

A STUDY OF LIPID METABOLISM AND OXIDATIVE STRESS IN RATS WITH CHRONIC NICKEL NITRATE POISONING IN THE BACKGROUND OF EXPERIMENTAL ATHEROSCLEROSIS UNDER THE INFLUENCE OF A COMPLEX ANTITOXICANT

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The purpose of the research was to study the effect of a complex plant antitoxicant from the flora of Azerbaijan consisting of a mixture of licorice, wild rose, grape seeds, oat bran, and burdock in a ratio of 3:2:1:1:2 (Eurasian patent 201600043 dated 06/25/2018) on lipid metabolism and oxidative stress in rats chronically poisoned with nickel nitrate against the background of experimental atherosclerosis. It was shown that in experimental atherosclerosis, after exposure to nickel nitrate, lipid metabolism and oxidative stress disorders were aggravated. A proportional relationship was found between the severity of disorders and the duration of intoxication with nickel nitrate, with a maximum of disorders on the 60th day after exposure. In the experimental group, after chronic intoxication with nickel nitrate, a complex plant antioxidant implementation led to a significant improvement in lipid metabolism and oxidative stress. The revealed corrective effect of the plant antitoxicant indicates its detoxifying effect and the possibility of its clinical approbation both for the prevention and treatment of chronic nickel nitrate poisoning in patients with existing atherosclerotic vascular lesions.

Keywords: plant antitoxicant, lipid metabolism, oxidative stress, nickel nitrate, experimental atherosclerosis.

INTRODUCTION

One of the most harmful pollutants for the Earth's biosphere, which has a wide range of dangerous consequences for both human health and the lives of living organisms, is heavy metal pollution. High concentrations of heavy metals, caused by technogenic processes as a result of bioaccumulation, are currently found in all natural environments and eventually enter the human body through the food chain [13]. An increase in the scale of environmental pollution turns into an increase in genetic mutations,

oncological, cardiovascular, and occupational diseases, poisoning, dermatosis, reduced immunity, and concomitant diseases [3, 7, 8, 9]. Moreover, it is known that exposure to heavy metals in recent years is an important and underestimated risk factor in the pathogenesis of atherosclerosis, associated both with the development of atherosclerosis and with its consequences [1, 2, 4] (heart attack, stroke, sudden death), from which about 65% of all people worldwide die [6].

Despite optimal treatment using modern technologies and pharmacological preparations,

the risk of death after acute complications of atherosclerotic vascular lesions remains unacceptable, which requires the development of new approaches to the development of prevention and treatment [5].

Based on the foregoing, reducing the risk of heavy metal intoxication to prevent the development of severe complications of atherosclerosis, which is especially important for older age groups, is one of the urgent tasks of medicine today. The study of the effects of safe phyto-preparations for the prevention and treatment of chronic heavy metal poisoning seems very important and promising, especially in the presence of atherosclerotic lesions in the body.

The aim of the study was to study the effect of a complex plant antitoxicant from the flora of Azerbaijan on lipid metabolism and oxidative stress in chronic nickel nitrate poisoning against the background of experimental atherosclerosis.

MATERIALS AND METHODS

The studies were carried out on 55 white non-linear male rats weighing 200–250 g. The model of atherosclerosis was created according to I.V. Savitsky et al. (2016) [14] based on the polyetiological theory of the development of the disease. Animals received Mercazolil at 25 mg/kg of body weight, methylprednisolone at 0.17 mg/kg of animal weight, and a 15% aqueous solution of ethyl alcohol in free access instead of water against the background of an atherogenic diet for 2 weeks. To confirm atherosclerotic changes after 2 weeks, blood was taken from rats to study total cholesterol (TC), high-density lipoproteins (HDL), and low-density lipoproteins (LDL) in blood serum. After modeling atherosclerosis, animals were chronically exposed to nickel nitrate via drinking water for 60 days at a dose of 2 mg/kg. The mother solution of nickel nitrate was prepared in accordance with the calculation according to the equation $A=(X*B)*C$, where X-factor = 6.77; B - the average weight of a rat; C is the average daily water consumption by the animals, and a drinker was added to the drinking water.

Lipid metabolism was monitored by the level of TC, HDL, and LDL in blood serum using a standard set of reagents on a BioScreen MS-2000 biochemical analyzer (USA). The processes of oxidative stress were monitored by the level of malondialdehyde (MDA) by the method of V.P. Gavrilov (1987) [11] and catalase (CA) by the method of M.A. Korolyuk (1988) [12]. The dynamics of indicators were monitored before and after modeling atherosclerosis and, respectively, 30 and 60 days after the poisoning, as well as after the use of an antitoxicant for a month.

