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# Hippocampal Metabolism of Biogenic Metals and Selenium in Patients With Chronic Manganese Intoxication

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## ABSTRACT

**BACKGROUND:** The stability of trace element composition within the organism is crucial for maintaining the vital biochemical and biophysical processes. The severity of diseases associated with heavy metal accumulation is largely attributable to the irreversibility of this process and the persistent disturbances in metabolic systems. Therefore, investigating the imbalance of biogenic elements in patients with chronic heavy metal intoxication is highly relevant.

**AIM:** The work aimed to determine the variations in the levels of biogenic metals and selenium with chronic manganese chloride intoxication.

**METHODS:** The experiments were conducted on 12 male white outbred rats weighing 180–220 g. The experimental group ( $n = 6$ ) received a 0.2% manganese chloride solution via automatic dispensers for 3 months, and the control group ( $n = 6$ ) was given tap water. The concentrations of manganese, copper, zinc, selenium, calcium, iron, and magnesium were measured in the left and right hippocampi using atomic emission spectroscopy with PerkinElmer Optima 7000 DV ICP-OES Spectrometer (USA).

**RESULTS:** Based on the hippocampal content, the analyzed biogenic elements were arranged in the ascending order of concentration as follows:  $[Mn] < [Cu] < [Zn] = [Se] < [Mg] < [Fe] < [Ca]$ . No evidence of asymmetry was observed in the levels of these metals and selenium across any of the animal groups. In rats that received the manganese solution, the hippocampal levels of manganese were more than twice as high compared to the control group ( $p < 0.01$ ). In the experimental group, the copper concentrations were found to be significantly higher ( $p < 0.01$ ), whereas the selenium levels were lower ( $p < 0.01$ ) compared to the control group. These effects demonstrated a bilateral pattern, affecting both the left and right hippocampi. The levels of iron, zinc, calcium, and magnesium remained unchanged.

**CONCLUSION:** It can be hypothesized that the observed variations in biogenic elements may be responsible for the impairment of enzymatic systems, which include manganese, copper, and selenium.

**Keywords:** hippocampus; copper; manganese; selenium; manganese intoxication; biogenic metals.

## For citation

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# Об особенностях обмена биогенных металлов и селена в гиппокампе при хроническом отравлении марганцем

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## АННОТАЦИЯ

**Актуальность.** Постоянство микроэлементного состава в организме крайне важно для поддержания биохимических и биофизических процессов жизнедеятельности. Тяжесть заболеваний, связанных с накоплением тяжелых металлов в организме, обусловлена необратимостью данного процесса и стойкостью нарушений работы метаболических систем. Таким образом, представляется актуальным изучение изменения баланса биогенных элементов при хроническом отравлении тяжелыми металлами.

**Цель** — определить изменение содержания биогенных металлов и селена при хроническом отравлении хлоридом марганца.

**Материалы и методы.** Эксперименты проводили на 12 белых беспородных крысах-самцах массой 180–220 г. Крысы опытной группы ( $n=6$ ) в течение 3 мес. получали в автопоилках 0,2% раствор хлорида марганца, крысы контрольной группы ( $n=6$ ) — водопроводную воду. В левом и правом гиппокампе методом атомно-эмиссионной спектроскопии определяли содержание марганца, меди, цинка, селена, кальция, железа и магния с использованием анализатора Optima 7000 DV ICP-OES, (PerkinElmer, США).

**Результаты.** По содержанию в гиппокампе исследованные биогенные элементы располагались в следующем порядке (по возрастанию концентраций):  $[Mn] < [Cu] < [Zn] = [Se] < [Mg] < [Fe] < [Ca]$ . Асимметрии по уровню исследованных металлов и селена ни у одной из групп животных выявлено не было. У крыс, потреблявших раствор марганца, его содержание в гиппокампе более чем в 2 раза превышало данный показатель у животных контрольной группы ( $p < 0,01$ ). При этом у крыс экспериментальной группы, по сравнению с контрольной, концентрация меди была значимо выше ( $p < 0,01$ ), а селена — ниже ( $p < 0,01$ ). Указанные эффекты проявлялись билатерально — как в левом, так и в правом гиппокампе. Содержание железа, цинка, кальция и магния не изменялось.

**Заключение.** Можно предположить, что обнаруженные нами изменения биогенных элементов может быть причиной нарушения ферментативных систем, в которые, помимо марганца, включены, медь и селен.

