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Research Article

Parameters of The Redox System State in Case of Acute Intraabdominal Infection and Underlying Acute Nephrosis-Nephritis: An Experimental Study

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Abstract

Background: The ROR studies show AOS disorders in nephritis and in IAI. But there is no data on the ROR characteristics if IAI and nephritis are associated.

Materials and Methods: 100 albino rats: intact (10), with simulated NN (10), with simulated IAI (40) with simulated NN and IAI (40). MDA, CP, SHG, PPOM parameters were studied.

Results: In 12 h since NN simulating, the increase in CP, SHG, the decrease in PPOM, the same MDA parameters compared to intact rats were found. Since IAI induction in intact rats, ROR activity progressed with a maximum in 12 h and stabilized in 24 h. The lipid oxidation intensity decreased, and the glutathione oxidation intensity increased in 48 h, while the AOS ability decreased. Instead, in rats with IAI and NN models, ROR were activated slower. Various links of the oxidative reactions, for the most part, were activated asynchronously. During the IAI progression, signs of the permanent oxidative reactions' imbalance against the background of the ROS dysfunction were found. The maximum activation of oxidative reactions occurs in 48 h on the background AOS failure. Taking into account our data, it is expedient to determine the ROR markers in patients and prescribe medication correction taking into account these markers.

Conclusion: The development of acute IAI and underlying acute NN is characterized by late activation of oxidative reactions, permanent oxidative reactions' imbalance, ROS dysfunction, late maximal activity of oxidative reactions with the simultaneous AOS failure.

Keywords: Nephritis; intraabdominal infections; malondialdehyde; protein oxidation; ceruloplasmin; glutathione

Abbreviations

AOS: Antioxidant System

CP: Ceruloplasmin

NN: Nephrosis-Nephritis

IAI: Intraabdominal Infection

MDA: Malondialdehyde

PPOM: Plasma Protein Oxidative Modification

ROR: Redox Reactions

ROS: Redox System

SHG: Sulfhydryl Groups

Introduction

The global burden of kidney disease, in particular, different types of nephritis, is rapidly increasing worldwide [1-4]. Studies show a negative correlation between kidney disease and health. Pathological disorders of the kidneys negatively affect the condition of all organs and systems [5-7]. At the same time, the prevalence of intraabdominal infections (IAI) is constant. Therefore, the number of patients with acute IAI associated with kidney disease is constantly increasing. In patients with kidney disease, clinical changes, and an increase in the number of postoperative complications are observed [8,9]. Kidney disease is one of the risk factors for mortality in IAI [10]. Moreover, hemodialysis can be complicated by peritonitis in patients with renal failure [11]. And such peritonitis is characterized by severity and negative consequences of treatment [12]. So, such comorbidity requires changes in diagnostic tools and management [13].

Controversial data about the changes in pathophysiological mechanisms if IAI and kidney diseases are associated among the reasons for the unsatisfactory management results of patients with this comorbidity [14,15]. The one of the important mechanisms of homeostasis regulation are redox reactions (ROR). This is due to their participation in the processes of adaptive restructuring in various physiological and pathological conditions [16]. ROR components are among the regulators of the inflammatory process, immune response, regeneration, etc. [17]. Researchers of these problems quite often recommend antioxidant drugs to correct ROR [18,19] in particular, with kidney diseases [20]. But some researchers note the negative results of antioxidants because the elimination of reactive oxygen species, which are physiological signaling messengers, can disrupt physiological responses [21].

Changes in ROR are important in the development of kidney disease, in particular, different types of nephritis and their complications [22,23]. Disorders of the redox system (ROS) are also one of the leading links in the pathogenesis of acute intraabdominal infection (IAI) [24,25]. But there is no data on the characteristics of ROS condition if IAI and kidney diseases are associated. Therefore, the study of ROS condition peculiarities if IAI and kidney diseases are associated is important. Such studies are also important because guidelines for the IAI management do not recommend the use of adjuvant drugs, in particular, antioxidants, because its effectiveness has not been proven. And some studies indicate negative results of the antioxidants used in IAI [26].

