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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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ავტორთა საყურადღებოდ!

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1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

ლობის მაღალი მაჩვენებლები (52%), განსაკუთრებით მოზარდებში (47%), აბორტების მაღალი მაჩვენებელი (31%), ჩვენების გარეშე საკეისრო კვეთების მაღალი პროცენტი მოზარდებში (25%).

ორსულობაზე და ორსულობის შედეგებზე ზედამხედველობა რეგისტრის ტიპის სისტემების მეშვეობით არის ინოვაციური მიდგომა დაბალი და საშუალო შემოსავლის მქონე ქვეყნებისათვის,რაც იძლევა საშუალებას ქალთა პოპულაციაში გამოავლინოს ზოგიერთი სოციალურ-ეკონომიკური და ქცევითი მახასიათებლების გავლენა დედათა და ბავშვთა ჯანმრთელობაზე. მონაცემებზე დაფუძნებით შესაძლებელია პრევენციული ინტერვენციების დაგეგმვა, რომლებიც მიზნად დაისახავს დაბალი და საშუალო შემოსავლის მქონე ქვეყნებში დედის და პერინატალური ავადობისა და სიკვდილიანობის შემცირებას.

THE INFLUENCE OF CHRONIC HYPERHOMOCYSTEINEMIA ON PHAGOCYTIC AND METABOLIC ACTIVITY OF PERIPHERAL BLOOD NEUTROPHILS IN CASE OF LIPOPOLYSACCHARIDE-INDUCED PERIODONTITIS

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Periodontal disease, which is usually defined as an inflammatory disorder, which involves both soft and hard periodontal structures (ie, gingivitis and periodontitis), is the second most common oral health problem after caries and has serious health and economic consequences, which significantly impairs quality of life for those affected [18,27]. It should be noted that the prevalence of periodontal disease differs in both developed and developing countries [8]. So, in Europe severe periodontal disease is found in 5-20% of 35-44 years adults, and up to 40% of older people [20]. At the same time in Ukraine, the prevalence of periodontal disease among the population over the age of 35 reaches 85-95% [24].

In the pathogenesis of periodontitis, as well as any other inflammatory processes that accompany tissue damage, an important role belongs to cellular defense mechanisms and especially phagocytic cells – neutrophils and macrophages. The first to enter the site of inflammation are neutrophils, which participate in the neutralization of pathogens, absorbing them through phagocytosis (although less effective as monocytes/macrophages) [28] and releasing a large number of free radicals (respiratory burst), which have a pronounced bactericidal effect [9]. Moreover, neutrophilic granules contain a spectrum of substances intended to destroy the bacterial cell wall (lysozyme, lactoferrin) and hydrolytic enzymes (proteases, peptidases, oxidases, deoxyribonucleases and lipases) [25]. In recent years, a new antibacterial defense mechanism has been discovered – formation of neutrophil extracellular traps, which main function appears to be evacuation of dental plaque pathogen-associated molecular patterns [29]. According to Andryukov B.H. and co-authors neutrophils are not only modulators of inflammation, but also active effectors of immune responses [3]. At the same time excessive activation of neutrophils and hyperproduction of reactive oxygen species (ROS) in response to periodontal pathogens can induce tissue damage and lead to periodontitis persistence [13]. So, determining the functional state of neutrophils is important in understanding the periodontitis pathogenesis.

It should be noted that the progression of destructive phenomena in periodontal tissues depends on a number of adverse exogenous and endogenous factors, one of which may be high level of homocysteine (Hcys) – hyperhomocysteinemia (HHcy).

Therefore, the aim of our study was to investigate the phagocytic and metabolic activity of peripheral blood neutrophils in rats with lipopolysaccharide-induced periodontitis combined with chronic thiolactone HHcy.

Material and methods. The study included mature inbred white male rats (n=48) with a body weight of 180-200 g. During the period of the experiment, animals were kept in controlled-temperature (22±2ºC) room with an adjustable light cycle (12/12) and unrestricted access to water and food at the animal facility of I. Horbachevsky Ternopil National Medical University, Ternopil. Animal treatment and all experimental procedures were performed in compliance with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (European convention for the protection of vertebrate animals used for experimental and other scientific purposes 1986). The Bioethics Commission of I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine approved the protocol of the experiment.