**Ключевые слова:** гиппокамп; медь; марганец; селен; марганцевая интоксикация; биогенные металлы.

## Как цитировать

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## BACKGROUND

The stability of trace element composition within the organism is crucial for maintaining the vital biochemical and biophysical processes [1]. In clinical medicine, there are diseases associated with the accumulation of heavy metals in the body and their incorporation [2, 3]. In morbidity structure, heavy metal poisoning predominantly falls under the occupational disease category and is characterized by persistent impairments involving various organs and systems.

Manganese intoxication holds a special place among heavy metal-related diseases, as chronic poisoning clinically mimics the neurodegenerative disorder of Parkinson disease (PD) [4]. The common clinical features of manganese intoxication and PD include neurological and psychiatric disturbances [4, 5]. Cognitive impairments are observed in some patients with PD, similar to those in patients with manganese intoxication [4, 6]. The hippocampus, as the central component of the limbic system, is considered responsible for memory function in the brain [7]. Researchers note that biogenic metals essential for biochemical processes underlying cognitive abilities are required to maintain physiological memory function [7]. Therefore, studying the content of biogenic elements in hippocampal tissue will enhance understanding of biochemical changes observed in chronic manganese intoxication and clarify potential links between clinical manifestations of this pathological condition and alterations in biogenic metals and selenium.

The aim of this study was to determine the variations in the levels of biogenic metals and selenium in chronic manganese chloride intoxication.

## METHODS

The experiments included 12 white outbred male rats weighing 180–220 g. All animals were obtained from the Rappolovo breeding colony (Leningrad Region, Russia). The rats were housed under standard conditions with *ad libitum* access to food and water<sup>1</sup>.

To model chronic manganese poisoning, we adapted a protocol of chronic semi-forced intake of excessive manganese via drinking water [8].

Prior to the experiments, all animals were randomly divided into two groups: group 1, control group ( $n = 6$ ) receiving tap water via automatic dispensers, and group 2, experimental group ( $n = 6$ ) receiving water supplemented with manganese chloride. Manganese chloride solution was prepared by adding manganese(II) chloride tetrahydrate ( $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ , Lenreaktiv, Russia) to tap water to a final concentration of 0.2% [8]. All animals consumed water *ad libitum* for

3 months. This deviation from the original 10-month exposure protocol [8] was based on recommendations permitting the reduction of factor exposure duration to 3 months in chronic experiments on biological subjects [9].

After three months, the rats were decapitated, and the hippocampi were dissected from both cerebral hemispheres and weighed with an accuracy of 1 mg. Collected samples were digested with nitric acid in a high-frequency demineralizer at 190 °C and a power of 800–1100 W. The resulting mineralizate was dissolved in water and analyzed for manganese, copper, zinc, selenium, magnesium, iron, and calcium content using atomic emission spectroscopy with Optima 7000 DV ICP-OES Spectrometer (PerkinElmer, USA). Quality control and analytical validity were ensured using certified reference materials (State Standard Sample 6077-91). The analysis yielded metal concentration values in the hippocampi ( $\mu\text{g/g}$ ).

Data analysis was performed using GraphPad Prism 6.0 statistical software (GraphPad Software, USA). Nonparametric statistical methods were applied for small sample sizes. The Wilcoxon signed-rank test was used for paired comparisons of right and left hippocampal parameters within each group, whereas the Mann–Whitney  $U$  test was employed for intergroup comparisons. Differences were considered significant at  $p < 0.05$ . Sample features are presented as medians ( $Me$ ) with interquartile ranges [ $Q_1$ ;  $Q_3$ ].

## RESULTS

The concentrations of biogenic metals and selenium in rats from the control group (CG) and experimental group (EG) are presented in Table 1 and Figure 1.

Analysis of biogenic element content in rat hippocampi revealed that manganese was the least abundant. Copper content exceeded this value by one order of magnitude; zinc and selenium—by two orders of magnitude; and calcium, magnesium, and iron—by three orders of magnitude (Table 1). No significant differences in element content were found between the left and right hippocampi.

The study demonstrated that experimental exposure resulted in more than a 2-fold increase in manganese content in the rat hippocampi ( $p < 0.01$ ; Table 1, Fig. 1, *a*).

Despite manganese's lowest concentration compared to other elements, this trace element significantly contributes to biogenic element metabolism by influencing copper and selenium levels.

