ENGLISH VERSION: PAIRING ANTIOXIDANT AND PROOXIDANT SYSTEMS IN WHITE RATS AT SUBACUTE EFFECTOF OLIGOETHERS

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New oligoethers group on the basis of oxide ethylene and propylene is absolutely unstudied and available data on acute toxicity parameters do not open pathophysiological fundamentals of structural and metabolic violations of homeostatic functions of the organism. The need to study the systemic anti-systemic interactions is dictated primarily by their importance in ensuring the stability of the internal environment of the body and prognostic assessment of possible risk of dysfunction of the oxidant-antioxidant system, which form the membrane pathology. the purpose of the work was to study the status of cooperative interaction oxidant-antioxidant system in white rats exposed to subacute oligoethers experience and justification criterion-relevant indicators diagnostic molecular pathology. In the work of 100 white rats (9 experiment groups and 1 control group, total N = 100) in the subacute experience was study action small subtoxic doses a new chemical substances, to simple polyethers - L-501-2-100, L-1601- 2 -50 "B" and L-1601-2-50 "P". The following doses were used: 1/10 LD_{50}, 1/100 LD_{50} and 1/1000 LD_{50}. The control group received the appropriate volume of drinking water. In blood and blood sera improving activity of antioxidant and prooxidant system was detected. Statistical processing of the results was carried out using Student'- Fisher t test. The differences between control and experience are significant on level significance at p <0.05. Investigations showed significant changes experiments indicators in rat, was influence impact oligoethers doses 1/10 and 1/100 LD_{50}. In 1/1000 LD_{50} xenobiotic does not effect on the activity of antioxidant and prooxidant system. More specifically, an increase content was revealed 2,4-DNFKG 78,5%; 38,9% and 56,1%; 2,4 DNFKG-100,6%; 52,3% to 73,07%; Schiff bases – 43,6%; 20,4% to 28,96%; DK – 103,5%; 58,3% and 78,2%; malondialdehyde – 255,5%; 156,5% and 192,9%; and AST activity by 285,1%; 192,5% and 235,8%, ALT – 333,3%; 229,6% and 296,3%; γ-HT – 61,7%; 40,1% and 50,3%, respectively, under the influence of L-501-2-100, L-1601-2-50 "B" and L -1601-2-50 'P' as compared with the control group. Investigations showed that under dose of 1/10 LD_{50} oligoethers inhibit activation of antioxidant system and xenobiotics detoxification system, and activate freeradical processes, lipid peroxidation, that is evidence of adaptic mechanisms frustration and dysfunction of systemic-antisystemic interactions of oxidant and antioxidant systems. With higher than dose of 1/10 LD50 oligoethers have inhibition activity of antioxidant system and detoxification system in terms of xenobiotic activation of freeradical processes, lipid peroxidation. Conclusions: oligoethers L-501-2-100, L-1601-2-50 "B", and A-1601-2- 50 "R" in dose of 1/100 LD_{50} under subacute effect on white rats stimulate in organism freeradical processes, lipid peroxidation, antiradical and antiperoxide defense system activation against a background of significant stress of adaptic mechanisms. With higher dose of 1/10 LD50 oligoethers have inhibition activity of antioxidant system and detoxification system in terms of xenobiotic activation of freeradical processes, lipid peroxidation, wich indicates antiperoxide defense system activation against a background of significant stress of adaptic mechanisms. In 1/1000 LD_{50} xenobiotic does not affect the activity of antioxidant and prooxidant system in the blood and blood sera of white rats.

Key words: *xenobiotics, oxidant and antioxidant homeostasis, white rats, subacute experiment.*

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Introduction

In the face of increased anthropogenic chemical load on the biosphere one of the most important tasks of medical science is the early diagnosis of disorders of homeostatic functions of the body, the rationale for the development of environmentally sound mechanisms of pathological conditions and methods for their pathogenetic correction [1 - 4]. In this regard, relevant is the study of the pathogenesis of structural and metabolic disorders and metabolic identifying leading indicators on the basis of systemic anti-system estimates a state of homeostasis. The need to study the systemic anti-systemic interactions is dictated primarily by their importance in ensuring the stability of the internal environment of the body and prognostic assessment of possible risk of dysfunction of the oxidant-antioxidant system, which form the membrane pathology. Analysis of the literature [1 - 4] showed that the new group oligoethers based on ethylene and propylene oxide has not been studied, and the available data on acute toxicity parameters do not reveal the pathophysiological basis of the structural and metabolic disturbances of homeostatic functions of the body. Based on the above, the purpose of the work was to study the status of cooperative interaction oxidant-antioxidant system in white rats exposed to subacute oligoethers experience and justification criterion-relevant indicators diagnostic molecular pathology.

