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EXPERIMENTAL STUDY OF THE INFLUENCE OF IRON OXIDE COLLOIDAL SOLUTIONS WITH NANOPARTICLES ON THE CARDIOVASCULAR SYSTEM OF RATS

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The purpose of the study was to establish the toxic effect of Fe_2O_3 nanoparticles of different sizes on the cardiovascular system after long-term exposure. Experimental rats were injected intraperitoneally 5 times a week with colloidal solutions of Fe_2O_3 (with particles of 19, 75 and 400 nm) in a dose of 1 mmol (0.112 mg/ml of iron) per 100 g of the rat's body weight, a total of 30 injections. To establish the cardiotoxic effect of Fe_2O_3 colloidal solutions, haematological, biochemical and electrocardiographic parameters were determined and compared with the data in the control group. It was established that the long-term intake of Fe_2O_3 solutions caused disruptions in the process of hemoglobin synthesis; changes in blood coagulation parameters with signs of hypercoagulation; damage to liver and heart cells and increased activity of AST, ALT, AP, LDG, total CK and CK-MB enzymes. The cardiotoxic effect due to the exposure to Fe_2O_3 colloidal solutions was manifested by disruptions of the contractile and conduction function of the heart. It was noted that the $Fe_2O_3$with 19 nm NPs had a more pronounced effect on the cardiovascular system of rats.

Key words: iron oxide nanoparticles, cardiovascular system, toxicity.

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ЕКСПЕРИМЕНТАЛЬНЕ ДОСЛІДЖЕННЯ ВПЛИВУ КОЛОЇДНИХ РОЗЧИНІВ ОКСИДУ ЗАЛІЗА З НАНОЧАСТИНКАМИ НА СЕРЦЕВО-СУДИННУ СИСТЕМУ ЩУРІВ

Метою дослідження було встановлення токсичної дії наночастинок Fe_2O_3 різного розміру на серцево-судинну систему за умовиїх тривалого надходженняв організм щурів. Піддослідним щурам уводили в очеревину 5 разів на тиждень колоїдні розчини Fe_2O_3 (з частинками 19, 75 і 400 нм) удозі 1 мл (0,112 мг/мл заліза) на 100 гмаси тіла щура, всього 30 введень. Для встановлення кардіотоксичної дії колоїдних розчинів Fe_2O_3 визначали гематологічні, біохімічні та електрокардіографічні показники, які порівнювали з даними в контрольній групі щурів. Встановлено, що тривале надходження розчинів Fe_2O_3 в організм щурів викликало порушення процесу синтезу гемоглобіну; зміни показників згортання крові з ознакамигіперкоагуляції;ушкодження клітин печінки, серця та збільшення активності ферментів АСТ, АЛТ, ЛФ, ЛДГ, КК загальна і КК-МВ. Кардіотоксичний ефект за впливу колоїдних розчинів Fe_2O_3проявлявся порушенням скорочувальної та провідної функції серця. Відзначено, що більш виразну дію на серцево-судинну системущурів чинив розчин Fe_2O_3з НЧ19 нм.

Ключові слова: наночастинки оксиду заліза, серцево-судинна система, токсичність.

The work is a fragment of the research project "Investigation ofcardiovasotoxic action the mechanisms of heavy metal (on the problem of biosafety of nanomaterials)", state registration No. 0119U100182.

Iron is a vital trace element and plays a key role in many intracellular biological processes in the human body. Iron deficiency causes the development of anemia, changes in the functioning of the cardiovascular system, neurological disorders, and suppression of immunity. At the same time, the excess intake of iron in the body beyond the physiological need together with the disruption of control mechanisms for its redistribution and utilization leads to the accumulation of this metal in organs and tissues. This can stimulate oxidative stress, lipid peroxidation, the formation of reactive radicals, cell apoptosis and the development of pathological changes in the body [5].

