UDC 613-615.092.044:616.099.036
http://orcid.org/0000-0003-2118-5035

CROWN-ETHER INFLUENCE ON RAT ANTIOXIDANT SYSTEM IN SUB-ACUTE EXPERIMENT

R.I. Kratenko, *Ph.D. (byology), assistant professor*

H.S. Skovoroda Kharkiv National Pedagogical University, Kharkiv, Ukraine
freesword@ukr.net

The present article illustrates the experimental results of investigation of antiradical defense system state at conditions of crown-ethers action upon the organism of warm-blooded animals. The research program used sub-acute toxicological experiment on sexually mature white male rats of WAG population (body mass - 180-220 g). The animals were administered with water emulsion of investigated crown-ethers (12-crown-4, 15-crown-5, and 18-crown-6) in 1/100 and 1/1000 LD_{50} daily, within 30 days perorally. The animals of the control group were given water at the same conditions. On the 30^{th} day of the experiment the rats of all groups were anesthetized by sodium thiopental (50 mg/kg) and slaughtered by decapitation with the Guillotine knife. Oxidant-antioxidant interaction was evaluated using the following indexes: SH-groups, vitamin C, vitamin E contents; haptoglobin, MDA, and DC concentrations; ceruloplasmin, catalase, peroxidase, SOD, GP activities.

All crown-ethers 1/1000 LD_{50} (subtoxic dose) increased blood serum contents of DC by 80.1; 75.4; 70.2% and MDA 108.9; 130.8; 82.4% for 12-crown-4, 15-crown-5, 18-crown-6, respectively. Their action also resulted in enhancing the activity of investigated antioxidant system enzymes – blood catalase (by 35% on average), blood peroxidase (by 80% on average), blood GP (by 60% on average) and blood SOD (by 40% on average). Crown-ethers significantly increased concentrations of serum ceruloplasmin (by 85% on average) and haptoglobin (by 82% on average). The concentration of the main antioxidant peptide glutathione (reduced form) was higher in blood of the experimental rats, whereas the general contents of SH-groups became diminished. The contents of adrenal gland vitamin C got increased (by more than 40%) in the action of crown-ethers on the background of decreasing in serum vitamin E concentration.

The action of 12-crown-4, 15-crown-5 and 18-crown-6 1/100 LD_{50} resulted in the pronounced increase in blood serum contents of DC by 152; 138; 144% and MDA by 178; 162; 154%, respectively. The blood contents of SH-groups did not significantly changed at the influence of the investigated compounds.

This dosage of crown-ethers further activated free-radical processes and lipid peroxidation, inhibiting antioxidant system, which was connected with membranes pathology development being at the base of structure-metabolic disturbances in different organs and tissues of the organism.

Key words: crown-ethers, free-radical oxidation, lipid peroxidation, antioxidant system.

Вплив краун-етерів на стан антиоксидантної системи щурів у підгострому експерименті. Кратенко Р.І. − В роботі викладені результати експериментів з вивчення стану системи антирадикального захисту за умов дії краун-етерів на організм теплокровних тварин. Програма дослідження базувалася на використанні підгострого токсикологічного експерименту на статевозрілих білих щурах-самцях популяції WAG масою тіла 180-220г. Тваринам вводили водну емульсію досліджуваних речовин (12-краун-4, 15-краун-5, 18-краун-6) у 1/100 та 1/1000 LD_{50}, щоденно, перорально впродовж 30-ти днів. Тварини

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контрольної групи одержували воду за аналогічних умов. На 30-й день експерименту тварин усіх груп анестезували тиопенталом натрію (50 мг/кг) і забивали декапітацією гільйотинним ножем. Оксидант-антиоксидантна взаємодія оцінювалася за допомогою наступних індексів: вміст SH-груп, вітаміна Е, вітаміна С; концентрації ДК, МДА, гаптоглобіну; активності церулоплазміну, каталази, пероксидази, СОД, глутатіонпероксидази.

Всі досліджувані краун-етери в 1/1000 LD_{50} (субтоксична доза), підвищували у сироватці крові вміст ДК на 80.1; 75.4; 70.2% та МДА на 108.9; 130.8; 82.4% для 12-краун-4, 15-краун-5, 18-краун-6 відповідно. Їх дія також призводила до підвищення активності досліджуваних ферментів антиоксидантної системи: каталази крові (в середньому на 35%), пероксидази крові (в середньому на 80%), ГП крові (в середньому на 60%), СОД крові (в середньому на 40%). Краун-етери достовірно підвищували концентрації церулоплазміну (в середньому на 85%) та гаптоглобіну (в середньому на 82%) у сироватці крові. Концентрація основного антиоксидантного пептиду – глутатіону (відновлена форма) була вище у крові експериментальних груп щурів, у той час, як загальний вміст SH-груп зменшувався. Вміст вітаміну С в наднирниках підвищувався (більш ніж на 40%) при дії краун-етерів, на фоні зниження концентрації вітаміну Е в сироватці крові.

