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I.M. Bagirov
Azerbaijan Medical University, Baku, Azerbaijan

OXIDATIVE STRESS IN LIVER TISSUES AT ALCOHOLIC HEPATITIS AND ITS CORRECTION BY A COMPLEX COMPOUND SYNTHESIZED ON THE BASIS OF PALLADIUM AND MEXIDOL

e-mail: med_avtor@mail.ru

An experiment was conducted on 20 white rats bred in vivarium conditions at the Research Center of the Azerbaijan Medical University, and divided into 4 groups. The 1st group included intact experimental animals, the 2nd-4th groups – experimental animals simulating alcoholic hepatitis. A complex compound (mexidazole) synthesized on the basis of palladium and mexidol was injected into the abdominal cavity of group 3 animals for 3 days, and group 4 animals – for 7 days at a dose of 0.02 mg/kg. A model of alcoholic hepatitis has been developed. In the homogenate, the average concentrations of surface-located SH-groups, internal protein-SH-groups, peroxidase, catalase and total antioxidant activity decreased compared to the intact state. In the blood of experimental animals, due to the action of alcohol, the activity of liver enzymes significantly increased, free lipid peroxidation increased in the liver tissue. The body's antioxidant defense system has significantly weakened. The results of the 3rd group of experimental animals showed that oxidative stress in the liver continues even after 10 days since the creation of the alcoholic hepatitis model. After injection of 0.02 mg/kg of mexidozole into the abdominal cavity for 3 days, the concentration of these enzymes in the blood tended to decrease. After daily administration of mexidozole at a dose of 0.02 mg/kg for 3 days into the abdominal cavity of white rats against the background of an alcoholic hepatitis model, pronounced positive changes in the dynamics of oxidative stress were noted.

Key words: alcohol, hepatitis, enzymes, oxidative stress, palladium and mexidol.

І.М. Багіров

ОКИСЛЮВАЛЬНИЙ СТРЕС У ТКАНИНАХ ПЕЧІНКИ ПРИ АЛКОГОЛЬНОМУ ГЕПАТИТІ ТА ЙОГО КОРЕКЦІЯ КОМПЛЕКСНОЮ СПОЛУКОЮ, СИНТЕЗОВАНОЮ НА ОСНОВІ ПАЛАДІЮ І МЕКСИДОЛУ

Було проведено експеримент на 20 білих щурах, розділених на 4 групи. До 1-ї групи увійшли інтактні експериментальні тварини, до 2–4-ї груп – експериментальні тварини, у яких моделювали алкогольний гепатит. Комплексну сполуку (мексидазол), синтезовану на основі паладію та мексидолу, вводили в черевну порожнину тваринам 3-ї групи протягом 3-х діб, а тваринам 4-ї групи – протягом 7 діб у дозі 0,02 мг/кг. Розроблено модель алкогольного гепатиту. У гомогенаті середні значення концентрації поверхнево-розташованих SH-груп, внутрішніх білково-SH-груп, пероксидази, каталази та загальної антиоксидантної активності порівняно з інтактним станом зменшилися. У крові піддослідних тварин за рахунок дії алкоголю значно збільшились показники активності печінкових ферментів, у тканинах печінки посилювалося вільне перекисне окиснення ліпідів. Система антиоксидантного захисту організму значно послабшала. Результати 3-ї групи піддослідних тварин показали, що окислювальний стрес у печінці триває навіть через 10 днів з моменту створення моделі алкогольного гепатиту. Після введення в черевну порожнину 0,02 мг/кг мексидозолу протягом 3 днів концентрація цих ферментів у крові мала тенденцію до зниження. Після щоденного введення мексидозолу в дозі 0,02 мг/кг протягом 3 днів у черевну порожнину білих щурів на фоні моделі алкогольного гепатиту відмічені виражені позитивні зміни в динаміці оксидативного стресу.

Ключові слова: алкоголь, гепатит, ферменти, окислювальний стрес, паладій та мексидол.