According to the literature, iron is important in the development of hepatitis, diabetes, pneumosclerosis, rheumatoid arthritis, atherosclerosis and its complications (myocardial infarction, stroke), pathological changes in the nervous system (Alzheimer's and Parkinson's diseases), cataracts and cancer [2].

The role of iron in the development of diseases of the cardiovascular system was confirmed by numerous epidemiological studies, which revealed a positive correlation between excess accumulation of iron in the body and cardiovascular diseases [7]. Research by other authors [15] confirms that the use of excess iron with food products increases the risk of developing atherosclerosis, coronary disease in both men and women, especially in old age. In all of the above studies, we are talking about iron anionic compounds.

The modern development of nanotechnology contributes to the synthesis of innovative medicines based on nanoparticles (NPs) of iron and its oxides, which are used as anti-anemic agents, as well as for the treatment and diagnosis of oncological diseases [14].

Today, it is known that metal NPs due to their ultra-small size (<100 nm) can overcome biological barriers, penetrate cells, initiate the formation of reactive oxygen compounds and inflammation, damage organelles and DNA, lead to apoptosis and necrosis of cells and tissues, have a cardiotoxic effect [8, 12]. That is why the study of Fe_2O_3 NPs toxicity and safety is an important issue for preventive medicine and toxicology.

The purpose of the study was to establish the toxic effect of Fe_2O_3 NPs of different sizes on the cardiovascular system of rats under long-term exposure.

Materials and methods. We studied colloidal solutions of 19 nm, 75 nm, and 400 nm particles of iron oxide, which were synthesized in the reaction: $2Fe(NO_3)_3+6NH_3+3H_2O=Fe_2O_3+6NH_4NO_3$using reagents supplied by Aldrich (USA): $Fe(NO_3)_3 \cdot 9H_2O$, 25 %NH_3 aqueous solution, gelatin and distilled water. The concentration of iron in all colloidal solutions was 0.112 mg/ml. The size of NPs in solutions was determined using ANALYSETTE 12 laser particle analyzer (Germany).

The study of the effects of Fe_2O_3colloidal solutions on the cardiovascular system of rats was carried out by modelling isolated subchronic intoxications. The experiment was performed on 40 male Wistar rats with a body weight of 260–280 g, which were kept in stationary vivarium conditions, on a standard food and water regimen. The rats were divided into 3 experimental and 1 control groups (10 animals per group). Fe_2O_3colloidal solutions with NPs of different size were injected into the peritoneum of rats 5 times a week at a dose of 1 ml per 100 g of the rat's body weight; 30 injections in total. Rats of the 1st group were injected $Fe_2O_3$with 19 nm NPs; the 2nd group – $Fe_2O_3$with 75 nm NPs; and 3rd group – $Fe_2O_3$with 400 nm NPs. Control group animals were injected with 0.9 % physiological solution. At the end of the experiment, blood and organs were taken from the animals after euthanasia with 1.0 % propofol. All manipulations were carried out in accordance with the principles of bioethics in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, Strasbourg, 1986). "On the protection of animals against cruel treatment" (No. 1759-VI of 15.12.2009) and the European Union Directive2010/10/63 EU on animal experiments, confirmed by the Commission on Bioethics of SI "Kundiiev Institute of Occupational Health of the National Academy of Medical Sciences of Ukraine" (protocol No. 1 dated 20.04.2018).

