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Low Doses Of Zinc Chloride Decrease The Activation Of Lipid Peroxidation And The Hemodynamic Effects Of Toxic Doses Of Cobalt Small Doses Of Zinc Attenuate The Effects Of Cobalt In Rats

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Abstract

The authors carried out a study aimed at analyzing the specificity of changes in the parameters of systemic hemodynamics and lipid peroxidation against the background of the introduction of small doses of zinc chloride in conditions of combined and isolated administration of heavy metal salts of cobalt. Experimental cobalt intoxication in Wistar rats was created by daily single administration of cobalt chloride (4 mg/kg) intragastrically using a probe. Zinc chloride (1 mg/kg) was administered in a similar manner, daily for 1 month. The purpose of the experimental studies was to assess the functional state of the cardiovascular system, indicators of which are traditionally the parameters of systemic hemodynamics. Blood pressure was determined invasively by inserting a catheter into the femoral artery; the minute blood volume was assessed by the thermodilution method, for which a thermistor was inserted through the left common carotid artery into the aortic arch. Indicators such as mean arterial pressure, stroke index, cardiac index, specific peripheral vascular resistance were calculated using special formulas.In order to assess the processes of lipid peroxidation, the concentration of hydroperoxides and malondialdehyde in the blood was calculated based on its interaction with thiobarbituric acid. The state of the antioxidant system of rats was assessed by determining the activity of enzymes such as catalase and superoxide dismutase.

Studies have shown that with monthly intragastric isolated administration of cobalt chloride, the development of arterial hypertension of the hypokinetic type is observed. The experimentally specified combined administration of low doses of zinc

chloride and toxic doses of cobalt has a protective effect on the onset and progression of symptoms of cobalt intoxication. The combined administration of cobalt and zinc salts causes a less pronounced effect on the parameters of systemic hemodynamics and enhances antioxidant protection.

Keywords: heavy metals; cobalt chloride; zinc chloride; systemic hemodynamics; arterial hypertension; lipid peroxidation.

Introduction

Zinc is one of the most important microelementsof the body, participating in various biological processes in animals and humans. The human body cannot accumulate zinc reserves, so zinc deficiency can arise relatively quickly, for example, as a result of an improper diet. It is believed that the human proteome is 10% composed of zinc-binding proteins, where zinc performs catalytic and structural functions (12, p. 982). It is an integral part of such metalloenzymes as carboxypeptidase, carbonic anhydrase, and DNA polymerase, as well as a cofactor for more than 300 metalloenzymes and more than 200 transcription factors. Recent studies on animals have revealed the importance of zinc in the prenatal and postnatal periods of development (11, p. 718). Thus, zinc, in particular, is of great importance for the formation of the structure and functioning of neurons in young rats (8, p. 656).

Zinc also takes an active part in the process of stabilizing the cell membrane and is a powerful component of the antioxidant system. The effects of magnesium, zinc and their combinations on lipid peroxidation indices in rats exposed to cadmium, where zinc chloride plays the leading role, have been described (20, p. 46; 7, p. 1).

Cobalt in certain dosages (3, p. 311) is vital for the normal functioning of the organism, both human and animal; without it, the full functioning of various systems and organs is impossible (10, p. 1). The foregoing considers cobalt as essential microelement, however, its excessive concentrations in the body are extremely toxic, and when certain indicators are reached, they even pose a threat to life.

The features of the processes in which cobalt in high concentrations becomes dangerous to the life of a living organism are not completely obvious, but there is an assumption that its toxic effect is based on the ability to replace bivalent positive ions in metal-active enzymes (6, p. 89).

The toxicity of cobalt is partly explained by its high affinity for sulfhydryl groups of protein molecules, which leads to inhibition of the main enzymes of mitochondrial respiration and to the triggering of the “hypoxia activator factor” found in all cells and leading to the development of numerous pathological effects (5, p. 200).

The environmental impact of cobalt, which leads to an excess of the MAC, leads to excessive accumulation of metal in the tissues of the body (17, p. 1). Cobalt accumulates in the brain, lungs, heart, which leads to structural damage to the cells of these organs, and their functional activity decreases (4, p. 447).

Studies have sufficiently touched upon such an aspect as the damaging mechanisms of excessive penetration of cobalt and zinc into the body with isolated channels of their intake. However, there are not

enough studies in the scientific literature in which the problem of the combined administration of zinc and cobalt would be considered, their effect on systemic hemodynamics, as well as on lipid peroxidation, would be analyzed. The foregoing determines the relevance of this study.