Copper concentration in the left and right hippocampi of the EG rats was statistically significantly higher than the in the CG animals ( $p < 0.01$ , Fig. 1, *b*). As previously noted, no interhemispheric differences in this parameter were observed in either group.

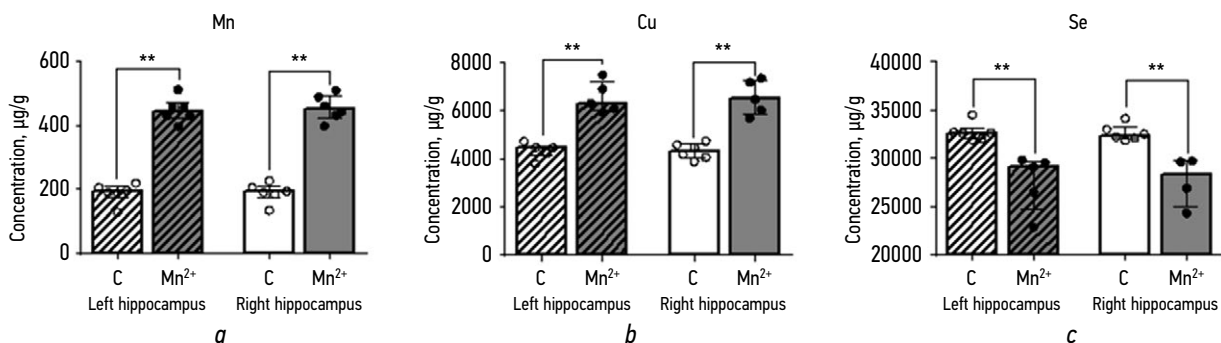
The rats chronically receiving manganese chloride in drinking water showed significantly lower selenium content compared to the CG animals. These differences were observed in both right and left hippocampi ( $p < 0.01$ ), with no interhemispheric differences (Fig. 1, *c*).

<sup>1</sup> GOST 33216-2014. *Guidelines for Accommodation and Care of Animals. Species-Specific Provisions for Laboratory Rodents and Rabbits*, dated July 1, 2016; GOST 33215-2014 *Guidelines for Accommodation and Care of Animals. Environment, Housing and Management*, dated July 1, 2016.

**Table 1.** Variations in the hippocampal levels of biogenic metals and selenium ( $\mu\text{g/g}$ ) in rats following chronic exposure to manganese chloride solution

Elements	Rats			
	receiving potable tap water (control group)		receiving manganese chloride (experimental group)	
	hippocampus		hippocampus	
	left	right	left	right
Manganese	0.19 [0.17; 0.21]	0.19 [0.17; 0.21]	<b>0.44**</b> [0.42; 0.47]	<b>0.45**</b> [0.42; 0.49]
Copper	4.47 [4.12; 4.54]	4.32 [4.02; 4.62]	<b>6.30**</b> [6.00; 7.18]	<b>6.47**</b> [5.86; 7.25]
Zinc	30.8 [30.2; 35.4]	31.6 [30.2; 34.6]	31.7 [25.8; 37.3]	28.8 [24.5; 36.6]
Selenium	32.6 [32.0; 33.2]	32.4 [32.1; 33.3]	<b>29.1**</b> [24.7; 29.7]	<b>29.6**</b> [25.6; 30.2]
Magnesium	131.7 [124.7; 150.5]	127.2 [122.4; 135.3]	122.2 [101.5; 134.2]	118.0 [99.5; 135.9]
Iron	192.5 [185.6; 198.4]	189.1 [184.4; 197.7]	185.3 [137.4; 190.9]	177.2 [136.1; 190.5]
Calcium	444.9 [394.8; 495.0]	447.7 [390.0; 475.4]	465.7 [398.6; 484.7]	467.9 [396.8; 484.0]

Note. The data are presented as medians (*Me*) and interquartile ranges [ $Q_1$ ;  $Q_3$ ]. \*\*  $p < 0.01$ , statistically significant differences from the concentration of this element recorded in rats of the control group on the corresponding side of the brain (according to the Mann–Whitney criterion).



**Fig. 1.** Variations in the hippocampal levels of manganese (Mn), copper (Cu), and selenium (Se) ( $\mu\text{g/g}$ ) in rats following chronic exposure to manganese chloride solution. The data are expressed as medians (bar heights) and quartile intervals (strokes). The light bars and dots correspond to the hippocampal levels of trace elements in control rats (C), and the dark bars and dots correspond to the levels measured in rats treated with manganese chloride solution ( $\text{Mn}^{2+}$ ). The shaded bars represent the values obtained for the left hippocampus, whereas the plain bars depict the values obtained for the right hippocampus. \*\* statistically significant differences,  $p < 0.01$  (Mann–Whitney test).