In the experimental group, a month after the poisoning against the background of simulated atherosclerosis, the animals received a complex plant antitoxicant obtained from the flora of Azerbaijan, consisting of a mixture of licorice, wild rose, grape seeds, oat bran, and burdock in a ratio of 3:2:1:1:2 (Eurasian patent 201600043 dated 06/25/2018). An antitoxicant was added to drinking water at a dose of 8 mg/kg for a month.

At the end of the experiment, the animals were decapitated under thiopental anesthesia, with a subsequent sampling of the biomaterial (whole blood) for biochemical analysis. The results obtained were statistically processed using the Statistica 8.0 software package. Numerical results were processed using the Student's t-test (differences were accepted as significant, starting from $p<0.05$). With regard to experimental animals, all the rules and recommendations of the European Convention for the Protection of Vertebrate Animals used in experimental work were observed.

RESULTS AND DISCUSSION

The results of the study of lipid metabolism showed that after modeling atherosclerosis, the content of TC and LDL in blood serum increased by an average of 21% ($p<0.05$) and 36% ($p<0.05$) compared with the initial level, respectively. The level of HDL decreased by 19% ($p<0.05$) compared with the data before atherosclerosis modeling (Table 1, Fig. 1).

As can be seen in Table 1, after the start of exposure to nickel nitrate against the background of the atherosclerosis model, lipid

metabolism disorders were aggravated. Thus, the level of TC after 30 and 60 days under the influence of nickel nitrate increased by an average of 30% ($p<0.05$) and 59% ($p<0.01$), respectively, compared with the level of this indicator before treatment against the background of experimental atherosclerosis.

The level of LDL compared with the value before the poisoning increased on the 30th and

60th days of intoxication with nickel nitrate by an average of 46% ($p<0.05$) and 60% ($p<0.01$), respectively. The content of HDL on the 30th and 60th days of the study after exposure to nickel nitrate decreased on average by 25% ($p<0.05$) and 37% ($p<0.01$), respectively, compared with the values of the studied parameter before modeling atherosclerosis.

Table 1.

Indicators of lipid metabolism in the blood serum of rats with chronic exposure to nickel nitrate against the background of experimental atherosclerosis under the influence of a complex antitoxicant ($M\pm m$, $n=10$).

| Indicators | Terms of research | | | | |
|-------------|-------------------|-------------------|------------------------|------------------------|-----------------------------------|
| | Before modeling | After modeling | 30 days after exposure | 60 days after exposure | 30 days after use of antitoxicant |
| TC, mmol/l | 2.42 ± 0.15 | $2.94 \pm 0.09^*$ | $3.15 \pm 0.19^*$ | $3.85 \pm 0.11^*$ | 3.25 ± 0.112 |
| HDL, mmol/l | 1.28 ± 0.09 | $1.14 \pm 0.07^*$ | $0.96 \pm 0.2^*$ | $0.81 \pm 0.3^*$ | $1.12 \pm 0.03^*$ |
| LDL, mmol/l | 1.13 ± 0.06 | $1.54 \pm 0.04^*$ | $1.65 \pm 0.10^{**}$ | $1.81 \pm 0.15^{**}$ | $1.55 \pm 0.2^{**}$ |

Notes: * - $p < 0.05$, ** - $p < 0.01$ (compared with baseline)

