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INTENSITY OF LIPID OXIDATION AND OXIDATIVEMODIFICATION OF PROTEINS IN BLOOD OF RATS UNDER THE CONDITIONS OF CHRONIC INFLUENCE OF MIXTURE OF NANO PARTICLESOF METALS AND THEIR MACRO-DISPERSE ANALOGUE

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Abstract. *In this article we studied the chronic oral effects of the NPMe mixture (Ag, Cu, Fe, Mn dioxide) in comparison with its macro-dispersed analogue on the intensity of oxidative processes in the blood of white rats. Research has established that chronic oral reception of a mixture of metals in various disperse forms caused in the blood of experimental rats different-directional changes in the formation of products of lipoperoxidation in the dynamics of the experiment. All animals were monitored for 90 days (main period). On the 15th, 30th and 60th day after the start of feeding, and in 30 days after termination of feeding (on the 90th day) the mixture of NPMe and metal salts, there were taken blood samples from 5 animals from each group after inhalation chloroform anesthesia. After that blood plasma was obtained for biochemical studies.Regarding results of strengthening the endogenous AOA against the background of storage of physiological levels of the intensity of the processes of LPO and OMB in experimental rats under the action of a mixture of NPMe in a dose of 0.3 mg/kg of body weight, it can be argued about its antioxidant effect, and in subsequent studies it can be taken into account for the purpose of creation nanonutraceutical of adaptogenic orientation.*

Keywords.*antioxidant system, metal nanocomposite, oxidative modification of proteins, lipid peroxidation, metal salts, plasma, chronic toxicity, rats*

Introduction. An important direction in the use of nanotechnologies in feeding animals and poultry is the receipt of nanonutrients in order to enrich feed with them,and, first of all, micro elements - essential biometals. At the same time, feed as an element of the environment must be biotic, that is, on the one hand, it should not contain and bring into the internal environment of the body toxic and reactive substances, and on the other hand, contain as many nutrients as possible in the chemical form in which they are in macroorganism.

Analysis of recent researches and publications. To date, the first nanomaterials, which meet all the conditions for functional biomaterials, have been developed and tested in animal husbandry and veterinary practice, and they have received the general name of aqueous colloidal solutions of metal nanoparticles [1, 2]. One of the decisive biochemical mechanisms of action of risk factors is an imbalance between the intensity of the oxidation processes of the main structural components of cell membranes - lipids and proteins and their AO-regulation [3-7].

According to the results of our previous studies there has been proved [8-10] thatat the experimental simulationof acute toxicity on the model of white rats, the biological effect of the NPMe mixture (Ag, Cu, Fe, Mn dioxide) is essentially different in terms of the toxicodynamics and toxicokinetics of this substance in the form of macroscopic dispersions (mixture of salts of the corresponding metals).

Purpose. Therefore, the purpose of the study was to study the chronic oral effects of the NPMe mixture (Ag, Cu, Fe, Mn dioxide) in comparison with its macro-dispersed analogue on the intensity of oxidative processes in the blood of white rats.

Methods. The experiment was conducted in the Department of Toxicology, Safety and Quality of Agricultural Products and in the condition of the vivarium of the NSC "IECVM" on the sexually mature male rats. For this purpose, on the principle of analogues, four groups of male rats (n = 80) of the Wistar line, weight (120-140) g, were formed per 20 animals in each.

Experimental studies on rats were conducted taking into account the basic principles of bioethics. Keeping, care and feeding of animals were carried out in accordance with the standards and rations recommended for this type of laboratory animal. During the experiment animals of all groups had free access to water.

We used a mixture of the following NPMe in the form of colloidal dispersions: Ag average 30 nm, Fe - 100 nm, Mn dioxide 50 nm, Cu - 70 nm in an aliquot, in which the initial concentration of metals was 100 μg / cm^3, respectively.

As a comparison preparation, a solution of a mixture of salts of the corresponding metals in ionic form was used - AgNO3, (CuSO4 • 5H2O), (MnSO4 •

5H2O) and (FeSO4 • 7H2O), concentration of which was 100 μg/cm^3, respectively, for each metal.

After keeping the experimental rats of all groups on a standard diet for 7 days, the animals of experimental groups (I, II, III group) received with feed solutions of mixture of salts of corresponding metals (I group) and mixtures NPMe (II, III group).

Rats of the experimental group I, weregiven a mixture of salts of metals at a dose of 0.3 mg/kg of body weight, and rats of experimental group II - a mixture of NPMe at a dose of 0.3 mg /kg of body weight (biotic dose established according to previous studies in acute toxicity study) , and the third experimental group - a mixture of NPMe at a dose of 4.0 mg /kg of body weight (toxic (dangerous) dose, established according to previous studies in the context of study of acute toxicity).