Дія 12-краун-4, 15-краун-5 та 18-краун-6 у 1/100 LD_{50} призводила до достовірного підвищення в сироватці крові вмісту ДК на 152; 138; 144%, та МДА на 178; 162; 154% відповідно. Вміст SH-груп в крові суттєво не змінювався під впливом досліджуваних речовин.

Ця доза краун-етерів в подальшому активувала вільнорадикальні процеси та перекисне окислення ліпідів, інгібуючи антиоксидантну систему, що було пов’язано з розвитком мембранної патології, яка лежить в основі структурно-метаболічних порушень в різних органах та тканинах організму.

Ключові слова: краун-етери, вільно-радикальне окислення, перекисне окислення ліпідів, антиоксидантна система.

INTRODUCTION

One of the actual scientific problems nowadays should be the investigation of antioxidant processes, which are closely associated with organism chemical stress development. By the opinion of many authors, the main leading link in the development of toxic stress is the activation of free radical processes and lipid peroxidation [1, 5]. This is mostly connected with the fact, that, disturbances in the mentioned metabolic link may significantly inhibit organism resistance to the various harmful factors of internal and external nature. The latter could provoke the onset of different diseases and impairment of vital organs, i.e. heart, lungs, kidneys, liver etc. The characteristic particularity of organism toxic stress reaction evoked by intake of many chemicals (chemical or toxic stress) is disturbances of cellular membranes and inhibition of antioxidant defense which might result in starting dystrophic and destructive processes [5,8].

At the same time one should mention lipid peroxidation to be a main metabolic link for the organism normal functioning biological membranes. Such essential processes as electron transport chain, oxidative phosphorylation, methylation and hydroxylation of exo- and endogenic substrates by endoplasmic reticulum enzymes, and even cells division are accompanied by certain changes in free radical processes and lipid peroxidation proceeding intensity [1,5,8]. Lipid peroxides are normal

necessary products for prostaglandins, progesterone, leukotriens biosynthesis; they participate in hydroxylation of cholesterol perhydrophenanthrene ring [8].

On the other hand, there are many literature data signifying lipid peroxides, which are formed as a result of functioning many enzyme systems or/and non-enzyme auto-oxidation to be participating in the development of different pathological processes (radiation impairments, tumor cells growth, inflammation processes, etc) [1, 5, 8, 15]. The lipo-peroxides increased levels are known to inhibit some enzymes, induce cellular membrane permeability, decrease sulf-hydrylic groups quantity [9]. This may lessen cells division and reductive syntheses [9, 15]. The induction of fatty acids free radical oxidation obligatory results in formation of secondary reactive oxidants (aldehydes, ketones, alcohols, dialdehydes etc.), which are able to interact with certain functional groups of proteins. This may lead to protein native conformation loss and conglomeration of protein molecules. The process is known as protein peroxidation. Besides, accumulation of lipo-peroxides in the hydrophobic part of the membrane alters ionic transport, conformational and metabolic properties of lipids and proteins. Many researchers showed lipid peroxidation products emergence in membrane lipid composition to be the crucial factor for hydrophobic metabolism, viscosity, electric charge, membrane-structured enzymes activity of biological membranes [1, 5, 8, 9, 15].

The action of many xenobiotics is established to result in accumulation of dienic conjugates (DC) and malonic dialdehyde (MDA) in liver. The given compounds appear on the stage of free radicals formation and signify the tissue increase in peroxides and hydroperoxides. The compounds cause destructive effects on cells and their intracellular structure-functional ensembles (endoplasmic reticulum, Goldgi apparatus, nucleus, etc). DC – fatty acids molecules, containing double bonds are considered as intermediate products of lipid peroxidation, whereas MDA – as the end product.

Complex of biologically active compounds of non-enzyme and enzyme nature, which counteracts effects of free radical oxidation, is known as antioxidant system [1, 15]. Quite active common antioxidants are tocopherol, ascorbic acid, superoxide dismutase (SOD), catalase, glutathione peroxidase (GP), ceruloplasmin, etc.