Iron concentration was measured in the blood and internal organs of rats after mineralization by atomic emission spectroscopy with inductively coupled plasma on Perkin Elmer ICP Optima 2100 DV (USA). Peripheral blood parameters were determined in all groups of rats on the Elite 3 hematological analyzer (Czech Republic); coagulometric parameters: prothrombin index (PTI), activated partial thromboplastin time (APTT) and fibrinogen on Humaclot Junior (Germany) according to the manuals of each device. Biochemical studies with the determination of parameters characterizing the functional state of the liver, heart and kidneys, lipid and protein metabolism, were performed using a Key-Lab biochemical analyzer (Italy) and RANDOX (Great Britain) and ELiTech (France) test kits. In blood serum, the activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP); the content of uric acid, low molecular nitrogen substances (urea, creatinine), parameters of protein (total protein, albumin, globulin), carbohydrate (glucose, α-amylase) and lipid (cholesterol, triglycerides) metabolism were measured. Among the parameters indicating heart damage, the activity of lactate dehydrogenase (LDG), total creatine kinase (CK) and its isoenzyme creatine kinase MB (CK-MB) was determined. The functional state of the heart in experimental and control rats was assessed by electrocardiogram (ECG), which was recorded in standard II lead (right front and left hind paws) using the NEUROKOM electro-encephalographic device (XAI-MEDICA, Ukraine, Kharkiv). When deciphering the ECG, the elongation of the P wave, the RR and PQ intervals, the QRS complex, the height of the P and R waves were determined [3].

Statistical processing of data was carried out using the STATISTICA 13.3 program (Stat Soft; AXA9051924220FAACD-N). The reliability of intergroup and inter-group differences was assessed using Student's parametric criteria (t), in other cases – by non-parametric Mann-Whitney (U) criteria [1]. The critical level of statistical significance (p) was taken as ≤5 % ($p<0.05$).

The study was carried out in the laboratory of industrial toxicology and occupational hygiene when using chemicals, which is accredited by the National Accreditation Agency of Ukraine (NAAU) in accordance with the requirements of DSTU EN ISO/IEC 17021:2019. The accreditation certificate was registered in the Register on 6 August 2021, No. 201487. The measuring capabilities of the laboratory are

recognized by the "UKRMETRTESTSTANDART" SE, certificate No. PT-472/20 dated 10 December 2020. All units of measurement and parameters used in the study are given in accordance with the International System of Units.

Results of the study and their discussion. Measurement of the iron content in the blood and internal organs of control and experimental rats showed changes in the distribution and accumulation of metal in tissues and organs, represented in Fig. 1.

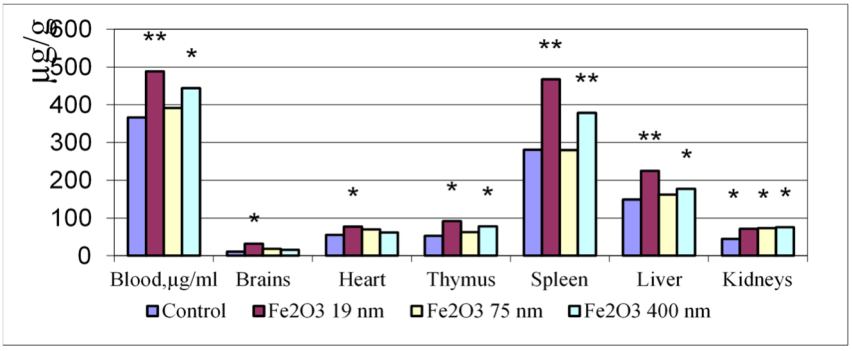

Fig. 1. Iron concentration in whole blood (μg/ml) and organs (μg/g) of control and experimental groups of rats after 30 administrations of Fe_2O_3colloidal solutions. (** – a significant difference in parameters of the experimental groups of rats compared to the control ones ($p<0.01$); * – ($p<0.05$))

It was established that the administration of Fe_2O_3 colloidal solutions, regardless of particle size, led to an increase in the iron content in the blood and organs of experimental rats. A particularly pronounced increase in the concentration of Fe in the blood occurred in the group of rats injected with Fe_2O_3 19 nm NPs by 30 % compared to the control group, $p<0.05$.

