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CHANGES IN STATE OF THE THIOL LINKAGES OF AN ANTIOXIDANT SYSTEM DURING ISCHEMIA AND REPERFUSION, AGAINST A BACKGROUND OF VASCULAR EXCLUSION IN THE RAT LIVER

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ИЗМЕНЕНИЯ СОСТОЯНИЯ ТИОЛОВОГО ЗВЕНА АНТИОКСИДАНТНОЙ СИСТЕМЫ В ИШЕМИЧЕСКИЙ И РАННИЙ РЕПЕРФУЗИОННЫЙ ПЕРИОДЫ ПРИ ВАСКУЛЯРНОЙ ЭКСКЛЮЗИИ ПЕЧЕНИ КРЫС

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The dynamic activities of glutathione reductase (GR) and glutathione peroxidase (GPO), as well as the concentration of reduced glutathione (GSH), were examined at both the organ and systemic levels in a liver ischemia-reperfusion model. Samples were collected at 5 min intervals from rats (n=95) during a 20 min ischemic

period and after 20 min reperfusion. There was an adaptive increase (30–50 %) in GR activity and GSH concentration in erythrocytes during the ischemic period. Within 10 min of ischemia, there was a 1.5- to 2-fold decrease in all parameters measured in the liver tissue. Liver reperfusion was accompanied by greater decreases in GR and GPO activities, as well as increased GSH concentrations, in the erythrocytes. In liver tissue, against the background of increased oxygen toxicity, there was a 2- to 3-fold increase in GPO activity. GSH concentration and the GR activity remain decreased during 10 min reperfusion but then returned to control levels. These findings provide information about the pathogenesis of ischemic reperfusion and also illustrate pathobiochemical links that are potentially subject to beneficial metabolic correction.

Keywords: ischemia-reperfusion syndrome, liver, antioxidant system, glutathione

Изучена динамика активности глутатионредуктазы (ГР), глутатионпероксидазы (ГПО) и концентрации восстановленного глутатиона (GSH) на органном и системном уровнях при ишемически-реперфузионном поражении печени. Были сформированы группы крыс (n=95), биологический материал которых забирался с интервалом 5 минут в течение 20 минут ишемического периода и 20 минут после восстановления кровотока. Установлено адаптивное увеличение на 30–50 % активности ГР и концентрации GSH эритроцитов в ишемический период. В ткани печени в течение 10 минут ишемии наблюдалось снижение в 1,5–2 раза всех изученных показателей. Реперфузия печени сопровождалась выраженным увеличением активности ГР и ГПО с увеличением концентрации GSH в эритроцитах. На фоне относительной гипероксии в ткани печени наблюдалось увеличение активности ГПО в 2–3 раза. Концентрация GSH и активность ГР в течение 10 минут реперфузии оставались сниженными с последующей нормализацией. Полученные данные расширяют представления о патогенезе ишемически-реперфузионных нарушений, показывая чувствительные патобиохимические звенья, воздействие на которые является перспективным для метаболической коррекции.

Ключевые слова: ишемически-реперфузионный синдром, печень, антиоксидантная система, глутатион

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HDL – Hepatic–Duodenal Ligament
GPO – Glutathione Peroxidase
GR – Glutathione Reductase

GSH – Reduced Glutathione
NADPH – Nicotinamide Adenine Dinucleotide Phosphate Reconstituted

Prevention and treatment of acute ischemia and reperfusion induced injuries in organs are among the most urgent challenges in modern medicine. Reasons include the widespread prevalence of cardiovascular disease and of surgical interventions, including transplantations, requiring that organs be temporarily disconnected from the systemic blood supply. There is much accumulated information on the mechanisms of development of liver damage under acute ischemia. A study of effects of hepatic-duodenal ligament (HDL) clamping procedures in the liver showed ultrastructural changes in the endoplasmic reticulum and mitochondria, and the severity of such changes correlated with duration of vascular isolation of the organ [1]. There have been many animal studies examining changes in biochemical parameters during experimental ischemia-reperfusion induced liver damage [1–4]. However, a holistic picture of the pathobiochemistry of the hypoxic pathology of the hepatobiliary zone is still lacking. Such studies would be necessary to understand in detail the compensatory capabilities of various humoral homeostatic regulatory systems [4, 5] to identify new directions for metabolic correction of the effects of hypoxia and reperfusion in livers that are temporarily isolated from systemic blood flow [6–8].

The aim of our study was to describe dynamics of the activities of glutathione reductase (GR) and glutathione

peroxidase (GPO), as well as the concentration of reduced glutathione (GSH), at both organ and systemic levels in an experimental model of liver ischemia-reperfusion injury.

