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Characteristics of lipid peroxidation processes and factors of the antioxidant defense system in chronic atrophic gastritis and gastric cancer

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ABSTRACT

Background. The problem of gastric cancer remains unresolved throughout the world, while chronic atrophic gastritis (CAG) increases the likelihood of its development by 15 times. In the Russian Federation, the incidence of gastric cancer (GC) is among the highest, with it prevailing among males. One of the leading mechanisms in molecular pathology of membranes is lipid peroxidation (LPO). The severity of oxidative membrane damage depends on concomitant diseases, contributing to emergence and progression of pathological processes and development of cancer. Currently, the problem of LPO is unsolved in biological systems.

The aim of this study was to investigate the state of LPO and antioxidant defense system in CAG and GC.

Materials and methods. The parameters were studied in 45 patients with CAG and 50 patients with GC. The control group included 50 practically healthy volunteers without gastrointestinal complaints, who did not have changes in the gastric mucosa according to the fibroesophagogastroduodenoscopy (FEGDS) findings.

Results. In patients with CAG, an increase in malondialdehyde, superoxide dismutase, catalase, glutathione S-transferase, and glutathione peroxidase was found in the blood plasma compared with the control group. In patients with CAG, lipid peroxidation was activated, and the malondialdehyde level increased by 3.5 times relative to normal values. At the same time, the body fought against oxidative stress by increasing the activity of antioxidant enzymes, such as superoxide dismutase, catalase, glutathione S-transferase, and glutathione peroxidase. All patients with GC showed pronounced oxidative stress in the blood plasma in the form of a 45-fold increase in malondialdehyde. The activity of the main antioxidant enzyme superoxide dismutase was reduced in GC. Catalase was activated, which indicated pronounced oxidative stress, significant damage to blood vessels, and massive cell death. Glutathione-related enzymes (glutathione S-transferase and glutathione peroxidase) and the antioxidant protein ceruloplasmin were activated, which also indicated significant oxidative stress and severe intoxication in patients with GC.

Conclusion. Depending on the stage and type of cancer, an in-depth study of lipid peroxidation and factors of the antioxidant defense system can be used to correct therapy and prevent cancer and can serve as markers of progression and prognosis in gastric cancer.

Key words: chronic gastritis, gastric cancer, chemiluminescent activity of neutrophil granulocytes, Eastern Siberia.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All individuals signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at the Federal Research Center "Krasnoyarsk Science Center of the Siberian Branch of the Russian Academy of Sciences" (Protocol No. 4 of 02.08.2019).

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Характеристика процессов липопероксидации и факторов системы антиоксидантной защиты при хроническом атрофическом гастрите и раке желудка

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РЕЗЮМЕ

Актуальность. Проблема рака желудка является нерешенной во всем мире, при этом хронический атрофический гастрит (ХАГ) повышает вероятность его развития в 15 раз. В России показатели заболеваемости раком желудка (РЖ) – одни из самых высоких, мужская заболеваемость здесь лидирует. Одним из ведущих механизмов молекулярной патологии мембран является перекисное окисление липидов (ПОЛ). Выраженность окислительной деструкции мембран зависит от сопутствующих заболеваний, способствуя возникновению и прогрессированию патологических процессов, развитию онкологического заболевания. В настоящее время проблема ПОЛ является нерешенной в биологических системах.

Целью настоящего исследования явилось изучение состояния ПОЛ и антиоксидантной защиты при ХАГ и РЖ.

Материалы и методы. Изучены показатели у 45 пациентов с ХАГ и 50 больных РЖ. Контрольная группа представлена 50 практически здоровыми добровольцами, не имеющими гастроэнтерологических жалоб, у которых отсутствовали изменения слизистой оболочки желудка по результатам фиброэзофагогастродуоденоскопии.