Accumulation of iron in the organs of experimental rats was also more significant after the administration of Fe_2O_3 19 nm NPs. This indicates that smaller NPs had a greater cumulative capacity. An increase in the content of iron in the brains of experimental animals after the introduction of Fe_2O_3 19 nm and 75 nm NPs compared to the control group (by 2.9 and 1.6 times, respectively, $p<0.05$), indicates that the nanoparticles actively overcome the blood-brain barrier.The highest concentrations of iron were determined in the spleen and liver of experimental animals, while in heart tissue it exceeded the control value only after the introduction of Fe_2O_3 19 nm NPs, while in the kidneys the highest metal concentration was determined after the introduction ofFe_2O_3 400 nm. The obtained data indicate that $Fe_2O_3$19 nm NPs had greater cumulative activity, particles larger than 400 nm were more actively excreted from the body, and liver and spleen were the depot organs.

It was established that long-term administration of Fe_2O_3 colloidal solutions caused changes in the composition of peripheral blood (Table 1).

Table1

Peripheral blood parameters of control and experimental groups of rats after 30 administrations of Fe_2O_3colloidal solutions(M±m)

Parameters	Groups of rats			
	Control	Fe_2O_3 19 nm	$Fe_2O_3$75 nm	$Fe_2O_3$400 nm
ZPP, mM/M of hem	70.75±4.38	135.63±2.58*	110.75±4.40*	70.75±4.38
Hemoglobin, g/l	157.10±2.80	141.50±0.19*	127.10±5.3*	145.10±1.50
Erythrocytes,10^9/ml	9.25±0.33	8.18±0.09$^+$	8.69±0.15	7.61±0.28 *
Hematocrit, %	49.27±0.97	44.22±0.55$^+$	47.02±0.95	47.59±0.75
Leukocytes,10^6/ml	11.88±0.99	5.74±0.38*	9.71±0.97$^+$	11.77±0.94
Lymphocytes, %	61.05±3.83	65.81±3.06	56.14±2.03	62.87±3.83
Monocytes, %	5.87±0.33	4.73±0.40	8.15±0.60*	7.93±0.57*
Segmented neutrophils, %	26.89±4.01	22.59±1.15	28.13±1.94	32.52±1.64*
Banded neutrophils, %	2.70±0.31	2.52±0.41	3.46±0.19*	2.33±0.42
Eosinophils, %	2.29±0.31	1.52±0.41*	4.15±0.60*	2.00±0.68
Trombocytes,10^6/ml	586.6±19.9	653.6±12.9	689.5±63.6*	889.6±22.4*
Trombocrit, %	0.49±0.04	0.61±0.03*	0.73±0.05*	0.72±0.04*
Prothrombin index (PTI), %	87.2±2.4	47.0±1.6*	55.2±1.85*	76.6±1.29*
APTT, s	60.0±0.7	44.0±1.05*	39.4±1.08*	26.2±0.37*
Fibrinogen, mg/dl	240.0±6.1	295.4±5.0*	400.0±8.0*	260.0±6.0*

Notes: * – a significant difference in parameters of the experimental groups of rats compared to the control ones ($p<0.05$); + – ($p<0.1$)

A significant increase by 2.0 times in the level of zinc protoporphyrin (ZPP), a slight decrease by 12.5 % in the number of erythrocytes and by 10.0 % in the concentration of hemoglobin and by 10.3 % in hematocrit were observed in rats injected with Fe_2O_3 19 nm NPs. After the injection of Fe_2O_3 75 nm NPs, an increase in the level of ZPP by56.5 % and a slight decrease in the level of hemoglobin by 8.3 %, and

after the injection of Fe_2O_3 400 nm NPs, a decrease in the number of erythrocytes by 17.7 %, hemoglobin level by 20.1 % was observed compared to the control. A decrease in the level of hemoglobin in the blood at the background of an increase in ZPP is the first sign of a violation of the heme synthesis process and may indicate the development of anemia.