Alcohol is the main cause of liver damage and contributes significantly to the genesis of overall morbidity and mortality. Today, alcohol consumption is especially common among the general population. The problem of alcoholic liver damage still does not lose its relevance. Today, alcohol consumption is especially common among the general population. The study of its negative impact on human health and the organization of its rehabilitation is one of the priority tasks facing medicine. The

incidence of this problem among the younger generation is increasing day by day, and at the same time, this pathology has become a social problem, as it is widespread among the elderly population and leads to disability. [1, 4].

It has been established that pathological changes in the function of a number of organs and systems of the body occur under the influence of alcohol [5, 7]. The liver is most susceptible to these changes. Thus, under the influence of alcohol, a number of physiological functions of the liver are disrupted, and in some cases, cirrhosis of the liver develops as a result of chronic hepatitis. It is known from the literature that the pathogenesis of alcoholic hepatitis is multifactorial and is the end result of a complex interaction of ethanol metabolism, inflammation and immunological reactions [8]. The number of chronic liver diseases continues to increase due to the increasing propensity of the population to alcohol [8]. The results of the conducted studies show that for many years, moving away from medical control, alcoholic hepatitis becomes chronic and, as a result, makes the quality of life of patients low, and in many cases critical, easily turning into cirrhosis of the liver, increasing the likelihood of death. This situation is more typical for elderly and senile patients [2, 14].

Many medications have been proposed for the treatment of chronic alcoholic liver disease and especially cirrhosis. Despite numerous attempts to improve treatment outcomes and patient survival, the medications used in almost 40 % of patients with severe forms of liver damage do not allow for achieving clinically significant improvement [9, 10]. However, the use of numerous drugs in the treatment plays an important role in liver dysfunction. In this regard, the synthesis of combined biologically active substances has become an urgent problem of our time.

Among the group of drugs for the treatment of hepatitis, platinum derivatives are considered one of the most effective. But the use of such drugs is limited by high hepatotoxicity. Palladium compounds turned out to be the most promising among the complex compounds of other platinum group metals, which have a pronounced antitumor and significantly less toxic effect on the body as a whole [10, 15].

Considering the importance of the problem, a complex compound based on palladium and mexidol was synthesized at the Research Center of Azerbaijan Medical University. This substance with the chemical structure 2-ethyl-6-methyl-3-hydrospyridine tetrachloro-palladium-mexidol was tentatively named mexidazole.

The purpose of the study was to create a biologically active substance (mexidazole) obtained from a combination of palladium, used against tumors, but having a toxic effect on the liver, and mexidol, used in medical practice as an antioxidant, and to determine its hepatoprotective and antioxidant properties in an experiment by injection into the body.

Materials and methods. The experiments were carried out on 20 mongrel white rats, weighing 140–260 g, raised in vivarium conditions. Depending on the purpose of the study, the experimental animals were divided into 4 groups.

Group 1 – animals in an intact state, group 2 – a model of chronic alcohol, group 3 – 10 days after the creation of an alcoholic model, and group 4 – the introduction of 0.02 mg./kg of a dose of mexidazole into the abdominal cavity of experimental animals against the background of an alcoholic model for 3 days.

The experiments were carried out in accordance with the recommendations of the European Commission on Bioethics (Strasbourg, 1986).

In the vivarium, groups of experimental animals were placed in cages at 20 ° C and fed according to the required diet.

At the end of the experiments, the animals were decapitated under anesthesia by injecting 0.5 ml of calypsol solution into the abdominal cavity. For the tests, blood was taken and liver homogenate was prepared.

To assess changes in liver metabolism in the blood, the activity level of aspartate aminopherase (AST), alanine aminotransferase (ALT), glutamine transferase (γ-GT), creatine phosphokinase (CPK), lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) was determined. The concentrations of these enzymes were determined on the Bio Ssgeep MS-2000 analyzer (USA), operating in semi-automatic mode, using reagent kits manufactured by "Human".