The animals were randomly divided into the following groups: group 1: control (n=12); group 2: animals with a model of periodontitis (n=12). For two weeks, the rats in this group were injected 40 μL (1 mg/mL) of E. coli lipopolysaccharide (LPS) (manufactured by Sigma-Aldrich, USA) into gingival tissues every other day [25]; group 3 – rats with chronic thiolactone HHcy (n=12). Homocysteine thiolactone was administered intragastrically (100 mg/kg of body weight in 1 % solution of starch) once a day for 42 days [26]; group 4 – animals with a model of periodontitis combined with HHcy (n=12). In animals of this group chronic thiolactone HHcy was caused as described above. From the 29th day after the start of HHcy induction, animals were injected into the gum tissue with LPS for 14 days in parallel with thiolactone homocysteine in accordance to the above scheme.

The rats were euthanized under deep thiopental-sodium anesthesia by cardiac puncture the day after the last LPS injection (group 2 and 4) or the day after the last homocysteine thiolactone administration (group 3). Blood samples were used for further investigations. The population of peripheral blood neutrophils was obtained by blood centrifugation at double density gradient 1.077 and 1.093 of ficoll-urografin [21].

As a test system for studying phagocytic activity of neutrophils were used standard latex particles for phagocytosis (10% polystyrene suspension) with a diameter of 1.5 μm («Diaem», Russia). The neutrophil cell suspension was added to test tube in an amount of 0.1 ml and incubated at 37 ° C for 60 min with 0.1 ml of latex suspension. Then smears were prepared on slides, dried, fixed and stained with 1% solution of methylene blue. 100 neutrophils were counted in each smear [10].

As indices of phagocytosis were determined: phagocytic activity (PA) by the number of phagocytic cells out of 100 counted (%); phagocytic index (PI) – the number of phagocytosed latex particles that are captured by a single cell; phagocytic number (PN) – the number of phagocytic latex particles per 100 counted cells.

PN and PI were calculated by the formulas: PI = number of phagocytosed latex particles/ PA; PN = number of phagocytosed latex particles/100.

Oxygen-dependent bactericidal activity of peripheral blood neutrophils was studied using nitroblue tetrazolium test (NBT-test). This assay is based on the use of NBT, a yellow, water-soluble, nitro-substituted aromatic tetrazolium salt (2,20-bis(4-nitrophenyl)-5,50-diphenyl-3,30-(3,30-dimethoxy-4,40-diphenylene)ditetrazolium chloride), with the ability to interact with intracellular superoxide to create formazan. Neutrophils are incubated in the presence of the tetrazolium salt and subsequently take up NBT into their cytoplasm where it is transformed by superoxide radicals to purple-blue and water insoluble formazan crystals. While formazan is trapped intracellularly, it may be observed within the cells using an optical microscope [11].

During the spontaneous NBT-test (ST), the cell suspension of neutrophils was introduced into a test tube in an amount of 0.1 ml, added 0.1 ml of 0.1% aqueous solution of nitroblue tetrazolium and incubated at 37 ° C for 40 min with 0.1 ml of saline. During the activated NBT-test (AT), the cell suspension of neutrophils was introduced to a test tube in an amount of 0.1 ml, added 0.1 ml of 0.1% aqueous solution of nitroblue tetrazolium and incubated at 37 ° C for 40 min with 0.1 ml of latex suspension.

The reaction was evaluated by counting 100 neutrophils for the presence of formazan crystals in the cytoplasm. In the cytoplasm of cells that react positively with NBT, the precipitation of purple-blue formazan crystals was recorded. In the cytoplasm of cells that react negatively with NBT, formazan crystals were absent. The percentage of formazan-positive cells (dye granules occupy at least ¼ part of the cytoplasm) was calculated in a spontaneous test and in an activated test.

Reserve ratio (RR) and metabolic activation coefficient (MAC) were determined to characterize the reserve capacity of oxygen-dependent metabolism. RR and MAC were calculated by the formulas: RR=AT/ST; MAC=AT – ST/AT, where AT – % of formazan-positive cells in activated NBT-test; ST – % of formazan-positive cells in spontaneous NBT-test.

