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HEMODYNAMIC CHANGES IN NICKEL INTOXICATION AND THEIR EXPERIMENTAL CORRECTION WITH ORGANIC SELENIUM AND SMALL DOSES OF ZINC

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ABSTRACT

The purpose of the study is to investigate the effect of organic selenium and low doses of zinc on nickel intoxication. Selenium and zinc were administered once daily at a dose of 4 and 1 mg/ kg. Nickel chloride (5 mg/kg) was administered intragastrically using a probe, daily for one month. At the end of the experiment time (30 days), the main parameters of systemic hemodynamics were determined. The arterial blood pressure from the femoral artery was measured and the mean (MAP) was calculated. Cardiac output was determined by thermal dilution, heart rate (HR) was recorded; cardiac index, shock index and specific peripheral vascular resistance were calculated using special formulas.

Our findings showed that nickel leads to significant disruptions in hemodynamics and heart function of rats, manifested in an increase in MAP, a change in heart rate, a decrease in systolic output. The introduction of selenium or small doses of zinc in rats exposed to nickel, produced a noticeable decrease in the cardiotoxic effects of this metal. There was also a decrease in the hypertensive effect of the metal. Thus, it has been established that antioxidants selenium and zinc can effectively reduce nickel toxicity.

Keywords: organic selenium, zinc chloride, nickel chloride, hemodynamics

INTRODUCTION

Nickel is a widely used metal in various industries such as printing inks, welding, alloys, electronics and electrical engineering. Exposure to nickel at work or in the environment can lead to cancer, allergic reaction, nephrotoxicity, hepatotoxicity, neurotoxicity, as well as cell damage, apoptosis and oxidative stress [5]. It is a toxic metal that can cause serious diseases, including asthma, chronic bronchitis, pneumonia and lung cancer. However, the most serious is its cardiotoxic effect. In particular, it has been shown that nickel can cause various disorders of cardiac activity and blood circulation - changes in heart rhythm, arrhythmias, increased blood pressure, impaired calcium metabolism, etc. [4].

Scientific literature demonstrates that prolonged intoxication with nickel cause cardiovascular diseases [8]. The experimental data highlights a coronary vasoconstrictor effect caused by low doses of nickel [1].

It was found that in workers exposed to an increased nickel concentration in the air there were changes in the functional state of the heart, intracardiac and peripheral hemodynamics. Some aspects of the mechanisms of toxic action of non-ferrous metals remain undisclosed. In their development, the main role is played by the imbalance of pro- and antioxidant systems, the generation of oxygen free radicals, the intensification of lipid peroxidation processes against the background of inhibition of energy production by mitochondria and a decrease in the energy potential of the cell [3,11].

Zinc is the most important trace element of the body, participating in various biological processes in animals and humans. The human body does not accumulate zinc, so its deficiency can occur relatively quickly, for example, as a result of an improper diet [2].

Zinc is a component of such metalloenzymes as carboxypeptidase, carbonic anhydrase and DNA polymerase, as well as a cofactor of more than 300 metalloenzymes and more than 200 transcription factors. Recent animal studies have revealed the importance of zinc in the prenatal and postnatal periods of development [7].

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 parameters in rats exposed to cadmium, where zinc chloride plays a leading role, are described [9].

Selenium is a vital trace element present as selenocysteine in proteins that are known as selenoproteins. Humans have 25 selenoproteins, most of which are functionally characterized as oxidoreductases, where the protein residue plays a catalytic role in redox regulation and antioxidant activity.

The bioavailability of selenium in various tissues and organs after absorption is very high, performing important biological functions, it regulates the synthesis of selenoproteins, being included in the composition of proteins. In addition, some selenoproteins are also involved in regulating the activation of signaling pathways and cellular functions [10].

Antioxidant enzymes such as superoxide dismutase, catalase and other redox enzymes, including selenoproteins, and low-weight antioxidant molecules such as carotenoids, ascorbic acid, vitamin E, are necessary to maintain the concentration of stable reactive oxygen species, which helps regulate the redox balance and maintain cellular homeostasis.

Increased environmental pollution by heavy metal compounds, including nickel, requires studying the mechanisms of possible development of toxic effects and the need to develop methods of prevention and correction.

MATERIALS AND METHODS

The experiment was performed on 84 Wistar male rats weighing 250-280 g. The investigations were carried out in 7 experimental groups: 1st group of animals - control, 2nd group – animals with intragastric administration of selenium (selexene, organic selenium) at a dose of 4 mg/ kg, 3rd group - animals with intragastric administration of zinc chloride at a dose of 1 mg/ kg, 4th group - with intragastric administration of nickel chloride at a dose of 5 mg / kg, group 5 - rats with intragastric combined administration of nickel and zinc chloride, group 6 - rats with intragastric combined administration of nickel and selenium, group 7 - rats with intragastric combined administration of nickel, zinc chloride, and selenium.

During the experiment, the animals were on a standard diet, had free access to water and food during the day. The animals were housed in natural light mode.

At the end of the experiment time (30 days), the functional state of the cardiovascular system was investigated, determining the main parameters of systemic hemodynamics. The study was conducted in accordance with the ethical standards established by the 1964 Helsinki Declaration, "International Recommendations for conducting Biomedical research using Animals" (1985) and the Rules of Laboratory Practice in the Russian Federation (Order of the Ministry of Health of the Russian Federation No. 267 of 06/19/2003)

The determination of hemodynamic parameters was carried out in an acute experiment. Rats were anesthetized by intraperitoneal Zoletil injection (0.1 ml/100g). The following indicators were determined: blood pressure – invasively by inserting into the femoral artery a plastic catheter filled with a 10% heparin solution and connected to an electromanometer "DDA". To measure the minute volume of blood through the left common carotid artery, a thermistor MT-54M was inserted into the aortic arch. A 0.2ml fixed temperature saline solution was injected into the right atrium through the catheterized right jugular vein. Thermodilution curves were recorded on the EPP-5 recorder. The readings were recorded using the MX-04 monitor. The mean arterial pressure (MAP) was calculated using the formula MAP = DP + 1/3 PP, where DP-diastolic pressure, PP is pulse pressure; heart rate (HR) – using the MX–04 monitor; heart index (HI), shock index (SI) and specific peripheral vascular pressure were calculated using special formulas.

