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EFFECT OF OLIGORIBONUCLEOTIDES WITH D-MANNITOL COMPLEXES ON OXIDATIVE STRESS INDICATORS AGAINST THIOACETAMIDE-INDUCED LIVER FIBROSIS

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The aim of the study. *To determine the effect of oligoribonucleotides-D-mannitol complexes (ORN-D-M) on the indicators of oxidative destruction of biomolecules and the antioxidant system of cells in thioacetamide (TAA)-induced liver fibrosis.*

Materials and methods. *Liver fibrosis was induced for 8 weeks by intraperitoneal administration of TAA (150 mg/kg body weight). ORN-D-M (200 mg/kg per os) was administered orally during intoxication. At the end of the experiment, the liver was excised and examined for the content of oxidative stress products and the activity of antioxidant enzymes. Data were analyzed using the ANOVA test followed by Tukey post hoc testing.*

Results. *It is shown that the monotherapeutic treatment of ORN-D-M in TAA-induced liver fibrosis has a pronounced protective effect, which is manifested in the reduction of oxidative stress. ORN-D-M led to the attenuation of free radical damage of biopolymers, which was manifested in a decrease in the levels of peroxidation products of lipids and proteins with a simultaneous increase in the level of protein thiol groups and reduced glutathione. In addition, treatment with complexes increased the activity of the antioxidant defence system of cells.*

Conclusions. *The obtained results indicate that ORN-D-M complexes have a potential hepatoprotective effect in TAA-induced liver fibrosis. The complexes are able to effectively reduce the indicators of oxidative damage of biomolecules with a simultaneous increase in the activity of enzymes of the antioxidant system in TAA-induced fibrosis*

Keywords: *oxidative stress, antioxidant defence system, complexes of oligoribonucleotides with D-mannitol, liver fibrosis*

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1. Introduction

Liver fibrosis is a complex and dynamic process of connective tissue accumulation, which can be caused by various etiological factors [1]. Regardless of the nature of the factor, chronic liver disease is characterized by parenchymal necrosis, inflammation [2], and qualitative and quantitative changes in the components of the extracellular matrix [3]. No less important role in the development of fibrosis is played by oxidative stress, which is a reflection of the imbalance between the production of reactive oxygen species (ROS) and nitrogen and the work of the antioxidant cell defense [4]. Excessive amounts of ROS, which are formed as a result of oxidative reactions, interfere with the normal functioning of liver cells, triggering a cascade of events leading to liver fibrosis. In this case, Kupffer cells, resident macrophages of the liver, are the main effectors that generate ROS [5]. The molecular mechanism of pathogenesis is the release of Kupffer cells of biologically active mediators (cytokines, chemokines, adhesion molecules, ROS) in response to the damaging factor [6]. Due to intercellular communication, the released mediators activate "quiet" stellate cells and have a damaging effect on neighboring hepatocytes [7].

It is known that to date there is no approved hepatoprotective drug by the Food and Drug Administration (FDA) [8]. Therefore, the treatment of liver fibrosis is based on the use of oral agents mainly with antioxidant, antihypoxic and membrane stabilizing activities. However, the use of modern synthetic drugs is often accompanied by the development of side effects with prolonged use [9]. This fact limits the use of chemicals and prefers drugs of natural origin.

2. Literature review

Potentially promising molecules for the development of hepatoprotective agents are ORN-D-M complexes. They are compounds consisting of total yeast RNA with a dominant fraction of 5–8 nucleotides and D-mannitol [10, 11]. ORN-D-M are formed due to the formation of hydrogen bonds between the parallel hydroxyl OH groups of D-mannitol and the centers of hydrogen bond generation in nucleoside heterocycles [12]. The optimal ratio at which ORN-D-M have biological activity is: ORN: D-M – 2.5: 1 [13]. It is known that the complexes have a wide range of biological activity. In particular, ORN-D-M are effective in the monotherapeutic treatment of chronic viral hepatitis B and C with a low level of viral load (<800,000 IU/l) [14]. In addition, ORN-D-M have found their application in combination therapy with phospholipids against non-alcoholic steatohepatitis [15]. We have previously shown that the complexes are effective in the treatment of acute TAA-induced hepatotoxicity [16, 17].

Since hepatitis B and C viruses are one of the main etiological factors leading to chronic hepatitis, fi-

brosis, cirrhosis and hepatocellular carcinoma, it is promising to find drugs that have both antiviral and hepatoprotective activities.