The experimental data were processed and analyzed using MS Office 2016 EXCEL (Microsoft Corp., USA) and Statistica 7.0 software (StatSoft Inc., USA). The distribution of data was analyzed in

Table 1. The indices of functional state of peripheral blood neutrophils in rats with LPS-induced periodontitis without comorbid pathology and combined with chronic thiolactone HHcy (Me [Q25–Q75])

Parameter	Experimental group			
	Control	Periodontitis	HHcy	Periodontitis + HHcy
	1	2	3	4
Suspension of peripheral blood neutrophils				
Phagocytic activity (PA), %	69.50 (64.00; 71.00)	86.00 (84.00; 95.50)	79.00 (76.00; 81.00)	60.00 (57.00; 64.00)
	Kruskal-Wallis criterion H=38.29; p<0.001*			
	p_{1-2}<0.001* p_{1-3}=0.360 p_{1-4}=0.512	p_{2-3}=0.138 p_{2-4}<0.001*	p_{3-4}<0.002*	–
Phagocytic number (PN)	4.73 (4.40; 4.98)	4.10 (3.89; 4.45)	4.63 (4.35; 4.93)	2.01 (1.73; 2.37)
	Kruskal-Wallis criterion H=31.35; p<0.001*			
	p_{1-2}=0.256 p_{1-3}=0.999 p_{1-4}<0.001*	p_{2-3}=0.452 p_{2-4}=0.020*	p_{3-4}<0.001*	–
Phagocytic index (PI)	6.97 (6.44; 7.42)	4.64 (4.37; 5.02)	6.05 (5.69; 6.25)	3.40 (2.74; 3.79)
	Kruskal-Wallis criterion H=40.72; p<0.001*			
	p_{1-2}<0.001* p_{1-3}=0.528 p_{1-4}<0.001*	p_{2-3}=0.127 p_{2-4}=0.315	p_{3-4}<0.001*	–

*Note 1. p_{1-2}, p_{1-3}, p_{1-4} - the probability of differences between control and experimental groups; p_{2-3} - the probability of differences between the group with periodontitis and group with HHcy; p_{2-4} - the probability of differences between the group with periodontitis and group with periodontitis combined with HHcy; p_{3-4} - the probability of differences between the group with HHcy and group with periodontitis combined with HHcy. Note 2. * – statistically significant results*

accordance with the assessment of normality by the Kolmogorov-Smirnov test. The obtained values had not a normal distribution, so comparison of three or more groups on a quantitative basis was carried out using Kruskal-Wallis test followed by the Mann-Whitney test for pairwise comparison of groups, taking into account the Bonferroni correction. All data were presented as a median and quartiles (lower and upper) – Me (Lq; Uq). A probability level (p-value) of less than 0.05 was considered to be statistically significant.

Results and discussion. The results of our studies showed an increase of neutrophils' PA in rats with only LPS-induced periodontitis by 23.7% (p<0.001) vs. control group (table 1).

In rats with LPS-induced periodontitis combined with chronic thiolactone HHcy, a decrease of this index by 13.7% relative to control was found, but these changes were not significant (p=0.512). It should be noted that the PA of neutrophils in this group of animals was significantly lower by 30.2% relative to rats with only LPS-induced periodontitis.

Regarding PN, this index in rats with only LPS-induced periodontitis significantly did not change vs. control group. In rats with LPS-induced periodontitis combined with chronic thiolactone HHcy, this index was decreased by 2.4 times vs. control (p <0.001), which was 2.0 times lower than in rats with only LPS-induced periodontitis.

PI in rats with LPS-induced periodontitis without comorbid pathology significantly decreased by 33.4% vs. control group. In rats with LPS-induced periodontitis combined with chronic thiolactone HHcy, this index was decreased by 51.2% (p<0.001) vs. control and by 26.7% vs. rats with only LPS-induced periodontitis, but these changes were not significant (p=0.315).

The number of formazan-positive neutrophils in the spontaneous NBT-test in rats with LPS-induced periodontitis increased by 25.8% (p=0.003), and in the activated – by 42.9% (p= 0.001) vs. control group (table 2). The MAC of peripheral blood neutrophils significantly increased by 44.2%, and RR did not change significantly vs. control group.