Material and Methods

100 albino non-pedigree female rats. All rats were sexually mature (age 6 months). The rats' mass was from 180 to 200 g. Intact rats were kept in a vivarium. Housing and feeding conditions were the same for all rats. After the nephrosis-nephritis (NN) and IAI simulation, the rats were in the same stay conditions and had the same drink. The rats were divided into 4 groups: 1st - intact (10), 2nd - NN model (10), 3rd - IAI model (40), 4th - NN and IAI model (40). NN was simulated by subcutaneous introduction of 5% sodium nitrite solution on distilled water in the dose of 0,5 mg per 100 g of mass. IAI was simulated by intraabdominal injection of 20% autofaeces suspension in the dose of 10 ml per 100 g of mass. IAI was induced 12 h since NN was simulated. Blood from the jugular vein was taken for analysis in rats of the 1st and 2nd groups, and in rats of the 3rd and 4th groups in 6, 12, 24, 48 h since IAI was induced.

The parameters of malondialdehyde (MDA) in erythrocytes, the level of plasma protein oxidative modification (PPOM), the parameters of ceruloplasmin (CP) and sulfhydryl groups (SHG) in blood plasma were detected. All manipulations were performed under sevorane anesthesia. The animals were taken out of the experiment by an overdose of sevorane. While performing the work, the norms of conducting research in the field of biology and medicine were observed: the Vancouver Conventions on Biomedical Research (1979, 1994), the Council of Europe Convention on the Protection of Vertebrate Animals Used in Experiments and for Other Scientific Purposes (1986) as well as the national law.

Statistical analysis

The hypothesis of normal data distribution (Gaussian distribution) was tested in samples by Shapiro-Wilk criterion. Verification of the hypothesis of average data equality was carried out by Wilcoxon and Mann-Whitney-Wilcoxon criterion. To discover the strength of a link between sets of data the Spearman's Rank Correlation Coefficient was used. The significance level (alpha) 0.05 was set in the study. The results of the study were statistically processed by the Microsoft® Office Excel (build 11.5612.5703) tables.

Results

The initial MDA parameters had almost no differences in the 1st and 2nd groups (Table 1). PPOM parameters in the 2nd group were significantly less. CP and SGH parameters in the 2nd group were significantly higher. An inverse significant correlation ($r=-0.88$, $p<0.05$) was between MDA and CP parameters in the 1st group. A direct non-significant correlation ($r=0.6$, $p>0.05$) was between PPOM and SHG parameters. An inverse significant correlation ($r=-0.88$, $p<0.01$) was between PPOM and SHG parameters in the 2nd group. A little inverse correlation ($r=-0.5$, $p>0.05$) was between CP and MDA parameters. In the 6 h since IAI was induced, it was found that MDA parameters increased significantly (Figure 1) in the 3rd group, compared to the initial ones (1st group). PPOM parameters decreased significantly (Figure 2). CP parameters decreased significantly (Figure 3). SHG parameters decreased significantly (Figure 4).

Table 1: Parameters of the redox system in rats of the 1st and 2nd groups.

Marker	1st group	2nd group
Malondialdehyde (μmol/l)	13.600 ± 0.057	13.600 ± 0.389
Plasma Protein Oxidative Modification (u.u.g/l)	2.030 ± 0.057	1.430 ± 0.035**
Ceruloplasmin (mg/l)	192.000 ± 3.391	210.800 ± 4.831*
SH-groups (μmol/l)	2.798 ± 0.050	5.134 ± 0.065**

