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INFLUENCE OF VITAMIN E ON THE HAEMODYNAMIC EFFECTS OF INTRAGASTRIC CHROMIUM INTAKE AND LIPID PEROXIDATION IN EXPERIMENTAL RATS

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ABSTRACT

Purpose: To examine the possibility of using vitamin E for the correction of free radical oxidation disorders and haemodynamic effects of potassium bichromate. **Methods:** Experiments were performed in 90 male Wistar rats; the study included 9 experimental groups. Vitamin E and sunflower oil (control) were injected daily intragastrically through an atraumatic tube into the stomach. At the end of the experimental period (30 days and 60 days), the main parameters of systemic hemodynamics and values of lipid peroxidation were measured. Differences between groups were analyzed using Student's t-test.

Results: The analysis of basic parameters of systemic haemodynamics showed that PO administration of potassium bichromate promoted an increase in mean arterial pressure due to the increase in normalized peripheral vascular resistance (systemic vascular resistance, SVR). At the same time there was a decrease in the stroke volume index. The haemodynamic effects of chromium were more pronounced with prolonged administration. Parameters of systemic hemodynamics in combined administration of potassium bichromate and sunflower oil changed similarly to the effects of combined administration of the metal and vitamin E, but changes were less pronounced. A decrease in SVR and the restoration of the stroke volume index were observed.

The isolated administration of the metal for thirty days resulted in an increase in lipid peroxidation (LPO) accompanied by a stimulation of catalase and superoxide dismutase activity. During prolonged (2 months) isolated administration of potassium bichromate, a more pronounced increase in LPO was observed along with the depletion of the antioxidant system.

The prevention of chromium intoxication using vitamin E during the first month of administration reduced lipoperoxidation phenomena accompanying increased antioxidant defense activity. These dynamics persisted after two months of the combination of vitamin E and potassium bichromate.

Conclusions: The intragastric administration of potassium bichromate for 30 and 60 days resulted in arterial hypertension in a rat model. The administration of toxic doses of potassium bichromate to laboratory animals may lead to the activation of lipid peroxidation. The administration of vitamin E may attenuate the haemodynamic effects of chromium intoxication and the activation of lipid peroxidation.

Keywords: potassium bichromate, systemic haemodynamics, lipid peroxidation, vitamin E.

INTRODUCTION

The contamination of the environment with heavy metals is a frequent phenomenon. This can be due to many factors, e.g. man-made disasters, road transport, violation of the rules of disposal of heavy metal products, etc. By getting into water, soil, plants and animal organisms, and through those to humans, chromium compounds contribute to the development of many diseases [3, 12, 18].

Chromium is widely used in the production of stainless steel, industrial pigments, ceramic raw materials, rubber, paints, leather products, power generation facilities and metal parts [22]

Chromium is considered an important micronutrient for mammals that plays a major role in maintaining proper carbohydrate, lipid and protein metabolism through an insulin-related mechanism. Trivalent chromium can enhance the action of insulin, cellular glucose uptake and intracellular carbohydrate and lipid metabolism [4, 5, 11]. The positive effects of chromium on metabolism are determined by its concentration in the body; its excessive intake causes general intoxication, threatening human health. These toxic effects are due to the rapid penetration of chromium into cell membranes and its subsequent interaction with proteins and nucleic acids in cells [19].

Chromium compounds can enter the body through inhalation, skin contact and ingestion and mainly accumulate in the liver, kidneys, heart, blood and endocrine glands. Long-term exposure to chromium can lead to dermatitis, bronchitis, pulmonary inflammation, congestion and oedema, gastrointestinal ulcers, tumours and tissue damage. [1, 2, 7, 17, 20]

The heart is one of the target tissues of chronic exposure to heavy metals, including chromium. [15]. Chromium has been shown to cause cardiac dysfunction in laboratory animals by affecting certain Sesn2 regulator proteins (Sesn2) (21). In addition, the occurrence of cardiovascular pathologies is most often closely associated with mitochondrial dysfunction of cardiomyocytes; the main cause of this dysfunction is related to oxidative stress and the initiation of an inflammatory process accompanying reduced adenosine triphosphatase (ATPase) activity and irreversible protein modification with the formation of carbonyl protein, an oxidative damage marker. [8, 9, 10].

