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RESEARCH ARTICLE

MAGNESIUM AND ITS ROLE IN CHANGING THE SPECIFIC NUMBER AND INTENSITY OF EXPRESSION OF GELATINASE B IN THE TISSUES OF THE STOMACH IN AN EXPERIMENTAL ULCERATION

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ABSTRACT

Purpose: To determine the role of magnesium in the changing of intensity of the expression of specific Gelatinase B in the gastric tissue in an experimental ulcer.
Material and Methods: The experiment was performed on 24 white Wistar rats. The Acetate gastric ulcer was simulated according to Ocabe S.
The Investigation of Gelatinase B by immunohistochemistry was performed by standard methods. The magnesium levels in plasma and lymph were determined with a special set (Lachema), while the content of magnesium in red blood cells was judged based on the reaction with titan yellow. The magnesium-containing composition was used for the correction of the magnesium level.
Results and discussion: There is a negative relation between the decrease of magnesium in red cells from the subclavian vein and activity of gelatinase B and a positive relation between the decrease of magnesium in red cells from the subclavian vein and the area of the ulcer. Using of magnesium-containing composition causes the increase of magnesium in red blood cells and the decrease of the activity of gelatinase B and the area of the ulcer.
Conclusions: The results shows the optimize role of magnesium in activity of gelatinase B in gastric tissue in case of the gastric ulcer.

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INTRODUCTION

Gastric and duodenum ulcers are the zone of acute or chronic inflammation. They depend on the causative agent which causes the destructive processes. Destructive processes are invoked and supported by purported aggression factors (Okorokov, 2002; Povetkina, 2013). In cases of acute aseptic inflammation and chronic autoimmune inflammation there is an increase of matrix metalloprotease's activity in the serum. They destroy the intracellular matrix and stimulate proliferation with cytokines. Free radicals and cytokines play a key role in the activation of MMP. As it is known, a deficiency of magnesium causes the activation of MMP associated with systemic connective-tissue dysplasia (Povetkina and Rogova, 2011; Hasigov, 2001; Rogova, 2015). Purpose: To determine the role of magnesium in the changing of intensity of the expression of specific Gelatinase B in the gastric tissue in an experimental ulcer.

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MATERIAL AND METHODS

The experiment was performed on 18 white Wistar rats, consisting of both sexes, weighing 198±3 gr. kept on standard diet. The rules of the animals were observed. (ETS-123 from 18.03.1986; Beuchamp T.L.) Childress O.F., Principles of Biomedical Ethics, Oxford, 1989Federal Law of April 24, 1995 № 52 -F3 "On the animal world "; The Convention on the Protection of the Rights and Dignity of Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS № 164) Oviedo, 4 April 1997), standards of GLP - rules of good laboratory practice (order of the Ministry of Health of the Russian Federation 19.06 .2003 , №266). The Rats were divided into 3 groups: Intact, control, and intervention. Each group consisting of six rats. The Acetate gastric ulcer was simulated on the intervention group according to Ocabe (2005) under nembutal anesthesia. (30 mg/cg weight) (Okabe, 2005). The rats in the control group were subjected to the same intervention as intervention group yet without any stomach wall lesion. There were 6 rats in each group. The rats were discharged from the experiment 7 days after the simulation, with the samples to be drawn further – blood from subclavian and portal veins,

lymph from the common intestinal lymphatic duct and gastric tissues (pyloric part of the stomach). Fixation of the specimens, dehudrotation, preparation of paraffin sections, and hematoxylin-eosin staining were performed based on the conventional method (Aruin *et al*., 1998). The morphological changes and the number of cells in the inflammatory infiltrates were evaluated in the specimens through a visual analog scale within the lamina propria of the stomach (LPS) and its submucous layer (SL) (Aruin *et al*., 1998; Rogova, 2015). The Investigation of Gelatinase B by immunohistochemistry was performed by standard methods using antibodies firm «Novocastra».