Rats of the control group were given each 2 cm^{3}of physiological solution of sodium chloride by similar regulations.

All animals were monitored for 90 days (main period). Onthe 15th, 30th and 60th day after the start of feeding, and in 30 days after termination of feeding (on the 90th day) the mixture of NPMe and metal salts, there were taken blood samples from 5 animals from each group after inhalation chloroform anesthesia. After that blood plasma was obtained for biochemical studies.

The intensity of the LPO processes was estimated by determining in blood plasma the concentration of its products - DC and MDA - in heptane-isopropanol extracts using the methods of Gavrilova V. B. and Mishorudnaya M. I. [11]. The state of the indicators of the antioxidant system (AOS) was investigated by activity of catalase (KF 1.11.1.6) using H_2O_2 at a wavelength of 410 nm, as described in the work of Korolyuk M.O. [12]. The total plasma AOA of blood plasma lipids was determined as described in the work of Klebanov G.I. [13].

The intensity of OMB in blood plasma was determined by the registration of the formation of carboxylic derivatives of neutral (NC) and basic character (BC) by the method of Archakova O. I. and Mihosoyev I. M. (1998) [14]. Aldehyd- and ketoderivatives of neutral character were determined at wavelengths of 370 nm, and

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the basic character - 430 nm, respectively, taking into account the value of the molar coefficient of extinction ($2.1 \times 104\ M^{-1}\ cm^{-1}$).

The results of the research were statistically processed using the Microsoft Excel 2003 software package (for Windows XP), the probability of the data obtained was estimated by the Student criterion.

Results. The results of the study of the intensity of the LPO and OMB processes in the blood plasma of experimental rats in the dynamics of the experiment are given in Table 1.

Research has established that chronic oral reception of a mixture of metals in various disperse forms caused in the blood of experimental rats different-directional changes in the formation of products of lipoperoxidation in the dynamics of the experiment.

1. State of indicators of the intensity of the LPO and OMB processes in blood plasma of rats under the chronic per oral effect of a mixture of metal salts and a mixture of NPMe in the dynamics for 90 days (M ± m; n = 5)

№ , Animal group	Term of research, day	Intensity of LPO, products		Intensity of OMB carboxylic derivatives	
		DC, μmol/l	MDA, ΔD	NC, mmol/g of protein	BC, mmol/g of protein
Control	15	38,9±2,5	5,52±0,20	549,2±64,2	274,2±24,0
	30	41,5±0,7	4,88±0,16	547,4±44,0	300,5±18,0
	60	39,4±3,2	5,11±0,234	597,9±22,8	302,0±34,3
	90	38,2±2,2	5,40±0,67	539,3±33,36	292,2±26,9
I experiment: Mixture of salts Me, 0,3 mg/kg	15	39,1±1,2	5,46±0,27	568,2±10,2	285,8±21,8
	30	45,8±2,3	4,41±0,22	498,7±62,6	307,1±36,7
	60	**51,2±2,6***	**6,89±0,12***	544,2±50,2	277,5±26,8
	90	**57,4±3,7***	**6,91±0,45***	581,4±52,8	311,0±23,4
II experiment: Mixture NPMe, 0,3 mg/kg	15	37,92±1,5	5,34±0,22	550,1±23,7	277,7±25,0
	30	40,8±0,5	4,80±0,32	573,8±37,4	326,7±18,0
	60	39,5±2,8	5,77±0,20	523,7±41,7	280,7±16,7
	90	**28,3±0,8***	5,01±0,28	526,8±26,0	322,6±40,0
III experiment: Mixture NPMe, 4,0 mg/kg	15	35,6±0,2	5,04±0,12	**671,7±26,2***	**388,2±25,0***
	30	**28,0±0,8***	**4,02±0,15***	557,9±33,0	328,4±20,5
	60	**26,4±0,5***	**4,14±0,12***	587,4±25,6	310,5±32,6
	90	**25,8±2,5***	**3,11±0,06***	556,2±38,6	302,2±24,8
Note. * - the difference of valuesis probable at (p≤0,05) relative to the values of such an indicator in control animals.					

Thus, in blood plasma of rats (Experiment I), which received a mixture of metal salts, there was determined the gradual increase in the intensity of LPO processes, which reached a probable growth rate on the 60th and 90th days of the experiment by the values of DC and MDA - an average on 29.9 and 34.8% and 50.3 and 28.0%, respectively, relative to their control indices.

In the blood of rats, under the conditions of the NPMe mixture reception, a reverse picture was recorded. Thus, in the plasma of animals (Experiment II) receiving the biotic dose of the NPMe mixture, only on the 90th day of the experiment, the reduction in the content of DC was determined on average by 15.9%, and in animals (III experiment) receiving the maximum dose, starting from the 30th day of the experiment, the content of both products of lipoperoxidation - DC and MDA - by 30.0% and 30.4% ($p \leq 0.05$), respectively, relative to the level of control indicators.