Material and Methods. The study was performed with 95 white nonlinear adult male rats weighing 240–280 g, maintained in the vivarium of Kuban State Medical University. The studies were performed in accordance with the «Rules Adopted in the European Convention for the Protection of Vertebrate Animals» (Strasbourg, 1986) and were approved by the local ethical committee of the Federal State Educational Establishment of Health Care at the Kubmin Medical Center of the Ministry of Health of the Russian Federation (Minutes № 51 of May 23, 2017). All painful manipulations were performed under general anesthesia with Zoletil 100 (Virbac Sante Animale, Carros Cedux, France), given intramuscularly at 10 mg/kg.

Animals were divided into groups and biological samples collected at 5 min intervals during a 20 min ischemic period and, subsequently, for 20 min after restoration of blood flow. Ischemic liver damage was induced by clamping the HDL, using a vascular clamp, after performing a mid-laparotomy. Because blood and liver samples were repeatedly taken from the same animals, groups of control rats were included to assess effects of blood loss or liver damage caused by partial resection. In these control rats, samples were taken at the same time intervals, but there was no HDL clamping. Blood samples of 150 µl each were collected from the caudal hollow

vein in syringes with 10–15 μ l sodium heparin. Animals in the first control group (n=12) had blood sampled 5, 10 and 15 min after the laparotomy. Animals in the second control group (n=10) had blood sampled 5, 10, 15 and 20 min after the laparotomy. Animals in the first test group (n=15), after mid-laparotomy, underwent HDL clamping for 15 min with blood sampling at 5, 10 and 15 minutes after the onset of ischemia. Animals in the second test group (n=14) underwent 15 min HDL clamping, with blood sampling at 5, 10, 15 and 20 min after restoration of blood flow. To assess changes at the organ level, liver sampling was performed on four similar groups. At each time point, a liver sample weighing 150–200 mg was removed from each rat by partial resection. The site of resection was then electrocoagulated. Animals in the third control group (n=10) had liver samples taken at 5, 10, 15 and 20 min after the laparotomy. Those in the fourth control group (n=10) had liver samples taken at 5, 10, 15 and 20 min later, at 20 min after the laparotomy. Animals in the third test group (n=12), after mid-laparotomy, underwent HDL clamping for 20 min with liver tissue sampling at 5, 10, 15 and 20 min of ischemia. Animals in the fourth experimental group (n=12) underwent HDL clamping for 20 min, with liver sampling at 5, 10, 15 and 20 min of reperfusion.

To assess changes in the enzymes affecting thiol moieties in the antioxidant systems of erythrocytes and liver tissue, GPO and GR activities were measured. GPO activity was assayed based on the glutathione oxidation rate in a reaction with tert-butyl hydroperoxide. GR activity was assessed based on the rate of NADPH consumption during reduction of the oxidized form of glutathione [9]. The content of reduced glutathione (GSH) in erythrocyte suspensions and liver homogenates was determined by its reaction with dithiobisnitrobenzoic acid, after deproteinization of the sample with sulfosalicylic acid. In the liver homogenates, protein concentrations were determined by the Bradford method using Coomassie dye [10] and calculations of enzymatic activities and GSH concentrations were expressed per g homogenate protein.

Data were statistically analyzed using a Stat plus LE (AnalystSoft Inc., Walnut, CA, USA). The data were expressed using median (Me) and 25th and 75th percentile ratio (p0.25/p0.75) values. Mann-Whitney criteria were used to assess differences among groups. The Wilcoxon test was used to assess differences among animals in the same group. Differences at $p < 0.05$ were considered to be significant.

Results and Discussion. To assess the dynamics of antioxidant balance dysregulation in ischemia-reperfusion induced liver damage, the state of thiol groups, among the most sensitive regulators of redox homeostasis, was determined. The major intracellular thiol containing compound is glutathione. Therefore, the concentration of its reduced form, GSH, and the activities of its metabolizing enzymes were determined. These enzymes were GR, which regenerates the oxidized form of glutathione, and GPO, which uses the thiol group of GSH to reduce various substrates, including organic peroxides [11–12].

