EFFECT OF SUBCHRONIC EXPOSURE TO MANGANESE ON MINERAL METABOLISM IN WISTAR RATS

Kazakova T.V.,
Marshinskaia O.V.,
Notova S.V.

Federal Research Centre of Biological Systems and Agrotechnologies of the Russian Academy of Sciences (9 Yanvarya str. 29, Orenburg 460000, Russian Federation)

Corresponding author:
Tatiana V. Kazakova,
e-mail: vaisvais13@mail.ru

ABSTRACT

Background. *The presence of increased manganese concentrations in soils and water intakes areas for drinking and household purposes in a number of the Russian Federation subjects indicates the chronic influence of this metal on all segments of the population. This situation is aggravated by violation of the optimal nutrition principles, which leads to changes in the organism absorption of micronutrients. In this regard, the study of the elemental status of an organism against the background of manganese exposure is of particular importance.*

The aim of the study. *To study the effects of subchronic exposure to manganese on the mineral status of Wistar rats.*

Materials and methods. *To conduct the study, 20 mature rats were selected, from which two groups were formed – control (n = 10) and experimental (n = 10). Animals in the control group received a general diet, animals in the experimental group received a diet with additional administration of manganese sulfate at a dose of 1433 mg/kg for 28 days. At the end of the preparatory period, blood and brain samples were taken to determine the content of chemical elements using inductively coupled plasma mass spectrometry and of metal-ligand manganese forms using high-performance liquid chromatography combined with inductively coupled plasma mass spectrometry.*

Results. *It has been established that subchronic oral exposure to manganese leads to an increase in the content of this microelement in the blood serum and to a decrease in the levels of calcium, potassium, magnesium, iron and copper. In the cerebral cortex, the level of manganese, lead, mercury and strontium increases against the background of a decrease in iron and iodine levels. An increase in the gross content of manganese in blood serum leads to an overload of the main high-molecular carriers and initiates the formation of low-molecular forms of manganese.*

Conclusion. *Subchronic oral exposure to manganese leads to the accumulation of this microelement in the body of animals and to the development of an imbalance of a number of macro- and microelements.*

Key words: *mineral metabolism, manganese, microelements, analysis of the content of chemical forms of elements, toxicity*

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ВЛИЯНИЕ СУБХРОНИЧЕСКОГО ВОЗДЕЙСТВИЯ МАРГАНЦА НА МИНЕРАЛЬНЫЙ ОБМЕН КРЫС ЛИНИИ WISTAR

Казакова Т.В.,
Маршинская О.В.,
Нотова С.В.

ФГБНУ «Федеральный научный центр биологических систем и агротехнологий Российской академии наук»
(460000, г. Оренбург, ул. 9 Января, 29, Россия)

Автор, ответственный за переписку:
Казакова Татьяна Витальевна,
e-mail: vaisvais13@mail.ru

РЕЗЮМЕ

Обоснование. *Наличие повышенных концентраций марганца в почвах, на водозаборах питьевого и хозяйственно-бытового назначения в ряде субъектов Российской Федерации свидетельствует о хроническом влиянии данного металла на все слои населения. Усугубляет данное положение нарушение принципов оптимального питания, что приводит к изменению усвоения микронутриентов организмом. В связи с этим особое значение приобретает изучение элементного статуса организма на фоне воздействия марганца.*
Цель исследования. *Изучить эффекты субхронического воздействия марганца на минеральный статус крыс линии Wistar.*
Материалы и методы. *Для проведения исследования было отобрано 20 половозрелых крыс, из которых были сформированы две группы – контрольная (n = 10) и опытная (n = 10). Животные контрольной группы получали общий рацион, животные опытной группы – рацион с дополнительным введением сульфата марганца в дозе 1433 мг/кг в течение 28 дней. По окончании подготовительного периода осуществлялся забор крови и головного мозга для определения содержания химических элементов методом масс-спектрометрии с индуктивно связанной плазмой и металл-лигандных форм марганца методом высокоэффективной жидкостной хроматографии в сочетании с масс-спектрометрией с индуктивно-связанной плазмой.*
Результаты. *Установлено, что субхроническое пероральное воздействие марганца приводит к повышению содержания данного микроэлемента в сыворотке крови, снижению уровня кальция, калия, магния, железа и меди. В коре головного мозга повышается уровень марганца, свинца, ртути и стронция на фоне снижения железа и йода. Повышение валового содержания марганца в сыворотке крови приводит к перегрузке основных высокомолекулярных носителей и инициирует образование низкомолекулярных форм марганца.*
Заключение. *Субхроническое пероральное воздействие марганца приводит к кумуляции данного микроэлемента в организме животных и развитию дисбаланса ряда макро- и микроэлементов.*