At the end of the experiment, the liver was extracted and placed in porcelain dishes for washing with saline solution and homogenate was prepared. The concentration of markers of oxidative stress was determined in liver homogenate.

To assess the intensity of free lipid peroxidation, concentrations of hydrogen peroxide (H_2O_2) were determined by the method of Askawat, Matusushita S., and diene conjugates (DC) by the method of I.D.

Stalnaya, malondialdehyde (MDA) by the method of Uchiyama, Michara. To assess the overall antioxidant activity, the following markers were identified.

1. The SH group is a protein located on the surface and inside the structure.
2. Catalase or reduced glutathione (peroxidase).
3. Total antioxidant activity (TAA).

The statistical significance of the differences obtained as a result of experiments was calculated on a personal computer using Microsoft Office Excel application programs, using the Student's t-test and the nonparametric Wilcoxon-Mann–Whitney U–test based on modern recommendations [13]. The statistical difference was considered reliable at a value of $p < 0.05$. The correlation analysis was carried out using the Broys-Pearson method, and the correlation dependence was confirmed at $p > 0.07$.

We have developed a model of alcoholic hepatitis (MAH). To facilitate the absorption of alcohol from the stomach, alcoholic hepatitis in white rats was created in 3 stages. At the 1st stage, 1 ml of alcohol was injected into the stomach 3 times a day through a small diameter probe to each white rat, then the probe was removed and water was given. At the 2nd stage, at the end of the meal, 5 ml of alcohol mixed with 100 ml of water was placed in the cage, and after finishing the rats to the end, the drinkers were removed from the cage. At the 3rd stage, rats were given 5 ml of pure alcohol daily for 6 days. 20 minutes after taking alcohol, 100 ml of pure water was given. At the end of the experiments, the animals were decapitated and the liver was removed.

To prepare liver homogenate, at the end of the experiments, 0.1 ml of calypsol solution per kg of weight was injected into the abdominal cavity of white rats, the abdominal cavity was opened, the liver was removed, placed in porcelain dishes and washed with saline solution. Then they were transferred to another porcelain dish and crushed into small pieces with a sharp scalpel. The resulting pieces were further crushed using an IKA ULTRA-TURRAX T18 homogenizer until a homogeneous mass was obtained and diluted with the addition of saline solution in a ratio of 1:2. The resulting solution was centrifuged for 10 minutes at 3000 rpm. The liquid part was taken to epindorph to determine markers of oxidative stress. The method of obtaining homogenate was developed at the Research Center of the Azerbaijan Medical University.

Results of the study and their discussion. The results of a group of intact experimental animals were accepted as normal. Quantitative indicators obtained in further experiments were compared with intact ones. It was determined that the average AST activity in the blood taken from group 1 animals was 29.4±1.50 units/l, ALT – 35.2±1.85 units/l, γ-GT – 43.2±5.43 units/l, LDH 260.4±6.00 units/l, ALP 234±27.13 units/L.

When determining markers of oxidative stress, the following results were obtained. The average concentration of H_2O_2 in liver homogenate was 2.0±0.13 cu, DC – 1.42±0.12 D232/ml, MDA – 1.14±0.09 nmol/mg.

Based on the determination of markers of the antioxidant protection system in liver homogenate, it was found that the average concentration of the surface protein-SH group (SP-SH) in the liver of intact white rats was 31.1±0.51 nmol/mg, and the average concentration of the internal protein-SH group (IP-SH) was 21.2±0.38 nmol/mg, the average concentration of peroxidase was 11.2±0.38 nmol/mg, the average concentration of catalase was 247.4±12.42 nmol/mg, the average value of TAA was 40.56±0.96%.

In contrast to group 1, experimental animals with the alcoholic hepatitis model have impaired liver enzyme metabolism under the influence of alcohol and the average concentrations of liver enzymes in the blood have increased significantly.

Thus, in the blood of experimental animals included in group 2, the average enzyme activity increased: AST by 56 % ($P<0.05$), ALT – 61 % ($P<0.001$), γ-GT – 67 % ($P<0.05$), LDH by 66 % ($P<0.001$), CPK by 123 % ($P<0.001$), ALP by 88 % ($P<0.01$).

