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EFFECT OF COMBINED USE OF PLANT ANTITOXICANT AND PROBIOTIC ON LIPID METABOLISM AND ANXIETY DURING INTOXICATION WITH NICKEL AGAINST THE BACKGROUND OF EXPERIMENTAL ATHEROSCLEROSIS

Actuality. *In recent years have appeared the data regarding the toxic effects of such a heavy metal as nickel, however, studies about its effect on the atherosclerotic processes, behavioral reactions, or about methods for correcting its toxic effects have not been found.*

The aim of the study *was to study the state of lipid metabolism and behavioral reactions during intoxication with nickel against the background of experimental atherosclerosis under the influence of experimental therapy using a plant antitoxicant and a probiotic together.*

Materials and methods. *The experiments were conducted on 100 white nonlinear male rats in 5 series: Series 1 – healthy intact animals (control); Series 2 – animals with experimental atherosclerosis; Series 3 and 4 – animals with experimental atherosclerosis, which poisoned with nickel nitrate for 15 and 30 days, and Series 5 – animals that, after 30 days of nickel intoxication against the background of experimental atherosclerosis, received a plant antitoxicant and a probiotic for a month.*

Research results. *It was shown that nickel intoxication aggravates both dyslipidemic and behavioral disorders occurring after modeling experimental atherosclerosis. Maximum anxiety disorders are noted by the end of 30 days of intoxication and indicate on significant neurotoxic effect of nickel against the background of dyslipidemic changes.*

Conclusions. *The combined use of a plant antitoxicant and a probiotic is a safe and highly effective method of detoxification poisoning with nickel nitrate against the background of experimental atherosclerosis. It is likely that the positive effect of complex therapy is associated with the enhancement of the detoxifying effect of symbiotic bacteria by a plant antitoxicant, which has both a prebiotic and antioxidant, antihypoxic, membranotropic and stress protective properties effect, which is inherent in its plant components.*

Key words: *plant antitoxicant, probiotic, lipid metabolism, anxiety, nickel, atherosclerosis.*

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ВПЛИВ ПОЄДНАНОГО ЗАСТОСУВАННЯ РОСЛИННОГО АНТИТОКСИКАНТУ ТА ПРОБІОТИКА НА ЛІПІДНИЙ ОБМІН І ПОВЕДІНКОВУ РЕАКЦІЮ ПІД ЧАС ІНТОКСИКАЦІЇ НІКЕЛЕМ НА ТЛІ ЕКСПЕРИМЕНТАЛЬНОГО АТЕРОСКЛЕРОЗУ

Актуальність. *Останнім часом з’явилися дані про токсичну дію такого важкого металу, як нікель. Однак досліджень щодо його впливу на перебіг атеросклеротичних процесів, поведінкових реакцій або методів корекції його токсичної дії не знайдено.*

Мета дослідження. *Вивчити стан ліпідного обміну та поведінкові реакції за інтоксикації нікелем на тлі експериментального атеросклерозу під впливом експериментальної терапії із застосуванням рослинного антитоксиканту та пробіотика разом.*

Матеріали та методи. *Досліди проводили на 100 білих нелінійних щурах-самцях у 5 групах: 1-ша група – здорові інтактні тварини (контроль); 2-га група – тварини з експериментальним атеросклерозом; 3-тя і 4-та групи – тварини з експериментальним атеросклерозом, які отруїлися нітратом нікелю протягом 15 і 30 днів, і 5-та група – тварини, які після 30 днів інтоксикації нікелем на тлі експериментального атеросклерозу отримували рослинний антитоксикант і пробіотик протягом місяця.*

Результати досліджень. *Доведено, що інтоксикація нікелем посилює як дисліпідемічні, так і поведінкові розлади, які виникають під час моделювання експериментального атеросклерозу. Максимальні тривожні розлади відзначаються до кінця 30-денної інтоксикації і свідчать про значну нейротоксичну дію нікелю на фоні атеросклеротичних змін.*

Висновки. *Комбіноване застосування рослинного антитоксиканту і пробіотика є безпечним і високоефективним методом детоксикації отруєнь нітратом нікелю на тлі експериментального атеросклерозу. Імовірно, позитивний ефект комплексної терапії пов'язаний із посиленням детоксикаційної дії симбіотичних бактерій рослинним антитоксикантом, який має як пробіотичну, так і антиоксидантну, антигіпоксичну, мембранотропну та стреспротективну дію, притаманну його рослинним компонентам.*