It is known that the toxic effect of chromium is associated with the stimulation of free radical processes, as well as the formation of intermediate products during the reduction of hexavalent chromium, which have a high reactivity [20]. These reactive chromium intermediates are capable of generating reactive oxygen species (ROS) [6], which cause oxidation of protein and lipid macromolecules with damage to organs and systems [14, 22], and exhibit neuro-, hepato-, nephro-, cardio-, gene- and immunotoxicity and carcinogenicity [9, 13, 16].

Based on the evidence from literature showing that chromium induces lipid peroxidation processes, it was decided to use vitamin E to correct free radical oxidation.

METHODS

The work was performed in 90 mature male Wistar rats with an average weight of 260g±20g. The study included nine experimental groups of animals: Group 1 - control; Group 2 - animals with intragastric administration of vitamin E in a dose of 200 mg/kg (daily dose) (animals eliminated from the experiment after 30 days) ; Group 3 - animals with intragastric administration of vitamin E in a dose of 200 mg/kg (animals eliminated from the experiment after 60 days); Group 4 - animals with isolated intragastric (IG) injection of potassium bichromate in a dose of 5 mg/kg (daily dose), (animals eliminated from the experiment after 30 days); Group 5 - animals with isolated IG injection of potassium bichromate in a dose of 5 mg/kg (daily dose), (animals eliminated from the experiment after 60 days); Group 6 - animals with combined potassium bichromate and vitamin E administration (animals kept for removal from the experiment after 30 days); Group 7 - animals with combined potassium bichromate and vitamin E administration (animals kept for removal from the experiment after 60 days); Group 8 - combined administration of potassium bichromate and sunflower oil - control with vitamin E diluent (animals eliminated from the experiment after 30 days); Group 9 - combined administration of potassium bichromate and sunflower oil - control with vitamin E diluent (animals eliminated from the experiment after 60 days).

During the first month, the cycle dose of administered potassium bichromate per animal was 150 mg/kg, during the second month it was 300 mg/kg. The animals were fed a standard diet, had free access to water and food, and a natural light regime was maintained. The study was conducted in the spring period of the year. The experiments were guided by Article 11 of the Declaration of Helsinki of the World Medical Association, "International Recommendations for Biomedical Research Using Laboratory Animals" (1985)

(revision 2008) and the rules of laboratory practice in the Russian Federation (Order of the Ministry of Health of the Russian Federation No 199 of 01.04.2016). All investigations were performed under zoletilol anaesthesia (5 mg per 100g weight)

Vitamin E and sunflower oil were administered daily intragastrically through an atraumatic tube into the stomach at a dosage of 200 mg/kg (0.2 ml)/100 g body weight of the animal.

After the time of the experiment (30 days and 60 days), arterial pressure was measured by indirect catheterisation of the femoral artery. The catheter was filled with 10% heparin solution and connected to the "DDA" electromanometer of the MH-04 monitor. To measure the minute blood volume through the left common carotid artery, an MT-54M thermistor was inserted into the aortic arch; 0.2 ml of fixed room temperature physiological solution was injected into the right atrium through the catheterized right jugular vein. Thermodilution curves were recorded using an EPP-5 self-recorder. Mean arterial pressure (MAP), cardiac index (CI), stroke volume index (SVI) and normalized peripheral vascular resistance (systemic vascular resistance, SVR) were calculated. Heart rate (HR) was determined using an MH-04 monitor.

To assess lipid peroxidation processes, blood concentrations of hydroperoxides (in plasma) and malondialdehyde (MDA) (in erythrocytes) were measured using a technique based on its interaction with thiobarbituric acid. The state of the antioxidant system (AOS) was also explored by measuring the activity of catalase and superoxide dismutase in erythrocytes. The principle of the method is based on the ability to auto-oxidise adrenaline with previously occurring free-radical oxidation products.

Statistical analysis was performed using Student's t test, taking into account the number of samples and the normality of distribution of comparison series as determined by the Shapiro-Wilk test. All analyses were run using the the STATISTICA 10 software. Statistical significance was defined as p-value below 0.05.

