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DC–IMMUNOTHERAPY IN COMPLEX TREATMENT OF EARLY HIGH AGGRESSIV BREAST CANCER

Abstract: A method of anti-relapse autoimmunotherapy with antigen-specific dendritic cells was developed for patients with a primary highly aggressive Breast Cancer (BC). It is established that the proliferation of antigen-specific CD3 + T-cell lymphocytes with intracellular cytokine production evaluates the immunological efficacy of the treatment. The 5-year recurrence-free survival of patients with early aggressive cancer in clinical trials of the Method was approaching the overall 5-year survival of patients with early BC by Cancer – Registry, that indicates the effectiveness of the method in the complex treatment.

Keywords: dendritic cells, early biologically agressive Breast Cancer, specific immune response, duration of a non-recurring period.

Breast cancer (BC) is the most common malignant neoplasm in women in industrialized countries. The development of numerous projects for the early detection and systemic treatment of BC is explained by the steady increase in the number of cases in all countries, an average of 1, 2% per year [1].

The wide screening of BC and subsequent systemic therapy helped to identify early forms of malignant process, increase the duration and improve the quality of life of patients. According to the Belarusian Cancer Registry-2017 [2] 73,4% of newly diagnosed cases of BC belong to the I–II clinical stage of the disease, with a 5-year general survival rate of 88,2%. But the optimization of treatment of such patients is a widely discussed problem, as numerous international studies have established that 6–30% of such patients after the completion of primary treatment for a radical program, clinically undiagnosed micrometastases promote the progression of the malignant process [3].

The different disease-free survival rates of patients after systemic treatment of the same stage BC attracted the attention of clinicians to the study of the molecular biological characteristics of malignant cells, which contributed to the new approaches to diagnosis and treatment of tumors [4].

A long-term prospective study conducted in the Department of Clinical Mammology Belorussian Cancer Center of N. N. Alexandrov (1999–2008) revealed a close relationship between disease-free survival (n = 164) after primary comprehensive therapy for early breast cancer T1–2N0–1 G2 and presence of biological aggressiveness of tumors ($P_{log\text{-}rank}$ < 0,0001 – 0,0006). The biological aggressiveness of tumors was determined by the imbalance of the proliferative-apoptotic potential of malignant cells, characterized by high expression of growth factors against the background of a pronounced blockade of apoptosis. Highly aggressive tumors were recorded in 10% of patients with stage I and in 35% of patients with stage II breast cancer, which implies the introduction of additional adjuvant therapy in this category of patients [5]. The performed study allowed to determine the most vulnerable time intervals of primary disease progression after complex treatment of patients with breast cancer (BC) of early clinical stages. It was established that even at the average degree of histological malignancy of the removed tumors (stratification by criterion G_2) more than 40% of the first cases of disease progression after primary radical treatment (over 10 years of observation) were determined during the 2–3 years of the postoperative period [6].

New treatment standards introduced since 2004 have reduced the percentage of early disease returns. But the trend of disease returns towards the third year after systemic treatment is traced in the analysis of the recurrence-free survival in the population group of patients (in the country) treated for BC T1–2N0–1 (with tumors of varying degrees of malignancy G) – 75.4 ± 1.5% for the third year of the postoperative period [7].

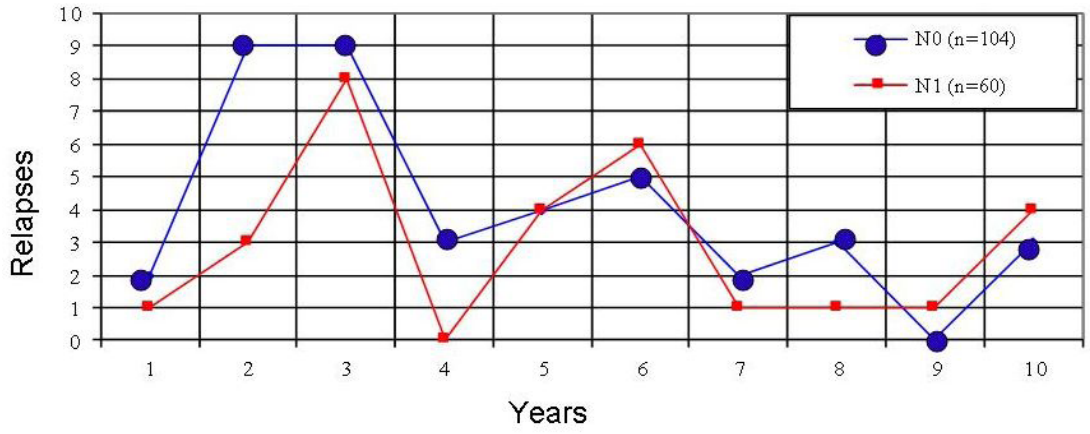

Figure 1. The first cases of tumor progressi after primary radical treatment of breast cancer $T_{1-2}N_{0-1}G_2$