It was determined that on the background of the absence of excessive production of LPO products, in the blood of experimental rats of group III, the probable increase in the content of OMB derivatives was observed on the 15th day of the experiment (Table 1). The percentage of increase in the level of derivatives of neutral and basic character in this term of research was 22.3% and 41.6% ($p \leq 0.05$), respectively, relative to their values in control animals.

In the blood plasma of experimental rats of groups I and II, which were given a mixture of Me salts and a mixture of NPMe in a biotic dose, there was not not recorded a probable changes in the values of carboxylic derivatives during the experiment.

Table 2 shows the dynamics of indicators characterizing the state of the enzymatic link and the total AOS in the body of experimental rats.

Thus, induction of catalase activity was recorded due to the reception of a mixture of metals in both disperse forms at a dose of 0.3 mg/kg of body weight in the blood of experimental rats (Experiments I and II). In rats of the experimental group I in the dynamics of the experiment, the increase in the activity of catalase had a gradual nature and on the 30th, 60th and 90th days averaged 25.3%, 49.2% and

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42.6% ($p \leq 0.05$) relative to its control values.

In the blood plasma of animals (III Experiment) that received a maximum dose of NPMe, the level of catalase activity declined over time with respect to that in the control group, whose percentage onthe 15th, 30th and 60th days from the beginning of the experiment was, on average, 18.3%, 25.9% and 22.9% ($p \leq 0.05$) respectively.

Due to the chronic supply of a mixture of metals in both disperse forms at a dose of 0.3 mg/kg of body weight, an increase in the level of total AOA in blood plasma of rats of the experimental group I on the 60th day was recorded on average by 8.3%, while the second group on the 15th and on the 30th day - by 9.0 and 18.1% ($p \leq 0.05$) relative to the control values of the indicator.

2.Status of AOS values in blood plasma of rats at long-term per oral effects of a mixture of metal salts and a mixture of NPMe in the dynamics for 90 days (M ± m; n = 5)

№, animal group	Term of research, day			
	15th	30th	60th	90th
Activity of catalase, nmol H_2O_2/sec mg of protein				
Control	123,2±10,0	127,2±8,9	126,5±10,8	118,3±8,3
I experiment: Mixture of salts Me, 0,3 mg/kg	132,7±13,7	**159,4±6,9***	**188,7±21,1***	**168,7±6,7***
II experiment: Mixture NPMe, 0,3 mg/kg of body weight	126,1±11,1	129,3±7,5	**139,2±11,8***	108,2±12,6
III experiment: Mixture NPMe,4,0 mg/kg of body weight	**100,6±8,2***	**94,2±5,8***	**97,5±6,0***	117,8±8,8
Total AOA,% of inhibition				
Control	66,8±4,7	67,6±5,0	69,0±5,8	71,3±4,6
I experiment: Mixture of salts Me, 0,3 mg/kg	61,8±8,2	69,0±3,5	**74,7±2,5***	68,4±7,8
II experiment: Mixture NPMe, 0,3 mg/kg of body weight	**72,8±4,6***	**79,8±3,13***	73,5±6,2	72,6±4,7
III experiment: Mixture NPMe,4,0 mg/kg of body weight	62,8±6,8	**60,3±2,6***	**58,0±4,6***	**44,2±2,5***
Note. * - the difference of valuesis probable at ($p \leq 0,05$) relative to the values of such an indicator in control animals.				

Gradual expenditure of endogenous AOA resources was recorded in rats due to the effect of a mixture of NPMe in a dose of 4.0 mg/kg of body weight (III Experiment), starting from the 30th and the 90th day inclusive. The smallest value of the total AOA in the blood plasma of the experimental rats was established even after 30 days after the reception of NPMe mixture was discontinued, its decrease was 38.0% ($p \leq 0.05$).

Based on the nature of the intensity of the formation of OMB derivatives and the content of LPO products in the blood of rats in the conditions of long-term reception both a mixture of metal salts (Experiment I) and NPMe mixtures in the maximum dose (Experiment III), there was not enough capacityof the AOS own resources of the organism of experimental animals to prevent the influence of the AISW and the corresponding inclusion of protective mechanisms.

However, it may be concluded that the possible induction of antioxidant resources by the action of a mixture of NPMe in a dose of 0.3 mg/kg of body weight for 30 days, that illustrates the strengthening of the activity of endogenous AOA on the background of storage of physiological levels of intensity of oxidation processes in experimental rats; Consider such a dose of NCMe as biotic, and in further research it is necessary to take into account when creating nanonutraceutic of adaptogenic orientation.