Ключевые слова: *минеральный обмен, марганец, микроэлементы, анализ содержания химических форм элементов, токсичность*

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INTRODUCTION

The vital activity of humans and animals has been substantiated to be closely related to the chemical composition of the environment and the content of various macro- and microelements, which take part in the formation of a number of adaptive mechanisms of the organism, including the functioning of vital systems, such as nervous, respiratory, cardiovascular, immune, digestive, endocrine [1].

One of the essential chemical elements associated with the geochemical parameters of the area is manganese. On the one hand, this metal is a vital trace element that controls a number of physiological processes in human and animal organisms [2]. Manganese is known to be involved in the regulation of carbohydrate, protein and lipid metabolism, protection of cells from oxidative stress, synthesis of neurotransmitters, and ensuring full reproductive function [3-5]. At the same time, at increased exogenous intake, manganese can have a negative effect on the functional state of the organism [6, 7]. This was first observed among miners, welders, smelters and other workers who were exposed to inhalation exposure to manganese as a result of the use of this metal in production cycles [8, 9]. However, it should be recognised that health risks are not limited to occupational exposures alone. The presence of manganese elevated concentrations in soils and water in a number of constituent entities of the Russian Federation indicates its chronic influence on the whole population [10]. This is especially true for the part of the population that lives near industrial areas and roads [11]. This situation is aggravated by the violation of the principles of optimal nutrition, which leads to changes in the absorption of chemical micronutrients by the body [12]. Consequently, it is food and drinking water that are the main intermediate link in the intake of manganese into the human and animal organism from the environment, largely determining the state of mineral metabolism [13]. Considering the above, the importance of studying the metabolism of macro- and microelements against the background of chronic exposure to manganese increases.

THE AIM OF THE STUDY

To evaluate the state of mineral metabolism of Wistar rats against the background of subchronic exposure to manganese.

MATERIALS AND METHODS

The experimental study was performed in full compliance with the ethical standards prescribed in the World Medical Association Declaration of Helsinki (1964, revised 2013). The design of the experiment was approved by the local ethical committee of the Federal Research Centre of Biological Systems and Agrotechnologies of the Russian Academy of Sciences (Orenburg). The study was performed using 20 sexually mature female Wistar rats. The age of the animals was 3 months at the time the experiment commenced. All animals received a basic diet (BD) in the form of a loose compound feed and were kept in plastic cages with sawdust bedding under conditions of artificial light (12-hour daylight hours) and supply and exhaust ventilation. The duration of the experiment was 4 weeks (28 days).

The animals were divided into two groups. Rats from the control group ($n = 10$) received the basic diet, animals of the experimental group ($n = 10$) – BD supplemented with pentahydrate manganese sulphate ($MnSO_4 \times 5H_2O$) at a dose of 1433 mg/kg. This salt is produced by JSC «Vekton» (St. Petersburg) with certified purity not less than 98 %, is a crystalline powder of white to pale pink colour (TS (technical specifications) 6-09-01-218-84). Dose selection of $MnSO_4 \times 5H_2O$ was based both on the GESTIS Substance Database and the European Chemicals Agency (ECHA) information systems.

After 28 days, the animals were removed from the experiment for the collection of biomaterials (blood, cerebral cortex) to evaluate the effect of manganese over mineral metabolism.