The **objective** of the present study is the investigation of antiradical defense system state at conditions of crown-ethers action upon the organism of warm-blooded animals.

MATERIALS AND METHODS

The research used three classic crown-ethers (12-crown-4, 15-crown-5, 18-crown-6), which are chemically heterocyclic polyethers. These compounds possess such unique properties as solubility in many non-aqueous mediums, high stability, selectivity of oxido-reductive reactions, ability to form complexes with metals, etc. Therefore, crown-ethers find growing application in electrochemistry, pharmacy, medicine. The given group of compounds belong to relatively toxic substances (3^d

class of hazard) possessing pronounced cumulative properties. Crown-ethers LD_{50} were established at the level of 1.17; 1.35; 1.27; 3.20 g/kg for 12-crown-4, 15-crown-5, 18-crown-6, 21-crown-7 respectively [18]. The choice of the new xenobiotics group was made due to the absence of their biological mechanism data from scientific literature as well as their large volume of production and wide contact of population with the substances and their derivatives.

The research program intended the performance of sub-acute toxicological experiment using sexually mature white male rats of WAG population (body mass – 180-220 g). The animals were administered with water emulsion of investigated crown-ethers in 1/100 and 1/1000 LD_{50} daily, within 30 days perorally. The animals of the control group were given water at the same conditions. On the 30^{th} day of the experiment the rats of all groups were anesthetized by sodium thiopental (50 mg/kg [7]) and slaughtered by decapitation with the Guillotine knife.

Oxidant-antioxidant interaction was evaluated using the following indexes: SH-groups, vitamin C, vitamin E contents; haptoglobin, MDA, and DC concentrations; ceruloplasmin, catalase, peroxidase, SOD, GP activities [11]. DC blood serum level was determined by spectrophotometric method, which is based on the phenomenon, that, primary products of free radical lipid oxidation possess a characteristic consumption of UV-spectrum with the maximum of 233 nm [6]. MDA blood serum level was determined spectrophotometrically, using the method principle, which is MDA ability to form a colored compound with 2-thiobarbiturate when heating. The compound maximum wave length absorbtion is 533 nm [16]. Catalase activity was evaluated by the velocity of H_2O_2 utilization from incubation medium in the colored qualitative reaction with ammonium molibdate by spectrophotometric method [4]. Peroxidase activity was determined by the rate of interaction between n-phenyldiamine and hydrogen peroxide [10]. GP activity was manifested by diminishing the glutathione contents in the colored reaction with sulf-hydrylic groups with Ellmann reagent spectrophotometrically (λ=412 nm) [12]. Blood SOD activity was determined by the enzyme's ability to compete with nitroblue tetrasolic dye to engage superoxide anions, which were formed as a result of $NADH_2$ and phenazine-metasulfate interaction [3]. The reaction between nitroblue tetrasolic dye and CO-radicals reduces the former to colored tetrazol hydrazine, λ=540 nm. The presence of SOD blocks the reaction. The reaction inhibition degree was determined spectrophotometrically [17]. The blood reduced glutathione was investigated by spectrophotometric method with Ellmann reagent (λ=412 nm) [14]. The method is based on the reaction of thioldisulfate exchange. In this reaction, Ellmann reagent gets easily reduced by SH-substances forming thionitrobenzoate of light-yellow color [14]. Blood serum ceruloplasmin level was determined by Rabbine method based by ceruloplasmin ability to oxidize a colorless reduced form of paraphenylendiamine to the colored blue-violet form (λ=530 nm) [13]. Sulfhydrylic groups of blood were determined by spectrophotometric method with Ellmann reagent (λ=412 nm) [14]. Vitamin E contents were investigated spectrophoto-

metrically after its preliminary extraction by column chromatography method in the reaction of oxidation by nitric acid with the formation of the red-pink product (λ=470 nm) [2]. Ascorbic acid in the adrenal cortex was determined by titrometric method based on the reaction with 2, 6-dihydrophenolindophenole [14].

Statistical analysis of digital material was performed with the usage of computer software instrumentation package for processing and analysis of statistical information – *Statistica 6.1* (StatSoft, Inc., USA). The primary statistical processing the digital data was started with the preliminary screening the assumption at the conformity of the samples to Gaussian distribution law. Quantitative traits, which had normal distribution, were described by parametric characteristics – arithmetic mean of variations number, i.e. Mean Values (M) with Standard Deviation (S). In the case of normal distribution absence, the quantitative traits were processed by non-parametric characteristics – median (Me) with interquartile swing. If, at the least, one of the distributions was not normal, then the comparison of independent samples was performed by Mann Whitney criterion. The differences between two samples were considered as significant if the probability of random difference was not higher then 0.05 ($p<0.05$).