The mean concentration of H_2O_2 in liver homogenate increased by 80 % compared to the intact state ($P<0.001$). The mean concentration of DC was slightly increased compared to H_2O_2. Compared with the intact state, the increase in the average concentration of DC in the blood of white rats against the background of the alcoholic hepatitis model was 26 % ($P>0.05$). The average concentration of MDA, which is one of the main indicators of lipid peroxidation, increased by 126 % compared to the intact state ($P<0.001$).

Thus, the results obtained from experimental animals belonging to group 2 showed that under the influence of alcohol, free lipid peroxidation in liver tissue increased. Despite this, the body's antioxidant defense system has significantly weakened.

In the homogenate, the average concentration of the SP-SH groups decreased by 39 % compared to the intact state ($P<0.001$), the average concentration of the IP-SH group was 30 %, the average

concentration of peroxidase was 16 %, the average catalase activity was 11 %, and the average TAA value was 44 % (P <0.001).

Thus, based on the analysis of our experiments (Groups 1 and 2), it can be assumed that alcohol intensifies free lipid peroxidation, blocking the general antioxidant system in liver tissue. Oxidative stress in the liver disrupts tissue metabolism and acts as a driving factor in the development of hepatitis.

The results of experimental animals included in group 3 show that on the 10th day of the model creation, the average enzyme activity indicators increased compared to the intact group: AST by 54 % (P<0.005) ALT by 60 % (P<0.001), γ-GT by 57 % (P<0.005), LDH by 65.5 % (P<0.01), CPK by 123 % (P<0.001), ALP by 85.5 % (P<0.01) (Table 1).

Table 1

The state of oxidative stress in liver tissue depending on the time of the creation of the alcoholic hepatitis model

№	Markers	1st group	2nd group	3rd group
1	H_2O_2	2.0±0.13	**** 3.6±0.17	**** 3.55±0.18
2	DC	1.42±0.12	* 1.8±0.14	* 1.76±0.16
3	MDA	1.14±0.09	**** 2.58±0.15	**** 2.59±0.18
4	SH-group surface protein	31.1±0.51	**** 18.9±2.08	**** 18.6±2.12
5	Structural internal protein of the SH-group	21.2±0.38	* 14.9±1.52	*** 14.72±1.44
6	Peroxidase	11.2±0.44	* 9.38±1.32	* 9.24±1.27
7	Catalase	247.4±12.42	* 220±17.96	** 214±16.99
8	Total antioxidant activity	40.56±0.96	**** 22.8±3.12	*** 21±3.03

Note: *P>0.05; ** P<0.05; *** P<0.01; **** P<0.001

Thus, the results obtained by us show that the violation of liver metabolism under the influence of alcohol is persistent. However, the concentration of these enzymes is lower than in animals of the 2nd group.

So, in comparison with the 2nd group, the average AST activity in the blood decreased by 1.6 %, γ-GT by 6 %, and ALP by 1 %. However, the values of ALT, LDH and CPK activity in the blood remained at the level of group 2.This indicates that the metabolism of liver enzymes is constantly disrupted due to the influence of alcohol.

The results of the 3rd group of experimental animals show that oxidative stress in the liver continues even after 10 days since the creation of the alcoholic hepatitis model. The average concentration of H_2O_2 in liver homogenate increased by 78 % compared to the intact state (P<0.001).

Although the increase in the average DC concentration is somewhat less, it is still 23.5 % higher than the level in the intact state (P<0.05).

In contrast to both markers, the average concentration of MDA, the final product of free lipid peroxidation, increased more. Compared to the 1st group, this difference was 123 % (P<0.001).

Thus, as a result of our experiments, it was found that the intensification of peroxidation of free lipids in the liver tissue of white rats continues 10 days after the creation of the alcoholic hepatitis model. Despite this, the overall antioxidant defense system in liver tissue continued to decline.