In animals with LPS-induced periodontitis combined with chronic thiolactone HHcy, the number of formazan-positive neutrophils in the spontaneous NBT-test increased more markedly – by 80.6% (p=0.001) vs control, which is 43.6% significantly higher than the data of rats with only LPS-induced periodontitis. Regarding the number of formazan-positive neutrophils in the activated NBT-test, this index significantly increased by 58.9% vs. control, but did not differ significantly from the data of animals with only LPS-induced periodontitis. A similar trend was observed with regard to the MAC of peripheral blood neutrophils. This index increased

Table 2 .The indices of peripheral blood neutrophils NBT-test in rats with LPS-induced periodontitis without comorbid pathology and combined with chronic thiolactone HHcy (Me [Q25–Q75])

Parameter	Experimental group			
	Control	Periodontitis	HHcy	Periodontitis + HHcy
	1	2	3	4
Suspension of peripheral blood neutrophils				
Formazan-positive cells in activated NBT-test (AT), %	28.00 (25.00; 32.50)	40.00 (36.50; 46.00)	30.00 (29.00; 32.50)	44.50 (40.00; 49.00)
	Kruskal-Wallis criterion H=33.34; p<0.001*			
	p_{1-2}=0.001* p_{1-3}=0.999 p_{1-4}<0.001*	p_{2-3}=0.006* p_{2-4}=0.999	p_{3-4}<0.001*	–
Formazan-positive cells in spontaneous NBT-test (ST), %	15.50 (15.00; 16.00)	19.50 (18.50; 22.00)	19.00 (18.00; 20.00)	28.00 (26.50; 29.50)
	Kruskal-Wallis criterion H=36.67; p<0.001*			
	p_{1-2}=0.003* p_{1-3}=0.034* p_{1-4}<0.001*	p_{2-3}=0.999 p_{2-4}=0.007*	p_{3-4}=0.003*	–
Metabolic activation coefficient (MAC)	27.41 (24.42; 32.03)	39.53 (35.97; 45.58)	29.43 (28.38; 31.92)	43.95 (39.29; 48.42)
	Kruskal-Wallis criterion H=32.36; p<0.001*			
	p_{1-2}=0.001* p_{1-3}=0.999 p_{1-4}<0.001*	p_{2-3}=0.003* p_{2-4}=0.999	p_{3-4}<0.001*	–
Reserve ratio (RR)	1.84 (1.68; 2.10)	2.02 (1.80; 2.19)	1.61 (1.53; 1.74)	1.58 (1.45; 1.68)
	Kruskal-Wallis criterion H=14.00; p=0.003*			
	p_{1-2}=0.999 p_{1-3}=0.138 p_{1-4}=0.129	p_{2-3}=0.003* p_{2-4}=0.003*	p_{3-4}=0.999	–

*Note 1. p_{1-2}, p_{1-3}, p_{1-4} - the probability of differences between control and experimental groups; p_{2-3} - the probability of differences between the group with periodontitis and group with HHcy; p_{2-4} - the probability of differences between the group with periodontitis and group with periodontitis combined with HHcy; p_{3-4} - the probability of differences between the group with HHcy and group with periodontitis combined with HHcy. Note 2. * – statistically significant results*

by 60.3% ($p<0.001$) vs. control group, which is 11.2% higher than the data of animals with only LPS-induced periodontitis, but these changes were not significant. The RR of peripheral blood neutrophils in rats with LPS-induced periodontitis combined with chronic thiolactone HHcy decreased by 14.1% vs. control group, but these changes were not significant. At the same time, the RR in this group of animals was significantly lower by 21.8% compared to animals with only LPS-induced periodontitis.

Thus, the study of the functional state of peripheral blood neutrophils in case of LPS-induced periodontitis showed an increase in their phagocytic activity with a simultaneous decrease of absorption capacity. Regarding the NBT-test, in animals of this group the number of formazan-positive neutrophils significantly increased in both spontaneous and activated NBT-test vs. control group, which indicates the activation of oxygen-dependent microbicidal mechanisms.

It is known that the destruction of absorbed microbes and viruses by phagocytes occurs with the involvement of oxygen-dependent microbicidal mechanisms, which are realized by generating of a number of ROS, such as superoxide radicals, hydrogen peroxide, hypochlorous acid, hydroxyl radicals, and chloramines, by an enzyme complex known as nicotinamide adenine dinucleotide phosphate-oxidase/Nox2 (NADPH) oxidase [15,19] and their effects on the absorbed object. Reducing of the bactericidal activity of phagocytes can contribute to the survival of bacteria, their reproduction and chronicity of the inflammatory process [23].