3. The purpose and objectives of the study

The aim of the study was to determine the effect of ORN-D-M complexes on the indicators of oxidative stress and activity of antioxidant enzymes in TAA-induced liver fibrosis.

To achieve this goal, the following tasks were set:

1. Determine the content of TBA-active compounds, protein carbonyl derivatives and protein thiol groups in liver samples in TAA-induced fibrosis in mice.

2. To investigate the activities of glutathione peroxidase, glutathione-S-transferase and the level of reduced glutathione in liver samples in TAA-induced fibrosis in mice.

4. Materials and methods

The study used C57BL/6 mice aged 2–2.5 months and weighing 18–20 g, which were raised in the vivarium of the Institute of Molecular Biology and Genetics of NASU. Animals were kept on a standard diet under conditions of free access of water and food in rooms with humidity of 50–70 % and a 12-hour light/dark cycle. The experiment with chronic liver damage was performed for 8 weeks on the basis of the vivarium of the Institute of Molecular Biology and Genetics of the National Academy of Sciences of Ukraine. The experimental design was reviewed and approved by the Bioethics Committee of the Institute of Molecular Biology and Genetics of NASU (protocol 16 of December 3, 2018).

Animals were kept and manipulated in accordance with the provisions of Article 26 of the Law of Ukraine No. 3447-IV of 21 February 2006 “On the Protection of Animals against Cruelty”, the European Convention for the Protection of Vertebrate Animals Used for Research and Scientific Purposes (Strasbourg, 1986), "General Ethical Principles of Animal Experiments", approved on September 20, 2001 by the First Ukrainian National Congress on Bioethics, and taking into account the provisions set forth in the NIH Guide for the Care and Use of Laboratory Animals.

The study used a model of TAA-induced chronic liver damage.

Animals were randomly (n = 6) divided into 5 groups:

NaCl – animals that received intraperitoneally 0.9 % NaCl solution three times a week for 8 weeks;

TAA – animals that received intraperitoneally a solution of TAA at a dose of 150 mg/kg body weight of mice three times a week for 8 weeks;

ORN-D-M – animals that received daily ORN-D-M (per os) at a dose of 200 mg/kg body weight for 8 weeks;

TAA+ORN-D-M 0 – animals that received intraperitoneally a solution of TAA at a dose of 150 mg/kg body weight of mice three times a week for 8 weeks and daily ORN-D-M (per os) at a dose of 200 mg/kg body weight body for 8 weeks;

TAA+ORN-D-M 4 – animals treated intraperitoneally with a solution of TAA at a dose of 150 mg/kg body weight of mice three times a week for 8 weeks and 4 weeks after the start of the experiment daily treatment with ORN-D-M (per os) at a dose of 200 mg/kg body weight up to end of the experiment.

Euthanasia of animals was performed under the action of ketamine / xylazine (100/15 mg/kg, respectively) 3 days after the last injection of the toxin. The liver was perfused, excised and washed with cold 0.9 % NaCl.

Evaluation of oxidative degradation of biomolecules was performed based on the determination of the content of TBA-active compounds, protein carbonyl derivatives and protein thiol groups in liver tissue.

The content of TBA-active products in the liver parenchyma was determined by the amount of formed colored raspberry complex, which was formed by the interaction of the products of secondary peroxidation of lipids with thiobarbituric acid [18].

The content of protein carbonyl derivatives was determined by the number of formed aldehyde and ketondinitrophenylhydrazones of neutral and basic nature [19].

The content of protein SH-groups was determined by the amount of formation of 2-nitro-6-mercaptobenzoic acid as a result of the interaction of Elman's reagent with protein SH-groups [20].

The activity of the glutathione link of antioxidant protection of cells from the action of hepatotoxin was performed on the basis of determining the level of reduced glutathione (GSH), and the activities of glutathione peroxidase (GP_x, 1.11.1.9) and glutathione-S-transferase (GST 2.5.1.18).

The content of reduced glutathione in the liver parenchyma was determined by the level of formation of thionitrophenyl anion due to the interaction of SH-groups of glutathione with 5,5′-dithiobis-2-nitrobenzoic acid and was determined by the calibration curve, which was constructed by introducing into the method from 0.0001 M to 0.005 M and expressed in μmol/mg protein [21].