Disscussion. 1. An antioxidant effect on the rat body of the NPMe mixture was established at a dose of 4.0 mg/kg of body weight, the maximum severity of which was recorded in 30 days after the start of oral administration, which was irreversible and persisted even in 30 days after stopping the receipt.

2. The mechanism of the prooxidant action of the NPMe mixture at a dose of 4.0 mg/ kg of body weight was in the formation oxidative stress in the body of rats due to the initial increase in the level of toxic OMB derivatives (on the 15th day), and subsequently (on the 30th day) - decrease in the formation of products of lipoperoxidation against the background of spending capacity of AO-resources atr inhibiting the activity of catalase and total AOA ($p \leq 0,05$).

3. Based on the results of strengthening the endogenous AOA against the background of storage of physiological levels of the intensity of the processes of LPO and OMB in experimental rats under the action of a mixture of NPMe in a dose of 0.3 mg/kg of body weight, it can be argued about its antioxidant effect, and in subsequent studies it canbe taken into account for the purpose of creation nano-nutraceuticalof adaptogenic orientation.

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ІНТЕНСИВНІСТЬ ЛІПОПЕРОКСИДАЦІЇ ТА ОКИСНЮВАЛЬНОЇ МОДИФІКАЦІЇ БІЛКІВ У КРОВІ ЩУРІВ ЗА УМОВ ХРОНІЧНОГО ВПЛИВУ СУМІШІ НАНОЧАСТИНОК МЕТАЛІВ ТА ЇЇ МАКРОДИСПРЕСНОГО АНАЛОГА

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Анотація. *У даній статті ми вивчали хронічні побічні ефекти суміші NPMe (Ag, Cu, Fe, двоокис Mn) у порівнянні з його макродисперсним аналогом за інтенсивністю окислювальних процесів у крові білих щурів. У ході експерименту за тваринами спостерігали протягом 90 днів (основний період), проводили відбір проб крові із 5 тварин з кожної групи на 15-, 30- та 60-й день після початку та через 30 днів (на 90-й день) після закінчення годування суміші NPMe та солей металів для подальших біохімічних досліджень. У результаті дослідження встановлено, що тривале згодовування суміші металів у різних дисперсних формах викликає в крові експериментальних щурів різноспрямовані зміни в утворенні продуктів ліпопероксидації в динаміці експерименту. За визначенням підвищення рівня загальної АОА на тлі зберігання фізіологічних рівнів інтенсивності процесів ПОЛ та ОМБ в крові експериментальних щурів під дією суміші NPMe у дозі 0,3 мг/кг маси тіла, можна стверджувати про її антиоксидантний ефект, враховувати в подальших дослідженнях та використовувати з метою створення нанонутрицевтика адаптогенної орієнтації.*

Ключові слова: *антиоксидантна система, суміш наночастинок металів, окиснювальна модифікація білків, перекисне окиснення ліпідів, солі металів, плазма, хронічна токсичність, щури*

ИНТЕНСИВНОСТЬ ЛИПОПЕРОКСИДАЦИИ И ОКИСЛИТЕЛЬНОЙ МОДИФИКАЦИИ БЕЛКОВ В КРОВИ КРЫС В УСЛОВИЯХ ХРОНИЧЕСКОГО ВЛИЯНИЯ СМЕСИ НАНОЧАСТИЦ МЕТАЛЛОВ И ЕЕ МАКРОДИСПРЕСНОГО АНАЛОГА

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Аннотация. *В данной статье мы изучали хронические побочные эффекты смеси NPMe (Ag, Cu, Fe, двуокись Mn) в сравнении с ее макродисперсним аналогом по изменению интенсивности окислительных процессов в крови белых крыс. В ходе эксперимента за животными наблюдали в течение 90 дней (основной период), проводили отбор проб крови с 5 животных из каждой группы на 15-, 30- и 60-й день после начала и через 30 дней (на 90-й день) после окончания кормления для дальнейших биохимических исследований. В результате исследования установлено, что постоянное скармливание смеси металлов в различных дисперсных формах вызывает в крови экспериментальных крыс разнонаправленные изменения в образовании продуктов липопероксидации в динамике эксперимента. По установленному увеличению уровня общей АОА на фоне сохранения физиологических уровней интенсивности процессов ПОЛ и ОМБ в крови экспериментальных крыс под действием смеси NPMe в дозе 0,3 мг/кг массы тела можно утверждать о ее антиоксидантном эффекте, что можно учитывать в дальнейших исследованиях и использовать в целях создания нанонутрицевтика адаптогенной ориентации.*

Ключевые слова: *антиоксидантная система, смесь наночастиц металлов, окислительная модификация белков, перекисное окисление липидов, соли металлов, плазма, хроническая токсичность, крысы*