Materials and methods

In total, 60 sexually mature male Wistar rats were involved (vivarium of the Federal State Budgetary Educational Institution of Higher Education SOGMA, Ministry of Health of the Russian Federation). The average body weight of rats is 280g±20g. To carry out the experiment, it was considered rational to create 4 groups of experimental animals. The composition of the groups is as follows: 1 group — intact rats; 2 group — rats in whose body cobalt chloride is injected separately intragastrically (4 mg/kg); 3 group — animals in whose body zinc chloride is administered separately intragastrically (1 mg/kg); 4 group — rats with combined administration of low doses of zinc and toxic doses of cobalt.

Taking into account the daily administration of substances for 30 days, the dose of cobalt chloride is 120 mg/kg, zinc chloride — 30 mg/kg. The solution was prepared using distilled water. A natural light regime was maintained in the animal vivarium. Feeding the animals assumed that the feed was appropriate for the nutritional needs, and the drinking regime provided free access to clean drinking water. The experiment was carried out in the spring.

During the study, all ethical principles were observed in accordance with the World Medical Association Declaration of Helsinki (2000), the Rules of Good Laboratory Practice (Order of the Ministry of Health of the Russian Federation dated 04/01/2016 No. 199) and “International Recommendations for Biomedical Research Using Laboratory Animals” (1985). All procedures involving animals were performed under anesthesia using sodium thiopental intravenously (0.4 g per 100 g).

The activity of the cardiovascular system was assessed using a monitor (MX-04). Hemodynamic parameters were assessed as follows: blood pressure was measured invasively by catheterization of the femoral artery: a catheter (1 mm diameter) was inserted into the lumen of the vessel. First, to avoid thrombosis, the catheter is filled with a rinsing solution of heparin (10%). The catheter was connected to an electrical DDA manometer.Such an indicator of general circulation as the minute blood volume was also measured by the invasive method by passing an MT-54M thermistor through the left common carotid artery into the aortic arch. The catheter was inserted into the right jugular vein for the purpose of injecting physiological solution (0.2 ml) into the right atrium. Mean arterial pressure (MAP) was calculated using the formula (2(DBP)+MAP)/3. Specific peripheral vascular resistance (PSVR) was determined by calculation. Stroke index (SI) and cardiac index (CI) were measuredby the area of the thermal dilution curves. The heart rate (HR) was recorded on the MX-04 monitor.

An assessment of lipid peroxidation (LPO) was made by the method of Gavrilova V.B., Gavrilova A.R. and Mazhul L.M. (18, p. 1). In addition to hydroperoxides, the quantitative determination of

malondialdehyde in the blood was carried out on the basis of the reaction product with thiobarbituric acid (TBA). The assessment of the antioxidant system (AOS) was carried out according to the indicators of catalase activity, for which the standard method of E. Beutler (2, p. 1) and superoxide dismutase was used.

Statistical analysis of the data was carried out using the STATISTICA version 10. Statistical processing of the data was carried out using the Mann-Whitney U test. The selection and distribution of comparison series were established using the Shapiro-Wilk test (Wf>>Wm). Differences in experimental indicators and specificity of factorial influences were taken at a critical level of reliability (p) less than 0.05.

Literature review

The problem of the influence of zinc chloride on hemodynamic processes and LPO in the situation of their correlation with cobalt has been described by numerous foreign researchers (3, p. 311; 7, p. 1), whose points of view coincide in the statement that, being, on the one hand, substances, necessary for the life of any living organism, zinc and cobalt, accumulating in tissues, can cause serious deviations from the standard indicators, on the other hand. In the context of our study, we are interested in systemic hemodynamic disorders and LPO processes. The issue of the genesis of these disorders and, especially, with their combined intake into the body in the literature, is given an insignificant place. A similar situation is observed in the Russian scientific literature (19, p. 16; 20, p. 46).

Noteworthy are the studies of Chinese scientistsfocusing on the meta-analysis between the content of zinc in the blood serum and preeclampsia (11, p. 519; 12, p. 718). The mechanisms of interdependence between these factors are also still not fully established. It can beexplaned by the fact that zinc alleviates oxidative stress by increasing the activity of antioxidants or acts as a component of substrates or a cofactor for adequate activation of antioxidant enzymes such as superoxide dismutase. Zinc is a cofactor of this enzyme, therefore, its deficiency can lead to a decrease in the activity of superoxide dismutase, which leads to a violation of the cellular antioxidant capacity and the balance of oxidant and antioxidants (14, p. 110).

Results and discussions

In conditions of isolated intragastric administration of cobalt chloride (4 mg/kg), an increase in lipid peroxidation was observed, which was reliably confirmed by an increase in the content of malondialdehyde in erythrocytes. There was also an increase in indicators of hydroperoxides in the blood plasma of laboratory animals. This trend was observed in comparison with all experimental groups (Table 1).

