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THE CONCEPT OF NITRO-OXIDATIVE STRESS IN ACUTE GENERALIZED PERITONITIS ON THE BACKGROUND OF OBESITY IN EXPERIMENT

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Globally, acute generalized peritonitis (AGP) is a common medical and surgical emergency, which is a major cause of mortality, and the number of obese populations is constantly increasing every year. Aim was to study the state of the indicators of the nitric oxide system in the body of experimental animals with simulated AGP against the background of obesity and compare them with groups of obese animals and with animals with AGP. 64 white Wistar rats were used, which were divided into three groups: the main group – 24 animals with AGP simulation on the background of obesity; comparison group – 8 animals with obesity simulation; another comparison group – 24 animals with GPP modeling; control – 8 intact animals. AGP was modeled by injecting 10 % filtered fecal suspension into the abdominal cavity. Obesity was simulated using a high-calorie diet. On the 1st day, the level of NOx metabolites in the blood serum of the group of animals with AGP on the background of obesity was 9 % significantly higher than that of the group of animals with isolated GPP, on the 3rd day – by 8 %, and on the 7th day – by 7 %, respectively ($p < 0,05$). Comparing the indicators of NO-synthase activity in the liver of the rats of the main group and the comparison group, we obtained higher indicators in the animals of the AGP group and the background of obesity during all periods of the experiment: on the 1st day – by 16 %, on the 3rd day – by 14 %, and on the 7th day – by 13 % ($p < 0,05$).

The mechanisms of nitrooxidative stress are significantly increased in animals with AGP against the background of obesity during all periods of the experiment, which is confirmed by statistically significantly higher levels of NO-synthase in the liver and the content of nitrates and nitrites in blood serum compared to animals with isolated obesity or animals with AGP.

Key words: nitro-oxidative stress; acute generalized peritonitis; obesity.

The connection of the publication with planned research works.

The work was performed within the framework of the planned scientific topic of I. Horbachevsky Ternopil National Medical University « Experimental study of metabolic disorders in the body under the action of exogenous desiccants and in various pathological conditions», state registration number 0120U104148.

Introduction.

Worldwide, acute generalized peritonitis (AGP) is a common medical and surgical emergency that is a major cause of mortality, despite improvements in diagnosis and surgical and intensive care [1-2]. Despite the obvious successes of diagnostics, the use of various antibacterial drugs of the new generation, the introduction of modern methods of minimally invasive treatment, the mortality rate in AGP ranges from 12.5% to 39.2% [3-4]. The basis of the severe course and high mortality rates in acute

peritonitis is often a concomitant pathology, among which obesity accounts for 7.5% to 14.0% [5-6]. The effectiveness of using different criteria to detect obesity is not equal, which requires a necessary discussion and comparative analysis of existing diagnostic criteria and requires further, more in-depth study of biochemical indicators under conditions of obesity.

Another no less important aspect of research in the pathogenesis of obesity is the study of the role of mediators of intercellular interaction, which includes nitric oxide and its metabolites. Nitric oxide is a universal regulator of various biochemical processes [7]. Previously, the role of nitric oxide was associated only with inflammation, but it is involved in many physiological and pathophysiological reactions of the body, including apoptosis reactions. Nitric oxide and its metabolites play a significant role in the development of obesity complications. It is known that obesity is

accompanied by endothelial dysfunction, which is characterized by increased production of nitric oxide [8]. Therefore, increased attention of researchers is focused on the problem of endothelial dysfunction, oxide. Insufficient or excessive production of nitric oxide characterizes the presence of endothelium dysfunction, which is associated with a violation of the antioxidant system under the influence of free radical oxidation. This phenomenon is the main risk factor for the occurrence and complications of various diseases, including obesity [9].