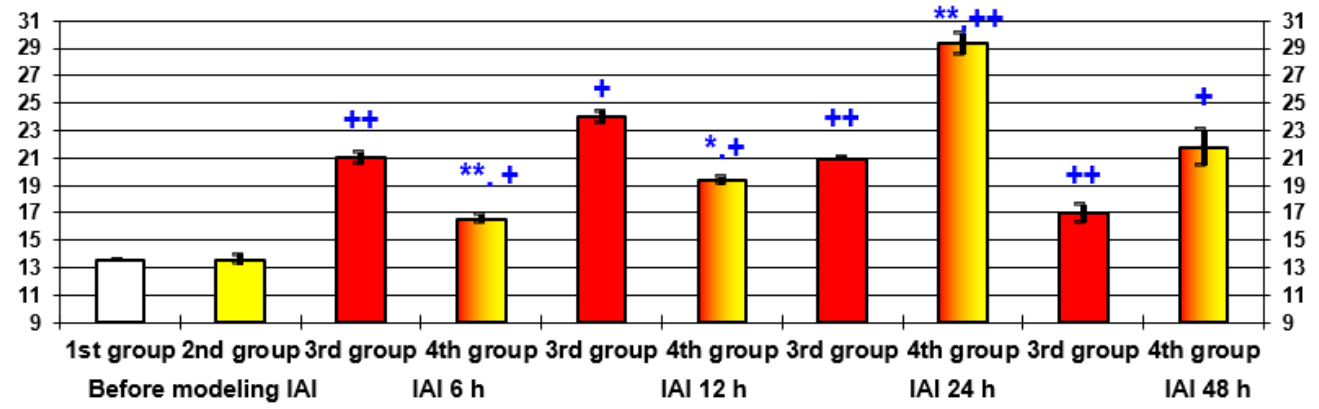

Figure 1: The dynamics of MDA parameters in experimental animals (M±m).

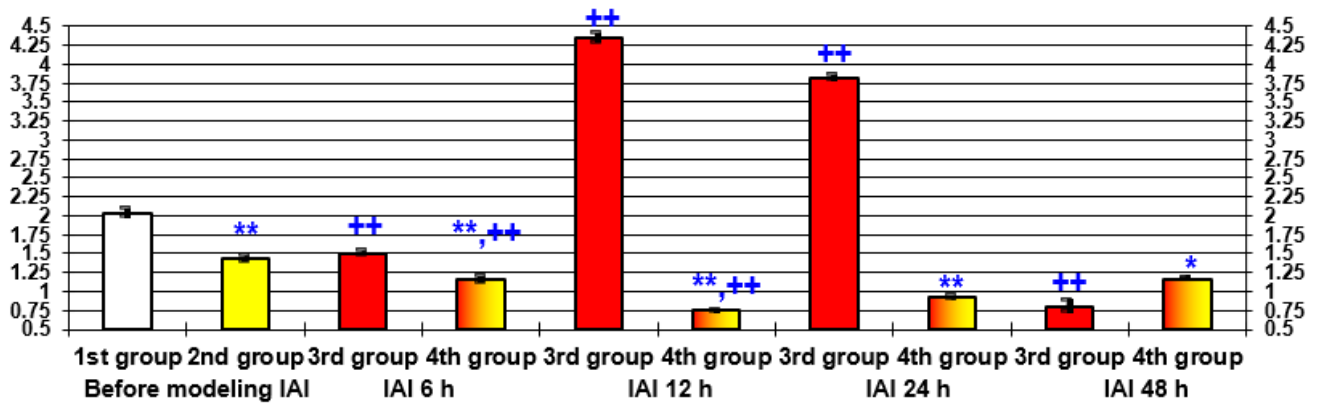

Figure 2: The dynamics of PPOM level in experimental animals (M±m).