Результаты. У больных ХАГ в плазме крови обнаруживалось увеличение малонового диальдегида, активности супероксиддисмутазы, каталазы, глутатион-S-трансферазы, глутатионпероксидазы относительно контрольной группы. У больных ХАГ происходит активация перекисного окисления липидов, увеличение малонового диальдегида в 3,5 раза относительно нормальных величин. При этом сам организм борется с окислительным стрессом, увеличивая активность антиоксидантных ферментов (супероксиддисмутазы, каталазы, глутатион-S-трансферазы, глутатионпероксидазы). У всех больных РЖ в плазме крови выявлялся выраженный окислительный стресс в виде повышения в 45 раз малонового диальдегида. Активность основного фермента антиоксидантной защиты (супероксиддисмутазы) снижена при РЖ. Активирована каталаза, которая свидетельствует о выраженном окислительном стрессе и значительном повреждении сосудов, о массовом клеточном распаде. Активны ферменты глутатионового звена (глутатион-S-трансфераза и глутатионпероксидаза), антиоксидантный белок (церулоплазмин), которые также указывают на значительный окислительный стресс и выраженный интоксикационный синдром у больных РЖ.

Заключение. Углубленное изучение процессов перекисного окисления липидов и факторов системы антиоксидантной защиты в зависимости от стадии онкопроцесса и типов рака может использоваться для коррекции терапии и профилактики онкозаболеваний, а также в качестве маркеров прогрессирования и прогноза рака желудка.

Ключевые слова: хронический гастрит, рак желудка, хемилюминесцентная активность нейтрофильных гранулоцитов, Восточная Сибирь.

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

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INTRODUCTION

The problem of gastric cancer (GC) remains unresolved all over the world, while chronic atrophic gastritis increases the likelihood of its development by 15 times. In the Russian Federation, the incidence rate of GC is among the highest, with it prevailing among men [1–3]. Low survival rates are due to late diagnosis of a malignant disease and low treatment efficiency at the end stages of the disease. GC is characterized by regional variability; the disease is 2 times more common in the Far East, Eastern Siberia, and the North of the European part of Russia [4, 5]. One of the leading mechanisms in the molecular pathology of membranes is lipid peroxidation (LPO). The severity of oxidative damage to membranes depends on concomitant diseases, contributing to the emergence and progression of pathological processes and development of cancer. Currently, the problem of LPO is unsolved in biological systems. According to the Correa cascade, a precancerous condition of the stomach (chronic atrophic gastritis) associated with *Helicobacter pylori* infection can advance to GC (adenocarcinoma) [6–8]. Atrophic changes in the gastric mucosa trigger membrane destruction, and produced reactive oxygen species (ROS) contribute to oxidative damage to tissues, enhancing lipid peroxidation in cell membranes [9–11]. The role of toxic products of LPO and free radicals in the development of chronic oxidative stress and advancement of the disease to GC is not excluded. Progression of the malignant disease aggravates disorders in LPO and antioxidant defense (AOD) systems, reduces tumor resistance in patients with GC, and causes the emergence of histotoxic hypoxia, disorders of tissue respiration, and an increase in LPO products, closing the vicious pathogenetic circle [12–14].

The aim of this study was to research the state of lipid peroxidation and antioxidant defense systems in chronic atrophic gastritis and gastric cancer.

MATERIALS AND METHODS

The parameters were studied in 45 patients with chronic atrophic gastritis (CAG) and 50 patients with gastric cancer (GC). The control group encompassed 50 practically healthy volunteers who did not have gastroenterological complaints or changes in the gastric mucosa (GM) according to the results of fibroesophagogastroduodenoscopy. The study was approved by the local Ethics Committee at the Federal Research Center of the KSC SB RAS (Protocol No. 4 of 02.08.2019). All ethical principles imposed by Art. 24 of the Constitution of the Russian Federation and the Declaration of Helsinki by the World Medical Association were observed in the study. Each participant confirmed that they take part in the study voluntarily by signing a voluntary informed consent to participate in the study.

The diagnosis of CAG was verified according to the clinical data, medical history data, fibroesophagogastroduodenoscopy, and morphological examination of the mucous membrane of the greater and lesser curvature of the stomach using the updated Sydney System. Diagnosis of GC was carried out by oncologists at Krasnoyarsk Regional Oncology Dispensary, taking into account the full range of instrumental and morphological examination. This study included patients with GC associated with *Helicobacter pylori* infection and adenocarcinoma as a histological variant of the tumor.