These results showed several changes in components of the glutathione system, at both the systemic and organ levels. The GSH concentration was elevated by 20–40 % (2.4 μ mol/ml), compared with controls, in erythrocyte suspensions from venous blood during the ischemic period, with the most noticeable effect detectable at 5 min HDL clamping. During the reperfusion period, GSH concentration continued to increase slightly, by 10–20 % (2.8 μ mol/ml), compared with during the ischemic period

(Fig. 1). It is likely that 15 min isolation of the liver from systemic blood flow was not sufficient to cause serious damage to the metabolic systems in the blood. The increased GSH concentrations during the reperfusion period might be associated with a washing out of the lysed hepatocytes, especially because the highest GSH concentrations were reported in lens and liver tissues [11, 12]. In the liver homogenates, meanwhile, decreased GSH concentrations were observed in our study. The lowest GSH level (1.8 μ mol/g) was observed during the ischemic period, when GSH levels were 2- to 3-fold lower than in controls. After restoration of the liver blood supply, GSH concentrations were immediately markedly increased, to only 15 % below control values (3.7 μ mol/g) within 5 min (Fig. 2). The temporary decrease in GSH concentration at 10 min reperfusion was attributable to significant fluctuations in this parameter soon after blood flow restoration, related to its direct participation in regulation of redox homeostasis and the relative hyperoxia of the liver during reperfusion.

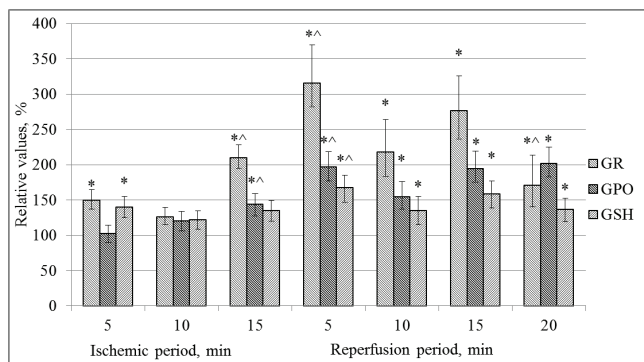


Fig. 1. Changes in activities of thiol antioxidant defense enzymes and in reduced glutathione concentrations in erythrocyte suspensions from a rat liver ischemia-reperfusion model (Me (p0.25/p0.75)). * – significant differences ($p < 0.05$) from corresponding control group values; ^ – significant differences ($p < 0.05$) between two parameters, determined within a 5 min interval of ischemia-reperfusion. (Values of the control group parameters are expressed as 100 %)

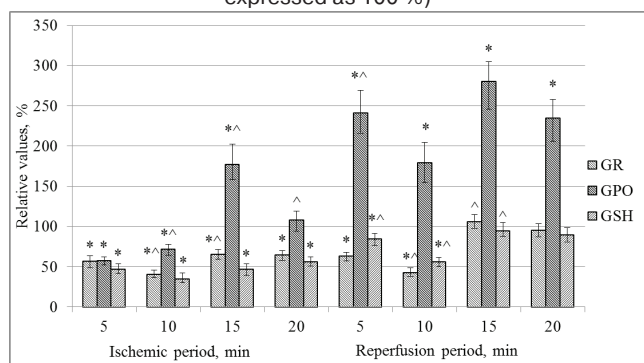


Fig. 2. Changes in activities of thiol antioxidant defense enzymes and in reduced glutathione concentrations in liver homogenates during ischemia-reperfusion induced injury (Me (p0.25 / p0.75)) * – significant differences ($p < 0.05$) from corresponding control group values; ^ – significant differences ($p < 0.05$) between two parameters, determined within a 5 min interval of ischemia-reperfusion. (Values of the control group parameters are expressed as 100 %)

Activities of the glutathione metabolism enzymes were also variable in blood and liver tissue. GR activity in erythrocyte suspensions showed a slight tendency to increase during the ischemic period, by 50 % at 5 min and

up to 2-fold (592 $\mu\text{mol}/\text{min}/\text{ml}$) at 15 min HDL clamping. Perhaps this is a mechanism for ensuring maintenance of high GSH levels, to avoid disruption of glucose metabolism in erythrocytes and enable sufficient reaction rates in the pentose phosphate pathway. During the reperfusion period, GR activity was even more increased, up to 3-fold (1044 $\mu\text{mol}/\text{min}/\text{ml}$), compared with in the corresponding control group, by 5 min, an effect that would further increase GSH concentration. Later, at 10–20 min reperfusion, GR activity remained elevated 1.5- to 2.5-fold, compared with in the controls. GR activity in erythrocytes at 5–10 min during the ischemic period remained at the control level (841 $\mu\text{mol}/\text{min}/\text{ml}$), possibly because there was no need to neutralize the active forms of oxygen at this stage of the pathological process. GPO activity in the erythrocyte suspensions after 15 min HDL was increased by 44 % above that in the control group. During the reperfusion period, against a background of expected increases in free radical levels, GPO activity was doubled (1820 $\mu\text{mol}/\text{min}/\text{ml}$), relative to controls and remained elevated for at least 20 min.