Materials and methods of research

Selection of new group oligoethers justified by large volumes of production, a wide range of products and use on the basis of various sectors of the economy and the lack of prognostic assessment of potential risks to warm-blooded animals and humans. In this work three new chemicals with regulated physico-chemical properties and related oligoethers following grades were used: L - 501-2-100 (polyoxyethylene glycol monomethyl ether acetals), L-1601-2-50 "B" (polyoxypropyleneoxyethylene glycol butilallilovy ether) and L-1601-2-50 "P" (acetals monobutyl ether polyoxypropylene oxyethylene glycol) with regulated physicochemical properties. The presence in the molecule oligoethers hydrophilic groups and hydrophobic radicals gives them surface-active properties, which is a prognostic significance in the selection and justification of research methods. Based on the results of acute toxicological data oligoethers are moderate and low-toxic compounds, with no cumulative properties. The mean lethal dose (LD50) for white rats were set at 3.46; 3.85 and 5.17 g/kg body weight, and the coefficients of cumulation (CK) levels: 9.8; 9.17; and 7.13, respectively,

for the L-501-2-100, L-1601-2-50 "B" and the L-1601-2-50 "P".

The research program included a subacute toxicological experiment on mature white male rats of Wistar weighing 0.18-0.20 kg. While in vivarium under standard conditions and feeding the animals. Were administered the studied oligoethers intragastrically with aqueous solutions, using a metal probe daily in the morning before feeding for 45 days. We used the following doses: 1/10 LD_{50}, 1/100 LD_{50} and 1/1000 LD_{50}. A control group of animals received corresponding volumes of drinking water. In the experiments, 100 rats were used. Nine experimental and one control group, there were 10 animals in each of them (total N = 100). Experiments were carried out in compliance with the requirements and principles of bioethics "European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes" (Strasbourg, 1986).

To assess the state of the oxidant-antioxidant homeostasis after subacute exposure oligoethers we determined the intensity of free radical processes and lipid peroxidation (LPO) on the content of the final and intermediate products of oxidation of proteins and lipids on the background of the study of antiradical, antiperoxide defense. In the blood serum by conventional biochemical methods [5 - 7] we determined the content of carbonylated proteins - 2,4- dinitrophenyl-aldogidrazonov (2,4-DNFAG), 2,4-dinitrophenyl-ketogidrazonov - 2.4 DNFKG, fluorescent product type schiff bases; dienes conjugates (DC); TBA - active products; reduced glutathione; sulfhydryl groups [SH]; haptoglobin; ceruloplasmin, and the enzyme activity of catalase; superoxide dismutase (SOD); glutathione peroxidase (GP); glutathione transferase (GT); aspartic (AST) and alanine aminotransferase (ALT), gamma-glutamattransferazy (γ-HT). Statistical processing of the results of research wascarried out using Student - Fisher t-test. The differences between the control and experiment were considered significant at the level of $p < 0.05$.

Results and discussion

The study revealed significant changes of performance indicators in rats exposed to oligoethers in doses 1/10 and 1/100 LD_{50}. At 1/1000 LD_{50} xenobiotics do not effect on the activity of the antioxidant and prooxidant system - this dose was not significant for the below mentioned conclusions. The results of the study of the impact of oligoethers at a dose of 1/10 LD_{50} on state of the oxidant-antioxidant homeostasis are presented in Table 1. As we can see, xenobiotics in serum increased in general content of 2.4 - DNFAG 2.4 - DNFKG, schiff bases, DC, malondialdehyde and activity of enzymes ALT, AST, γ-HT. Against this background, a decrease of levels of reduced glutathione, sulfhydryl groups, haptoglobin, ceruloplasmin and catalase activity, SOD, GP, GT. More specifically, the observed increase in the content of 2,4-DNFKG by 78.5%; 38.9% and 561%; 2.4 DNFKG-100.6%; 52.3% and 73.07%; Schiff bases - 43.6%; 20.4% and 28.96%; DK - 103.5%; 58.3% and 78.2%; malondialdehyde - 255.5%; 156.5% and 192.9%; and AST to 285.1%; 192.5% and 235.8%, ALT - 333.3%; 229.6% and 296.3%; γ -GT - 61.7%; 40.1% and 50.3%, respectively, under the influence of L-501-2-100, L-1601-2-50 "B" and L-1601 -2-50 "P" as compared with the control group.

