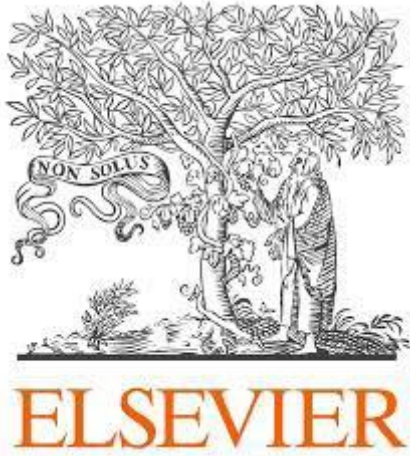


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The background is a solid blue color. On the right side, there is a large, light blue geometric shape that resembles a stylized 'L' or a corner cut. This shape is composed of several horizontal bars of varying lengths, creating a stepped effect. The top bar is the longest, and each subsequent bar below it is shorter, extending further to the right. The overall composition is clean and modern.



BioScience

Issue 12 (2), December 2017

VOLUME 67

Oxford University Press

2017

*BioScience, Issue 12 (2), (December), Volume 67. Oxford University Press, 2017. -
Pages 1350-1549.*

Proceedings of the Journal are located in the **Databases Scopus and Web of Science.**

Source Normalized Impact per Paper (SNIP): 2.261

SCImago Journal Rank (SJR): 2.374

Impact factor: 4.294

5-Yr impact factor: 6.607

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ISSN 0006-3568

EISSN 1525-3244

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The state of glutathione system in rats' liver with sodium fluoride in subtoxic doses

Abstract: On 60 white Wistar rats' population subacute experiment was investigated to determine the effects of small doses of subtoxic chemical substance belonging to sodium fluoride liver detoxication system. There were 5 experimental groups and one control with 10 animals in each (N=60). Content glutathione reduced and enzyme activity glutathione system investigated parameters of liver homogenate of rats. Studies increase liver glutathione's content within 10 days of action at a dose of sodium fluoride 1/10 LD₅₀ and within 30 days of the action of sodium fluoride in 1/100 LD₅₀ dose can be considered as the activation of defense reactions, and further decrease as maladjustment organism rats.

The revealed changes in the content of reduced glutathione and antioxidant enzymes activity glutathione dependent antioxidant enzymes rat liver indicate destabilization glutathione system, which may contribute to violations of adaptation in response to the development of oxidative stress as a result of fluoride intoxication.

Keywords: liver detoxication system, reduced glutathione, glutathione system of enzyme's activity, liver homogenate, Wistar rats' populations, sodium fluoride.

Introduction

Investigation was performed at the Department of Clinical Pathophysiology, Topographical Anatomy and Operative Surgery at Kharkiv Medical Academy of Postgraduate Education according to the issue "Radiotoxins' pathophysiological mechanisms on the body and methods of early diagnostics and correction".

There are geochemical province of excessive fluoride content in water in Ukraine. It is known that the increasing concentration of fluoride in the soil and in the water spreads pathology among children and adults, which can occur dental fluorosis, disorder of bone mineralization tissue [1].

At the heart of biotransformation harmful environmental factors are enzymatic conversion of molecules. This protective function of the body is until exhausted spare capacity of the body. It is known that the metabolism of chemicals in the body comes in two phases: the first phase - is the oxidation and hydrolysis recovery, and the second phase - a glucuronidation, sulfonation methylation and binding to glutathione [2-6].

To understand the state of prooxidant and antioxidant balance in rats under the influence of sodium fluoride (FS) experiment the antioxidant status was investigated. The most reactive antioxidants include glutathione system components which the pool restored and oxidized forms tripeptide glutathione and enzymes, ensuring reduced of glutathione, utilization of hydrogen peroxide and lipoperoxid - glutathione reductase (GR), glutathione peroxidase (GPO) glutathione transferase (GT).