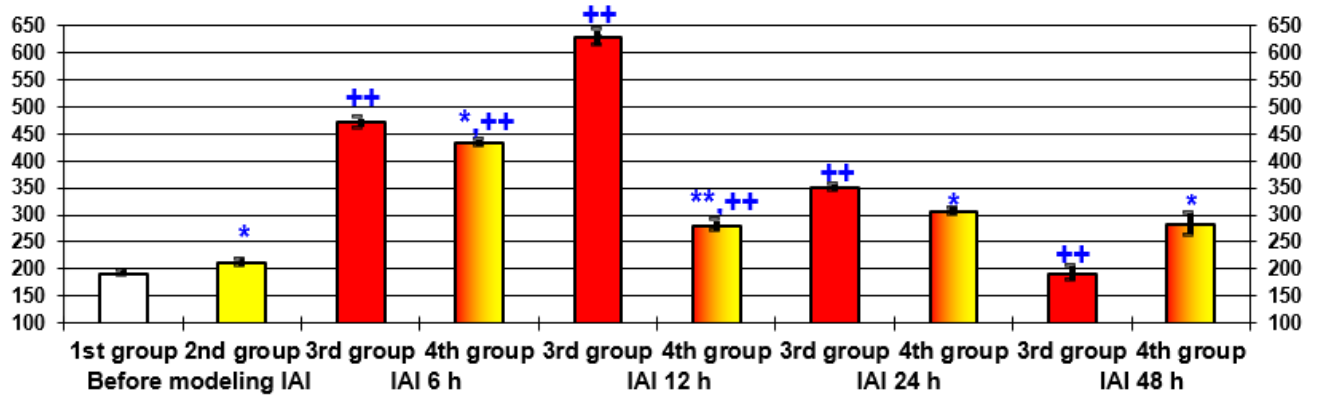

Figure 3: The dynamics of CP parameters in experimental animals (M±m).

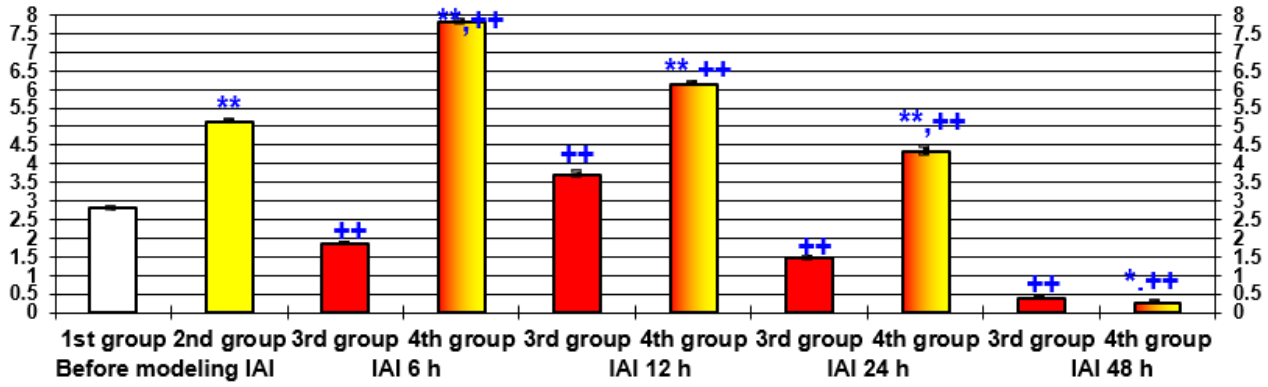

Figure 4: The dynamics of SHG parameters in experimental animals (M±m).

MDA, CP and SHG parameters increased significantly in the 4th group, compared to the initial ones (2nd group), instead PPOM parameters decreased significantly. MDA, PPOM and CP and parameters were significantly less than in the 3rd group, instead SHG parameters were significantly higher. A direct significant correlation (r=0.71, p<0.05) was between MDA and PPOM parameters in the 3rd group. The correlation between PPOM and SHG parameters decreased (r=0.5, p>0.05). An inverse little correlation was between SHG and PPOM parameters (r=0.58, p>0.05) in the 4th group. A direct little correlation was between SHG and CP parameters (r=0.58, p>0.05). After 12 h since IAI was induced, all markers' parameters increased significantly in the 3rd group. Instead, all markers' parameters decreased significantly in the 4th group. MDA, PPOM and CP parameters in the 4th group were significantly less than in the 3rd group.