The material of the study was venous blood which was drawn from the cubital vein in the morning, from 8 to 9 o'clock, on an empty stomach, upon admission of the patient to the hospital before

the start of pathogen-specific therapy. The presence of *H. pylori* was detected in all patients included in the study by ELISA to determine the titer of specific IgG antibodies to the *H. pylori* CagA antigen. If the titer of antibodies to *H. pylori* corresponded to 30 EIU or more, it was assessed as a positive result. If the antibody titer was less than 30 EIU, it was assessed as a negative result.

In addition, for chronic atrophic gastritis, serological diagnosis was performed to determine pepsinogens in the blood serum. The diagnosis of severe CAG of the gastric mucosa was made when the level of pepsinogen-1 was less than 25 μg/l and the value of the pepsinogen-1/pepsinogen-2 ratio was less than 3. The final diagnosis was always verified by the results of a morphological examination of the gastric mucosa (GM).

In the blood serum, spectrophotometric methods were used to determine the LPO-AOD parameters: malondialdehyde, activity of glutathione S-transferase, glutathione peroxidase, superoxide dismutase, catalase, and ceruloplasmin. The ratio of pro- and antioxidant factors was used to calculate an integral coefficient of individual oxidative stress assessment (coefficient of oxidative stress – COS).

$$COS = \frac{(DC_i/DC_n) \times (KD \text{ and } CT_i/KD \text{ and } CT_n) \times (TBA - AP_i/TBA - AP_n)}{(SOD_i/SOD_n \times (GSH_i/GSH_n) \times (\alpha - \text{tocopherol}_i/\alpha - \text{tocopherol}_n/) \times (\text{retinol}_i/\text{retinol}_n)}$$

where *i* – the levels of the parameter in the examined patients; *n* – the level of the parameter in the control group. With COS> 1, the development of oxidative stress was recorded.

Statistical analysis of the results was carried out using the Statistica for Windows 8.0 (StatSoft Inc., USA, 2008) and Microsoft Excel, 2007 (Microsoft, USA) software packages [15]. Nonparametric data were determined: the median and the interquartile range *Me* (C_{25} – C_{75}). Statistically significant differences were established using the Mann – Whitney test. The critical level of statistical significance when testing scientific hypotheses was considered equal to $p < 0.05$.

RESULTS

We studied the features of LPO and AOD systems in the blood plasma of patients with CAG and GC. The level of malondialdehyde indicated the severity of oxidative stress in the blood plasma. The products of LPO are opposed by the activity of antioxidant enzymes (superoxide dismutase (SOD), catalase, glutathione S-transferase, glutathione peroxidase) and the effect of the antioxidant protein ceruloplasmin.

The median plasma concentration of malondialdehyde in patients with CAG and GC increased relative to the control group (Table). An increase in the median concentration of malondialdehyde in the plasma was found in patients with GC (adenocarcinoma) compared with patients with CAG. Malondialdehyde is considered the end product of LPO and is a parameter of LPO processes triggered in cells by free radicals and ROS. Malondialdehyde, being an active compound, can react with proteins, carbohydrates, and nucleic acids, and the formed complexes reduce their biological activity.

Lipoprotein particles (very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL)) are a necessary component of LPO in the blood. Altered lipoproteins damage the endothelial lining of blood vessels, contributing to the development of atherosclerosis. A significant increase in MDA in the blood plasma of patients with CAG and GC indicates excessive formation of ROS, which become an altering factor in the vascular endothelium.

The median plasma superoxide dismutase concentration increased in CAG patients in comparison with the control group. In contrast, in the patients with GC, a decrease in the median concentration of superoxide dismutase was found compared with the CAG. Superoxide dismutase is the most important enzyme of the antioxidant defense system; at the stage of one-electron oxygen reduction, it interrupts the chain of free-radical processes at its inception with the formation of a superoxide anion radical. The extracellular SOD isoform is active in the blood plasma. As a rule, an increase in its activity indicates an increase in the number of free radicals and reactive oxygen species in the intercellular fluid. Excessive production of this enzyme is due to increased activity of glial cells and fibroblasts.

The median concentration of catalase in the blood plasma increased in the patients with CAG and GC compared with the control group. Significant catalase activity indicated damage to the endothelium of blood vessels following oxidative stress.