The results we received are consistent with the results of E.V. Mokrenko and P.D. Shabanov, who simulated inflammatory-degenerative lesions of the soft tissues of the periodontium in rats and found a significant increase of PN (by 26%) and the index of phagocytosis' completion (by 22%) on the background of a decrease (by 31%) of the count of neutrophils involved in phagocytosis [16]. Along with this, the indices of the spontaneous NBT-test increased by 63%, and the activated – by 35%. At the same time data on phagocytosis by neutrophils from peripheral blood in individuals with periodontitis are controversial. There are data both of reduction [4] and increase of phagocytosis by neutrophils [17]. V. M. A. Carneiro et al. evaluated the phagocytic function of peripheral blood neutrophils in periodontal disease (30 subjects), in comparison with 27 control individuals without periodontal disease [6]. A significant reduction in phagocyte functions was observed in individuals with periodontitis. Other researchers, examining the indices of spontaneous NBT-test in patients with chronic generalized periodontitis, found that in all individuals they were significantly higher than in healthy controls, although they decreased with the increasing of the severity of the disease [1]. There are data that in case of moderate and severe generalized periodontitis, the number of neutrophils with incomplete phagocytosis in the oral fluid increases. In addition, the decrease of the absorption capacity of phagocytic polymorphonuclear leukocytes of blood and gums occurs on the background of high activation of cells to phagocytosis [22].

Chronic thiolactone HHcy adversely affects the functional and metabolic activity of peripheral blood neutrophils in case of LPS-induced periodontitis in rats, which is confirmed by a violation of the process of phagocytosis, a more pronounced decrease of absorption capacity and depletion of reserves of these cells. Influence of Hcys on neutrophils is less understood. In rat neutrophils, Bryushkova and co-authors [5], showed expression of N-methyl D-aspartate (NMDA) receptors and subsequent oxidative burst in response to Hcys. Researchers concluded that expression of NMDA receptors on neutrophil membrane makes neutrophils sensitive to Hcys. Thus, HHcy may induce additional stimulation of immune competent cells. Álvarez-Maqueda M. and co-authors [2] demonstrated that Hcys increased superoxide anion release by neutrophils to the extracellular medium, and that this effect was inhibited by superoxide dismutase and diphenyleneiodonium, an inhibitor of NADPH oxidase activity. They also showed that Hcys increased intracellular hydrogen peroxide production by neutrophils, that Hcys enhanced the activation and phosphorylation of mitogen-activated protein kinases (MAPKs), specifically p38-MAPK and extracellular signal-regulated kinase 1/2 (ERK1/2) cascade, and that the migration of neutrophils was increased by Hcys. Requirement of protein kinase B (a set of three serine/threonine-specific protein kinases - Akt) and Erk1/2 signaling in inducing neutrophil extracellular traps have been demonstrated by different researchers [7, 12], but Joshi MB and co-authors showed an induction of Erk1/2 and Akt phosphorylation in response to Hcys in neutrophils [14].

Conclusion. LPS-induced periodontitis in rats is accompanied by dysfunction of phagocytosis (increased phagocytic activity with a simultaneous decrease of absorption capacity) and activation of oxygen-dependent microbicidal mechanisms of peripheral blood neutrophils, as indicated by an increase of indices of spontaneous and activated NBT-test. Chronic thiolactone HHcy adversely affects the functional and metabolic activity of peripheral blood neutrophils in case of periodontitis, which is confirmed by a violation of the process of phagocytosis, a more pronounced decrease in absorption capacity and depletion of metabolic reserves of these cells in rats with comorbid course of LPS-induced periodontitis vs. animals with only LPS-induced periodontitis. The observed disorders in the process of phagocytosis in rats with comorbid course of periodontitis are an important factor in reducing the non-specific organism resistance which contributes to the progression of periodontitis. The obtained results reveal new aspects of the high Hcys plasma level influence on the course of inflammatory process in periodontal tissues, which opens opportunities for improving pathogenetic therapy in patients with periodontal disease combined with chronic HHcy.