It is known that nitric oxide can cause both protective and damaging effects. It plays an insignificant role in the processes that regulate the production of free radicals. Its molecule itself, as one of the reactive forms of oxygen, participates in the initiation of oxidative stress, which has independent antioxidant properties [10]. However, the pathogenetic mechanisms that explain the role of nitrooxidative stress, lipoperoxidation processes, and the state of the antioxidant system in the development of obesity and its complications have not been fully explored [11]. There are no clear criteria that would make it possible to have an idea of the course of this pathology, to make it possible to predict the course of the disease and to prevent unwanted consequences. In the available literature, the question of the role of the activity of nitric oxide, lipoperoxidation processes, and antioxidant enzymes in the pathogenesis of systemic abnormalities in AGP against the background of obesity remains to be fully clarified.

The aim of the study.

To study the state of the indicators of the nitric oxide system in the body of experimental animals with simulated AGP against the background of obesity and compare it with groups of obese animals and with animals with AGP.

Object and research methods.

The experiments were carried out in the Central Research Laboratory of I. Horbachevsky Ternopil National Medical University. The experiment used 64 white Wistar rats, which were divided into three groups: the main group – 24 animals with AGP modeling against the background of obesity; the comparison group – 8 animals with modeling of obesity only; another

comparison group – 24 animals with only AGP simulation; the control group consisted of 8 intact animals kept in standard vivarium conditions. All compared groups of animals were of the same weight, sex, and age.

Male rats of the control group were fed a normal control diet. Male rats of the main group (n=24) were fed a high-fat diet (more than 60% of energy from fat) for 16 weeks [12], thus simulating the development of obesity in them.

AGP was modeled by injecting 10% of filtered fecal suspension into the abdominal cavity at a dose of 0.5 ml per 100 g of animal weight according to V.A. Lazarenko and co-authors (2008) [13]. Fecal suspension was obtained by mixing the isotonic solution and cecal contents of three intact animals and filtering it twice through a double layer of gauze. Fecal suspension was administered no later than 20 minutes after its preparation. In order to prevent damage to internal organs, the animals were kept in a vertical position, with the caudal end up. Using the method of ventral wall puncture in the center of the midline of the anterior abdominal wall, directing the end of the needle alternately into the area of the right and left hypochondrium, into the right and left pubic areas, the required amount of fecal suspension was injected.

In terms of etiological factors, clinical manifestations and phasic course, this model is close to a similar process in humans. Experimental animals were removed from the experiment by overdose of sodium thiopental (at the rate of 100 mg/kg of weight).

The state of the nitric oxide system was judged by the level of the total content of nitrates and nitrites, as well as by the total activity of NO-synthase.

The total content of nitrates and nitrites was determined by the Griess method after the reduction of nitrates to nitrites with the help of Cadmium [14]. The total activity of NO-synthase in liver tissue was determined colorimetrically. The indicators of the nitric oxide system were determined on the 1st, 3rd and 7th day after the AGP simulation.

Research was conducted in accordance with "General Ethical Principles of Animal Experiments", approved by the First National Congress in Bioethics (Kyiv, 2001) in accordance with the provisions of the "European Convention for the Protection of Vertebrates used in experiments and other educational purposes" (Strasbourg, 18 March 1986).

Statistical processing of digital data was carried out using Excel and STATISTICA software using parametric and non-parametric methods of evaluating the obtained data. For all indicators, the value of the arithmetic mean of the sample (M), its variance and the error of the mean (m) were calculated. The reliability of the difference in values between independent quantitative values was determined in the case of a normal distribution using the Student's t-test, in other cases – using the Mann-Whitney U-test (differences at $p < 0.05$ were considered reliable).

Research results and their discussion.