At the same time, SHG parameters in the 4th group stayed significantly higher. An inverse significant correlation (r=-0.67, p<0.05) was between PPOM and CP parameters in the 3rd group. A direct significant correlation (r=0.89, p<0.01) was between PPOM and SHG parameters. An inverse significant correlation (r=-0.89, p<0.01) was between CP and SHG parameters. An inverse significant correlation was between MA and CP parameters (r=-0.96, p<0.01) as well as between CP and SHG parameters (r=-0.96, p<0.01) in the 4th group. In the 24 h since IAI was induced, all markers' parameters decreased significantly in the 3rd group. MDA parameters increased significantly in the 4th group and became significantly higher than parameters in 3rd group. PPOM and CP parameters increased a little but stayed significantly less than parameters in 3rd group. SHG parameters decreased significantly but stayed significantly higher than parameters in the 3rd group.

An inverse insignificant correlation (r=-0.56, p>0.05) was between MA and PPOM parameters in the 3rd group. A direct little correlation was between PPOM and CP parameters (r=0.51, p>0.05). A direct significant correlation (r=0.68, p<0.05) was between PPOM and SHG parameters. A direct significant correlation (r=0.78, p<0.05) was between CP and SHG parameters. An inverse little correlation (r=-0.59, p>0.05) was between MDA and CP parameters in the 4th group. A direct insignificant correlation (r=0.6, p>0.05) was between MDA and SHG parameters. An inverse significant correlation (r=-0.79, p<0.05) was between CP and PPOM parameters. In 48 h since IAI was induced, all markers' parameters decreased in the 3rd group. MDA parameters were significantly higher compared to the initial ones (1st group). PPOM and SHG parameters were significantly less compared to the initial ones. CP parameters were almost the same as the initial ones.

MDA parameters decreased significantly in the 4th group but stayed significantly higher than in the 3rd group and were significantly higher compared to the initial ones (2nd group). PPOM parameters increased a little and became significantly higher than in the 3rd group and were significantly less compared to the initial ones. CP parameters decreased a little and were significantly higher compared to the initial ones. SHG parameters decreased significantly and became significantly less than in the 3rd group and significantly less compared to the initial ones. A significant inverse correlation was between MDA and PPOM parameters (r=-0.79, p<0.05) and between MDA and CP parameters (r=-0.81, p<0.01) in the 3rd group. Correlation between markers's parameters in the 4th group was not found. Notes (here and in Fig. 2, 3, 4): * - p < 0.05 between groups; ** — p < 0.01; «+»- p < 0.05 between adjacent terms of observation; «++»- p < 0.01 (only statistically significant differences are given).

Discussion

The differences in parameters that were found in the 1st and 2nd groups indicate differences of the ROS state in rats with NN models. On the one hand, the same MDA parameters in both groups indicate the stability of lipid peroxidation reactions in rats with NN models. On the other hand, the high CP parameters, which is the main antioxidant of blood plasma, in the 2nd group indicate intense AOS activation. Increased SHG parameters in the 2nd group indicate the glutathione reductase activation, which deoxidates glutathione which also indicates AOS activation. The results of the correlation analysis also indicate differences in the ROR state in both groups. The correlation coefficients in the 1st group demonstrate known

interactions between different links of ROS. The correlation coefficients in the 2nd group demonstrate transformations in the interaction of the ROS links, which are due to the ROR activation. The cause for the AOS activation is an increase in the peroxidation reactions activity.

However, the absence of an increase in MDA parameters indicates an effective deactivation of the primary lipid oxidation products, which indicates a sufficient AOS functional capacity. The causes for the significant decrease in the PPOM level in the 2nd group could be different. This could be a consequence of significant AOS activation. In particular, the PPOM level could decrease due to the glutathione reductase high activity. It is possible that the decrease in the PPOM level could be a consequence of changes in the proteins blood plasma structure caused by other processes that occur in NN. But proteins oxidative modification is an important component of various regulatory mechanisms [27]. Therefore, PPOM disruption may be one of the causes for disruption of these mechanisms in NN. The increase in MDA parameters found in 6 h since IAI was induced in the 3rd group indicates the activation of lipid oxidation reactions.