This system, in addition, participates in the mechanisms of non-specific responses and adaptation to the factors of different nature, including chemical [2, 3]. Glutathione is synthesized and metabolized primarily in the liver, which is in violation activity glutathione defense system suffers primarily [7-12].

The aim was to study the subacute experiment on white rats the influence of sodium fluoride on antioxidant system and detoxification processes of the liver and justification of informative indicators of dysfunction.

Materials and methods

As objects of the study sodium fluoride was selected. Based on the parameters of acute toxicity of the compound belongs to the second class of potential danger, which has cumulative properties. The animals were subjected to oral the seed animals probe using aqueous solutions of compounds once daily for 60 days at doses of 1/10, 1/100LD₅₀. Median lethal dose (LD₅₀) were set at 20 mg/kg and 2 mg/kg animals respectively. Due to lack of scientific literature, the prognostic characteristics of the potential dangers of sodium fluoride to warm-blooded animals and humans has identified the need to explore pathophysiological mechanisms of disorders in the body influenced by the subtoxic doses. Effect of sodium fluoride on antioxidant system and detoxification function of the liver as the main decontaminating laboratory, studied under conditions subacute toxicological experiment on white rats' Wistar population. Sexually mature animals weighing 180-200 g were daily influence by oral xenobiotics' action within 60 days.

The substance in the form of aqueous solutions administered in doses 1/10; 1/100LD₅₀ stomach using a metal probe in the morning on an empty stomach before feeding animals. The control group animals received appropriate volumes of drinking water. In each group - research and control were 10 animals.

All stages of a scientific experiment carried out while respecting bioethics rules of humane treatment of animals and requirements of the European Convention for the Protection of vertebrate animals used in scientific experiments (Strasbourg, 1986). In total, subacute experiment 60 animals were studied (N=60).

Program study included:

1) the study of the effect of sodium fluoride on the function of liver detoxification by the following indicators - the enzyme activity glutathione system in rat liver homogenate by the action of sodium fluoride in subtoxic doses;

2) the study of oxidant-antioxidant system interaction by glutathione content.

The activity of glutathione transferase was studied by the formation of conjugates 1-chlorine-2,4-dinitrobenzene [15, 16]. The content of reduced glutathione was defined in glutathione transferase reaction [17]. Content glutathione reduced enzyme activity was investigated glutathione system in rat liver homogenate [13, 14, 15, 18, 19]. To assess the statistical group differences used options - test Student - Fisher.

Results and discussion

In the liver to oral the seed of rats sodium fluoride 1/10 LD₅₀ dose on the 10th day of the experiment a statistically significant increase ($p < 0.001$) 51% of glutathione reduced compared with the control was observed. Starting from the 20th to the 60th day of the experiment recorded a gradual reduction of glutathione - 40, 61, 73 and 76%. Oral administration to rats in doses of FS 1/100 LD₅₀ at first was accompanied by a statistically significant ($p < 0.001$) increase in the level of viral hepatitis - by 34, 54 and 72%, respectively 10, 20 and 30th day relative to control. 50 and 60-day observation that the level of this indicator decreased by 34-40%.

Reduction of glutathione almost the entire duration of the FS in a dose of 1/10 LD₅₀ and at the end of the FS term in a dose 1/100 LD₅₀ probably due to, on the one hand, violation of the synthesis by the hepatotoxic effect of FS, on the other hand, increased use of the reduced form of glutathione for neutralization products of free radical oxidation and lipid peroxidation, which are formed in the large amounts in case of prolonged admission of FS. The gradual reduction of viral hepatitis in the

case of oral administration to rats in doses of FS 1/10 LD₅₀ with a significant degree of certainty suggests the intensification of lipid peroxidation, which confirmed in earlier studies [2, 5]. In addition, glutathione performs a central role in the inactivation of toxic and reactive products which are generated during biotransformation of xenobiotics. Therefore, the observed reduction of viral hepatitis may contribute to the accumulation and the consequent intensification of LPO. Increase of glutathione within 10 days of action in FS 1/10 LD₅₀ dose and within 30 days of action in FS 1/100 LD₅₀ dose can be considered as the activation of defense reactions.