As a result of the homogenate study, it was found that the average concentration of SP-SH was 40 % (P<0.001), the average concentration of IP-SH was 30.5 % (P<0.01), the average concentration of peroxidase was 17.5 % (P<0.05), the average catalase activity was 13.5 % (P>0.05), the average value of TAA was 48 % (P<0.01), which was higher compared to the intact state.

The results of our experiments show that oxidative stress is too massive even after 10 days of creating a model of alcoholic hepatitis.

The experimental animals of the 4th group were injected with mexidol at a dose of 0.02 mg/kg per day for 3 days after creating a model of alcoholic hepatitis.

It was determined that the average activity of AST enzymes in the blood was 46 % (P<0.05), ALT – 48 % (P<0.001), γ-GT – 45 % (P>0.05), LDH was 58 % (P<0.01), CPK was 110 % (P<0.001), and the ALP is 73 % (P<0.01). As can be seen, despite the introduction of mexidol into the abdominal cavity for 3 days, the average level of liver enzymes still remained above normal.

However, intraabdominal administration of the complex compound significantly reduced the activity of liver metabolism enzymes compared to group 3 animals.

Thus, the results of our experiments showed that the concentration of liver enzymes in the blood of animals created on the model of alcoholic hepatitis increased. After the injection of 0.02 mg/ kg of mexidol into the abdominal cavity for 3 days, the concentration of these enzymes in the blood tended to decrease (Fig. 1).

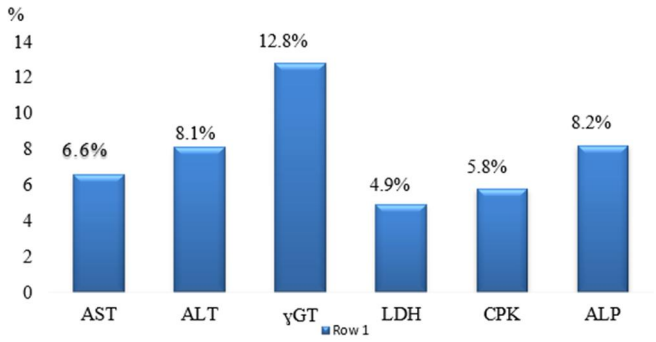

Fig. 1. Percentages of decrease in the concentration of the enzyme in the blood after intraperitoneal administration of 0.02 mg/ kg of a compound based on mexidosol in the simulation of alcoholic hepatitis in white rats.

It should be noted that the activity of the enzyme γ-GT decreased by 13 % more than the rest.

After daily administration of mexidol at a dose of 0.02 mg/kg for 3 days into the abdominal cavity of white rats against the background of an alcoholic hepatitis model, pronounced positive changes in liver homogenate were noted. Positive changes were also recorded in the dynamics of oxidative stress. The average concentration of H_2O_2 in liver homogenate decreased by 14 % compared to experimental animals with alcoholic hepatitis. Despite the decrease in the concentration of H_2O_2, the value did not reach a normal level, but remained 55 % higher (P<0.01), and the concentration of the primary product of H_2O_2 lipid peroxidation in the blood of 100 % of experimental animals was higher than that of intact animals.

The mean concentration of DC, an intermediate product of free lipid peroxidation, decreased by 11.7 %. Unlike H_2O_2, the concentration of DC in the liver homogenate of most experimental white rats reached a normal level. In this regard, the average concentration of DC in liver tissue was closer to normal and exceeded it only in 12 % (P>0.05), i.e. in 8 animals. However, the concentration of DC in the liver tissue continued to remain at a level higher than normal.

The mean concentration of MDA, the final product of free lipid peroxidation, decreased by 11.6 %. Despite this, in comparison with the intact state in 100% of animals, its concentration remained high. Thus, the introduction of 0.02 mg/kg of mexidol into the abdominal cavity of experimental animals with a model of alcoholic hepatitis for 3 days could not completely eliminate the intensity of lipid peroxidation.