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SUMMARY

THE INFLUENCE OF CHRONIC HYPERHOMOCYSTEINEMIA ON PHAGOCYTIC AND METABOLIC ACTIVITY OF PERIPHERAL BLOOD NEUTROPHILS IN CASE OF LIPOPOLYSACCHARIDE-INDUCED PERIODONTITIS

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The aim of the study was to investigate the phagocytic and metabolic activity of peripheral blood neutrophils in rats with lipopolysaccharide (LPS)-induced periodontitis combined with chronic thiolactone hyperhomocysteinemia (HHcy).

The experiment included non-linear mature male rats (n=48), which were divided into 4 groups: control; animals with a periodontitis model; animals with a model of chronic thiolactone HHcy; animals with a model of periodontitis in combination with chronic thiolactone HHcy. Phagocytic activity, phagocytic index and phagocytic number were determined as indicators of phagocytosis of peripheral blood neutrophils. The oxygen-dependent bactericidal activity of peripheral blood neutrophils was studied using nitroblue tetrazolium test (NBT-test).

Our research has found that LPS-induced periodontitis in rats is accompanied by dysfunction of phagocytosis process (increased phagocytic activity with a simultaneous decrease of absorption capacity) and activation of oxygen-dependent microbicidal mechanisms of peripheral blood neutrophils, as indicated by an increase of indices of spontaneous and activated NBT-test. Chronic thiolactone HHcy adversely affects the functional and metabolic activity of peripheral blood neutrophils in case of periodontitis, which is confirmed by a violation of the process of phagocytosis, a more pronounced decrease in absorption capacity and depletion of metabolic reserves of these cells in rats

with comorbid course of LPS-induced periodontitis vs. animals with only LPS-induced periodontitis. The observed disorders in the process of phagocytosis in rats with comorbid course of periodontitis are an important factor in reducing the non-specific organism resistance which contributes to the progression of periodontitis. The obtained results reveal new aspects of the high Hcys plasma level influence on the course of inflammatory process in periodontal tissues, which opens opportunities for improving pathogenetic therapy in patients with periodontal disease combined with chronic HHcy.

Keywords: periodontitis, hyperhomocysteinemia, phagocytosis, peripheral blood neutrophils.

РЕЗЮМЕ

ВЛИЯНИЕ ХРОНИЧЕСКОЙ ГИПЕРГОМОЦИСТЕИНЕМИИ НА ФАГОЦИТАРНУЮ И МЕТАБОЛИЧЕСКУЮ АКТИВНОСТЬ НЕЙТРОФИЛОВ КРОВИ В УСЛОВИЯХ ЛИПОПОЛИСАХАРИД-ИНДУЦИРОВАННОГО ПАРОДОНТИТА

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Целью исследования явилось определить фагоцитарную и метаболическую активность нейтрофилов периферической крови у крыс с липополисахарид-индуцированным пародонтитом в сочетании с хронической тиолактоновой гипергомоцистеинемией.

В эксперимент включены нелинейные половозрелые крысы-самцы (n=48), которые разделены на 4 группы: контроль; животные с моделью пародонтита; животные с моделью хронической тиолактоновой гипергомоцистеинемии (ГГЦ); животные с моделью пародонтита в сочетании с хронической тиолактоновой ГГЦ. Определяли фагоцитарную активность, фагоцитарный индекс и фагоцитарное число. Оксиген-зависимую бактерицидную активность нейтрофилов крови изучали с помощью теста с нитросиним тетразолием (НСТ-тест).

Проведенное исследование у крыс с липополисахарид (ЛПС)-индуцированным пародонтитом выявило нарушение процесса фагоцитоза (повышение фагоцитарной активности с одновременным снижением нейтрофилов поглощающей способности) и повышение оксиген-зависимой бактерицидной активности нейтрофилов крови, на что указывает увеличение показателей спонтанного и активированного НСТ-теста. Хроническая тиолактоновая ГГЦ негативно влияет на функциональную и метаболическую активность нейтрофилов крови, что подтверждается нарушением процесса фагоцитоза, более выраженным уменьшением поглощающей способности и истощением метаболических резервов этих клеток у крыс с коморбидным течением ЛПС-индуцированного пародонтита относительно животных с изолированным ЛПС-индуцированным пародонтитом. Наблюдаемые расстройства процесса фагоцитоза у крыс с коморбидным течением пародонтита являются значимым фактором снижения неспецифической резистентности организма, что способствует прогрессированию пародонтита. Полученные результаты раскрывают новые аспекты влияния высокого уровня гомоцистеина в плазме крови на течение воспалительного процесса в тканях пародонта, открывая возможности улучшения патогенетической терапии пациентов с пародонтитом в сочетании с хронической гипергомоцистеинемией.