Ключові слова: *рослинний антитоксикант, пробіотик, ліпідний обмін, тривога, нікель, атеросклероз.*

Introduction. Heavy metal pollution is a major global environmental problem that increases the risk of many human diseases (Briffa, 2020). According to literature data, one of the common key mechanisms of action of heavy metals is the development of oxidative stress that destroys biological macromolecules, which leads to the development of various pathologies (Jomova, Valko, 2011; Killian, Yuan, Tsai, Chiu, Chen, Chan, 2020). An analysis of the literature in recent years shows that exposure to heavy metals is an important and underestimated risk factor for the development of atherosclerosis and its consequences (Kim, Kang, Cho, Lim, Yoo, Park, Lee, 2021; Barregard, Sallsten, Harari, Andersson, Forsgard, Hjelmgren, Angerås, 2021) and there is also a link between exposure to heavy metals and development of mental disorders (Lee, Chou M., Chou W., Huang, Kuo, Lee, Wang, 2018; Yu, Wu, Su, Ji, Zhou, Wu, Tang, 2024).

In addition, the latest research shows that changes in the gut microbiota also play an important role in the development of various diseases (Madhogaria, Bhowmik, Kundu, 2022). Experimental studies have clearly shown that the intake of heavy metals through the gastrointestinal tract alters the diversity and composition of the gut microbiota (Richardson, Dancy, Horton, Lee, Madejczyk, Xu, Zhenjiang, 2018; Giambò, Italia, Teodoro, Briguglio, Furnari, Catanoso, Costa, Fenga, 2021). There is a correlation between changes in the intestinal microbiome and the development of atherosclerosis (Lindskog, Caesar, Akrami, Reinhardt, Fåk, Borén, Bäckhed, 2018) and a number of nervous diseases (Qian, Song, Liu, Chen, Tang, 2021; Forero-Rodríguez, Zimmermann, Taubenheim, Arias-Rodríguez, Caicedo-Narvaez, Best, Mendieta, 2024).

It has long been established that there is a bidirectional communication between the gut and the brain, referred to as the “brain-gut axis.” The interactions between heavy metals, the gut microbiota, and the central nervous system are thought to suggest that heavy metals may cause direct brain changes through alteration of the complex microbiota-gut-brain axis, contributing to neurotoxicity and neuropsychological disorders (Bicknell, Liebert, Borody, Herkes, McLachlan, Kiat, 2023; Yu, Wu, Su, Ji, Zhou, Wu, Tang, 2024).

The above data convincingly indicate a connection between atherosclerotic and neurotoxic changes and exposure to heavy metals, which in turn is interconnected with changes at the level of the intestinal microbiota.

Today, the main method of removing heavy metals in various diseases is chelation therapy, however, the available literature data, especially in reducing cardiovascular events, have recently been conflicting (Lamas, Anstrom, Navas-Acien, Boineau, Nemeth, Huang, Wen, 2024).

An innovative approach to the development of treatment methods for heavy metal poisoning today is considered the use of probiotics (Rodríguez-Viso, Domene, Vélez, Devesa, Zúñiga, Monedero, 2024; Skalny, Aschner, Gritsenko, Martins, Tizabi, Korobeinikova, Paoliello, 2024) and herbal remedies (Bhattacharya, 2020; Liu, Sun, Wang, Zhou, Sun, Li, Liu, Xu, 2023), suggesting enhanced protective properties of gut microbiota against heavy metal toxicity.

In the literature of recent years there are separate works on the toxic effect of such a metal as nickel, long-term exposure to which has a genotoxic, hematotoxic, teratogenic, immunotoxic and carcinogenic effect (Son 2020; Genchi, Carocci, Lauria, Sinicropi, Catalano 2020). However, no studies on its effect on the course of atherosclerotic processes and behavioral disorders could be identified.

The aim of the study. Based on the above, it seemed interesting to study the state of lipid metabolism and behavioral reactions when poisoned with nickel nitrate against the background of experimental atherosclerosis and to develop a method of experimental therapy based on the combined use of a plant antitoxicant and a probiotic.

Materials and methods. The experiments were conducted on 100 white nonlinear male rats in accordance with the principles of the "European Convention for the Protection of Vertebrate Animals used for Experimental and Scientific Purposes" (Strasbourg, 1986). The animals were obtained from the vivarium of the Azerbaijan Medical University. During the study period, the rats were in a natural light regime, received a standard diet and had free access to water and food. At the end of the experiment, the animals were decapitated under diethyl ether anesthesia, followed by whole blood sampling for biochemical analysis. This study was approved by the Ethics Committee of the Azerbaijan Medical University (protocol N31 dated 02.02.2024).