Blood was sampled from the cardiac artery into 6 ml VACUETTE vacuum tubes with clotting activator and gel (Greiner Bio-One International AG, Austria). Centrifugation of tubes for 10 minutes at 1000 g using ELMI CM-6M centrifuge (Latvia) was performed to obtain serum. The separated serum was stored at a temperature of -70 °C in Eppendorf-type test tubes. Immediately after rapid extraction of the brain, a tissue slice was performed from the surface of the hemisphere with a thickness of about 1–1.5 mm. Samples were weighed and stored at -20 °C until analyzed.

The content of macro- and microelements in blood serum and cerebral cortex samples was analysed using a NexION 300D mass spectrometer (PerkinElmer Inc., USA) by inductively coupled plasma mass spectrometry (ICP-MS). Determination of individual chemical forms of manganese in blood serum was performed using a NexION 300D mass spectrometer (PerkinElmer Inc., USA) in combination with a PerkinElmer Series 200 liquid chromatograph (PerkinElmer Inc., USA) by high-performance liquid chromatography with inductively coupled plasma mass spectrometry (HPLC-ICP-MS). This stage of the study was conducted in the certified laboratory of Micronutrients LLC (Moscow; licence registration number L041-01137-77/00370156).

The data obtained were processed by variation statistics methods using Statistica 10 statistical package (StatSoft Inc., USA). A hypothesis that the data belong to the normal distribution was rejected in all cases with a probability of 95 %, which justified the use of non-parametric procedures for processing statistical populations (Mann – Whitney *U*-criterion). The findings are presented as median (Me) and 25th and 75th percentiles (Q_{25}–Q_{75}). The relationships between the parameters were evaluated using Spearman's Rank Correlation Coefficient. A correlation coefficient (r) was calculated to determine the closeness of the relationship between the studied features. Correlation coefficients were evaluated as follows:

less than 0.3 – weak relationship; 0.3 to 0.5 – moderate; 0.5 to 0.7 – significant; 0.7 to 0.9 – strong; more than 0.9 – very strong [14].

RESULTS

The results of the study revealed that subchronic oral exposure to manganese did not lead to changes in the external signs of the animals and their activity level. However, a comparative analysis of the macro- and microelements content in blood serum revealed that in the experimental group by the end of the experiment the level of manganese statistically significantly exceeded the control values by 70 %; a tendency to increase the content of iodine and selenium was also observed. Against this background, it was revealed that the serum level of potassium was statistically significantly lower than in the control by 25 %, copper by 24 %, magnesium by 19 %, iron by 10 %, calcium by 8 %; there was a tendency to decrease phosphorus and zinc (Fig. 1).

Increased sensitivity to toxic factors of phylo- and ontogenetically younger and higher located parts of the brain compared to older and lower located parts is a general pattern for the central nervous system, in this connection we also analysed the elemental composition of the cerebral cortex [15] (Fig. 2).

It was revealed that in the grey matter of animals from the experimental group the content of a number of heavy metals was statistically significantly higher than the control values: the level of manganese exceeded the control by 19 %, strontium – by 57 %, mercury