Evaluating the content of nitrates and nitrites (NOx) in the blood serum of experimental rats, we established that in all experimental groups the level of these indicators was statistically significantly higher than the level of the control group (table 1). As for the isolated obese animals, nitrate and nitrite levels were statistically

Table 1 – Indicators of the content of nitrates and nitrites (NOx) in the blood serum of rats with simulated AGP and obesity (M±m)

Groups of animals	The term of observation		
	1st day (n=8)	3rd day (n=8)	7th day (n=8)
AGP (n=24)	8,16±1,48**	8,57±1,18**	9,17±1,01**
AGP + obesity (n=24)	8,87±0,66** $p_1 < 0,05$	9,34±0,59** $p_2 < 0,05$	9,79±0,54** $p_3 < 0,05$
Obesity (n=8)	7,18±1,07*		
Control (n=8)	4,08±0,49		

Notes: * – reliability of the difference of indicators with the control;
– reliability of the difference in indicators with the obesity group;
 p_1 – reliability of the difference in indicators with the AGP group for 1st day;
 p_2 – reliability of the difference in indicators with the AGP group for 3rd day;
 p_3 – reliability of the difference in indicators with the AGP group for 7th day.

significantly lower in these animals compared to those in the group of animals with simulated AGP and obesity and animals with AGP ($p < 0,05$).

Analyzing the indicators of the content of nitrites and nitrates in the blood serum of the main group and the comparison group, we established a clear tendency to increase depending on the increase in the duration of the experiment after AGP modeling in these two studied groups. Thus, on the 1st day, the level of NOx metabolites in the blood serum of the group of animals with AGP on the background of obesity was 9% significantly higher than that of the group of animals with isolated AGP, on the 3rd day – by 8%, and on the 7th day – by 7% in accordance ($p < 0,05$).

Nitric oxide is a universal regulator of various biochemical processes. Previously, the role of nitric oxide was associated only with inflammation, such as acute inflammation of the peritoneum, but it is involved in many physiological and pathophysiological reactions of the body, including apoptosis. Nitric oxide and its metabolites play a significant role in the development of obesity. It is known that obesity is accompanied by endothelial dysfunction, which is characterized by increased production of nitric oxide [15-16]. The data we obtained show that the combination of AGP and obesity contribute to the development of nitrooxidative stress much more than with the isolated course of AGP or obesity. Analyzing the indicators of nitrites and nitrates (NOx) in the blood serum of animals with a combination of AGP and obesity and a group of animals with isolated AGP, we established a clear tendency for their level to increase depending on the increase in the duration of the experiment after AGP modeling. Therefore, in the dynamics of the development of acute inflammation of the peritoneum, nitrooxidative stress deepens.

When evaluating NO-synthase (NOS) activity indicators in the liver of rats, we obtained the same picture as with the levels of nitrates and nitrites in the blood serum of experimental animals (**table 2**). Thus, the activity of NO-synthase in the liver of rats was reliably significantly higher in all comparison groups compared to the control. As for the obese group, the activity of NO synthase in this group was reliably significantly lower compared to animals with AGP on the background of obesity and with animals with AGP (except for animals with AGP for 1st day).

Comparing the indicators of NO-synthase activity in the liver of rats of the main group and the comparison group, we obtained reliably significantly higher indicators in animals of the AGP group and against the background of obesity during all periods of the experiment: on day 1st – by 16%, on 3rd day – by 14%, and on the 7th day – by 13%, respectively. Therefore, in animals with AGP on the background of obesity, the mechanisms of nitrooxidative stress during all periods of the experiment increase the most compared to animals with isolated obesity and animals with AGP.

Currently, it is known that NO is synthesized in the body from the amino acid L-arginine. This process is a complex oxidative reaction catalyzed by the enzyme NO-synthase, which attaches molecular oxygen to the terminal nitrogen atom in the guanidine group of L-arginine. NO-synthase isoforms are usually divided into constitutive (cNOS) and inducible (iNOS) nitric oxide synthases [17].

Table 2 – Indicators of NO-synthase (NOS) activity in the liver of rats with simulated AGP and obesity ($M \pm m$)

Groups of animals	The term of observation		
	1 day (n=8)	3 day (n=8)	7 day (n=8)
AGP (n=24)	6,70±0,97*	7,21±0,47**	7,74±0,36**
AGP + obesity (n=24)	7,99±0,32*# $p_1 < 0,05$	8,43±0,45*# $p_2 < 0,05$	8,89±0,37*# $p_3 < 0,05$
Obesity (n=8)	6,87±0,26*		
Control (n=8)	3,99±0,97		

Notes: * – reliability of the difference of indicators with the control; # – reliability of the difference in indicators with the obesity group; p_1 – reliability of the difference in indicators with the AGP group for 1st day; p_2 – reliability of the difference in indicators with the AGP group for 3rd day; p_3 – reliability of the difference in indicators with the AGP group for 7th day.