The studies were conducted in 5 series: Series 1 – intact animals (control); Series 2 – animals with experimental atherosclerosis; Series 3 and 4 – animals with experimental atherosclerosis, with nickel nitrate inoculation for 15 and 30 days, and Series 5 – animals that, after 30 days of nickel intoxication against the background of experimental atherosclerosis, simultaneously received a plant antitoxicant and probiotic for a month (10 rats at each study period).

The atherosclerosis model was created according to I.V. Savitsky et al. (2016) and is based on the polyetiological theory of disease development. The rats received mercazolil – 25 mg/kg of body weight, methylprednisolone – 0.17 mg/kg of animal weight and 15% aqueous solution of ethyl alcohol in free access instead of water against the background of an atherogenic diet (1% cholesterol, 20% unsaturated and 20% saturated fat) for 2 weeks. After 2 weeks, total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides (TG) in the blood serum were determined for confirming dyslipidemic changes, and was calculated the atherogenic index (AI) using the formula AI = TC – HDL/HDL. After modeling dyslipidemia, the animals were exposed to nickel nitrate through drinking water for 30 days at a dose of 2 mg/kg.

The anxiety study was conducted using a standard elevated plus maze setup. The elevated plus maze test is considered one of the most adequate and sensitive for assessing the effects of chemical and physical agents and is considered one of the most sensitive models for studying animal anxiety. The setup uses the conflict between the natural fear of animals of open space, height, novelty and the simultaneous desire to explore these unknown conditions (Rorgers, Shepherd 1993; Walf, Frye 2007). The elevated plus maze setup for rats TS0502-R3 (PC Open Science, Russia) was used.

Each animal was tested once at the appropriate time during the study before being removed from the experiment. The testing time was 5 minutes, and the following were recorded: time spent in the open arms, number of peeking out of closed arms, vertical stands, hanging from open arms and grooming.

The mixture of herbal preparations was used as an antitoxicant for which there is a Eurasian patent, obtained by employees of the Department of Medicines Technology of the Azerbaijan Medical University (Eurasian patent N030858 dated 31.10.2018, title – "Use of a product to cleanse the body of toxins"). The used plant antitoxicant included a mixture of licorice, rose hips, grape seeds, oat bran and burdock in a ratio of 3:2:1:1:2 and was added to drinking water in drinking bowls at a dose of 8 mg/kg for a month.

Symbiolact compositum was used as a probiotic, which was added to drinking water at a dose of 8 mg/kg for a month. Symbiolact compositum (Symbiopharm, Germany) contains several 6 types of symbiotic microorganisms (Lactobacillus acidophilus (2.0 x 10 CFU), Lactobacillus casei (2.0 x 10 CFU), Bifidobacterium bidum (1.0 x 10 CFU), Bifidobacterium lactis (1.0 x 10 CFU), Lactococcus lactis (2.0 x 10 CFU), Lactobacillus salivarius (2 x 10^7).

The obtained digital results were processed using the programs "Microsoft Excel 2010", "BioStat 6.0", "Statistica 10.0". The group indicators were arranged in a variation series and for each group the arithmetic mean (M), its standard error (m) was determined, and the width of the 95% confidence interval was also indicated. Due to the prevalence of parameters that had a distribution different from normal, statistical analysis of the study results was carried out using nonparametric analysis criteria: two independent groups were compared using the Mann-Whitney U criterion. The level of statistical significance was taken as a minimum at $p \leq 0.05$.

Results and discussion. The results of the study of lipid metabolism after poisoning with nickel nitrate and, accordingly, after the experimental therapy with the combined use of a probiotic and a plant antitoxicant are presented in Table 1.

A study of lipid metabolism indices after modeling dyslipidemia showed statistically significant changes in biochemical indices of lipid metabolism. Thus, after modeling dyslipidemic disorders was characterized by a reliable increase in the TC level by an average of 29% compared to the data of intact rats. The LDL level increased sharply – by an average of 60% more than the indicator of control intact animals. The TG content increased by an average of 10% compared to the data of intact animals. In parallel, a statistically significant decrease in the HDL content by an average of 28% was recorded. This nature of the change in lipid status indicators led to an increase in AI almost 3 times compared to the indicators of animals in an intact state.