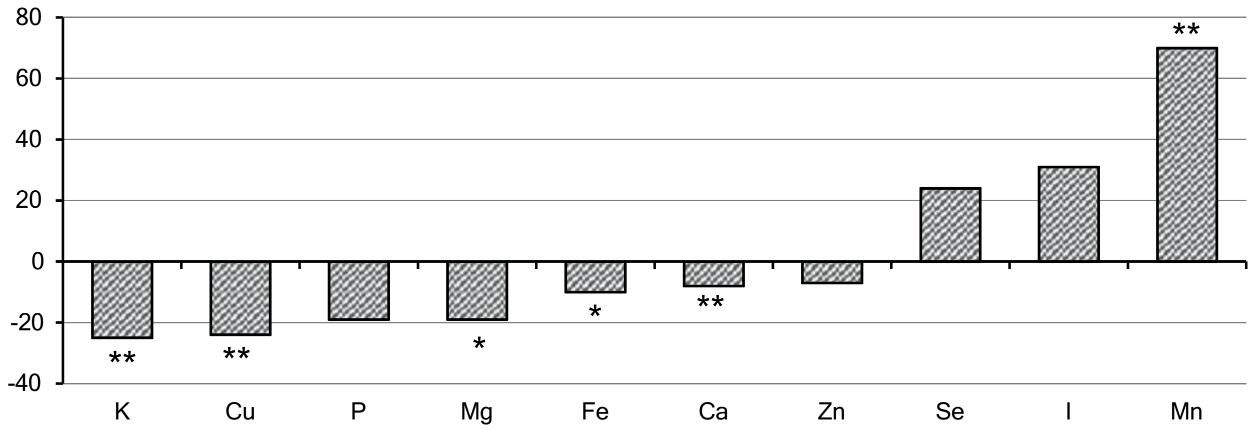

FIG. 1.
*Relative values of chemical elements content in blood serum of animals from the experimental group (%): X axis (0) – level of elements in the control group; * – statistically significant difference between the experimental group and control at p ≤ 0.05; ** – statistically significant difference between the experimental group and control at p ≤ 0.01*

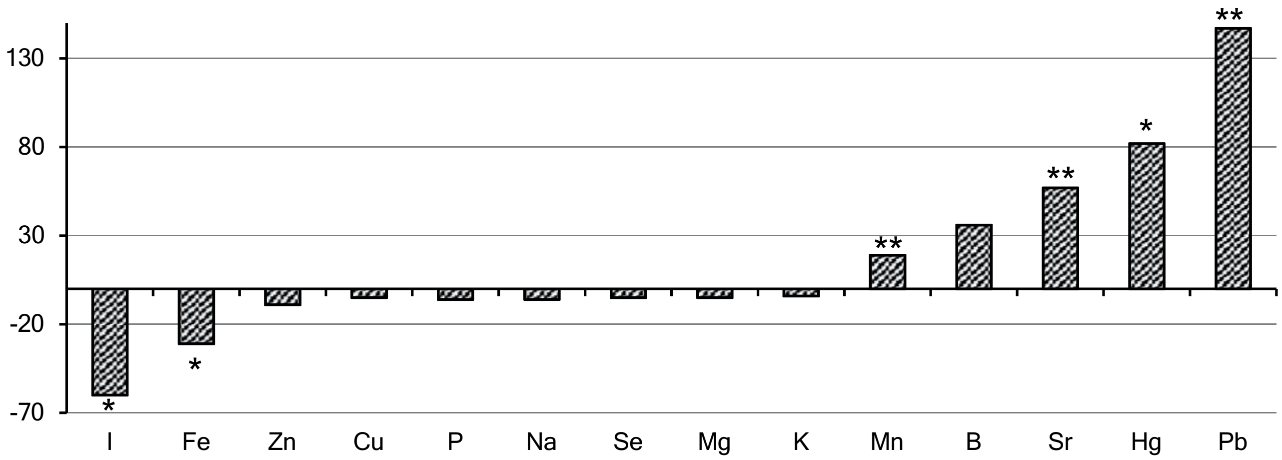

FIG. 2.
*Relative values of chemical elements content in the cerebral cortex of animals from the experimental group (%): X axis (0) – level of elements in the control group; * – statistically significant difference between the experimental group and control at p ≤ 0.05; ** – statistically significant difference between the experimental group and control at p ≤ 0.01*

– by 82 %, lead – by 147 %. In contrast, iron and iodine levels were statistically significantly lower than the control, by 31 % and 60 %, respectively.

From a diagnostic point of view, it is of particular interest to identify possible relationships between serum and cortical chemical elements, as the latter do not have equivalent *in vivo* measurements. Correlation matrix analysis showed that serum magnesium level was statistically significantly positively associated with cortical magnesium ($r \geq 0.3$), while serum copper level was positively correlated with brain copper ($r \geq 0.3$).

Manganese is known to be a rather active chemical element, as a result of which in the body it is stabilised in complex with various biological ligands. We have therefore analysed the chemical forms of this metal (speciation analysis). It was revealed that serum manganese of Wistar rats is mainly associated with high molecular weight compounds – such fractions as transferrin/albumin (Mn-Tf/Alb), in smaller amounts – with α-2-macroglobulin fraction (Mn-A2M); with low molecular weight compounds (Mn-LMM), and is also represented by free inorganic form (Mn-free) (Fig. 3).