Table

Parameters of pro- and antioxidant systems in the blood plasma in patients with chronic atrophic gastritis and gastric cancer compared with the control group, *Me* (C_{25}–C_{75})

Parameter	Control, *n* = 50 (1)	CAG, *n* = 45 (2)	GC, *n* = 50 (3)
MDA, μmol / 1 g protein	1.6 (0.96–2.24)	5.24 (4.38–5.88) $p_{1-2} < 0.001$	56.35(32.46–101.74) $p_{1-3} < 0.001$; $p_{2-3} < 0.001$
SOD, units / min / 1 g protein	204.41 (151.05–250.32)	570.5 (314–670.8) $p_{1-2} < 0.001$	235.2 (133.7–462.27) $p_{2-3} < 0.001$
CAT, μmol / s / 1 g protein	0.27 (0.16–0.39)	0.66 (0.42–0.71) $p_{1-2} = 0.03$	0.87 (0.67–1.01) $p_{1-3} = 0.02$
GST, mmol / min / 1 g protein	41.3 (37.7–42.64)	70.6 (63.5–105.7) $p_{1-2} < 0.001$	83.5 (79.3–110.6) $p_{1-3} < 0.001$
GPO, μmol / 1 g protein	105.9 (81.19–162.38)	177.5 (150.1–236.05) $p_{1-2} = 0.007$	168.6 (158.7–211.5) $p_{1-3} = 0.05$
CP, mg / l	192.5 (157.5–227.0)	149.6 (113.7–189.8)	375.8 (282.9–826.06) $p_{1-3} < 0.001$; $p_{2-3} < 0.001$

Note: statistically significant differences between the CAG patients and the control group – $p_{1-2,}$ between the GC patients and the control group – $p_{1-3,}$ between the CAG patients and the GC patients – $p_{2-3.}$

Catalase lacks an extracellular isoform, therefore, its high activity in the blood plasma is due to massive cell death, which proves histodestruction in CAG and GC.

Glutathione in the antioxidant defense system acts against endotoxicosis. The median concentration of glutathione S-transferase in the plasma in the patients with CAG and GC increased compared with the control group. In the patients with CAG and GC, the median concentration of glutathione S-transferase in the plasma was significantly higher than in the control group, as was the median concentration of glutathione peroxidase. Probably, the increased activity of these enzymes indicates the severity of intoxication, the presence of oxidative stress, and insufficient effectiveness of the antioxidant defense system in patients with CAG and GC.

The median ceruloplasmin level in the patients with GC was significantly elevated compared with all other studied groups, which proves an increase in oxidative stress in GC following the combined effect of various pathogenetic factors. Ceruloplasmin is an essential antioxidant copper-containing glycoprotein with ferroxidase and superoxide-removing activity. The protein ceruloplasmin inhibits superoxide and ferritin-dependent lipid peroxidation in lipoprotein particles of the blood plasma. According to the ratio of pro- and antioxidant components, COS was calculated for chronic atrophic gastritis (3.5) and for gastric cancer (45).

DISCUSSION

In the patients with CAG, an increase in malondialdehyde, superoxide dismutase, catalase, glutathione S-transferase, and glutathione peroxidase activity was found in the blood plasma compared with the control group. Thus, in the patients with CAG, lipid peroxidation was activated, and malondialdehyde increased by 3.5 times compared with normal values. At the same time, the body fought against oxidative stress by increasing the activity of antioxidant enzymes (superoxide dismutase, catalase, glutathione S-transferase, and glutathione peroxidase). Parameters of LPO and AOD in CAG prove the presence of cell destruction in the gastric mucosa infected with *Helicobacter pylori*.

All patients with GC showed pronounced oxidative stress in the blood plasma in the form of a 45-fold increase in the content of malondialdehyde. The activity of superoxide dismutase was reduced in GC. Activated catalase indicated massive cell death and significant vascular damage. Glutathione-related enzymes (glutathione S-transferase and glutathione peroxidase) and the antioxidant protein ceruloplasmin, which also combat oxidative stress and severe intoxication in GC patients, were activated. In patients with GC, multidirectional shifts in the activity of the antioxidant system enzymes were revealed. Compared with CAG, the activity of the main enzyme superoxide dismutase was reduced, which reflects the classic version of the peroxide theory of

carcinogenesis [16] with inhibition of antioxidant enzymes.