Data analysis was performed using Statistica 10.0 software («StatSoft, Inc», Russia). The normality distribution of continuous variables was tested with the Shapiro-Wilk test (Wf>>Wm). Statistical data processing was carried out using the "U" Mann-Whitney criterion. Differences in experimental parameters and the specificity of factor influences were taken at a critical confidence level (p) less than 0.05.

RESULTS AND DISCUSSION

Determination of the main parameters of systemic hemodynamics made it possible to establish that isolated oral administration of nickel chloride over thirty days leads to an increase in average blood pressure. This can be attributed to an increase in specific peripheral vascular resistance compared with the control group and the groups where small doses of zinc and selenium were administered in isolation. Under the influence of nickel intoxication, a change in the parameters characterizing the pumping activity of the heart was noted – the cardiac index fell critically as a result of a decrease in the shock index compared to the three control groups. At the same time, there was a significant increase in heart rate compared with the control group and with the groups receiving zinc and selenium in isolation.

Table 1. Indicators for parameters of systemic hemodynamics in experimental groups

Experience conditions	Stat. indic.	Average blood pressure (mmHg)	Heart rate (beats per minute)	Cardiac index (ml/100g)	Impact index(ml/100g)	Specific peripheral vascular resistance (conl. units)
Control	M±m	100,3±0,96	370±6,22	56,24±1,36	0,141±0,003	1,59±0,039
Control. Selenium	M±m	103,8±1,01	364±8,16	55,24±2,35	0,151±0,007	1,46±0,057
	P	*	-	-	-	*
Zinc Control	M±m	104,3±0,99	379±6,22	55,19±1,39	0,150±0,004	1,53±0,049
	P	*	-	-	*	-
Nickel Control	M±m	149,2±2,9	414±9,6	39,50±2,08	0,100±0,006	2,73±0,106
	P	*)**)#	*)**)#	*)**)#	*)**)#	*)**)#
Zinc+Nickel	M±m	122,3±2,21	380,5±8,79	45,64±1,03	0,117±0,002	2,37±0,071
	P	*)#)##	##	*)#)##	*)#)##	*)#)##
Selenium +Nickel	M±m	125,3±0,68	406,5±4,25	45,66±1,26	0,125±0,006	2,30±0,046
	P	*)**)##	*)**	*)**)##	*)**)##	*)**)##
Selenium +Nickel +Zinc	M±m	107,2±3,8	379±9	48,80±1,81	0,134±0,005	1,69±0,122
	P	*)##)!)!!	##)!!	*)**)#)##	**)#)##)!	**)##)!)!!

Note: (*) - significant (p <0.05) change compared to the background;
(**) - significant (p <0.05) change compared to the control selenium;
(#) - significant (p <0.05) change compared to the control zinc;
(##) - a significant (p <0.05) change compared to the control;
(!) - significant (p <0.05) change compared to zinc+nickel;
(!!) - a significant (p <0.05) change compared to selenium+nickel.

The parameters of systemic hemodynamics with combined intragastric administration of small doses of zinc and toxic doses of nickel changed unidirectionally to the effects of isolated nickel administration, but less pronouncedly. There was a significant increase in average blood pressure compared with the control group, and a significantly lower rise compared with isolated nickel administration.

With this combination of nickel administration, a change in the pumping activity of the heart was noted – there was a tendency to restore the cardiac and shock indices, but the values did not reach the control, being lower than at isolated nickel administration. The combination of nickel together with selenium caused similar changes described above.

The above changes indicate that the combination of selenium and nickel injections, as well as selenium and small doses of zinc, create a weak compensatory effect in relation to isolated nickel administration, however,

the degree of compensation is weak since the parameters do not reach the control values.

The combination of the introduction of small doses of zinc, selenium in the setting of nickel intoxication for 30 days leads to a sharp significant drop in average blood pressure, if we compare the values with isolated nickel management. However, if we compare these values with the control group, we can say that a powerful combination of two antioxidants leads to leveling or prevention of nickel intoxication. The restoration of pressure was facilitated by a significant increase in the specific peripheral vascular resistance.

As a result of the experiment, it was found that nickel leads to significant disruptions of the pumping function of the heart in rats, manifested in a change of heart rate, a decrease in cardiac output. When selenium or small doses of zinc were administered, especially when they were used together, a noticeable decrease in the cardiotoxic effects of this metal was found in rats exposed to nickel.

Thus, the results of our study confirm the role of lipid peroxidation in systemic hemodynamic disorders, since antioxidants selenium and zinc are effective for reducing nickel toxicity. The latter opens up new prospects for prevention and treatment of nickel poisoning

CONCLUSIONS

1. Intragastric administration of nickel chloride to laboratory animals for 30 days leads to development of arterial hypertension.
2. The combined administration of selenium and nickel, selenium and small doses of zinc mitigates the toxic effect of this metal on systemic hemodynamics.
3. The experimental combination of selenium, low doses of zinc under nickel intoxication significantly weakens the manifestations of nickel intoxication.

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