It was revealed that the main amount of manganese in the experimental group of animals was presented in the form of Mn-free fraction (6.6 μg/l), exceeding the control values by 1.8 times. Among the organic forms, it was observed that the concentrations of Mn-LMM and Mn-Tf/Alb were statistically significantly higher than the control, by a factor of 4 and 1.9, respectively. A tendency to decrease the content of the Mn-A2M fraction was observed against this background.

The results of the analysis concerning the percentage distribution of Mn by fractions against the background of its different content in the blood serum of animals are presented in Figure 4 for illustrative purposes.

According to correlation analysis, it was revealed that serum gross manganese content was statistically significantly positively associated with such fractions as Mn-free (r = 0.89), Mn-Tf/Alb (r = 0.81) and Mn-LMM (r = 0.63); a negative correlation with Mn-A2 (r = -0.6) was observed (Fig. 5).

The scatter graph illustrates the fact that the higher was the level of total manganese in serum among the animals of the experimental group, the higher was the concentration of Mn-free, Mn-LMM and Mn-Tf/Alb fractions and the lower became the concentration of Mn-A2 fraction. The graph also clearly illustrates that an increase in the total manganese concentration in rat serum (above 12 μg/L) leads to overloading of the major high molecular weight carriers and initiates even greater formation of low molecular weight forms of Mn.

DISCUSSION

Interest in research aimed at studying manganese metabolism in humans and animals, as well as possible adverse effects of manganese exposure, has increased significantly over the last decade. Much attention to this problem is caused by a number of objective reasons, among which the deterioration of the environmental situation takes the main place [16].

The conducted experimental study has revealed that subchronic oral exposure to manganese can lead to disturbance of the balance over chemical elements in the organism of animals.

The decrease in the levels of magnesium, iron and copper in blood serum revealed in the course of the analysis is associated with excessive intake of manganese, a functional antagonist of these metals, into the organism of laboratory animals. The absorption of these elements in the gastrointestinal tract is accomplished by common transport systems and, therefore, the nutritional status of manganese can influence the kinetics of these chemical elements [17, 18].

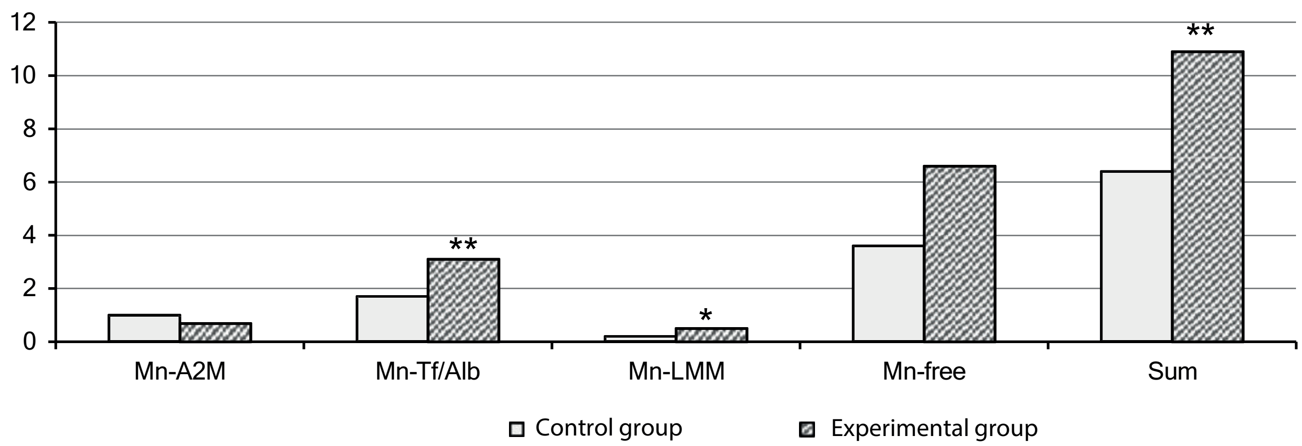

FIG. 3.
*Content of manganese fractions in serum of animals (μg/l): data are presented according to median values; * – statistically significant difference between experimental group and control at p ≤ 0.05; ** – statistically significant difference between experimental group and control at p ≤ 0.01*