Constitutive NOS (cNOS) is constantly present in the cytoplasm and promotes the release of small amounts of NO for a short period in response to receptor and physical stimulation. NO, generated by cNOS, acts as a transporter in a number of physiological responses [18]. Inducible NOS appears in cells only after their induction by bacterial endotoxins, such as during acute peritoneal inflammation. In particular, this process can be provoked by bacterial lipopolysaccharides, some endotoxins and cytokines. This is the mechanism of vasodilatation and exudation during inflammatory processes [19].

It is obvious that the increase in the total activity of NO-synthase registered by us in animals with AGP on the background of obesity and in animals with isolated AGP and obesity is a consequence of the activation of the inducible form of this enzyme. Moreover, we have proven much higher activity of this enzyme in animals with a combination of AGP and obesity compared to animals with AGP or obesity. Therefore, the activation of nitrooxidative stress in the combined pathology is much higher than in the isolated course of AGP or obesity.

Conclusions.

In animals with acute generalized peritonitis on the background of obesity, the mechanisms of nitrooxidative stress are significantly increased during all periods of the experiment, which is confirmed by statistically significantly higher levels of NO-synthase in the liver and the content of nitrates and nitrites in the blood serum and compared to animals with isolated obesity or animals with acute generalized peritonitis.

Prospects for further research.

To study the features of indicators of endogenous intoxication in animals with acute generalized peritonitis against the background of obesity.

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КОНЦЕПЦІЯ НІТРООКСИДАТИВНОГО СТРЕСУ ПРИ ГОСТРОМУ ПОШИРЕНОМУ ПЕРИТОНІТІ НА ТЛІ ОЖИРІННЯ В ЕКСПЕРИМЕНТІ

Малевиц Н. М., Кліщ І. М.

Резюме. Вступ. У всьому світі гострий поширений перитоніт (ГПП) є поширеною медичною та хірургічною невідкладною патологією, яка є основним чинником смертності. Незважаючи на очевидні успіхи діагностики, використання різноманітних антибактеріальних препаратів нового покоління, впровадження сучасних методів малоінвазивного лікування, летальність при ГПП сягає від 12,5% до 39,2%. Підґрунтям важкого перебігу та високих показників смертності при гострому запаленні очеревини часто є супутня патологія, серед котрої від 7,5% до 14,0% складає ожиріння.

Мета – визначити стан показників системи оксиду азоту в організмі піддослідних тварин при змодельованому ГПП на тлі ожиріння та порівняти їх із групами тварин із ожирінням та із тваринами з ГПП.

Матеріали й методи. Було використано 64 білих щурів лінії Wistar, яких було розподілено на три групи: основна група – 24 тварини з моделюванням ГПП на фоні ожиріння; група порівняння – 8 тварини з моделюванням ожиріння; ще одна група порівняння – 24 тварини з моделюванням ГПП; контроль – 8 інтактних тварин. ГПП моделювали шляхом введення 10 % профільованої калової суспензії у черевну порожнину. За допомогою висококалорійної дієти моделювали ожиріння. За допомогою фотоспектрометричного методу визначали вміст показників систему нітрит азоту у крові та печінці тварин.

Результати. Після аналізу показників вмісту нітритів і нітратів у сироватці крові основної групи та групи порівняння, ми встановили чітку тенденцію до зростання залежно від збільшення тривалості експерименту після моделювання ГПП у цих двох досліджуваних групах. На 1 добу рівень метаболітів NO_x в сироватці крові групи тварин із ГПП на тлі ожиріння був достовірно значимо вищим такого показника у групи тварин із ізолюваним ГПП (на 9%), на 3 добу – на 8%, а на 7 добу – на 7% відповідно (p<0,05). Порівнюючи показники активності NO-синтази у печінці щурів основної групи та групи порівняння, ми отримали вищі показники у тварин групи ГПП та тлі ожиріння протягом всіх термінів експерименту: на 1 добу – на 16%, на 3 добу – на 14%, а на 7 добу – на 13% (p<0,05).