GR activity in liver homogenates showed a decreasing trend during ischemia, so by 5 min ischemia its activity was 1.8-fold lower (493 $\mu\text{mol}/\text{min}/\text{g}$) than in the control group and by 10 min it was 2.5-fold lower. During the reperfusion period, GR activity remained low for the first 5–10 min, 1.6- to 2.3-fold below control values, but it was gradually increased to control values at 15–20 min (580–660 $\mu\text{mol}/\text{min}/\text{g}$). The decrease in GR activity during the ischemic period may have been caused by a redirection of glucose metabolism towards anaerobic glycolysis, with decreased involvement of the pentose phosphate pathway, while production of reduced coenzymes used for the regeneration of the oxidized form of glutathione was decreased. During such conditions of hypoxia, maintaining an adequate energy supply may be prioritized over the activities of detoxification and antioxidant enzymes. However, this may lead to further progression of oxidative disorders during the reperfusion period. GPO activity during the first 5–10 min of HDL clamping was significantly lower, by 30–40 % (480 $\mu\text{mol}/\text{min}/\text{g}$) than in the control but it was subsequently increased, reaching levels 70 % higher than control at 15 min ischemia. This effect might have been caused by an increased demand for utilization of organic peroxides. It is well known that vascular isolation is not accompanied by a drop in oxygen partial pressure in the tissue to zero. Thus, residual oxygen in the organ and oxygen delivered

by collateral circulation, when there is also a disturbance in energy metabolism, may be converted to free radicals and other reactive molecules. During the reperfusion period, as expected, GPO activity in liver homogenates was dramatically increased at 5 min after restoration of blood supply to the organ. At this time, GPO activity was increased 2.4-fold (2117 $\mu\text{mol}/\text{min}/\text{g}$) compared with control values, reaching a maximum 2.8-fold elevation after 15 min reperfusion. Significant differences in activity at different times during reperfusion could be caused by large fluctuations of GPO activity. Such variability, also a characteristic of GR activity and GSH concentration, was attributable to dynamic metabolic changes combined with a sudden restoration of blood flow. The characteristic metabolic changes during reperfusion reflect mechanisms by which the antioxidant system can maintain redox homeostasis in response to increased free radicals and relative hyperoxia, including through adaptive changes in the glutathione system.

Conclusions. These findings increase understanding of the dynamics of pathobiochemical changes during development of ischemia–reperfusion induced liver injury. This study showed development of an adaptive enhancement of the thiol moieties of the blood antioxidant system during ischemia, as manifested by increased GR activity and GSH concentration. In the liver tissue during the first 5–10 min ischemia, slightly decreased GR and GPO activities, as well as a lower GSH content, was observed. Such effects were probably caused by an initial attenuation of oxidative processes resulting from decreased oxygen partial pressure in the tissue. During the later periods of ischemia (15–20 min), GPO activity was increased in liver homogenates, an effect likely accompanied by increased generation of reactive oxygen species, attributable to an imbalance in use of the remaining oxygen in the organ, including that supplied by collateral circulation. Restoration of the blood supply to the liver was accompanied by even more pronounced adaptive changes in the blood glutathione system, including even greater increases in GR and GPO activities and in GSH concentration. In the liver tissue, an abrupt GPO response was observed, with a 2- to 3-fold increase in activity. GSH concentration and GR activity remained low during the first 10 min reperfusion, but were subsequently restored to control values. This reflected transition of metabolic systems to maintain the pro-oxidant-antioxidant balance.

Disclosures:

The authors declare no conflict of interest.

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DRUG INDUCED PATOMORPHOSIS IN PARODONT AND ENVIRONMENTAL BONE TISSUE IN EXPERIMENTAL USE OF CORTICOSTEROIDS

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ЛЕКАРСТВЕННЫЙ ПАТОМОРФОЗ В ПАРОДОНТЕ И ОКРУЖАЮЩЕЙ КОСТНОЙ ТКАНИ ПОД ВОЗДЕЙСТВИЕМ КОРТИКОСТЕРОИДОВ В ЭКСПЕРИМЕНТАЛЬНЫХ УСЛОВИЯХ

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This study was undertaken to evaluate the structure of bone and soft tissues of the rabbit oral cavity during and after long-term corticosteroid therapy. Osteoporotic changes in bone tissue were noted from the 12th day after the beginning of the experiment and progressed to the 30th day of the use of glucocorticoids. Dentin and tooth enamel were resistant to the action of the hormone. After the abolition of the 30-day course of hydrocortisone, normal structures were restored by day 16, and by the end of the experiment (day 30), there were no pathological changes in the bone or soft tissues of the teeth. Subsequently, the predentin zone was restored. These changes in bone tissue after the cessation of limiting therapy are reversible, which indicates the need for a more critical attitude towards those patients taking corticosteroids as an anti-inflammatory therapy.

Keywords: corticosteroid therapy, osteoporosis, bone tissue