A significant decrease in the relative number of leukocytes by 51.7 % and eosinophils by 33.7 % was observed after administration of Fe_2O_3 19 nm NPs compared to the control group. The number of lymphocytes, monocytes and neutrophils in the blood of rats of this group did not significantly differ from the values of control animals. An in ignificant decrease in the number of leukocytes by 19.0 %, lymphocytes by 9.0 %, but a significant increase in the relative number of monocytes by 38.8%, band neutrophils by 28.2 % and eosinophils by 81.2 % ($p<0.05$)was found in rats injected with Fe_2O_3 75 nm NPs. After 30 administrations of Fe_2O_3 400 nm, an increase in the number of monocytes by 35.0 % and segmented neutrophils by 20.9 % was determined ($p<0.05$). Such changes in blood composition may indicate the activation of cells (monocytes, neutrophils) involved in the formation of non-specific natural immunity and inflammatory reactions. In all three experimental groups of rats, compared to the control one, an increased number of platelets by 11.4 %, 17.5 % and 51.6 %, respectively and thrombocrit by 24.5 %, 48.9 % and46.9 % was found ($p<0.05$).

Significant changes in coagulogram parameters were also observed in experimental rats compared to the control group. In particular, in both the 1st and 2nd groups, a significant increase in the prothrombin index by 46.0 % and 36.7 %, respectively, a decrease in the activated partial thromboplastin time (APTT) by 26.7 % and 33.7 %, respectively, an increase in the level of fibrinogen by 23.0% and 66.7 %, respectively.

Studies of biochemical parameters of blood reflecting metabolic and exchange processes in cells, organs showed the changes represented in Table 2.

Table 2

Biochemical parameters of blood serum of control and experimental groups of rats after 30 administrations of Fe_2O_3colloidal solutions(M±m)

Parameters	Groups of rats			
	Control	Fe_2O_3 19 nm	Fe_2O_3 75 nm	$Fe_2O_3$400 nm
AST, IU/L	114.2±4.43	251.5±10.3**	338.0±9.95**	380.2±7.38**
ALT, IU/L	46.8±2.15	68.17±2.75*	85.60±2.34*	149.2±20.92**
de Ritis coefficient	2.44±0.15	3.69±0.11*	3.95±0.11*	2.55±0.21
AP, IU/L	195.0±3.54	565.00±14.1**	628.4±20.9**	820.8±19.6**
LDG, IU/L	682.2±17.88	1818.3±58.5**	2582.0±58.6**	2214.9±53.9**
CK, IU/L	2139.7±54.7	2359.7±139.6$^+$	3514.0±96.8**	6047.6±103.0**
CK-MB, IU/L	653.2±21.92	1265.3±116.1**	1895.8±71.7**	1457.6±101.4**
Total protein, g/l	74.14±1.53	74.40±1.24	72.46±1.22	75.08±2.25
Albumin, g/l	32.60±0.75	37.70±0.50$^+$	36.46±0.54	40.70±0.50*
Globulin, g/l	41.54±0.78	36.70±0.74$^+$	36.00±0.68$^+$	34.38±1.50*
Uric acid, μmol/l	82.10±2.42	154.17±4.66*	206.0±15.16*	470.3±43.37**
Urea, mmol/l	6.86±0.24	6.63±0.08	6.98±0.31	10.00±0.44*
Creatinine, μmol/l	63.40±1.60	33.83±1.08*	35.60±0.51*	46.00±2.21*
Cholesterol, mmol/l	1.30±0.03	1.14±0.20	1.37±0.10	1.69±0.15$^+$
Triglycerides, mmol/l	0.79±0.03	0.94±0.01*	0.80±0.07	1.49±0.08*
Glucose, mmol/l	4.85±0.10	3.42±0.14	4.49±0.15	3.76±0.17
α-amylase, IU/L	617.2±21.33	652.00±16.09	874.40±33.1*	885.50±14.97*

Notes: ** – a significant difference in parameters of the experimental groups of rats compared to the control ones ($p<0.01$); * – ($p<0.05$); + – ($p<0.1$)

After 30 injections of Fe_2O_3 19 nm, 75 nm and 400 nm NPs compared to the data in the control group, a significant increase in enzyme activity was determined: ASTby 2.2, 3.0 and 3.3 times, respectively ($p<0.01$), ALT by 1.5, 1.8, and 3.2 times, respectively ($p<0.05$). The obtained data may indicate damage to liver, heart, and kidney cells, while $Fe_2O_3$400 nm was found to be more toxic. The calculated de Ritis coefficient in groups of rats that were injected with $Fe_2O_3$19 nm and 75 nm NPs was > 3, which, together with an increase in the activity of the AST enzyme, may indicate toxic damage to cardiomyocytes.