Висновок. Отже, за статистично значимо вищими рівнями вмісту NO-синтази в печінці та вмісту нітратів і нітритів в сироватці крові тварин з ГПП на тлі ожиріння порівняно із тваринами з ізолюваним ожирінням чи тваринами із ГПП, ми встановили, суттєве підвищення механізмів нітрооксидативного стресу протягом всіх термінів експерименту у тварин із поєднанням ГПП та ожиріння.

Ключові слова: нітрооксидативний стрес; гострий поширений перитоніт; ожиріння.

THE CONCEPT OF NITRO-OXIDATIVE STRESS IN ACUTE GENERALIZED PERITONITIS ON THE BACKGROUND OF OBESITY IN EXPERIMENT

Malevych N. M., Klishch I. M.

Abstract. Worldwide, acute generalized peritonitis (AGP) is a common medical and surgical emergency and a major cause of mortality. Despite the obvious successes of diagnostics, the use of various antibacterial drugs of the new generation, the introduction of modern methods of minimally invasive treatment, the mortality rate in AGP ranges from 12.5% to 39.2%. The basis of the severe course and high mortality rates in acute peritonitis is often concomitant pathology, among which obesity is present in 7.5% to 14.0%.

Aim – to study the state of the indicators of the nitric oxide system in the body of experimental animals with simulated AGP against the background of obesity and compare them with groups of obese animals and with animals with AGP.

Materials and methods. 64 white Wistar rats were used, which were divided into three groups: the main group – 24 animals with GPP simulation on the background of obesity; comparison group – 8 animals with obesity simulation; another comparison group – 24 animals with GPP modeling; control – 8 intact animals. GPP was modeled by injecting 10% filtered fecal suspension into the abdominal cavity. Obesity was simulated using a high-calorie diet. Using the photospectrometric method, the content of indicators of the nitrogen nitrite system in the blood and liver of animals was determined.

Results. After analyzing the indicators of nitrites and nitrates in the blood serum of the main group and the comparison group, we established a clear tendency to increase depending on the increase in the duration of the experiment after GPP simulation in these two studied groups. On the 1st day, the level of NOx metabolites in the blood serum of the group of animals with GPP on the background of obesity was significantly higher than that in the group of animals with isolated GPP (by 9%), on the 3rd day – by 8%, and on the 7th day – by 7% respectively ($p < 0.05$). Comparing the indicators of NO-synthase activity in the liver of the rats of the main group and the comparison group, we obtained higher indicators in the animals of the GPP group and the background of obesity during all periods of the experiment: on the 1st day – by 16%, on the 3rd day – by 14%, and on the 7th day – by 13% ($p < 0.05$).

Conclusion. Therefore, based on the statistically significantly higher levels of NO-synthase in the liver and the content of nitrates and nitrites in the blood serum of animals with AGP on the background of obesity compared to animals with isolated obesity or animals with AGP, we established a significant increase in nitrooxidative stress mechanisms during all periods of the experiment in animals with a combination of AGP and obesity.

Key words: nitro-oxidative stress; acute generalized peritonitis; obesity.

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FINITE ELEMENT ANALYSIS OF THORACOLUMBAR JUNCTION TRANSPEDICULAR FIXATION VARIANTS AFTER RESECTION OF THE TH12 VERTEBRA WHILE FORWARD BENDING

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The zone of the thoracolumbar transition is one of the "most typical" areas of traumatic changes under the influence of mechanical stress on the human body. In modern clinical practice, many different types of surgical correction of traumatic injuries in this area are used, which ensure adequate decompression of the structures of the spinal canal, correct the axis of the spine and complete stabilization. Despite the achievements of modern medicine,