RESULTS AND THEIR DISCUSSION

The sub-acute experiment established all crown-ethers 1/1000 LD_{50} (subtoxic dose) to increase blood serum contents of DC by 80.1; 75.4; 70.2% and MDA 108.9; 130.8; 82.4% for 12-crown-4, 15-crown-5, 18-crown-6, respectively (tab. 1).

Table 1

Influence of crown-ethers 1/1000 LD_{50} on rats antioxidant system state (M±S)

Index	***Control***	***12-crown-4***	***15-crown-5***	***18-crown-6***
Serum DC, mcM	34.6±4.5	62.3±5.1*	60.7±4.6*	58.9±4.8*
Serum MDA, mcM	12.3±1.4	25.7±1.9*	22.5±2.6*	28.4±2.3*
Blood catalase, mcat/g Hb	5.52±0.48	7.4±0.5*	7.6±0.8*	7.5±0.5*
Blood peroxidase, mcat/g Hb	8.20±0.75	14.7±1.1*	13.5±1.2*	15.3±1.2*
Blood GP, mcat/g Hb	6.40±0.52	10.2±0.9*	10.3±0.9*	10.2±1.0*
Blood SOD, mcat/g Hb	0.58±0.04	0.88±0.09*	0.76±0.06*	0.75±0.06*
Serum ceruloplasmin, mkM	2.20±0.13	4.2±0.4*	4.5±0.5*	3.7±0.4*
Serum haptoglobin, g/l	1.80±0.16	3.20±0.31*	3.10±0.32*	3.50±0.34*
Blood glutathione, mM	1.50±0.08	2.25±0.21*	2.13±0.22*	2.15±0.19*
Blood SH-groups, mM	29.3±1.7	18.1±1.4*	14.5±1.3*	16.7±1.1*
Serum vitamin E, mcM	25.6±1.9	17.2±1.5*	18.7±1.6*	18.6±1.7*
Adrenal vitamin C, mg/g	18.2±1.6	27.3±2.5*	25.4±2.4*	30.4±3.1*

*Notes: n=8, * - $p < 0.05$*

The action of 12-crown-4, 15-crown-5 and 18-crown-6 also resulted in enhancing the activity of investigated antioxidant system enzymes – blood catalase (by 35 % on average), blood peroxidase (by 80% on average), blood GP (by 60% on average) and blood SOD (by 40 % on average, tab. 1). The antioxidant system protein-peptide components of experimental animals altered too in comparison with the control group. Crown-ethers significantly increased concentrations of serum ceruloplasmin (by 85% on average) and haptoglobin (by 82% on average, tab. 1). The concentration of the main antioxidant peptide glutathione (reduced form) was higher in blood of the experimental rats, whereas the general contents of SH-groups became diminished (tab. 1). The contents of adrenal gland vitamin C got increased (by more than 40%) in the action of crown-ethers on the background of decreasing in serum vitamin E concentration (tab. 1).

The results of investigation of the indexes evaluating oxidant-antioxidant processes showed the experimental crown-ethers in 1/1000 LD_{50} to activate free radical processes and lipid peroxidation significantly enhancing antiradical and antiperoxide defense at the same time. The results also display unidirectional influence of all the representatives of the investigated compounds upon antioxidant system state and oxidative processes occurrence.

It is worth mentioning, that, the animal toxification by substances 1/1000 LD_{50} was accompanied by increasing in serum concentration of ceruloplasmin and haptoglobin which are regarded to be proteins of inflammation acute faze. These data signify the development of inflammatory processes in the organism of experimental animals at the conditions of xenobiotics peroral toxification.

The increase in vitamin C adrenal contents in the organism of the experimental animals groups may be explained as compensatory mechanism activation against free radical processes evoked by crown-ethers. The organism of laboratory rats is capable of producing vitamin C from glucose in the liver. Therefore, the increased contents of the vitamin in rats adrenal cortex may be the consequence of induced synthesis of this most powerful water-soluble antioxidat, which, in turn, could be the response to free radical formation activation. These results perfectly correlate with the increase in glutathione concentration on the background of decreasing in the general contents of SH-groups in blood of experimental animals compared with the control group. Admittedly, it is the SH-groups of reduced glutathione, which participate in neutralization of oxygen active forms with the production of hydrogen peroxide, not SH-groups of various proteins. The latter may engage superoxide anions, but in this process, they become oxidized themselves, turning to HSO_3-groups, hence could occur the reduction of general SH-contents.