The modern stage of increasing the effectiveness of complex antitumor therapy is largely associated with discoveries in the field of molecular biology and oncoimmunology, the development of innovative technologies in the diagnosis of malignant process and the treatment of cancer patients. Identification of antigenic differences in malignantly transformed and normal cells is used for the recognition and directed destruction of tumor cells.

The real ways of inducing an immune effect on a particular tumor are determined, one of which is Dendritic-Cellular Immunotherapy (DC–IT), aimed directly at the tumor cells antigens. This treatment involves the creation in the body of a significant population of specific cytotoxic lymphocytes (CTL) against antigens of malignant cells. But the specific activation of CTL occurs only when antigens are presented to lymphocytes on the surface of antigen-presenting cells (APCs) in association with HLA molecules, costimulatory and adhesive molecular structures. This event is the determining factor in the directed activation of T cells and the formation of an effective immune response, including the antitumor effect. Dendritic-Cells are the most strong CTL activators [8; 9].

New biotechnological methods represent the possibility of obtaining human DC in vitro in sufficiently large amounts from the monocyte-macrophage fraction of the blood to conduct directed antigen-specific autoimmunotherapy. The primers of DC can be any antigens highly expressed in tumor cells against which vaccination is performed. The key point of directed immunotherapy is the identity of antigens – DC primers – with antigenic determinants of malignant cells.

The principle of antitumor immunotherapy with DC-autovaccines is the cultivation of DC in vitro from autologous monocyte precursors, their priming (under laboratory conditions) with antigens identical to the patient's tumor antigens, and subsequent reinjection to the patient in the mode of vaccine therapy.

The purpose of this study was to determine the efficacy and safety of using autologous Dendritic Cells primed with tumor-associated antigens for anti-relapse immunotherapy of Early High Aggressive Breast Cancer.

Materials and methods: The study includes 2 section:

1) a series of in vitro experiments with blood samples of aggressive breast cancer patients to study the effect of mature unprimed and primed DC on the proliferation of autologous cytotoxic T lymphocytes and the production of intracellular cytokines IL-2, INF-γ and TNF (determined by monoclonal antibodies "Becton Dickinson", "Beckman-Coulter", "Sigma", on the cytofluorimeter "FACSCalibur" – USA), characterizing the development of antigen-specific effect. DC cultures for active specific autoimmunotherapy were obtained by original technology (Patent BY12361, LP Titov, AE Goncharov) from the monocyte-macrophage fraction of peripheral blood of patients. Control was carried out on the number of DC, their viability, morphology, immunophenotype, microbiological purity. Primers of the DC were short-chain peptides (synthesized in the Research Institute of Highly Pure Biological Preparations, St. Petersburg), similar to the loci most susceptible to mutations in the DNA-binding domain of the suppressor protein p 53 (LLGRNSFEV, KLCPVQLWV, YLGSYGFRL, GLAPPQHLIRV), which was vosoko expressed by cells of distant malignant tumors.

To monitor the efficacy and safety of dendritic therapy, the immune status and patients were monitored after the initial complex antitumor therapy of BC before the initiation of immunotherapy with primed DC, during and after immunotherapy. The total number of leukocytes, monocytes; immunophenotype of peripheral blood lymphocytes (CD3, CD19, CD27, CD4, CD8, CD25, CD69, HLA-DR, CD28, CD16, CD56, TCR-αβ, TCR-γδ, CD95); Intracellular cytokines of peripheral blood lymphocytes (INF-γ, TNF, IL-17) after 6 hours of

stimulation with FMA, ionomycin and antigenic complex; antigen-specific T-lymphocytes were detected.