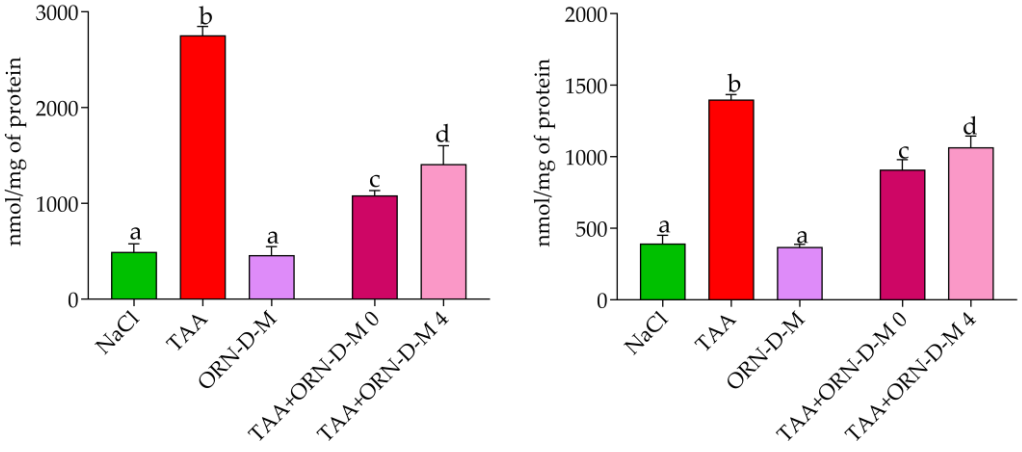
GP_x activity in the cytosolic fraction of the liver was determined by the rate of oxidation of GSH before and after incubation with hydrogen peroxide [22]. GST activity in the cytosolic fraction of the liver was determined by the reaction of GSH with 1-chloro-2,4-dinitrobenzene, which occurs with the formation of a conjugate with a maximum light absorption at 340 nm [23].

Data analysis was performed using Prism 6 software (GraphPad, La Jolla, Ca). Study data were expressed as mean ± standard deviation and analyzed by ANOVA test followed by sequential Tukey testing. The differences were considered significant at $P \leq 0.05$.

5. Research results

One of the leading places in the structure of chronic liver disease is liver fibrosis [24]. The pathogenesis of liver fibrosis is complex and involves hepatocellular damage, which is associated with inflammation and constant remodelling of extracellular matrix components [25, 26]. Oxidative stress plays an equally important role in the development of fibrosis – a state of imbalance between prooxidants and antioxidants, which can cause oxidative damage to biomolecular acyl chains of unsaturated fatty acids of membranes, thiol groups in proteins and nucleic acid bases.

The results of the studies showed that monotherapeutic treatment with complexes led to a decrease in oxidative damage to liver biopolymers. As shown in Fig. 1, *a*, *b*, the use of TAA to model liver fibrosis contributed to a significant (P<0.05) increase in the level of TBA-active compounds and protein carbonyls (TAA group), indicating severe damage to the hepatocyte membrane and oxidative damage to liver proteins. At the same time, the use of complexes from the beginning of the study helped to reduce the level of TBA-active compounds and protein carbonyls by 60 and 34 %, respectively, compared with the group of animals that received only hepatotoxin. Interestingly, the treatment of ORN-D-M 4 weeks after the first application of TAA also showed protective properties, which helped to reduce the level of markers of oxidative stress. It should be noted that the complexes themselves did not cause toxic liver damage with long-term use.