Positive changes were also observed in the antioxidant protection system in the liver homogenate of experimental animals belonging to this group.

The mean density of SP-SH was 21 % (P>0.05), the average density of IP-SH was 28 % (P>0.05), the average concentration of peroxidase was 63% (P <0.05), the mean catalase activity was 20.5 % (P>0.05), and the average value of TAA was 57 % (P<0.01), which was higher in comparison with these indicators in the liver homogenate of white rats against the background of the alcoholic hepatitis model.

However, despite such positive dynamics, the average concentrations of markers of the antioxidant defense system in the liver were below normal. This difference was 27 % (P<0.01) for the surface protein group-SH, 10 % (P>0.05) for the structural internal protein group-SH and 12 % (P<0.05) for TAA. The average concentrations of the other two markers of the general antioxidant defense system (peroxidase and catalase) reached normal values (Table 2).

Table 2

Dynamics of changes in liver enzymes and markers of oxidative stress in the blood of white rats after administration of mexidol for 3 days against the background of an alcoholic hepatitis model

Indices	1st group	2nd group	4th group
AST	29.4±1.50	45.8±4.88**	42.8±465**
ALT	35.2±1.85	56.6±3.33****	52±2.59****
γ-GT	43.2±5.43	72±10.68**	62.8±9.04*
LDH	368±28.53	610±43.93***	580±47.85***
CPK	260.4±6.0	581±31.85****	547±37.47****
ALP	234±27.13	440±32.71***	404±20.40***
H_2O_2	2.0±0.13	3.6±0.17***	3.1±0.24***
DC	1.42±0.12	1.8±0.14*	1.59±0.16*
MDA	1.14±0.09	2.58±0.15***	2.28±0.15***
SH-group surface protein	31.1±0.51	18.9±2.08****	22.8±2.42***
Structural internal protein of the SH-group	21.2±0.38	14.9±1.52*	19.08±1.89*
Peroxidase	11.2±0.44	9.38±1.32*	15.26±1.08**
Catalase	247.4±12.42	220±17.96*	265±13.78*
TAA	40.56±0.96	22.8±3.12****	35.8±1.74**

Note: *P<0.05; ***P<0.01; ****P<0.001

There are known data on platinum derivatives, which are considered one of the most effective and used for the treatment of hepatitis. So, one of these drugs is cisplatin. But the use of such drugs is limited by high hepatotoxicity. In the studies of Magerramova N.F. [6], a comparative analysis of the content of blood, bilirubin, urobilinogen, protein, ketones, nitrates, glucose, leukocytes in the daily urine of animals was studied against the background of the introduction of a complex compound synthesized on the basis of palladium and mexidol (CCSPM) and cisplatin. The study of these data showed that changes in the content of leukocytes, urobilinogen, bilirubin, proteins and blood in urine are of practical importance in urine. These indicators statistically significantly change less against the background of the use of (CCSPM) than against the background of the use of cisplatin, which is a confirmation of less damage to the liver and kidneys by the complex compound and, accordingly, indicate its lower toxicity to the liver and kidneys [3, 11].

In comparison with cisplatin, our study of a new complex compound based on palladium with mexidol showed a pronounced antitumor and significantly less toxic effect for the body as a whole.

Conclusion

The results of our experiments showed that in the liver of white rats against the background of the alcoholic hepatitis model, the antioxidant defense system of the body is sharply weakened. Intraperitoneal administration of a complex compound synthesized on the basis of palladium and mexidol at a dose of 0.02 mg/kg for 3 days plays an important role in increasing the antioxidant protection system of the liver. Based on the results obtained, it was found that mexidol reduces oxidative stress in liver tissue and promotes the restoration of hepatocyte function.

The peculiarity of this drug was its low toxicity, as well as the simultaneous content in its composition of both the function of suppressing the activity of lipid peroxidation and the function of enhancing antioxidant activity. Reducing oxidative stress in the liver to a normal level improves the metabolism of liver enzymes.

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