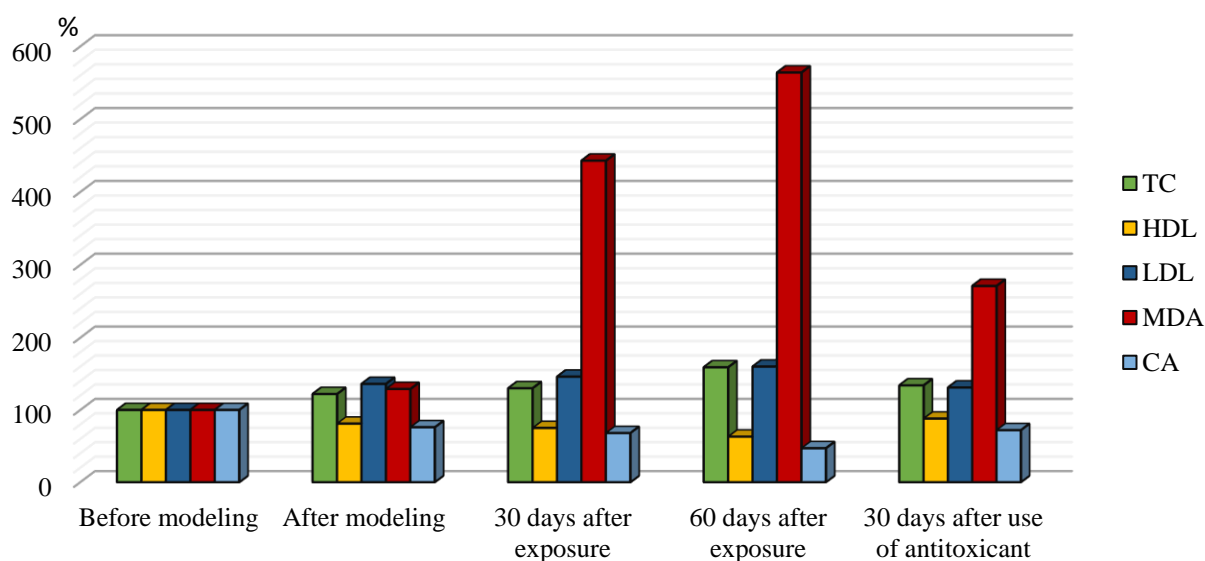


Figure 1. Indicators of lipid metabolism and lipid peroxidation in the blood serum of rats with chronic exposure to nickel nitrate against the background of experimental atherosclerosis under the influence of a complex antitoxicant.

The use of a complex plant antitoxicant after exposure to nickel nitrate against the background of experimental atherosclerosis led to a pronounced corrective effect, which was expressed in significant prevention of a further

increase in existing lipid metabolism disorders after a two-month exposure. Thus, the level of TC after the application of the antitoxicant exceeded the initial data by 34% ($p<0.01$) after poisoning with nickel nitrate compared with the

initial data. Compared with the data after a two-month poisoning, it was lower by 25%, respectively. The level of LDL decreased compared with the two-month study period after poisoning by 23% ($p<0.05$), while, compared with baseline values, it was 37% higher ($p<0.05$). The content of HDL increased by 24% compared with the two-month study period after exposure and was less than the original data by 13%.

The results of studies of indicators of oxidative stress showed the following (Table 2, Fig. 1). As can be seen from Table. 2, after modeling atherosclerosis, there was an increase in the level of MDA by 1.6 times ($p<0.05$) and a decrease in the level of KA by 24% compared

with the initial state. After 30 and 60 days after the start of the exposure against the background of atherosclerosis, there was a more pronounced trend towards an increase in the level of MDA and a decrease in the level of CA, i.e., there was an aggravation of violations of the processes of free-radical lipid oxidation that arose after modeling atherosclerosis. In particular, under the influence of nickel nitrate, the MDA level increased by an average of 4.4 times ($p<0.001$) and 5.6 times ($p<0.001$), respectively, compared with the initial value. The content of CA in the blood serum compared with the initial level decreased on the 30th and 60th days of the study after heavy metal exposure by an average of 32% ($p<0.05$) and 53% ($p<0.01$), respectively.

Table 2.

Changes in the level of MDA and catalase in blood serum after atherosclerosis modeling and in the dynamics of chronic exposure to nickel nitrate under the influence of a complex antitoxicant ($M\pm m$, $n=10$)

| Indicators | Terms of research | | | | |
|---|-------------------|--------------------|------------------------|------------------------|-----------------------------------|
| | Before modeling | After modeling | 30 days after exposure | 60 days after exposure | 30 days after use of antitoxicant |
| MDA (nmol/mg protein) | 0.014 \pm 0.011 | 0.018 \pm 0.007* | 0.062 \pm 0.011*** | 0.079 \pm 0.015*** | 0.038 \pm 0.005** |
| Catalase (mmol H ₂ O ₂ /mg protein·min) | 42.3 \pm 3.2 | 32.4 \pm 2.1* | 28.7 \pm 2.1 ** | 20.0 \pm 2.02*** | 30.4 \pm 2.2 ** |

The results of studies in the experimental group using a complex plant antioxidant showed a significant reduction in oxidative stress. Thus, the level of MDA exceeded the initial data by 2.7 times ($p<0.01$), which was almost 3 times less than 60 days after exposure ($p<0.01$). The level of CA after the application of a complex plant antitoxicant increased by 27% ($p<0.05$) within a month compared with the period after a two-month exposure to nickel nitrate.

Thus, in experimental atherosclerosis after chronic exposure to nickel nitrate, lipid metabolism and oxidative stress disorders were aggravated. Thus, there was an increase in the levels of TC, LDL, and MDA with a parallel

decrease in the levels of HDL and CA activity, which may be due to intoxication with nickel nitrate, which is a factor aggravating atherosclerotic processes. At the same time, a directly proportional dependence of the severity of disorders on the duration of intoxication with nickel nitrate was revealed, with a maximum of disorders on the 60th day after exposure.

The use of a complex plant antitoxicant from the flora of Azerbaijan for a month after a two-month intoxication with nickel nitrate led to an improvement in the state of both lipid metabolism and oxidative stress that occurred after chronic intoxication with nickel nitrate in experimental atherosclerosis.