In general terms, the level of glutathione of viral hepatitis in the liver determines the effectiveness of the cells' protection from oxidative stress products and depends on the rate of synthesis and breakdown, as well as the activity of enzymes that regulate the ratio of its oxidized and rehabilitative forms.

Prolonged exposure of FS doses 1/10 LD₅₀ led to a gradual decrease ($r \leq 0,001$) when compared to control GPO activity in rat liver (enzyme of neutralization of hydrogen peroxide, lipoperoxids which are formed as a result of activation of lipid peroxidation). Effect of FS in a dose 1/100 LD₅₀ thus was different. On 10, 20 and 30th day of the experiment in animals was noted statistically significant ($r \leq 0,002$) compared with control increased activity GPO respectively 10, 20 and 13%, and 50, the 60th day - decrease ($p < 0.001$) at 10-17%. Glutathione is the substrate of GPO, that's why the observed depletion of the pool of glutathione FS limited period of time in doses of 1/10 and 1/100 LD₅₀ can lead to inactivation of this enzyme. The decrease in activity of rat liver GPO for the duration of FS in a dose of 1/10 LD₅₀ and the end of the term of the FS in 1/100 LD₅₀ dose is an unfavorable factor of reduction in neutralization efficiency of peroxide radicals and can cause significant damage to the hepatocyte membrane. According to the literature [12], decreased activity GPO can be seen as a minimal manifestation of adaptive processes in the organism under conditions of oxidative stress.

The results showed a significant ($r \leq 0,001$), relative to the control group of animals, increased activity of GT (enzyme of peroxides detoxify) on 10 and 20th day of toxification of the rats FS in a dose of 1/10 LD₅₀, respectively, 70 and 119%. In subsequent periods of observation enzyme activity decreased ($p < 0.001$) at 45, 63 and 59%. Action FS in a dose 1/100 LD₅₀, by contrast, was characterized ($r \leq 0,019$) activity GT 10, 20 and 30th day, respectively 33, 101 and 64%, and 50, the 60th day - decrease 45-50%. Activity GT, usually induced by toxic electrophilic metabolites,

therefore, its increase may indicate the accumulation in the liver of experimental animals [8, 10, 12]. GT to perform its functions uses GT as a substrate because the gradual depletion pool SH by prolonged exposure FS may lead to decreased activity of the enzyme. It should be emphasized that GT is an important component of antioxidant that provides detoxification of lipid peroxidation products generated in the endoplasmic reticulum during the metabolism of xenobiotics [12-13].

In the liver of rats who were administered a long time FS in a dose of 1/10 and 1/100 LD₅₀, determined changes and GR activity (the enzyme responsible for the replenishment pool of glutathione). In the case of 1/10 LD₅₀ dose of enzyme activity statistically significantly ($p < 0.001$), when compared to control, increased only on the 10th day of observation of 99%. In the following activity timing GR gradually decreased ($r \leq 0,003$) 43, 53, 73 and 77%. Introduction in experimental animals FS 1/100 LD₅₀ dose led to an increase ($r \leq 0,002$) GR activity relative to controls at 10, 20 and 30th day, respectively 89, 75 and 31% in the next timing of FS in this dose recorded a decrease ($r \leq 0,003$) enzyme activity an average of 48-51%. Reduced activity of the GR indicates, above all, the failure of glutathione regeneration system. Increase enzyme activity can be seen as adaptive response to promote the necessary level of glutathione.

Conclusion. Thus, changes of glutathione content and the activity of glutathione dependent antioxidant enzymes in rats' liver indicate destabilization in glutathione system, which may contribute to violations of adaptation in response to the development of oxidative stress as a result of fluoride intoxication. Depletion of glutathione system in rats' liver in case of the action of FS in a dose of 1/10 LD₅₀ much more increases the process of lipid peroxidation, so that destructive changes in hepatocytes may be developed.

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BioScience

Issue 12 (2), December 2017

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