In experimental rats, after administration of all Fe_2O_3 solutions, a significant increase in the activity of the AP enzyme was determined, in the first group – by 3.0 times, in the second – by 3.2 times, in the third group – by 4.2 times compared to control animals ($p<0.01$). An increase in the activity of AP together with ALT and AST indicate a high hepatotoxic effect of Fe_2O_3 solutions. In rats injected with $Fe_2O_3$19 nm, 75 nm and 400 nm NPs, a significant increase in LDG activity was determined in the blood serum by 2.7 times, 3.8 times and 3.2 times respectively compared to the control group, $p<0.01$. This enzyme is contained

in the cells of most tissues of the body, but it is more active in the liver, erythrocytes and muscles; therefore, the observed data can also be considered as a sign of toxic damage to the liver and myocardium.

A significant increase in total CK activity was determined in the blood serum in all groups by 10.0 %, 1.6 times and 2.8 times. The activity of the CK-MB isozyme was also significantly higher than the control values in all experimental groups (2.0 times; 2.9 times and 2.2 times, respectively). In addition to the above parameters, in all three groups of rats, increased levels of uric acid content were found (by 87.8 %, 2.5 times and 5.7 times, respectively, $p<0.01$ compared to the control). Increased content of urea was determined only in animals of the third group by 45.7 %. In rats injected with $Fe_2O_3$19 nm and 75 nm NPs, a significant decrease in creatinine content was established (by46.6 % and 43.8 %, $p<0.05$), while under the exposure to $Fe_2O_3$400 nm, it decreased by 27.4 %. It should be noted that the content of total protein in the blood of all three experimental groups did not differ from the control.

As for lipid metabolism, changes in the cholesterol content in the blood serum compared to the control were observed only in rats injected with Fe_2O_3 400 nm (increase by 30.0 %), while the content of triglycerides in this group of rats increased by 88.6 % ($p<0.05$) compared to the control. Therefore, the obtained data may indicate the risk of developing atherosclerotic changes in rats after long-term administration of Fe_2O_3 solutions mostly with large particles.

There was a decrease in the glucose content in the blood serum of rats in the 1st and 3rd experimental groups compared to the control group by 29.5 % and 22.5 %, respectively, $p<0.05$. In rats injected with Fe_2O_3 75 nm and 400 nm, increased activity of α-amylase enzyme was determined (by 41.7 % and 43.5 %, $p<0.05$ compared to the control).

The functional state of the heart was assessed by electrocardiogram (ECG) parameters. The changes in ECG parameters are presented in fig. 2.

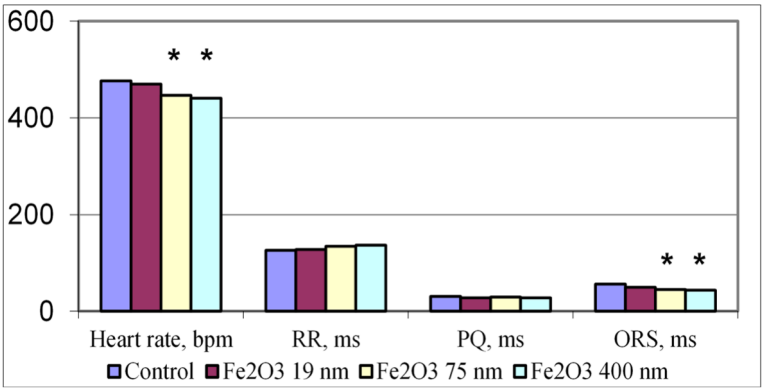

Fig. 2. Electrocardiogram parameters of control and experimental groups of rats after 30 administrations of Fe_2O_3colloidal solutions. (* – a significant difference in parameters of the experimental groups of rats compared to the control ones ($p<0.05$)).