Amazingly, the sub-toxic doses of crown-ethers serve as a trigger to activation of various enzymes in antiradical defense (SOD, GP, peroxidase, catalase). Apparently, 1/1000 LD_{50} of the xenobiotics is insufficient in inhibiting the antioxidant system proteins, but is quite capable of inducing them.

The alteration of the investigated indexes in the action of crown-ethers 1/100

LD_{50} had a somewhat different tendency compared with the previous one (tab. 2).

Table 2

Influence of crown-ethers 1/100 LD_{50} on rats antioxidant system state (M±S)

Index	Control	12-crown-4	15-crown-5	18-crown-6
Serum DC, mcM	34.6±4.5	87.3±6.8*	81.7±6.2*	82.4±7.1*
Serum MDA, mcM	12.3±1.4	34.2±3.1*	32.3±3.6*	31.2±2.7*
Blood catalase, mcat/g Hb	5.52±0.48	2.24±0.18*	2.51±0.21*	2.63±0.19*
Blood peroxidase, mcat/g Hb	8.20±0.75	5.32±0.48*	5.14±0.59*	5.30±0.51*
Blood GP, mcat/g Hb	6.40±0.52	4.21±0.52*	4.36±0.36*	5.1±0.41*
Blood SOD, mcat/g Hb	0.58±0.04	0.26±0.03*	0.28±0.01*	0.31±0.02*
Serum ceruloplasmin, mkM	2.20±0.13	1.13±0.12*	1.52±0.16*	1.48±0.14*
Serum haptoglobin, g/l	1.80±0.16	0.95±0.08*	0.99±0.12*	1.22±0.14*
Blood glutathione, mM	1.50±0.08	1.07±0.11*	1.13±0.12*	1.35±0.12
Blood SH-groups, mM	29.3±1.7	28.3±1.8	26.5±1.6*	28.2±1.9*
Serum vitamin E, mcM	25.6±1.9	17.2±1.5*	18.7±1.6*	18.6±1.7*
Adrenal vitamin C, mg/g	18.2±1.6	11.3±1.5*	12.5±1.3*	13.3±1.3*

*Notes: n=8, * - $p < 0.05$*

The action of 12-crown-4, 15-crown-5 and 18-crown-6 resulted in the pronounced increase in blood serum contents of DC by 152; 138; 144% and MDA 178; 162; 154%, respectively. The blood contents of SH-groups did not significantly changed at the influence of the investigated compounds. These data display the xenobiotics in 1/100 LD_{50} to cause even more powerful influence than in 1/1000 LD_{50} upon structure-metabolic state of organs and tissues, which is accompanied with the substantial accumulation of DC and MDA capable of impairing proteins, DNA, other macromolecules and structural components of biological membranes. The investigation results characterize exhaustion of the organism antiradical defense as a consequence of free-radical and lipid oxidation activation.

The crown-ethers action resulted in the inhibition of antioxidant system which is considered as a breakdown of defense-adapting mechanisms of homeostasis control. In the cases of chemical compounds influence upon the organism and/or at the conditions of increased formation of endogenous, as a rule, biologically active substances, homeostatic reaction includes primary detoxification mechanism as an obligatory element. Since the process of detoxification is performed with the participation of biological membranes (microsomal momooxigenase system), the necessary condition of the process effectiveness must be the membrane wholeness. Meddling the molecular mechanisms of biochemical systems (cellular membranes, receptors, enzymes, proteins et cet.) exogenous and endogenous chemical agents alter normal, physiological mechanisms of humoral, cellular and tissue homeostasis

maintenance, which is displayed by certain functional disturbances at the correspondent levels. The cellular level is characterized by two universal mechanisms of xenobiotics toxicity realization: irreversible covalent binding the chemical compound with biological molecules (ligands) on different cellular and intracellular structures, and oxidative stress, accompanied by activation of non-enzyme free-radical oxidation and lipid peroxidation [1]. Our previous investigations proved membranotropic activity of crown-ethers [19], i.e. their negative influence on phospholipids composition of cellular membrane and receptory and post-receptory links of signal transmission. The products of crown-ethers biotransformation including DC and MDA might have been the cause of the mentioned alterations.