RESULTS

The analysis of the main parameters of systemic hemodynamics showed that isolated oral administration of potassium bichromate for thirty days contributed to an increase in MAP, which was due to an increase in the SVR compared with the control group of animals. Under the influence of potassium bichromate, there was a change in the parameters characterizing the pumping activity of the heart - the CI decreased as a result of the reduction in the SVI compared to the control group. At the same time, an increase in heart rate was observed. The haemodynamic effects of chromium were more pronounced with prolonged administration for 60 days, with MAP increasing by 33% compared to the control group.

The combined administration of vitamin E and potassium bichromate for 30 days resulted in the same changes in systemic haemodynamics as those in the isolated administration of the metal: MAP was significantly higher than the control value, but vitamin E in oral administration of the metal contributed to a 4% decrease in MAP.

Table 1. Systemic haemodynamic parameters following the administration of potassium bichromate (isolated and combined) with or without vitamin E or sunflower oil administration.

Experimental conditions	Test statistic	MAP (mmHg)	Heart rate (bpm)	CI (ml/100g)	SVI(ml/100g)	SVR(units)
Control	M±m	104,2±3,7	383±9,8	53,73±1,91	0,147±0,005	1,53±0,136
Vitamin E 1 month	M±m	102,9±1,8	386±6,28	56,83±0,92	0,137±0,002	1,74±0,053
	p	-	-	-	-	-
Vitamin E 2 months	M±m	101±5,8	390±7,22	45,18±1,45	0,130±0,006	1,80±0,120
	p	-	-	*)**)	*	-
Potassium bichromate 1 month	M±m	122,2±2,6	390±5	49,82±1,41	0,126±0,005	1,99±0,016
	p	*	-	*	*	*

Potassium bichromate 2 months	M±m	139.±2.8	404±6.6	42.50±2.08	0.103±0.006	2.63±0.106
	p	*)##)	*)##)	*)##)	*)##)	*)##)
Potassium bichromate 1 month + Vitamin E	M±m	118,2±2,9	402±8,1	45,82±1,81	0,116±0,005	1,85±0,048
	p	*)**)	*)**)	*)**)##)	*)**))	*)**)##)
Potassium bichromate 2 months + Vitamin E	M±m	127,3±0,98	399.5±4.31	46,89±1,29	0,126±0.001	2,49±0.049
	p	*)#)!)!!)	*	*)!)	*)!)!!)	*)#)!!)
	p	!)^)^^)	!)^)	#)!)^)	#)!)^)	#)!)^)
Potassium bichromate 1 month + Sunflower oil	M±m	123.3±2.21	385.5±8.79	45,64±1,03	0,117±0,002	2.37±0.071
	p	*)^^)	^^)	*)##)	*)##)^^)	*)##)!!)^^)
Potassium bichromate 2 months + Sunflower oil	M±m	125,3±0,68	406.5±4.25	45,66±1,26	0,125±0.006	2,70±0.046
	p	*)!)^)	!)$)$)	*)$)	*)$)	*)^)$)$$)

Note: (*) - significant (p<0.05) change compared to background; (**) - significant (p<0.05) change compared to vitamin E 1 month; (#) - significant (p<0.05) change compared to vitamin E month 2; (##) - significant (p<0.05) change compared to Potassium Bichromate 1 month; (!) - significant (p < 0.05) change compared to Potassium Bichromate 2 months; (!!!) - significant (p <0.05) change compared to Potassium Bichromate 1 month + Vitamin E; (^) - significant (p<0.05) change compared to Potassium Bichromate 2 months + Vitamin E; ($$) - significant (p<0.05) change compared to Potassium Bichromate 1 month + Sunflower Oil; (&) - significant (p<0.05) change compared to Potassium Bichromate 2 month + Sunflower Oil;

In the long-term (60 days), combined administration of vitamin E and potassium bichromate, the parameters of systemic hemodynamics changed in a similar way, but the degree of recovery was higher than that in 30-day administration. It should also be noted that isolated administration of vitamin E for 30 and 60 days did not reliably change the parameters of systemic haemodynamics compared with the control group.

In combined intragastric administration of potassium bichromate and sunflower oil, the parameters of systemic hemodynamics changed similarly to those under the effects of combined administration of potassium bichromate and vitamin E, but changes were less pronounced. There was a significant increase in MAP compared with the control group. The increase in MAP was facilitated by the increase in SVR. It should also be noted that in these groups, the increase in MAP both in the first month of the experiment and in the second month was less pronounced than in the two months of combined administration of vitamin E and potassium bichromate.

