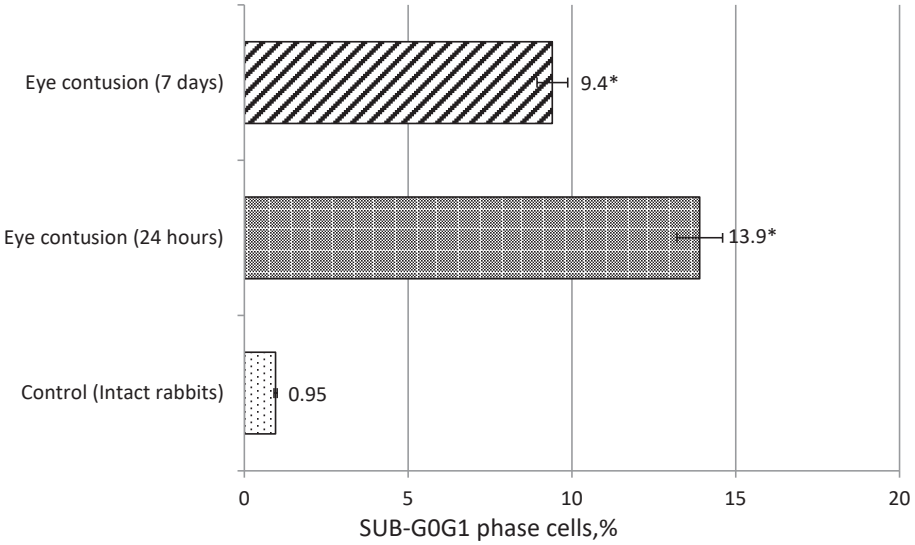

Fig. 3. Relative number of retinal cells in SUB-G0G1 phase in rabbits with model eye contusion (n=5, M±m). The reliability of the differences relatively to intact rabbits – * (p<0.01).

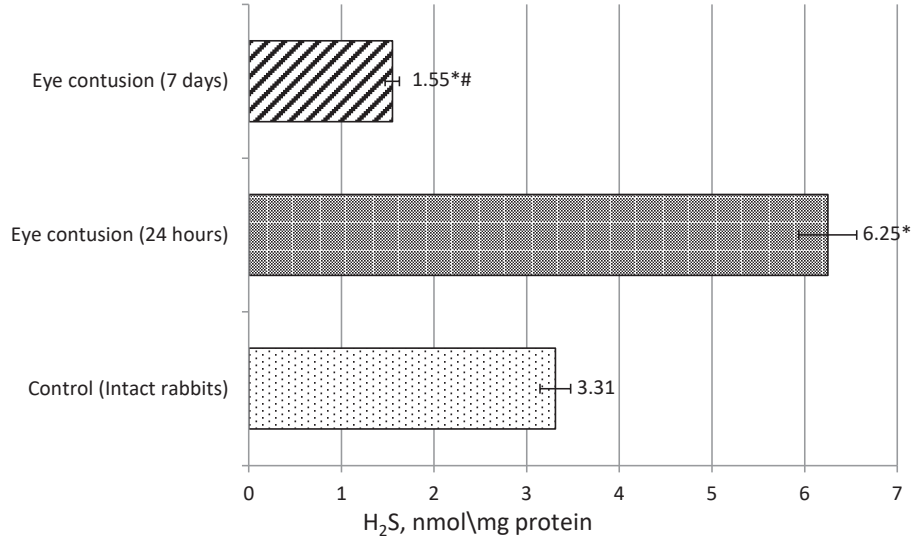

Fig. 4. H_2S level in retina of rabbits with model eye contusion (n=6–8, M±m). The reliability of the differences relatively the group of intact rabbits – * (p<0.01); relatively to the group of eye contusion 24 hours – # (p<0.05).

Thus, H_2S system is involved in the mechanisms of neuroretina destruction in the case of a contusive eye injury. Obviously, increase in H_2S level 24 hours after the eye injury may have a compensatory effect, while progression of post-contusion retinal destruction is associated with the formation of H_2S deficiency. As it is known, in physiological concentrations H_2S has cytoprotective, anti-inflammatory and anti-apoptotic effect, while at high concentrations it produces the opposite effect [12, 13]. H_2S is capable of modulating NMDA receptors activity by S-sulfhydration / desulfhydration [12, 14]. In glutamate-induced exitotoxicity, H_2S neuroprotective effect is mostly associated with cystine-glutamate transporter activation, cysteine concentration increase and glutathione synthesis activation in neurons and astrocytes [14]. Correcting of H_2S level in retina may prove to be a promising strategy in traumatic injury to the visual analyzer and this direction is appropriate for further research.

CONCLUSIONS. 1. The injury of the visual analyzer of traumatic genesis in rabbits is characterized by a significant increase of NSE and S100 protein levels in serum, and in retina of the eye – an increase of glutamate level and the number of cells in SUB-G0G1 phase (apoptotic marker) during the first day with the subsequent escalation of neuroretina destruction signs in 7 days.

2. Traumatic injury to the visual analyzer was characterized by an increase of H_2S level in retina 24 hours after contusion with further decrease of its level (2 times) in 7 days. Formation of H_2S deficiency in retina was significantly associated with aggravation of glutamate excitotoxicity and post-traumatic eye injury.