The formulations of the surface epithelium, and LPGM (cell components) at 400 - fold magnification were assessed a specific number (%) of positively stained cells. Reaction staining was evaluated on a three-point grading scale (Troshin and Gromova, 2008; Rogova *et al*., 2013; Okabe, 2005). Transportation and redistribution of magnesium were evaluated in their level in erythrocytic and plasmatic pools in the blood from the subclavicular and portal veins, lymph from the common intestinal lymphatic duct (CILD) and from tissue from the prepyloric ulcer zone. The magnesium levels in plasma and lymph were determined with a special set (Lachema), while the content of magnesium in red blood cells was judged based on the reaction with titan yellow (Kamyishnikov, 2004; Rogova *et al*., 2011; Rubin *et al*., 2003). The average was expressed as M±t. The importance of differences was evaluated according to the student's coefficient. If the distribution deviated from the normal it will expressed as the median (Me), 25/75 percentile. The significance oh the difference was evaluated using the Wilcoxon test under the significance level of Q>0,05. The outcomes were processed through the variation statistics method using the standard Data Analysis Tools of Excel.

and 1.5(1; 2) respectively, compared with 0.5 (0; 1), 1 (0.25; 1) and 0.5 (0;1) points in controls (Q>0.05) The control group showed no change in neutrophil, macrophage, lymphocyte, plasmocyte and eosinophil infiltration in the LPS and SL, if compared with the initial status. The specific number and activity of expression oh gelatinase B-positive cells in the gastric tissues of the intact animals was prominent neither in the number nor in the expression activity oh the antigen-positive cells. The control group showed some activation of gelatinase B, both in in the surface epitelium and in the LPS (cellular component) which was not statistically significant. In case of a developed EAGU, the surface epitelium oh the stomach shows a significantly higher expression to 3(3;3) (Q<0,05) against a tendency for an increase in the specific number of gelatinase B-positive cells. Besides, there was a simultaneous increase detected in the gelatinase B-positive cells in the LPS (cellular component) (Q>0.05), while during that the LPS (cellular component) reveled a more pronounced increase in the number of gelatinase B-positive cells to 77,5(55;100) at their top high expression activity to 3(3;3). (Table 1)

Homeostasis of gelatinase B has a known dual role: on the one hand it is used as metalloproteinase proliferation with increasing intensity, on the other hand it is used in the amplification of tissue destruction (Rogova, 2015). As it is known, the mucous membrane of the gastrointestinal tract renews at a high speed. A cell passes through the intestinal villi in 3-4 days. However, the increase of activity of gelatinase B according to morphological signs of inflammation on day 7 after the start of the simulation is evidence of the strengthing of the destructive process in the ulcer zone clearly indicate a destructive inflammatory process in the tissue of the ulcer area (Kamyishnikov, 2004).

Table 1. Specific number and expression activity of gelatinase B-positive cells in case of experimental acetate gastric ulcer, 7 days after start of simulation (25/75 percentile)

Index		Initial state	Control	Acetate gastric ulcer
Surface epitelium of the gastric mucosa	Specific number (%)	10(10;10)	42,5(17,5;48,75)	10(0;20)#
	Expression activity (points)	1,5(1;2)	1,5(1;2)	1(0;2)#
Gastric LPS (cellular component)	Specific number (%)	15(2,5;20)	32,5(12,5;48,75)	30(20;47,5)#
	Expression activity (points)	1,5(0,25;2)	2(1,25;2)	2(2;2,75)

*–significance----------(of the differences between the controls and in EAGU, Q<0,05

Table 2. Magnesium levels in concentrated red cella and blood plasma (mmol/l) in rats with experimental acetate gastric ulcer, 7 days after start of simulation (m±t)

Index	Initial state	Control	Acetate gastric ulcer	Acetate gastric ulcer + MSC
Subclavian vein (concentrated red cells), (mmol/l)	1,52±0,089	1,8±0,105 **	1,32±0,082 ** ¤	1,84±0,04 #
Portal vein (concentrated red cells), (mmol/l)	1,48±0,13	1,65±0,11	1,69±0,105	2,085±0,1#
Subclavian vein (plasma), (mmol/l)	0,981±0,015	0,917±0,011 *	0,914±0,026 **	0,882±0,006
Portal vein (plasma), (mmol/l)	1,02±0,013	0,884±0,006 ***	0,923±0,02 ***	0,947±0,016
Lymph	0,72±0,004	0,71±0,018	0,71±0,018	0,68±0,012

In relation to the initial state: * - p<0,05; ** - p<0,01; *** - p<0,001; In relation to the control: ¤ - p<0,05; # - p<0,001 - significance of the differences between the AGU and AGU + MSC