CONCLUSION

Thus, the obtained data showed that both lipid metabolism disorders and oxidative stress, observed after atherosclerosis modeling, are further aggravated by chronic exposure to nickel nitrate. The revealed corrective effect of the herbal complex antitoxicant from the flora of Azerbaijan indicates the detoxification effect of this plant complex and the possibility of its clinical approbation both for the prevention and treatment of chronic nickel nitrate poisoning in patients, especially those with atherosclerotic vascular lesions.

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KOMPLEKS ANTİTOKSİKANT TƏSİRİ ALTINDA EKSPERİMENTAL ATEROSKLEROZ FONUNDA NİKEL NİTRATLA XRONİKİ ZƏHƏRLƏNMƏSİ OLAN SIÇOVULLARDA LİPİD MÜBADİLƏSİNİN VƏ OKSİDİV STRESİN ÖYRƏNİLMƏSİ

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Eksperimental ateroskleroz fonunda xroniki nikel nitratla zəhərlənməsi olan siçovullarda 3:2:1:1:2 nisbətində biyan, it burnu, üzüm toxumu, yulaf kəpəyi və dulavratotu qarışığından ibarət (25.06.2018-ci il tarixli Avrasiya patenti 201600043) Azərbaycan florasından olan kompleks bitki antitoksikantının lipid mübadiləsinə və oksidativ stresə təsiri öyrənilmişdir. Eksperimental aterosklerozda nikel nitratla zəhərlənməyə məruz qaldıqdan sonra siçovullarda lipid mübadiləsi və oksidativ streslə bağlı pozulmalar daha da dərinləşmişdi, çünki nikel nitrat ilə intoksikasiya aterosklerotik prosesləri ağırlaşdıraraq amildir. Pozulmaların dərəcəsi ilə nikel nitrat ilə intoksikasiya müddəti arasında birbaşa mütənəssib əlaqə aşkar edilmişdir, pozulmaların maksimumu ekperimentin 60-cı günündə müşahidə olmuşdur. Əsas təcrübə qrupda nikel nitratla xroniki intoksikasiyadan sonra kompleks bitki antioksidantın istifadəsi lipid mübadiləsinin əhəmiyyətli dərəcədə yaxşılaşmasına və oksidativ stresin azalmasına səbəb olmuşdur. Bitki antitoksikantının aşkar edilmiş korreksiyaedici təsiri onun detoksikasiyaedici təsirini və mövcud aterosklerotik damar pozulmaları olan pasiyentlərdə xroniki nikel nitratla zəhərlənməsinin qarşısının alınması və müalicəsi üçün klinik sınaqdan keçirilmə imkanını göstərir.

Açar sözlər: bitki antitoksikantı, lipid mübadiləsi, oksidativ stres, nikel nitrat, eksperimental ateroskleroz

ИЗУЧЕНИЕ ЛИПИДНОГО ОБМЕНА И ОКСИДАТИВНОГО СТРЕССА У КРЫС С ХРОНИЧЕСКИМ ОТРАВЛЕНИЕМ НИТРАТОМ НИКЕЛЯ НА ФОНЕ ЭКСПЕРИМЕНТАЛЬНОГО АТЕРОСКЛЕРОЗА ПОД ВЛИЯНИЕМ КОМПЛЕКСНОГО АНТИТОКСИКАНТА

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Изучалось влияние комплексного растительного антиоксиданта из флоры Азербайджана, состоящего из смеси шрота солодки, шиповника, виноградных косточек, овсяных отрубей и лопуха в соотношении 3:2:1:1:2 (Евразийский патент 201600043 от 25.06.2018) на липидный обмен и оксидативного стресса у крыс при хроническом их отравлении нитратом никеля на фоне экспериментального атеросклероза. Показано, что при экспериментальном атеросклерозе после воздействия нитратом никеля усугублялись нарушения липидного обмена и оксидативного стресса, поскольку интоксикация нитратом никеля является фактором, усугубляющим атеросклеротические процессы. Выявлена прямая пропорциональная зависимость между степенью тяжести нарушений от продолжительности интоксикации нитратом никеля с максимумом нарушений на 60-й день после воздействия. В опытной же группе после хронической интоксикации нитратом никеля, применение комплексного растительного антиоксиданта приводило к достоверному улучшению состояния липидного обмена и оксидативного стресса. Выявленный корректирующий эффект растительного антиоксиданта свидетельствует о его детоксикационном действии и возможности его клинической апробации как для профилактики, так и для лечения хронических отравлений нитратом никеля у пациентов, с имеющимся атеросклеротическим поражением сосудов.

Ключевые слова: растительный антиоксидант, липидный обмен, оксидативный стресс, нитрат никеля, экспериментальный атеросклероз

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