The increase in SHG parameters indicates the activation of glutathione oxidation reactions. Peroxidation activation is a natural response to IAI. This is one of the inflammation regulation mechanisms. A parallel increase in the CP parameters indicates the AOS activation, which is aimed at inactivating toxic peroxidation products. The decrease in the PPOM level is apparently the result of the interaction of various links of ROR regulation. In particular, the significant correlation of the PPOM level with the MDA parameters indicates a relationship between lipid oxidation and PPOM. At the same time, PPOM depends on the activity of glutathione oxidation and deoxidation. Thus, in this case, the PPOM reduction may be the result of a high level of thiol groups oxidation, which protects plasma proteins from excessive oxidation. The increase in MDA and CP parameters in the 4th group also indicates the activation of lipid oxidation reactions and parallel AOS activation.

A high level of SHG, which parameters were the highest during the observation period, may indicate a high activity of glutathione reductase, and a decrease in PPOM parameters may be the result of the plasma proteins deoxidation activation. It cannot be excluded that differences in the peptides and proteins oxidation were the result of changes in their structure under the influence of other processes. It is also possible that the high activity of the AOS thiol link compensated for the insufficient activity of AOS mechanisms associated with CP. However, taking into account the parameters in the 3rd group, this indicates differences in the ROR state. The ratio between the basic parameters and parameters in 6 h since IAI was induced confirms these differences. The increase in MDA in the 3rd group was 1.54, and in the 4th group – 1.21 ($p<0.05$), the decrease in PPOM in the 3rd group was 1.35, and in the 4th group – 1.23 ($p>0.01$), the increase in CP in the 3rd group was 2.45, and in the 4th group – 2.05 ($p>0.05$), the decrease in SHG in the 3rd group was 1.52, instead, the increase in SHG in the group 4 was 1.52.

The indicated differences can be considered as the ROS response disorders to the occurrence of inflammation in the abdominal cavity. Given the role of oxidative reactions in the regulation of inflammation, this can be considered as a manifestation of the ROS dysfunction. The cause of the dysfunction can be considered changes in the ROS state caused by the NN simulation. The peak parameter of every marker that was found in 12 h since IAI induction in the 3rd group indicates the maximum intensity of ROR, which can be regarded as an «respiratory burst», which is an indispensable attribute of the protective reaction in IAI. The maximum activation of oxidative reactions is the result of an increase in the number of oxygen reactive forms, the main sources of which are stimulated phagocytic cells, polymorphonuclear leukocytes, and endothelial cells [28]. A simultaneous maximum increase in CP and SHG parameters shows a high AOS activity, which is aimed at neutralizing the negative affect of oxidative reactions.

Instead, the increase in MDA found at this time in the 4th group with the simultaneous decrease in PPOM, CP and SHG indicates the fundamental differences in the ROS state. First, the lipid oxidation intensity does not reach a maximum. Although the increase in MDA parameters in the 4th group (1.17) was greater than in the 3rd group (1.14), which indicates the greater lipid oxidation activity increase. Secondly, against the background of increased lipid oxidation activity, the activity of AOS mechanisms associated with CP and glutathione decreases. All this, together with a significant decrease in the PPOM level, which parameters were the smallest, indicates ROS imbalance and the suppression of the antioxidant mechanism's functional ability associated with CP and glutathione. Correlation analysis data support these interaction changes. Most of the correlation coefficients parameters differed from the parameters in the 3rd group. Given the importance of ROS in the inflammation regulation, this reaction is inadequate. The changes in parameters that found in 24 h since IAI induction in the 3rd group indicate the ROR intensity decrease. This shows the stabilization of peroxidation reactions after the previous explosive growth of their activity.