Hippocampal concentrations of iron, zinc, calcium, and magnesium showed no significant differences between the CG and EG rats (Table 1).

Thus, chronic manganese exposure alters trace element composition, manifesting as increased copper concentration and decreased selenium levels.

## DISCUSSION

We found no interhemispheric differences in the content of all studied elements, with all detected changes equally manifested in both hippocampi. However, previous studies

have shown that bilateral intranasal administration of the polypeptide (oxytocin) to mice increases its concentration exclusively in the left hippocampus [10]. It can be assumed that metals and selenium, due to their small size, freely cross brain barriers.

The mechanisms of negative impact of elevated manganese on brain function remain a subject of extensive research [11]. The potential oxidation of  $\text{Mn}^{2+}$  to  $\text{Mn}^{3+}$  in the mitochondrial matrix promotes the formation of a strong pro-oxidant species, leading to inhibition of oxidative phosphorylation and increased production of reactive oxygen species [11]. Manganese exhibits selective tropism for the brain's

cholinergic system [12]. It is hypothesized that mental impairments in Parkinson disease arise from degeneration of cholinergic fibers in the hippocampus [13]. Literature also describes more pronounced cholinergic changes in the hippocampus of highly stress-sensitive rats [14].

These data suggest that the hippocampus is particularly vulnerable to damage by reactive oxygen species, leading to alterations in the cellular antioxidant system, specifically in the concentrations of glutathione disulfide, glutathione peroxidase, and glutathione reductase—enzymes that contain selenium [15, 16]. Manganese intoxication-induced changes in the cellular antioxidant system may contribute to mediated neuroinflammation [17]. Our study demonstrated that chronic manganese intoxication reduces selenium levels in the hippocampus, a key component of the cellular antioxidant system. However, the mechanism of selenium elimination from hippocampal tissue remains unclear.

The observed increase in copper levels has not been previously described in the literature. However, excess copper is known to promote neuronal apoptosis in the hippocampus and may potentially contribute to dopaminergic neurodegenerative disorders [18, 19]. Elevated copper levels during chronic manganese exposure may result from altered blood-brain barrier function, manifesting as increased permeability to copper-transporting proteins. However, this hypothesis requires direct experimental validation.

## CONCLUSION

1. Chronic consumption of manganese chloride leads to increased copper concentrations in hippocampal tissue.

2. Chronic consumption of manganese chloride is associated with decreased selenium levels.

Thus, it can be hypothesized that manganese poisoning-induced alterations in biogenic elements may disrupt not only enzymatic systems directly associated with manganese but also those involving copper and selenium.

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## ADDITIONAL INFORMATION

**Authors contribution.** D.I. Klimenko, E.O. Demidova, P.N. Varioshkin, M.E. Shemaev, N.Yu. Grigorjeva: writing—original draft, data analysis; N.A. Belyakova, I.V. Karpova, N.V. Lapina: writing—review & editing, conceptualization. All authors made substantial contributions to the conceptualization, investigation, and manuscript preparation, and reviewed and approved the final version prior to publication.

**Competing interests.** The authors declare that they have no competing interests.

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**Ethical review.** The study was approved by the Local Ethics Committee of the Institute of Experimental Medicine (Minutes No. 2/23 dated June 15, 2023).

**Statement of originality.** The authors did not use previously published information (text, illustrations, data) to create this paper.

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**Provenance and peer-review.** This work was submitted to the journal on its own initiative and reviewed according to the standard procedure. Two external reviewers, and a member of the editorial board participated in the review.

## ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

**Вклад авторов.** Д.И. Клименко, Е.О. Демидова, П.Н. Вариошкин, М.Е. Шемаев, Н.Ю. Григорьева — написание статьи, анализ данных; Н.А. Белякова, И.В. Карпова, Н.В. Лапина — редактирование статьи, разработка общей концепции. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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**Оригинальность.** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

**Доступ к данным.** Все данные, полученные в настоящем исследовании, доступны в статье.

**Генеративный искусственный интеллект.** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовались.

**Рассмотрение и рецензирование.** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента и член редакционной коллегии.

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