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В. Л. Повх, Н. В. Заічко, А. В. Мельник, О. А. Ходаківський
ВІННИЦЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ М. І. ПИРОГОВА

ЗВ'ЯЗОК МАРКЕРІВ НЕЙРОРЕТИНОДЕСТРУКЦІЇ З РІВНЕМ ГІДРОГЕН СУЛЬФІДУ В СІТКІВЦІ ПРИ ТРАВМАТИЧНОМУ УРАЖЕННІ ЗОРОВОГО АНАЛІЗАТОРА

Резюме

Вступ. *Глутаматна ексайтотоксичність відіграє провідну роль в ураженні зорового аналізатора травматичного генезу. Нещодавно було засвідчено, що до регуляції нейротрансмісії, офтальмотонусу та нейроретинодеструкції залучена система гідроген сульфіду (H_2S), однак її роль у патогенезі посттравматичного ушкодження зорового аналізатора не з'ясовано.*

Мета дослідження *– оцінити зв'язок маркерів нейроретинодеструкції з рівнем гідроген сульфіду в сітківці при травматичному ураженні зорового аналізатора у кролів.*

Методи дослідження. *Досліди проведено на 24 кролях-самцях масою 3,0–3,9 кг. Травматичне ураження зорового аналізатора у тварин викликали дією потоку вуглекислого газу під тиском на рогівку ока. У сітківці ока визначали рівень H_2S, глутамату, цитометричні маркери апоптозу, в сироватці крові – рівень нейронспецифічної енолази (NSE) та білка S100.*

Результати й обговорення. *Травматичне ураження зорового аналізатора у кролів характеризувалось підвищенням у сироватці крові рівня маркерів нейродеструкції NSE та білка S100, а в сітківці ока – збільшенням рівня глутамату та кількості клітин у фазу SUB-G0G1 (маркера апоптозу) впродовж 24 год із подальшою ескалацією ознак нейроретинодеструкції через 7 діб. Через 24 год після травмування в сітківці спостерігали зростання рівня H_2S (у 2 рази), а через 7 діб цей показник достовірно знизився (в 4 рази). Формування дефіциту H_2S у сітківці асоціювалось із поглибленням ознак глутаматної ексайтотоксичності та нейроретинодеструкції.*

Висновки. *Система H_2S залучена в механізми ушкодження сітківки за умов контузійної травми ока. Корекція рівня H_2S у сітківці може виявитись перспективною стратегією за травматичного ушкодження зорового аналізатора, і цей напрямок є доцільним для подальшого вивчення.*

КЛЮЧОВІ СЛОВА: **зоровий аналізатор; контузія; гідроген сульфід; нейроретинодеструкція.**

В. Л. Повх, Н. В. Заичко, А. В. Мельник, А. А. Ходаковский
ВИННИЦКИЙ НАЦИОНАЛЬНЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ ИМЕНИ Н. И. ПИРОГОВА

СВЯЗЬ МАРКЕРОВ НЕЙРОРЕТИНОДЕСТРУКЦИИ С УРОВНЕМ ГИДРОГЕН СУЛЬФИДА В СЕТЧАТКЕ ПРИ ТРАВМАТИЧЕСКОМ ПОРАЖЕНИИ ЗРИТЕЛЬНОГО АНАЛИЗАТОРА

Резюме

Вступление. *Глутаматная эксайтотоксичность играет ведущую роль в поражении зрительного анализатора травматического генеза. Недавно было показано, что в регуляции нейротрансмиссии, офтальмотонуса и нейроретинодеструкции принимает участие система гироген сульфида (H_2S), однако ее роль в патогенезе посттравматического повреждения зрительного анализатора не выяснена.*

Цель исследования *– оценить связь маркеров нейроретинодеструкции с уровнем гидроген сульфида в сетчатке при травматическом поражении зрительного анализатора у кроликов.*

Методы исследования. *Опыты проведены на 24 кроликах-самцах массой 3,0–3,9 кг. Травматическое поражение зрительного анализатора у животных вызывали действием потока углекислого газа под давлением на роговицу глаза. В сетчатке глаза определяли уровень H_2S, глутамата, цитометрические маркеры апоптоза, в сыворотке крови – уровень нейронспецифической энолазы (NSE) и белка S100.*

Результаты и обсуждение. *Травматическое поражение зрительного анализатора у кроликов характеризовалось повышением в сыворотке крови уровня маркеров нейродеструкции NSE и белка S100, а в сетчатке глаза – увеличением уровня глутамата и количества клеток в фазе SUB-G0G1 (маркера апоптоза) в течение 24 ч с дальнейшей эскалацией признаков нейроретинодеструкции через 7 суток. Через 24 ч после травмирования в сетчатке наблюдали возрастание уровня H_2S (в 2 раза), а через 7 суток этот показатель достоверно снизился (в 4 раза). Формирование дефицита H_2S в сетчатке ассоциировалось с усилением признаков глутаматной эксайтотоксичности и нейроретинодеструкции.*

Выводы. *Система H_2S вовлечена в механизмы повреждения сетчатки в условиях контузионной травмы глаза. Коррекция уровня H_2S в сетчатке может оказаться перспективной стратегией при травматическом повреждении зрительного анализатора, и это направление целесообразно для дальнейшего изучения.*

КЛЮЧЕВЫЕ СЛОВА: **зрительный анализатор; контузия; гидроген сульфид; нейроретинодеструкция.**

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Address for correspondence: *V. L. Povh, M. Pyrohov Vinnytsia National Medical University, Pyrohov Street, 56, Vinnytsia, 21018, Ukraine, e-mail: biochem@vnmu.edu.ua.*