It is worth admitting, that, the modern scientific literature has recently been accumulating quite a stockpile of data about non-enzyme lipid peroxidation reactions having universal character, and being an index of metabolic stability in the organism [1, 8]. The reactions influence the organism adaptive potential and determine the possibility of pathology development. These properties are explained by high biological activity of the compounds formed in reactions of free radical oxidation and lipid peroxidation as well as by the complex of metabolism systemic alterations, and changes in the character of intercellular relations. Free radical processes may be considered as a normal physiological organism reacting, which is a link of general complex adaptation formation, having responded the irritation factors. On the other hand, the organism state of disadaptation, which may be a preface to a pathology onset, could be a consequence of enormous free radical processes triggering.

A distinctive feature of lipid peroxidation as a typical metabolic branched process is its high sensitivity to minor alterations in the oxidation components, inhibitors and activators concentration and composition. This attribute explains lipid peroxidation tremendous flexibility after the action of biologically active chemical factors. Its latter property is realized via changes in physico-chemical characteristics of cellular biological membranes, activity of membrane-localized and lipid-dependent enzymes (particularly, microsomal oxigenases), as well as reactivity of neuro-endocrine and immune organism systems.

CONCLUSIONS

1. The peroral administration of crown-ethers in 1/1000 LD_{50}, within one month stimulate free radical processes, lipid peroxidation and activate the system of antiradical and antiperoxide defence.

2. The higher dosage of crown-ethers (1/100 DL_{50}) further activates free-radical processes and lipid peroxidation, inhibiting antioxidant system, which is connected with membranes pathology development being at the base of structure-metabolic disturbances in different organs and tissues of the organism.

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Влияние краун-эфиров на состояние антиоксидантной системы крыс в подостром эксперименте. Кратенко Р.И. − В работе представлены результаты экспериментов по изучению состояния системы антирадикальной защиты в условиях действия краун-эфиров на организм теплокровных животных. Программа исследования базировалась на использовании подострого токсикологического эксперимента на половозрелых белых крысах-самцах популяции WAG массой тела 180-220г. Животным вводили водную эмульсию исследуемых веществ (12-краун-4, 15-краун-5, 18-краун-6) в 1/100 та 1/1000 LD_{50}, ежедневно, перорально на протяжении 30-ти дней. Животные контрольной группы получали воду при тех же условиях. На 30-й день эксперимента животных всех групп анестезировали тиопенталом натрия (50 мг/кг) и забивали декапитацией гильотинным ножом. Оксидант-антиоксидантнае взаимодействие оценивалось с помощью следующих индексов: содержание SH-групп, витамина Е, витамина С; концентрации ДК, МДА, гаптоглобина; активности церулоплазмина, каталазы, пероксидазы, СОД, глутатионпероксидазы.

Все исследуемые краун-эфиры в 1/1000 LD_{50} (субтоксическая доза), повышали в сыворотке крови содержание ДК на 80.1; 75.4; 70.2% и МДА на 108.9; 130.8; 82.4% для 12-краун-4, 15-краун-5, 18-краун-6 соответственно. Их действие также приводило к повышению активности исследуемых ферментов антиоксидантной системы: каталазы крови (в среднем на 35%), пероксидазы крови (в среднем на 80%), ГП крови (в среднем на 60%), СОД крови (в среднем на 40%). Краун-эфиры достоверно повышали концентрации церулоплазмина (в среднем на 85%) и гаптоглобина (в среднем на 82%) в сыворотке крови. Концентрация основного антиоксидантного пептида – глутатиона (восстановленная форма) была выше в крови экспериментальных групп крыс, в то время, как общее содержание SH-групп уменьшалось. Содержание витамина С в надпочечниках повышалось (более чем на 40%) при действии краун-эфиров, на фоне снижения концентрации витамина Е в сыворотке крови.

Действие 12-краун-4, 15-краун-5 та 18-краун-6 в 1/100 LD_{50} приводило к достоверному повышению в сыворотке крови содержания ДК на 152; 138; 144%, и МДА на 178; 162; 154% соответственно. Содержание SH-групп в крови существенно не менялось под влиянием исследуемых веществ.

Эта доза краун-эфиров в дальнейшем активировала свободнорадикальные процессы и перекисное окисление липидов, ингибируя антиоксидантную систему, что было связано с развитием мембранной патологии, которая может лежать в основе структурно-метаболических нарушений в разных органах и тканях организма.

Ключевые слова: краун-эфиры, свободнорадикальное окисление, перекисное окисление липидов, антиоксидантная система.