In rats injected with Fe_2O_3 19 nm NPs, the heart rate was 470.0±13.3 bpm, and in rats injected with Fe_2O_3 75 nm NPs, it was 446.8±13.2 bpm, which is lower than in the control group by 6.6 bpm and 29.8 bpm, respectively. Changes in the interdental intervals, in particular, a slight prolongation of the RR interval by9.0 % and a decrease in the QRS by 20.0 % were found in rats injected with $Fe_2O_3$75 nm NPs. Other ECG parameters remained within the control values.

Summarizing the results presented in the article, we can say that colloidal solutions of $Fe_2O_3$with different sizes NPs had a direct toxic effect on heart, as well as indirect effect through hematological and biochemical processes with disorders of the hematopoiesis and blood circulation. The obtained results well correspond with modern literature data.

According to the literature [10], disorders in the blood aggregate regulation system can affect the functioning of the cardiovascular system. Changes in the cellular (increase in the number of platelets) and humoral components of the blood coagulation system (increase in the level of fibrinogen) may indicate the hyper coagulative properties of Fe_2O_3colloidal solutions and an increased risk of blood clots and the development of cardiovascular diseases.

After 30 injections of Fe_2O_3 19 nm, 75 nm and 400 nm NPs compared to the data in the control group, a significant increase in enzyme activity (AST, ALT, AP, LDG) was determined. It is known that significant increase in enzyme activity in blood serum indicate damage to liver, heartand kidney cells [13]. The obtained data may indicate toxic damage to hepatocytes and cardiomyocytes.Under the exposure toFe_2O_3NPs, an increase in activity of total CK and CK-MB in blood serum was established, which is considered a specific diagnostic marker of acute myocardial infarction, and can also be a sign of toxic myocardial damage [6]. The increased level of triglycerides in rats after long-term administration of Fe_2O_3 solutions mostly with large particlesmay indicate the risk of developing atherosclerotic changes [11].

The study of super paramagnetic iron oxide polyacrylic acid coated γ-Fe_2O_3 nanoparticles (10 mg/kg) demonstrates that accumulation ofthis NPs does not affect kidney function in healthy mice but cause acute effect on the cardiovascular function [9]. In our study the increase in the level of uric acid and

a decrease in creatinine in blood serum under the exposure to Fe_2O_3 solutions indicates an impaired kidney function.

It is well known that ECG parameters, in particular the P wave reflects the excitation of the left and right atria, the PQ interval characterizes the time the impulse travels through the heart's conduction system from the atria to the ventricles, and the QRS complex reflects the excitation of both ventricles [3,4]. Determined changes in the interdental intervals (lengthening of the RR interval and reduction of the QRS) under the exposure to Fe_2O_3 colloidal solutions, especially with 75 nm and 400 nm NPs allow us to talk about their influence on the contractile and conduction function of the heart.

Conclusion

The long-term injection of Fe_2O_3colloidal solutions to rats led to the accumulation of iron in the blood, heart and depot organs (liver, spleen); caused a disorders in hemoglobin synthesis; changes in the cellular composition of blood with the development of inflammation, blood coagulation parameters with signs of hypercoagulation; damage to the cells of the liver and heart and, accordingly, an increase in the activity of AST, ALT, AP, LDG, CK and CK-MB enzymes. The cardiotoxic effect under the exposure to Fe_2O_3colloidal solutions was manifested by a disorders in the functional activity of the heart; in particular, such ECG parameters as reduction of the heart rate and lengthening of the QRS complex may point on a disorder of the contractile and conduction function of the heart. The toxic effect of Fe_2O_3colloidal solutions on the cardiovascular system of rats depended on the size of the particles, the most pronounced effect was under the exposure to 75 nm NPs.

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