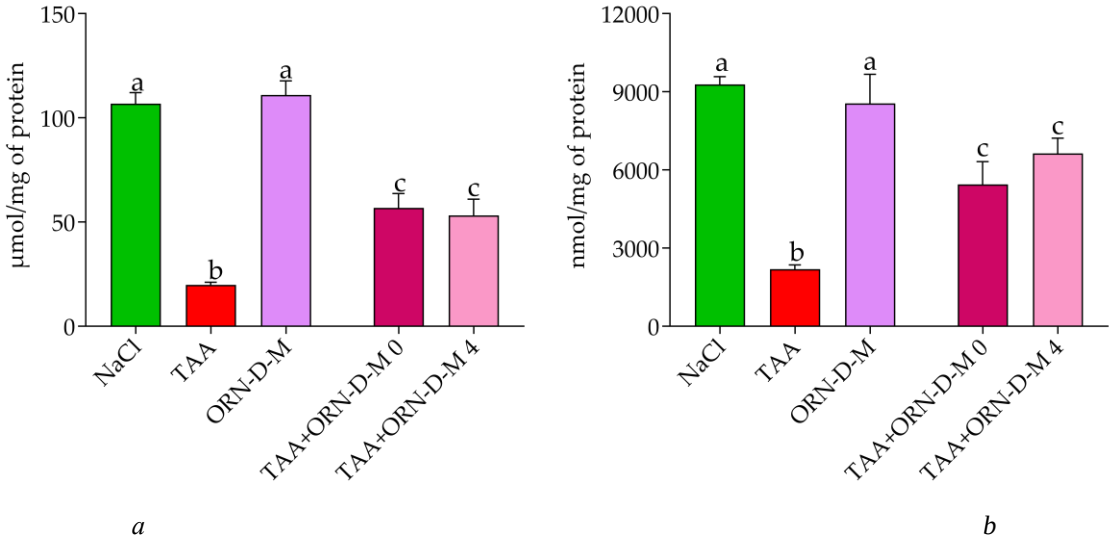
a *b*

Fig. 1. The content of products of oxidative degradation of cellular biomolecules in the liver: *a* – the content of TBA-active compounds; *b* – the content of protein carbonyls: values denoted by letter indices (a, b, c, d) are statistically significantly different, P<0.05; n=6 for each group

It was found that ORN-D-M have anti-inflammatory properties, inhibit oxidative processes in cell membranes and normalize the activity of inducible NO synthase [15, 27]. Thus, we suggest that the protective effect of ORNs-D-M may be related to the above-mentioned properties of the complexes. We also suggest that the complexes may take on the "first blow" of the active intermediates TAA and aldehydes formed as a result of peroxidation. The complexes act as proton donors for reactive oxygen species with unpaired electrons at the external electronic level, which leads to a decrease in oxidative stress in TAA-induced liver fibrosis.

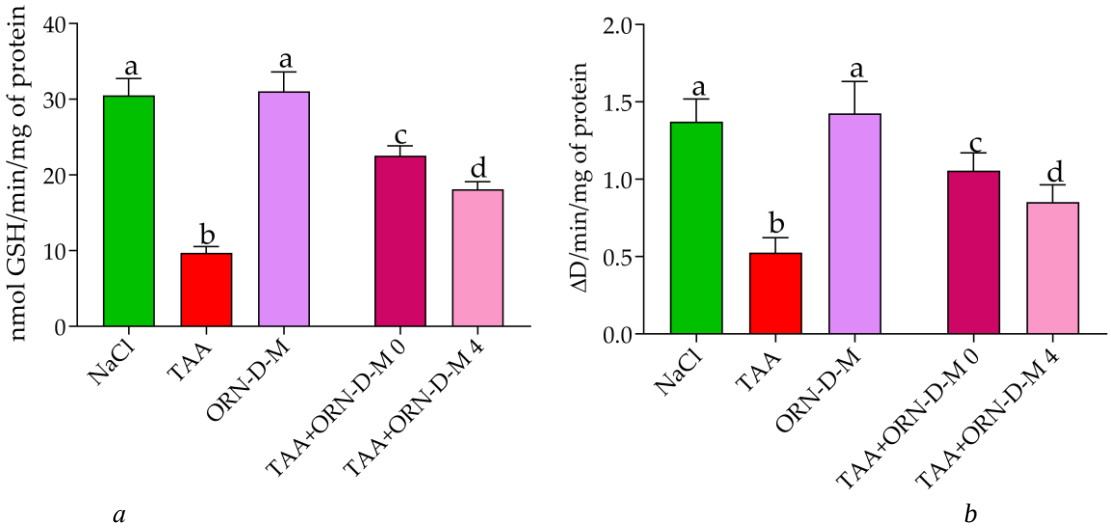
Because thiol groups are most sensitive to ROS, long-term use of TAA to induce fibrosis has been shown to significantly reduce levels of protein thiols and reduced glutathione (non-enzymatic cell defense) by 76.4 and 81.4 %, respectively, compared to carrier-only animals. However, ORN-D-M from the beginning of the study increased the decrease in the levels of protein thiols and reduced glutathione in 2.48 and 2.86, respectively, compared with the group of animals that received only the toxin (Fig. 2, *a*, *b*). It should be noted that a similar trend was observed in the group TAA + ORN-D-M 4. Treatment with complexes 4 weeks after the onset of fibrosis significantly increased levels of protein thiols and reduced glutathione by 148.4 % and 167 %, respectively, and did not differ statistically from the group TAA + ORN-D-M, who received treatment with complexes from the beginning of the study.