The isolated administration of potassium bichromate for thirty days led to an increase in lipid peroxidation (LPO), which was accompanied by stimulation of catalase and superoxide dismutase activity. During prolonged (2 months) isolated administration of potassium bichromate, a more pronounced increase in LPO products was observed along with depletion of the antioxidative system (AOS), which may be associated with the inhibitory effect of chromium on enzyme systems.

The prevention of chromium intoxication using vitamin E in the first month of administration reduced lipoperoxidation phenomena along with an increase in antioxidant defense activity. These dynamics persisted after two months of combination of vitamin E and potassium bichromate, with catalase and superoxide dismutase (SOD) activity being higher than the values obtained after one month of experiment.

Table 2. Parameters of lipid peroxidation (LPO) in potassium bichromate administration (isolated and combined) with or without vitamin E or sunflower oil administration.

Animal groups	Test statistic	MDA	Hydroperoxides	Catalase	SOD
Control	M±m	26,15±0,27	6,33±0,51	8,42±0,38	69,57±1,11
Administration of vitamin E for 1 month	M±m	24,82±0,94	5,54±0,36	9,6±0,52	78,66±0,83
	p	-	-	*	*
Administration of vitamin E for 2 months	M±m	25,61±1,02	6,15±0,45	10,02±1,05	81,6±0,41
	p	-	-	*	*)**)
Administration of potassium bichromate for 1 month	M±m	45,32±1,12	8,46±0,74	11,71±0,68	83,42±0,66
	p	*	*	*	*
Administration of potassium bichromate for 2 months	M±m	57,13±1,35	13,07±0,93	6,35±0,52	61,96±0,65
	p	*)##)	*)#)	*)##)	*)##)
Administration of potassium bichromate for 1 month + Vitamin E	M±m	36,46±0,91	7,83±0,68	10,37±0,41	73,26±1,27
	p	*)**)##)	*)**)	*)#)	*)**)##)
Administration of potassium bichromate for 2 months + Vitamin E	M±m	50,84±0,76	10,23±1,08	13,27±0,85	80,5±0,53
	p	*)#)!)	*)#)!!)	*)#)!)!!)	*)#)!)!!)
Administration of potassium bichromate for 1 month + sunflower oil	M±m	39,45±0,81	7,02±0,33	10,57±0,87	75,38±1,05
	p	*)##)!!)^^)	##	*	*)##)
Administration of potassium bichromate for 2 months + sunflower oil	M±m	53,32±1,27	11,19±0,86	7,28±0,61	71,96±1,17
	p	*)!)^)$)	*)!)$)$$)	*)^)$)$$)	!)^)

Note: (*) - significant (p<0.05) change compared to background; (**) - significant (p<0.05) change compared to vitamin E 1 month; (#) - significant (p<0.05) change compared to vitamin E 2 months; (##) - significant (p<0.05) change compared to potassium bichromate 1 month; (!) - significant (p < 0.05) change compared to potassium bichromate 2 months; (!!) - significant (p <0.05) change compared to potassium bichromate 1 month + Vitamin E; (^) - significant (p<0.05) change compared to potassium bichromate 2 months + Vitamin E; ($$) - significant (p<0.05) change compared to potassium bichromate 1 month + sunflower oil; (&) - significant (p < 0.05) change compared to potassium bichromate 2 months + Sunflower oil-;

It should also be noted that the isolated administration of vitamin E had no effect on the activity of antioxidative system enzymes (AOS).

The prevention of chromium intoxication with sunflower oil revealed the same effect as that of vitamin E, but significantly less pronounced. At the same time, after 2 months of the experiment, the catalase activity decreased below the control level, and SOD activity remained elevated.

CONCLUSIONS

1. Intragastric administration of potassium bichromate to laboratory animals for 30 and 60 days results in arterial hypertension.
2. Thirty-day isolated administration of toxic doses of potassium bichromate to laboratory animals leads to the activation of lipid peroxidation.
3. The use of vitamin E mitigates the toxic effects of potassium bichromate on systemic haemodynamics and lipid peroxidation.

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