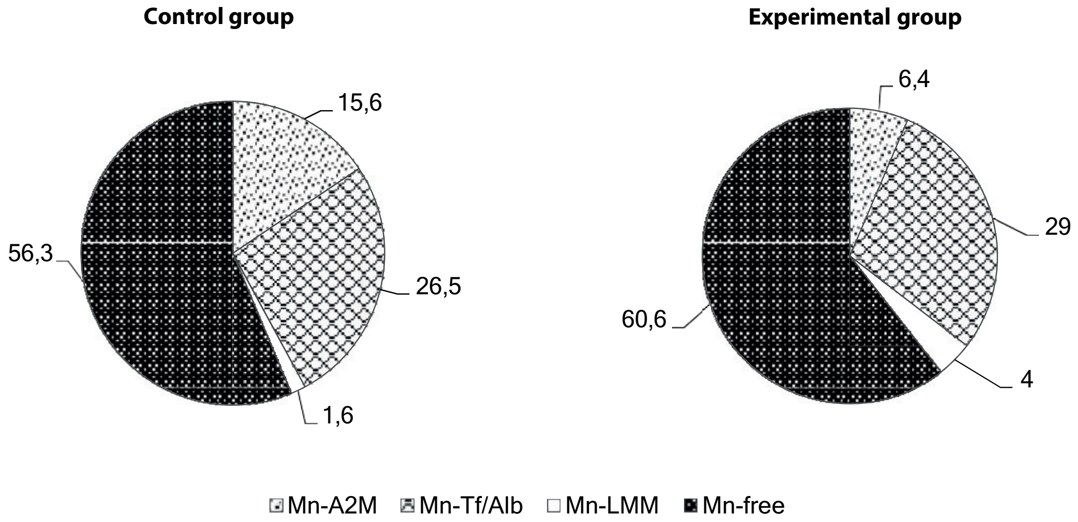

FIG. 4.
*Percentage distribution of manganese by fractions (%): * – statistically significant difference between the experimental group and control at p ≤ 0.05; ** – statistically significant difference between the experimental group and control at p ≤ 0.01*

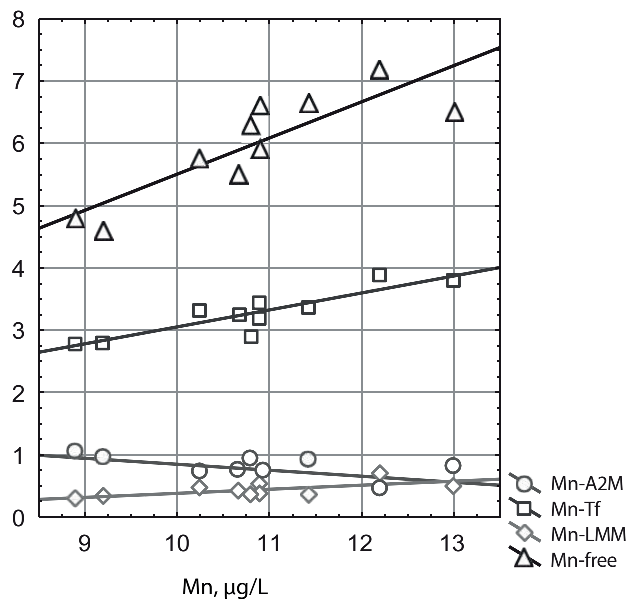

FIG. 5.
Correlation between the total concentration of manganese and its separate fractions in blood serum of animals from the experimental group (n = 10), µg/L

The observed tendency to increase iodine content may be associated with the blocking effect of manganese ions on iodine uptake by the thyroid gland [19]. Selenium compounds are well known to have an antitoxic effect in poisoning with salts of many heavy metals. The main blood selenoprotein SeP has a high affinity for heavy metals, as a result of which it is able to form complexes with metals and transport them [20, 21]. Specifically, a study by Chinese scientists revealed that mercury exposure affects the concentration of selenium and the distribution of selenoproteins in serum in a dose-dependent manner [22]. This may explain the trend towards higher selenium levels revealed in our study.