Subsequent intoxication with nickel nitrate against the background of experimental dyslipidemic disorders caused an increase in the intensity of lipid metabolism disorders. Thus, 15 and 30 days after intoxication, the TC content was higher than in intact animals, respectively, by an average of 30% and 39%. The LDL level on the 15th and 30th day of nickel nitrate intoxication increased, respectively, by more than 1.8 and 2 times relative to the data of intact rats. The TG content statistically significantly increased on the 15th day of intoxication by an average of 14% and by 27% on the 30th day compared to the data of the control animals. The HDL level 15 and 30 days after intoxication with nickel nitrate against the background of experimental atherosclerotic chances was lower by an average of 28% and 34.1%. AI after nickel nitrate intoxication increased by 3.8 times on the 15th day of challenge and by 4.8 times a month after poisoning relative to the data of intact rats. These changes in lipid metabolism due to nickel nitrate intoxication against the background of experimental atherosclerosis indicated further development and worsening of dyslipidemic disorders. The obtained data emphasize the important role of chronic poisoning with heavy metal salts in the process of worsening atherosclerotic processes and are consistent with the data of other studies on the pathogenetic role of heavy metals in the development of atherosclerotic processes (Kim, Kang, Cho, Lim, Yoo, Park, Lee, 2021; Barregard, Sallsten, Harari, Andersson, Forsgard, Hjelmgren, Angerås, 2021).

Conducting complex therapy with the simultaneous use of a probiotic and a plant antitoxicant showed the following results: the level of TC decreased by an average of 10%, LDL – by 40% and TG – by 18%, respectively, compared to the data before the start of treatment of animals. In parallel, a reliable increase in the level of HDL was recorded by an average of 17% and as a result, the AI decreased almost 1.6 times compared to the data before the start of treatment.

The results of the studies of behavioral reactions in the elevated maze test before and after the experimental therapy showed the changes presented in Table 2.

After modeling dyslipidemic disorders, the time spent in the open arms changed insignificantly compared to the data of intact animals. However, the number of hangings from the open arms decreased significantly by an average of 21%, the number of peeks out of the closed arms also decreased (by 9%) and the number of vertical stands in the closed arms (by an average of 7%) compared to the corresponding data of intact rats. The number of grooming after modeling atherosclerosis also increased significantly (by an average of 43%) compared to the data of intact animals.

Chronic poisoning of animals with nickel nitrate after modeling dyslipidemia resulted in significant changes

Table 1

Changes in lipid metabolism parameters in rat blood serum under the influence of combined use of a plant antitoxicant and a probiotic after nickel intoxication against the background of experimental atherosclerosis (M ± m, n = 10)

Indicators	Intact state	After modeling dyslipidemiya	15 days of intoxication	30 days of intoxication	30 days after treatment
OX mmol/l	1.86 ± 0.16	2.4 ± 0.34**	2.42 ± 0.21**	2.58 ± 0.16**	2.38 ± 0.2**
LDL mmol/l	0.17 ± 0.03	0.27 ± 0.03**	0.3 ± 0.02**	0.35 ± 0.03**	0.28 ± 0.04**
HDL mmol/l	1.33 ± 0.13	1.11 ± 0.1**	0.95 ± 0.1**	0.88 ± 0.05**	1.09 ± 0.31*
TG mmol /l	0.43 ± 0.06	0.47 ± 0.07	0.49 ± 0.06	0.54 ± 0.06**	0.47 ± 0.03
AI	0.4± 0.11	1.17 ± 0.29	1.57 ± 0.27	1.95 ± 0.27	1.31 ± 0.52*

Note: statistical significance compared with the indicators of intact animals: * – P ≤ 0,01; ** – P ≤ 0,001.

Table 2

Behavioral reactions of rats in the plus maze test under the influence of combined use of a plant antitoxicant and a probiotic after nickel poisoning against the background of experimental atherosclerosis (M ± m, n = 10)

Indicators	Initial data	After modeling dislipidemiya	15 days after poisoning	30 days after poisoning	30 days after treatment
Time in open arms	106.7 ± 16.5	111.4 ± 16.1	82.9 ± 13.3*	67.9 ± 9.3**	91.3 ± 8.1*
Hangings from open arms	6.2 ± 1.03	4.9 ± 0.74*	4.9 ± 0.99*	3.6 ± 0.84**	5.3 ± 0.95
Peeks out of closed arms	8 ± 1.16	7.3 ± 1.25	7.1 ± 0.99	5.8 ± 1.2*	6 ± 1.1*
Vertical stands	9.7 ± 1.64	9 ± 1.25	8.6 ± 0.97	4.7 ± 1.16**	7 ± 1.05**
Groomings	3.9 ± 0.99	5.6 ± 1.4*	4.6 ± 1.8	3.5 ± 0.97	4.2 ± 0.8