რეზიუმე

ქრონიკული ჰიპერჰომოცისტეინემიის გავლენა ნეიტროფილების ფაგოციტურ და მეტაბოლურ აქტივობაზე, ლიპოპოლისაქარიდებით ინდუცირებული პაროდონტიტის დროს

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კვლევის მიზანს წარმოადგენდა ნეიტროფილების ფაგოციტური და მეტაბოლური აქტივობის განსაზღვრა ლიპოპოლისაქარიდებით ინდუცირებული პაროდონტიტით და ქრონიკული თიოლაქტონური ჰიპერჰომოცისტეინემიით დაავადებული ვირთაგვების პერიფერიულ სისხლში.

ექსპერიმენტი ჩატარდა კვლევის ოთხ ჯგუფად დაყოფილ მამრ ვირთაგვებზე (n=48): საკონტროლო ჯგუფი, ვირთაგვები ექსპერიმენტული პაროდონტიტის მოდელით, ვირთაგვები ექსპერიმენტული ჰიპერჰომოცისტენემიის მოდელით, ვირთაგვები პაროდონტიტთან შეუღლებული ქრონიკული თიოლაქტონური ჰიპერჰომოცისტეინემიის მოდელით.

განისაზღვრა ფაგოციტური აქტივობა, ფაგოციტური ინდექსი და ფაგოციტური რიცხვი. სისხლის ნეიტროფილების ჟანგბადდამოკიდებულ ბაქტერიციდული აქტივობა განისაზღვრა ნიტრო-ლურჯი ტეტრაზოლიუმის ტესტით.

ჩატარებული კვლევით ვირთაგვებში ლიპოპოლისაქარიდ-ინდუცირებული პაროდონტიტით გამოვლინდა ფაგოციტოზის პროცესის დარღვევა (ფაგოციტური აქტივობის ზრდა, ამავდროულად ნეიტროფილების შთანთქმითი უნარის დაქვეითებით) და სისხლის ნეიტროფილების ჟანგბადდამოკიდებულ ბაქტერიციდული აქტივობის ზრდა, რაზეც მიუთითებს სპონტანური და აქტივირებული ნიტრო-ლურჯი ტეტრაზოლიუმის ტესტის მაჩვენებლების მატება.

ქრონიკული თიოლაქტონური ჰიპერჰომოცისტეინემია უარყოფითად მოქმედებს სისხლის ნეიტროფილების ფუნქციურ და მეტაბოლურ აქტივობაზე, რაც დასტურდება ფაგოციტოზის პროცესის დარღვევით, შთანთქმითი უნარის დაქვეითებით და ამ უჯრედების მეტაბოლური რეზერვების ამოწურვით ვირთაგვებში ლიპოპოლისაქარიდ-ინდუცირებული პაროდონტიტის კომორბიდული მიმდინარეობით, იზოლირებულ ლიპოპოლისაქარიდ-ინდუცირებულ პაროდონტიტთან შედარებით.

ფაგოციტოზის პროცესის აღწერილი დარღვევები ვირთაგვებში პაროდონტიტის კომორბიდული მიმდინარეობით წარმოადგენს ორგანიზმის არასპეციფიკური რეზისტენტობის დაქვეითების მნიშვნელოვან ფაქტორს, რაც ხელს უწყობს პაროდონტიტის პროგრესირებას. მიღებულმა შედეგებმა აჩვენა სისხლის

პლაზმაში ჰომოცისტეინის მაღალი დონის გავლენის ახალი ასპექტები ანთებითი პროცესის მიმდინარეობაზე პაროდონტის ქსოვილებში, რაც უზრუნველყოფს პათოგენეზური თერაპიის გაუმჯობესებას პაციენტებში პაროდონტიტით ქრონიკულ ჰიპერჰომოცისტეინემიასთან კომბინაციაში.