	Stat,indicator	Background	Co	Zn	Co+Zn
MDA	M±m	27,29±1,46	57,18±1,16	26,16±1,18	41,19±0,38
GP	M±m	5,26±0,38	8,84±0,27	6,12±0,40	7,83±0,85

	p	*	*	**	*#
Catalase	M±m	7,49±0,26	11,83±0,67	14,36±0,34	12,23±0,54
	p	#	*#	**	*#
SOD	M±m	70,78±1,12	83,67±0,58	73,63±1,19	79,55±1,13
	p	**#	*	**	*#
Note: (*)—reliable (p <0.001) measurement compared to the background; (**) — reliable (p <0,05) measurement compared to the background; (#)— reliable (p <0,001) measurement compared to the group No.2; (##) —reliable(p <0,05) measurement compared to the group No.3.					

Table 1. Indicators of the study of lipid peroxidation against the background of combined and isolated administration of cobalt 4 mg/kg and zinc 1 mg/kg

Against the background of the developed oxidative stress, the results of laboratory studies of experimental rats showed an increase in the activity of the catalase and superoxide dismutase enzymes in erythrocytes (9, p. 1), which was a consequence of the intragastric administration of large doses of the heavy metal cobalt.

The isolated administration of low doses of zinc (1 mg/kg) also led to a slight shift in the products of peroxidation, but only the activity of catalase was significantly increased. Other indicators of lipid peroxidation did not significantly differ from the background values.

In the group where the administration of cobalt chloride 4 mg/kg and zinc 1 mg/kg were combined, there was a decrease in the content of lipid peroxidation products relative to the isolated administration of cobalt, while the level of activity of antioxidant defense enzymes was also increased. It can be assumed that the introduction of low non-toxic doses of zinc enhances antioxidant protection due to at least three indirect mechanisms: activation of metallothioneins that prevent oxidative stress, regulation of the activity level of enzymes of the antioxidant system of protection against oxidation of sulfhydryl groups, as a result of which LPO processes are weakened (19, p. 16).

In the experimental group, where the animals received an isolated intragastric intake of cobalt chloride, the fact of an increase in SBP was stated. Also, an increase in specific peripheral resistance (SPR) was established. Such data were obtained as a result of comparison with the control group.

Experimentalconditions	Stat,indicator	SBP(mmHg)	Heartrate (bpm)	SI (ml/100g)	CI (ml/100g)	SPR
Backgro	M±m	103,3±0,81	380±5,20	0,141±0,003	54,24±1,35	1,55±0,044

und						
Co	M±m	127,4±3,31	400±10,46	0,114±0,005	44,32±1,78	2,31±0,089
	p	**)#	**)	**)#)	**)#)	**)#
Zn	M±m	112,2±2,6	388±10	0,116±0,005	43,82±1,81	1,90±0,01
	p	**)	*)	*)	*)	*)
Zn +Co	M±m	117±0,81	360±3,40	0,142±0,002	47,53±1,36	1,57±0,044
	p	**#	**#	**#	**#	**

Note:

(**) — reliable (p<0,05) measurement compared to the background;

(*) — reliable(p<0,001) measurement compared to the background;

(#)— reliable (p<0,001) measurement compared to the group No. 1;

(##) — reliable(p<0,05) measurement compared to the group No. 2;

(!!) — reliable(p<0,05) measurement compared to the group No. 3.

Table 2. Indicators of systemic hemodynamics with isolated and combined administration of zinc chloride 1 mg/kg and cobalt 4 mg/kg

In the experimental group, where the animals were injected with cobalt chloride, a change in the parameters was ascertained, that is a decrease in the cardiac index, which occurs as a result of a decrease in the SI. Such data were obtained as a result of comparison with the control group. The pumping activity of the heart is depressed. Heart rate is progressing (Table 2).

In the group of animals, where zinc chloride was administered orally in isolation at a dose of 1 mg/kg, statistically significant fluctuations in the indicators of systemic hemodynamics were not observed when compared with the control group, which significantly differed the state of geodynamics from that with isolated administration of cobalt, while there was only insignificant decreased heart index (Table 2).

The processing of the experimental results in the group where the administration of cobalt chloride and zinc chloride was combined showed that there was a significantly reduced increase in SBP compared to the group where cobalt chloride was administered in isolation. At the same time, there was no decrease in the cardiac index and a significantly weaker change in the stroke index.

Conclusion

1. Thirty-day isolated administration of toxic doses of cobalt chloride to laboratory animals leads to a powerful activation of lipid peroxidation.
2. Experimental administration of small doses of zinc weakens the effect of cobalt chloride on the intensity of lipid peroxidation when administered intragastrically.

3. A thirty-day isolated administration of toxic doses of cobalt chloride to laboratory animals leads to a persistent hypertensive reaction of the hypokinetic type.
4. Experimental administration of small doses of zinc softens the effect of cobalt chloride on the parameters of systemic hemodynamics during its intragastric administration.

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