The concentrations of glutathione were reduced by 69.24%; 58.9% and 51.3%; sulfhydryl groups - 57.1%; 44.9% and 38.5%; haptoglobin - 54.9%; 36.4% and 47.9%; ceruloplasmin - 60%; 31.15% and 42.8%; decreased catalase activity by 46.6%; 30.15% and 42.5%; SOD - 56.96%; 26.8% and 45.24%; GP - 45.75%; 23.94% and 33.6%; GT - 60.03%; 45.13% and 55.24%, respectively, under the influence of L-501-2-100, L-1601-2-50 "B" and the L-1601-2-50 "P".

Table 1

Subacute effects oligoethers at a dose of 1/10 LD_{50} on oxidant-antioxidant homeostasis in the body of white rats

Indicators (serum, blood)	Monitoring Group, M ± m			
	Control of	Л-501-2-100	Л-1601-2-50 «Б»	Л-1601-2-50 «Р»
2,4-DNFAG (ed.opt.plotn/1g protein, λ = 370nm), serum	26,5±2,4	47,30±3,5*	36,82±1,73*	41,35±2,68*
2,4-DNFKG (ed.opt.plotn/1g protein, λ = 370nm), serum	22,8±1,7	45,74±3,2*	34,73±2,65*	39,46±3,17*
Schiff Base (mkmol / L),serum	270,4±9,5	388,3±17,6*	325,6±12,8*	348,7±15,3*
Diene conjugates (mkmol / L), serum	20,3±1,6	41,32±3,60*	92,14±2,63*	36,18±2,74*
Malondialdehyde (mol/L), serum	4,95±0,53	17,6±1,4*	12,7±0,96*	14,5±1,23*
Reduced glutathione (mkmol/L), blood	2,340,16	0,72±0,05*	0,96±0,06*	1,14±0,12*
Sulfhydryl groups (mkmol/L), serum	24,7±1,8	10,6±1,4*	13,6±1,7*	15,2±1,2*
Haptoglobin (g/l), serum	1,73±0,16	0,78±0,06*	1,1±0,08*	0,9±0,05*
Ceruloplasmin (mkmol /l), serum	2,15±0,23	0,86±0,05*	1,48±0,13*	1,23±0,10*
Catalase (MAb/g Hb), blood	7,3±0,62	3,9±0,25*	5,1±0,46*	4,2±0,35*
SOD (U/ml serum • min)	1,68±0,05	0,74±0,04*	1,23±0,07*	0,92±0,05*
SE (mkmol/ml serum • min)	9,4±0,58	5,10±0,48*	7,15±0,68*	6,24±0,53*
HT (nmol/ml of serum • min)	38,6±2,8	15,43±0,97*	21,18±1,14*	17,28±1,32*
AST (mol/L • h), serum	0,67±0,05	2,58±0,32*	1,96±0,12*	2,25±0,18*
ALT levels (mmol/L • h), serum	0,540,63	2,34±0,26*	1,78±0,16*	2,14±0,21*
γ-HT (mkmol/L • h), serum	1,75±0,14	2,83±0,32*	2,45±0,22*	2,63±0,19*

*Note: * - the differences with control reliable, p <0,05.*

Analysis of the results found at the higher doses of oligoethers 1/10 LD_{50} have a significant effect on the activation of free radical processes, lipid peroxidation, protein and inhibition of antiradical and antiperoxide defense. Studied xenobiotic lead to depletion of antioxidant and organ dysfunction of their detoxification, primarily the liver, indicating the failure of protective-adaptive mechanisms of homeostasis.