Note: statistical significance compared with the indicators of intact animals: * – P ≤ 0,01; ** – P ≤ 0,001.

in the behavioral reactions of the rats. Thus, the time spent in the open arms began to decrease significantly in a progressive order – by 22% after 15 days, by 36% after a month after poisoning, respectively. The number of hanging from the open arms, already reduced after modeling atherosclerotic chances, continued to decrease and was significantly reduced on the 30th day of poisoning – on average by 42% compared to the data of intact animals. The number of peeks out of the closed arms and the number of stands in the closed arms after the start of poisoning also significantly decreased progressively. Thus, the number of peeks after poisoning after 15 days decreased by 11%, and after 30 days by an average of 27%), respectively, compared to the data of intact animals. The number of vertical stands relative to intact rats decreased by 11% after 15 days and by 51% after 30 days from the start of the intoxication. The number of grooming only after 15 days after the start of the poisoning was greater than that of intact animals by 18%, however, with the increase in the duration of the poisoning, the number of grooming decreased and after 30 days was already less than that of intact animals by 10%, respectively.

Summarizing the results of the study of the "elevated maze" test parameters, it can be said that after modeling atherosclerotic chances, minor certain changes were revealed that characterize the development of anxiety in the rats. However, after the start of nickel nitrate poisoning, the changes intensified and on the 30th day of intoxication, exhaustion of the animals and suppression of behavioral reactions were noted. In addition, it should be noted that as the poisoning period increased, the animals lost weight and consumed little water. All this indicates a suppressive effect of chronic nickel nitrate intoxication on the state of the central nervous system of the experimental rats and shows the toxic neurotropic effect of chronic nickel nitrate intoxication in experimental atherosclerosis.

Conducting experimental therapy of the identified behavioral disorders using the simultaneous use of a probiotic and a plant antitoxicant revealed a significant increase in the time spent by rats in open arms (by an average of 17%), the number of hangings (by an average of 28%), vertical stands (by an average of 23%) and grooming (by an average of 18%) compared to the data before the start of experimental therapy.

Thus, summarizing the obtained data, it can be stated that nickel plays a significant role both in the aggravation of dyslipidemia disorders and behavioral reactions that occur after modeling experimental atherosclerosis. The development and aggravation of behavioral disorders under the influence of nickel against the background of experimental atherosclerosis in our studies are consistent with the data of other researchers on the presence of a close relationship between heavy metal intoxication and disorders at the intestinal level and the development of neuropsychological disorders (Bicknell, Liebert, Borody, Herkes, McLachlan, Kiat, 2023; Yu, Wu, Su, Ji, Zhou, Wu, Tang, 2024).

The positive effect of the combination therapy can be explained by the fact that the probiotic probably exerts a protective effect on the intestinal microbiota by increasing both the number and composition of beneficial microorganisms and contributes to an increase in the production and recognition of neurochemicals that play an important role in the gut-brain axis, which in turn indirectly affects brain function and behavior. The effectiveness of the use of a complex plant antitoxicant can be explained by known facts about the antihypoxic (Gorchakova, Belenichev, Harnyk, Lukianchuk, Savchenko, Yakovleva, 2024), membrane-stabilizing (Gorchakova, Belenichev, Harnyk, Shumeiko, Klymenko, 2023) and anti-stress (Gorchakova, Belenichev, Harnyk, Zaichenko, Klymenko, Gorova, Shumeiko, Maslova, 2024) effects of herbal preparations. The combined use of a complex plant antitoxicant enhances the detoxifying effect of symbiotic bacteria, providing both a prebiotic, antioxidant, antihypoxic, membranotropic and stress protective effect, which is inherent in plant components.

Conclusions

1. İntoxication with nickel nitrate after modeling atherosclerosis leads to an increase in lipid metabolism disorders and anxiety in experimental rats.

2. The maximum disturbances in anxiety were by the end of 30 days after nickel intoxication and indicate a significant neurotoxic effect of nickel nitrate intoxication against the background of atherosclerotic changes.

3. The combined use of a plant antitoxicant and a probiotic is a safe and highly effective method for detoxification nickel nitrate poisoning against the background of dyslipidemia changes.

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