The obtained results clearly revealed that chronic exposure to manganese alters iron homeostasis in the systemic circulation, reducing its content in blood serum, as well as in the brain, which is consistent with the studies of foreign scientists [23]. Chemically, this is justified by the fact that manganese and iron are located next to each other in the periodic table, allowing them to compete for binding to transport proteins [24]. Generally, in iron-deficient brain regions, an increased accumulation of manganese occurs, leading to the activation of oxidative stress [25]. Manganese-induced oxidative stress appears likely to cause an increase in the permeability of the blood-brain barrier leading to an increased influx of heavy metals such as lead, mercury and strontium [26].

The development of analytical chemistry techniques has led to the realisation that the total concentration of chemical elements cannot provide complete information as regards their metabolism, bioavailability and possible toxic effects over living organisms. Only by knowledge of the chemical form of an element can provide information about potential chemical and biochemical processes and thus lead to a greater understanding of the toxicity or essentiality of the element [27, 28]. The obtained results of chemical element compound analysis (speciation analysis) clearly demonstrate that prolonged exposure to subchronic doses of manganese can lead to a shift of its metal-ligand forms towards low molecular weight compounds, as well as the inorganic fraction, which may be associated with overloading of other transport molecules. Mn-LMMs are assumed to be the ones capable of crossing the blood-brain barrier and accumulating in the brain, causing neurotoxic effects [29]. A perfusion study conducted by American scientists revealed that a higher inflow coefficient from blood to the brain is characteristic of Mn-LMM (3-fold higher) compared to Mn-free and Mn-Tf complexes [30].

CONCLUSION

The obtained results of the study allow us to conclude that subchronic oral exposure to manganese leads to its cumulation in the organism of animals and development of imbalance of a number of macro- and microelements. Such abnormalities can potentiate the development of functional disorders of the body systems. The excessive intake of manganese was revealed to contribute to a statistically significant increase in the content of this heavy metal in blood serum against the background of a statistically significant decrease in the level of calcium, potassium, magnesium, iron and copper. Simultaneously, the level of manganese, lead, mercury and strontium statistically significantly increased in the cerebral cortex; iron and iodine decreased.

The revealed correlations between the content of chemical elements in blood serum and cerebral cortex indicate that changes in serum levels of magnesium and copper may serve as a prognostic sign of disturbance of their homeostasis in the brain.

Redistribution of this metal to its metal-ligand forms occurs against the background of an increase in the gross content of manganese in blood serum. At manganese concentrations in rat serum above 12 μg/L, there is a shift of manganese fraction levels towards low molecular weight LMM compounds, which may be associated with an overload of other transport molecules and may be a new tool for prenosological diagnosis.

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Conflict of interest

The authors of this article declare no conflicts of interest.

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Information about the authors

Tatiana V. Kazakova – Junior Research Officer at the Laboratory of Molecular Genetic Research and Metallomics in Animal Husbandry, Federal Research Centre of Biological Systems and Agrotechnologies of the Russian Academy of Sciences, e-mail: vaisvais13@mail.ru, https://orcid.org/0000-0003-3717-4533

Olga V. Marshinskaia – Junior Research Officer at the Laboratory of Molecular Genetic Research and Metallomics in Animal Husbandry, Federal Research Centre of Biological Systems and Agrotechnologies of the Russian Academy of Sciences, e-mail: m.olja2013@yandex.ru, https://orcid.org/0000-0002-5611-5128

Svetlana V. Notova – Dr. Sc. (Med.), Professor, Acting Head of the Laboratory of Molecular Genetic Research and Metallomics in Animal Husbandry, Federal Research Centre of Biological Systems and Agrotechnologies of the Russian Academy of Sciences, e-mail: snotova@mail.ru, https://orcid.org/0000-0002-6378-4522