As shown in Fig. 3, a, b, in chronic liver intoxication there was a significant decrease in the activity of marker enzymes, including GST and GP_x by 61.3 and 68.2 %, respectively, compared with the control group of animals. However, the reduced activities of antioxidant enzymes under the action of TAA were significantly increased with daily use of ORN-D-M for therapeutic purposes. It was shown that the complexes increased the activities of GST and GP_x in 2 and 2.32 compared to animals that received only the toxin (Fig. 3, *a*, *b*). It should be noted that a similar trend was observed with daily treatment of ORN-D-M 4 weeks after 1 application of hepatotoxin. The complexes increased the reduced levels of GST and GP_x marker enzymes by 60 and 86.6 %, respectively.



a *b*

Fig. 2. Dynamics of changes in the index of non-enzymatic defense and protein thiols in the liver: *a* – the level of reduced glutathione; *b* – the level of protein thiols: values denoted by letter indices (a, b, c, d) are statistically significantly different, P<0.05; n=6 for each group.



a *b*

Fig. 3. Indicators of activity of enzymes of glutathione system of antioxidant link of protection of cells: a – glutathione peroxidase activity; b – glutathione-S-transferase activity: values denoted by letter indices (a, b, c, d) are statistically significantly different, P<0.05; n=6 for each group

6. Discussion of research results

Because one of the major mechanisms of liver fibrosis is the formation of free radicals in fibrosis [28], antioxidant activity and inhibition of free radical production are important to protect cells from TAA-induced hepatotoxicity.

Antioxidant enzymes, such as GPx and GST, play important functions in protecting against the harmful effects of free radicals in the liver. This study showed that monotherapeutic use of ORN-D-M from the beginning of the study and 4 weeks after the initiation of fibrosis, protects the liver from free radical oxidation, enhancing the activity of glutathione-dependent antioxidant protection. The action of the complexes is probably due to an increase in the level of reduced glutathione. Depletion of the reduced glutathione pool under oxidative stress affects the activity of GPx and GST, which use reduced glutathione as a substrate in xenobiotic biotransformation reactions. Therefore, we can assume that the complexes by increasing the level of reduced glutathione thereby increase the activity of antioxidant enzymes. These results suggest that ORN-D-M may have antioxidant properties in TAA-induced liver fibrosis.

We hypothesize that the main mechanisms by which ORN-D-M protect the liver from TAA-induced fibrosis are related to their anti-inflammatory, membrane-stabilizing, and antioxidant activities. On the other hand, we suggest that the complexes may modulate the signal-

ling pathways involved in the development of fibrosis, in particular TGF-β / SMAD3 signalling. TGF-β also activates SMAD-independent signalling pathways by increasing the production of reactive oxygen species, which leads to the activation of other signalling cascades and increased regulation of prophylactic genes [29]. Therefore, inhibition of TGF-β1-induced SMAD-dependent and SMAD-independent (P38 and MEK) pathways [30, 31] may be a key mechanism by which ORN-D-M exert their protective effects, which will be the subject of our future research.

Study limitations. This study examined the effect of ORN-D-M complexes on the activity of enzymes of phase I detoxification of xenobiotics, in particular the activity of cytochromes P450 and flavin-containing monooxygenases, but there was a limit to the availability of the necessary reagents. In addition, the study of inflammatory processes, which are an integral part of chronic toxic liver damage, in knockout mice by the IL-6 gene was envisaged, but at this stage this is not possible due to the lack of this line of mice in Ukraine.

Prospects for further research. In further studies, it is advisable to establish the relationship between the effects obtained and the effect of ORN-D-M complexes on the signalling pathways involved in the induction of oxidative stress. This will help establish the molecular mechanism of action of complexes in chronic hepatotoxicity.

6. Conclusions

1. Monotherapeutic use of ORN-D-M complexes in TAA-induced liver fibrosis in mice leads to a decrease in oxidative damage to hepatocyte biomolecules, which was manifested in a decrease in levels of TBA-active compounds and protein carbonyl derivatives with a simultaneous increase in protein thiolo levels.

2. The introduction of ORN-D-M complexes against the background of hepatotoxin increases the activity of enzymes of the antioxidant defense system, namely, glutathione peroxidase and glutathione-S-transferase, which protect cells from hepatotoxin. In addition, the use of complexes increases the content of reduced glutathione in the liver parenchyma.

Conflict of interest

The authors declare that they have no conflicts of interest.

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