At toxification of animals with 1/100 LD_{50} dose different dynamics of performance indicators was observed, all substances intensified free radical processes, lipid peroxidation and activity of antioxidant defense system (Table 2). Thus, increase of 2,4-DNFAG at 42.64%; 33.6% and 23.4%; DNFKG 2.4 - 52.26%; 35.1% and 41.6%; schiff bases - 21.4%; 14.8% and 22.2%; DK - 64.5%; 41.4% and 30.54%; malondialdehyde - 145.9%; 93.9% and 136.4%; reduced glutathione - 14.53%; 19.2% to 23.07%; sulfhydryl groups - 19.43%; 15.8% and 27.5%; haptoglobin - 46.8%; 52.02% and 60.1%; ceruloplasmin - 44.2%; 27.9% and 33.02%; catalase activity was increased by 21.9%; 24.6% and 27.9%, SOD - 36.9%; 54.15% and 47.02%, SE - 35.3%; 54.6% and 47.4%, HT - 17.4%; 20.5% and 16.13%, AST - 101.5%; 117.9% and 135.8%, ALT - 118.5%, 127.7% and 150% and ɣ - HT - 36%; 39.4% and 28.6%, respectively, under the influence of L-501-2-100, L-1601-2-50 "B" and the L-1601-2-50 "P" was found in the serum as compared with the reference group. The data obtained indicate that despite the enhancement of free-radical processes and lipid peroxidation in experimental animal body antioxidant mechanisms are activated and the system is influenced by detoxification of xenobiotics dose 1/100 LD_{50}, whereas at a dose of 1/10 LD_{50} oligoethers cause inhibition of antioxidant and activation of prooxidant systems.

Table 2

Influence of oligoethers on oxidant-antioxidant homeostasis in white rats under subacute experiment at a dose 1/100 LD50

Indicators (serum, blood)	Monitoring Group, M ± m			
	Control of	Л-501-2-100	Л-1601-2-50 «Б»	Л-1601-2-50 «Р»
2,4-DNFAG (ed.opt.plotn/1g protein, λ = 370nm), serum	26,5±2,4	37,8±2,2	35,4±1,6*	32,7±2,1*
2,4-DNFKG (ed.opt.plotn/1g protein, λ = 370nm), serum	22,8±1,7	35,4±1,9*	30,8±2,4*	32,3±1,7*
Schiff Base (mkmol / L),serum	270,4±9,5	328,3±12,5*	310,4±15,6*	330,4±10,8*
Diene conjugates (mkmol / L), serum	20,3±1,6	33,4±2,8*	28,7±1,4*	26,5±2,10*
Malondialdehyde (mol/L), serum	4,95±0,53	10,7±0,84*	9,6±0,73*	11,7±1,3*
Reduced glutathione (mkmol/L), blood	2,34±0,16	2,68±0,14*	2,79±0,16*	2,88±0,21*
Sulfhydryl groups (mkmol/L), serum	24,7±1,8	29,5±1,3*	28,6±1,10*	31,5±2,15*
Haptoglobin (g/l), serum	1,73±0,16	2,54±0,18*	2,63±0,21*	2,77±0,17*
Ceruloplasmin (mkmol /l), serum	2,15±0,23	3,10±0,24*	2,75±0,15*	2,86±0,27*
Catalase (MAb/g Hb), blood	7,3±0,62	8,9±0,56*	9,10±0,74*	9,34±0,68*
SOD (U/ml serum • min)	1,68±0,05	2,73±0,24*	2,59±0,18*	2,47±0,22*
SE (mkmol/ml serum • min)	9,4±0,58	12,72±0,83*	14,53±0,95*	13,86±0,73*
HT (nmol/ml of serum • min)	38,6±2,8	45,32±2,4*	46,51±2,72*	44,83±1,97*
AST (mol/L • h), serum	0,67±0,05	1,35±0,09*	1,46±0,13*	1,58±0,16*
ALT levels (mmol/L • h), serum	0,54±0,03	1,18±0,07*	1,23±0,09*	1,35±0,14*
ɣ-HT (mkmol/L • h), serum	1,75±0,14	2,38±0,17*	2,44±0,21*	2,25±0,19*

*Note: * - the differences with control reliable, p <0,05.*

Conclusions

1. The results of these studies allow us to judge that the oligo-L-501-2-100, L-1601-2-50 "B" and A-1601 -2-50 "P" in a dose of 1/100 LD50 in a subacute exposure to white rats promotes stimulation of free radical processes, lipid peroxidation and antiradical activity of antiperoxide protection against significant stress adaptive mechanisms aimed at ensuring the homeostatic functions of the body.

2. At the higher dose 1/10 LD50 oligoethers lead to inhibition of the activity of the antioxidant system and detoxification of xenobiotics in terms of activation of free radical processes, lipid peroxidation, indicating a failure of adaptive mechanisms and the development of membrane pathology in systemic dysfunction of anti-systemic interactions oxidant and antioxidant systems.

3. 1/1000 LD50 xenobiotics do not have any effect on the activity of the antioxidant and prooxidant system in the blood and serum of albino rats.

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