EARLY POSTNATAL DYSFUNCTIONING OF THE BRAIN MUSCARINIC CHOLINERGIC SYSTEM AND THE DISORDERS OF FEAR-MOTIVATED LEARNING AND MEMORY

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The aim of the study was to investigate the early postnatal dysfunctioning of the brain muscarinic cholinergic system as a major factor in the development of cognitive disorders similar with somewhat is noted in animal models of depression and in patients with Major Depressive Disease (MDD). The problem is highly topical because MDD is one of the most common diseases in the world and is a serious cause of human death. The appropriate strategy for treating of MDD is not fully understood yet. This is complicated by the fact that MDD is a complex, multidimensional, heterogeneous disease accompanied by a range of changes, including cognitive impairment, depressed mood, anhedonia, decreased appetite and libido and so on [12,13].

Therefore, it is very topical and important to search for new research approaches to elucidate the pathophysiology of MDD, for which we consider it necessary to thoroughly study the pathophysiological mechanisms of individual symptoms of MDD on adequate, valid, animal models of this disease. Such studies are of great importance in terms of both basic science and clinical medicine.

Such a minding of scientific thinking is very important since it is considered that the above-listed range of symptoms, accompanying MDD, should develop with the participation of various factors, particular specific symptoms may be served by dysfunctions of different neurotransmitters.

In the present study, special attention has been paid to the muscarinic cholinergic system of the brain, as this system is involved in the learning and memory mechanisms. In the central nervous system, acetylcholine promotes many functions such as learning, memory, attention, and motor control [7,14,16]. Muscarinic acetylcholine receptors (MAChRs) have recently been shown repeatedly to play a role in learning and memory [1,3,5]. Therefore, there is a suggestion and we also share this view that dysfunction of the cholinergic system may contribute to the development of cognitive disorders during MDD [2,8].

We hypothesize that for the investigation of the role of dysfunctioning the brain muscarinic cholinergic system as the main factor of cognitive impairment, accompanying various psychoneurological disorders, it is necessary to conduct experiments on animal models where the dysfunctioning of the brain muscarinic cholinergic system will be achieved without any specific (electrolytic, cytotoxic and so on) damaging of nervous cells by exogenous factors. Such a way is a completely new methodological approach, worked out by Nachkebia et.al. [11], which was also used in our study. The method involves dysfunctioning of the brain muscarinic cholinergic system during the early postnatal development (P7-P28) of rat pups and investigation of the long-term effects of this procedure after achieving the adult ages them. In general, the use of such a methodical approach allows obtaining a relatively pure effect of dysfunctioning of the brain muscarinic cholinergic system on the learning and memory in various separate tasks of declarative and non-declarative learning and memory. Studies conducted on such animal models are very important in terms of extrapolation to humans.

The present study examines the processes of learning and long-term retention of information obtained in the two important tasks of non-declarative memory - active avoidance, motivated by foot shock-induced fear, and the elevated plus-maze, based on the natural fear. We thought that the results obtained will answer the important question of whether the tasks of learning and memory motivated by the natural and/or procedural fear, are disturbed in animals that have been subjected, during early postnatal development, to the dysfunctioning of muscarinic cholinergic system.

The urgency of the issue is very high, as the lasting effects of early postnatal dysfunctioning of the brain muscarinic cholinergic system on learning and memory of the non-declarative fear-motivated tasks have been studied by us for the first time.

Material and methods. Experiments were carried out on male white wild rats (n=40). Four groups of animals were used with special procedures for each one.

Experimental group I - rat pups (n=15) received subcutaneously Scopolamine (Scop. n=10) 30 mg/kg two times daily during from postnatal day 7 (P7) to P28; Afterwards they were maintained in home cages under special care. After adult age (2.5-3 month) 5 rats were included in the experiments aimed to investigate the changes of learning and memory in the two-way active avoidance test. The second 5 rats received systemic injection of Scop (15 mg/kg) and 30 min after were included in the experiments aimed to investigate the changes of learning and memory in the two-way active avoidance test. The third 5 rats received systemic injection of Melipramin [(Mel) 15 mg/kg] and 30 min after were included in the experiments aimed to investigate the changes of learning and memory in the two-way active avoidance test.