The effect of antioxidant defense enzymes in GC has ambiguous changes: the activity of superoxide dismutase decreases, while the activity of the second line of defense (glutathione S-transferase and glutathione peroxidase) increases. Most likely, these processes are associated with the fact that an increase in the ROS level causes depletion of the enzymatic activity of AOD. ROS attack thiol proteins through interaction with the protein SH-group, changing their structural modification. These proteins are the key enzymes in the metabolism of nucleotides, carbohydrates, and the antiradical defense system (glutathione-related enzymes). This modification enhances the formation of the superoxide anion radical, therefore, ROS formation only increases.

In GC, hypoxia enhancing nitrate reductase activity is observed in the cell. Increased NO synthesis reacts with excess amount of superoxide anion radical to form peroxynitrite, causing the formation of carcinogenic nitrosamines. The resulting products interfere with apoptosis of tumor cells and enhance their metastasis. The tumor process in GC is associated with increased production of ROS, which at high concentrations can irreversibly damage tumor cells, while they themselves contribute to tumor progression. Strengthening the processes of free radical oxidation of membrane lipids and their interaction with LPO products lead to changes in lipid and protein domains. All this contributes to malignant transformation, invasiveness, uncontrolled tumor growth and metastasis [17] and affects the state of the antioxidant system enzymes, which are crucial for the malignant process [18, 19]. Therefore, in patients with GC, an imbalance of antiradical defense system is found, which contributes to better survival of tumor cells and tumor progression.

The activation of free radical oxidation is proved by the obtained results on the increase in LPO in the blood plasma of patients with CAG and GC. At the same time, the content of LPO products and pronounced disorders of the combined functioning of the antioxidant enzymes in the blood plasma increased in patients with GC [20]. Depending on the stage of cancer and its types, an in-depth study of LPO and AOD can be used to correct therapy and prevent cancer and can serve as markers of progression and prognosis in GC [21, 22].

CONCLUSION

The study of lipid peroxidation and antioxidant defense parameters in CAG and GC associated with *Helicobacter pylori* infection proved the importance of these biochemical processes in the pathogenesis of the diseases. In CAG, there is an increase in lipid peroxidation, which the body tries to compensate by activating the enzymes of AOD. The coefficient of oxidative stress (COS) in CAG is 3.5, which implies that the level of the end products of lipid peroxidation in CAG patients is 3.5 times higher than in healthy people. The increase in lipid peroxidation in CAG is probably due to morphological changes in the cells of the gastric mucosa. The higher the COS, the more structural changes in the gastric mucosa. Consequently, early detection of LPO and AOD parameters makes it possible to identify a risk group among CAG patients who need a more effective pathogen-specific therapy aimed at eliminating atrophic changes in the gastric mucosa.

In GC, tumor growth, intoxication, progressive destruction of healthy gastric mucosa, unresponsiveness of the immune system, etc. are revealed. All this causes a drastic rise in lipid peroxidation, and the coefficient of oxidative stress is 45. AOD is not effective; LPO, destroying membranes, enhances the decay of cells and tissues and complicates the clinical course of GC, hence, resulting in ineffective therapy in late stages of cancer. The established disturbances in the function of AOD have a significant impact on the viability and functions of cancer cells. The imbalance between lipid peroxidation and factors of the antioxidant defense system is closely related to enzymatic changes in the exchange of nucleotides, these processes regulating each other according to the feedback principle. The development of oxidative stress is accompanied by structural modification of biological membranes, enzymes, and nucleotides. The intensity of metabolic processes and rearrangements in the pathogenesis at the cellular level depend on the severity of all these disorders. Therefore, the key issue in the development of GC is the balance between prooxidants and antioxidants. Early diagnosis of patients with CAG and their complex pathogen-specific therapy will reduce the number of patients with advancement of the disease to gastric cancer and reduce the overall mortality and disability rates among the Russian population.

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Smirnova O.V. – conception and design, analysis and interpretation of data, drafting of the manuscript. Tsukanov V.V. – editing of the manuscript. Sinyakov A.A. – collection and processing of clinical material, statistical processing of data. Moskalenko O.L. – collection and processing of clinical material, statistical processing of data. Elmanova N.G. – collection and processing of clinical material. Ovcharenko E.S. – collection and processing of clinical material. Kasparov E.V. – editing of the manuscript.

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