At the same time, MDA decreased by 1.14 times, PPOM decreased by 1.13 times. But CP decreased by 1.79 times, SHG decreased by 2.54 times. This could be a sign of a somewhat inadequate AOS function. However, the effect of other AOS factors that we did not investigate cannot be excluded. The changes in parameters that occurred at that time in the 4th group indicate a fundamentally different ROR nature. Summarized significant increase in MDA, which parameters were the highest, with simultaneously increase in PPOM can be regarded as signs of a respiratory burst. But in contrast to the 3rd group, the respiratory burst develops with a delay. This confirms ROR imbalance, which signs were found after 12 h. In addition, during the respiratory burst simultaneously CP and SHG decreased. Moreover, SHG parameters were less than initial ones (2nd group). That is, in rats of 4th group, against the background of maximal oxidative reactions activity signs, manifestations of decreased antioxidant mechanisms activity were found.

This can be considered as signs of the AOS failure. Differences in the ROR orientation is also confirmed by correlation analysis. The changes in parameters that were found in 48 h since IAI induction in the 3rd group indicate a decrease in the lipids and

proteins oxidation intensity. On the one hand, this may be a sign of a decrease in the activity of oxidative reactions. But on the other hand, SHG decreased significantly, which indicates a high intensity of glutathione oxidation and low activity of its reduction reactions. CP also decreased significantly. The parameters of CP and MDA were significantly correlated. At the same time, MDA decreased by 1.24 times, SHG decreased by 1.83 times, and CP decreased by more than 4 times. So, in totality, these changes can be considered as signs of AOS functional ability inhibition. The changes in parameters that were at this time in the 4th group indicate a permanent ROR imbalance and progression of the AOS failure.

This is indicated by an increase in PPOM against the background of a decrease in MDA, which parameters, however, were 1.59 times greater than the initial ones (2nd group), as well as a decrease in CP and, especially, SHG which collapsed by 16 times and was the smallest in all observation time. At later times, studies were not performed because all animals with IAI models on the NN background died, in addition, some rats died before 48 h. Therefore, in 12 h since NN simulating, differences in the ROS state with signs of increased AOS activity and decreased PPOM levels were found in rats. Since IAI induction in intact rats, ROR activity progresses with a maximum in 12 h. Later, in 24 h, in intact rats with IAI models ROR stabilize, in 48 h the lipid oxidation intensity decreases, and the glutathione oxidation intensity increases. At the same time, the AOS ability decreases. Instead, in rats with IAI and NN models, ROR are activated late. Various links of the oxidative reactions, for the most part, were activated asynchronously.

During the IAI progression, signs of the permanent oxidative reactions' imbalance against the background of the ROS dysfunction were found. The maximum activation of oxidative reactions occurs on the background AOS failure. Given the role of ROS in the formation of inflammation, this may be one of the causes for the reactivity disruption found in NN patients with IAI. Therefore, the results of our study in some ways contradict the data of known studies, in which the linear dependence of AOS activity on the time of IAI is indicated. It is possible that such differences are caused by differences in the experimental models and differences in other experimental conditions. However, our data explain the ineffectiveness of antioxidants in IAI, as well as in NN. In our opinion, ROR interactions are much more complicated than some authors believe. It is worth noting that known recommendations for use of antioxidants did not significantly improve the results of treatment patients with IAI.

Taking into account our data, it is expedient to determine the ROR markers in patients and prescribe medication correction taking into account these markers, since the activity of different ROR components is different in different periods. Our study has a number of limitations. The study used a small sample (100 rats). To confirm the data, it is necessary to conduct additional experiments on a larger number of animals. Female rats were used in this study. Therefore, male rats should be used in future studies to confirm the data. Experiments with another NN and IAI models should be conducted to confirm the data. Research data must be verified on humans to definitively determine the validity of experimental data.

Conclusion

The development of acute IAI and underlying acute NN is characterized by late activation of oxidative reactions, permanent oxidative reactions' imbalance, ROS dysfunction, late maximal activity of oxidative reactions with the simultaneous AOS failure.

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Conflict of Interest

The authors declare no conflict of interest.

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