Results and discussion: Seven days after the start of the simulation a typical ulcer developed, usually crateriform, with a granulation bank, oedema, hyperaemia and hemorrahages in the mucosa with an area of 30,95±6,7 mm2 . The number of plasmocytes and eosinophiles in the LPS did not differ from the control values equaling 1(1; 1.75) and 2(1.25; 2) respectively, compared with 0(0;0) and 1(1;1,75) points in controls. Infiltration with macrophages, lymphocytes and neutrophilis increased reaching 2 (1.25; 2.75), 2 (1.25; 2.75)

This is supported by the correlation between the area of the ulcer and the specific number of gelatinase B-positive cells in the surface epitelium of the gastric mucosa (r=0,7), the number (r=0,33) and the intensity of the expression in the LPS (cellular component) (r=0,74). The increase of gelatinase B is the aggressive factor, which causes an increase of the area of the ulcer. The increase of gelatinase B in the zone of inflammatory infiltration according to the acetate ulcer is accompanied by the diminution of concentration of magnesium in blood from the subclavian vein (concentrated red cells) 1,3-fold (p<p0,05).

At the same time it's level stays invariable in the blood from the portal vein (p>0,01). The concentration of magnesium in plasma from the subclavian, and portal veins and from lymph in relation to the control didn't change (p>0,1), (p>0,1), (p>0,01). (Table 2) The analysis of results shows that optimum and identical concentration of magnesium in plasma from subclavian and portal viens according to simulated acetate ulcer in maintained by decreasing its level in red blood cells from the sublavian vien. Magnesium is known to activate more than 300 enzymes, energy production and energy consumption, and the synthesis of proteins, which are components of the proliferation process. It is noteworthy, that the concentration of magnesium in concentrated red cells from blood from the portal vien in the control group and acetate gastric ulcer group stays invariable. Perhaps this is due to the defect of mechanisms or mobilization, redistribution and consumption of magnesium from blood to intracellular space and GIT cells. As it is known, the level of magnesium decreases in the zone of the ulcer in the final period of simulation of the ulcer (Microelementoses, Rogova). It is evidence of the membrane's damage, which causes either an increase of its cell's losing or breach its cell's keeping.

These common factors coincide with Gromova's data OA (2008) which showed that the decrease in the percentage of intracellular magnesium with systemic mesenchymal dysplasia leads to the activation of metalloproteinases. The Correlation analysis showed the considerable negative relation between the level of magnesium in red cells from the subclavian vein,the specific number of gelatinase B- positive cells (r = - 0,59) and the area of the ulcer (r=-0,89). The damage of mechanisms of accumulation and consumption of magnesium by the cells, the considerable role of magnesium in the activation of enzymes of energy production and consumption and in the proliferative processes causing a slowing of the reparative processes in the ulcer. The magnesium-containing composition (MCC) was used for the correction of the magnesium level. There was a significant increase of magnesium concentration in red cells from blood from the subclavian vien by 28,26% (p>0,001), from the portal vein by 18,9% (p>0,001). Simultaneously the concentration of magnesium in plasma from the subclavian, portal vien and in the lymph didn't change (p>0,1).

The negative relation with the area of the ulcer was exposed (r=-0,65). The research showed that the increase of the intracellular/endoglobular magnesium in blood from the subclavian and portal viens causes a decrease in the number of gelatinase B – positive cells in the surface epitelium of the gastric mucosa from 52,5 (50; 62,5) to 10 (0;20) (Q<0,05) and in gastric LPS (cellular component) from 77,5 (55;100) to 30 (20; 47,5) (Q,<0,05). At the same time there were a significant decrease in expression of gelatinase B – positive cells in the surface epitelium of the gastric mucosa from from 3 (3;3) till 1 (0;2) (Q<0,05). The area of the ulcer decreased by 85,14 % (p<0,001). Furthermore, a negative correlation of magnesium level with the area of ulcerous defect (r=0,65) was established. Test analysis shows that the recovery of transport mechanisms and magnesium redistribution using MCC leads to gelatinase B normalization. In this regard, the magnesium level whether directly or indirectly regulates gelatinase B activity. Conclusions: In case of the experimental acetate gastric ulcer the decrease of endoglobular magnesium is associated with the increase in the specific number and expression of gelatinase B in the surface epitelium of the gastric mucosa and in the gastric LPS. Using of magnesium-containing composition causes the decrease of immunohystochemicrty signs of activity of gelatinase B and reduction in the area of the ulceration.

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