2) Clinical trials of anti-relapse DC-autoimmunotherapy approved by the Commission under the Ministry of Health of the RB are conducted in 22 patients aged 27 to 58 years after the initial complex treatment for aggressive BC II stage. The selection of patients for anti-relapse autoimmunotherapy was performed among 127 patients in accordance with the results of molecular-biological typing of tumors removed from them. According to the study protocol, tumors should be characterized by high expression of the mutant p53 protein chosen as an antigen target for DC vaccine therapy, overexpression of the Ki-67 proliferation marker, expression of the major histocompatibility complex molecules HLA-A2. DC-immunotherapy was carried out on an individual schedule and consisted of 5 courses of vaccinations (3 and 2 courses) with a three-month break. For each participant in the clinical trials, an individual temporary treatment plan has been developed that is consistent with the collection of blood and the manufacture of an antitumor vaccine. It was considered that possible cases of tumor progression after radical treatment may occur in 2–3 years of the postoperative period. Taking into account this fact and the duration of development of immunological effect, the most acceptable time to initiate anti-relapse DC-immunotherapy was 4 months after the end of 1 systemic treatment.

Results. DC in all the examined samples on the 7th day of cultivation were morphologically homogeneous, characterized by stellate cellular forms with the presence of cytoplasmic processes typical for DC (Figure 2).

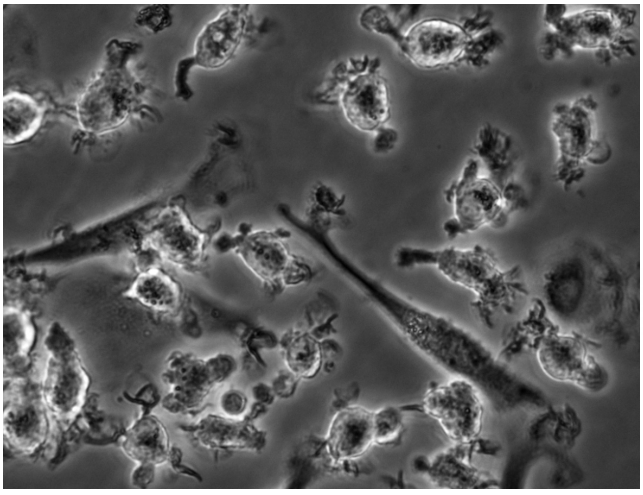

Figure 2. Micrograph of primary cultures

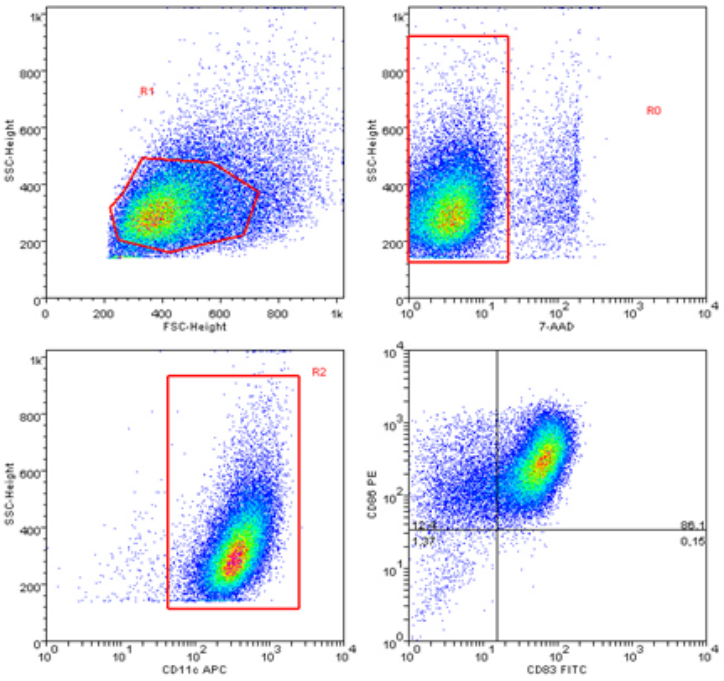

Figure 3. Immunophenotype of DC cultivation, increase of 400

In the culture of MDC, as a rule, there are single lymphocytes (small rounded cells), fibrocytes (oblong spindle-shaped cells) that make up no more than 25% of the number of DCs.

In order to control the immunophenotype of MDC from patients with breast cancer, the expression of the following molecules was studied: the total myeloid marker – the molecule of the integrins family – CD11c, involved in intercellular adhesion;

a highly specific marker of mature DC – CD83 molecule; Costimulatory molecule of CD86. All cultures of DC were characterized by a high density of expression of the studied molecules CD11c, CD86 and CD83, which is confirmed by high rates of their fluorescence intensity (Fig. 3).

The DC culture was considered to have passed immunophenotypic control in the presence of a relative number of DCs expressing the CD11c molecule – more than 90%, CD86 – more than 90% and CD83 – more than 50%. To each culture DC attached analytical passport. In the process of immunotherapy, there was no significant change in the quantitative indices of T-lymphocyte subpopulations, although there is a tendency to decrease the T-lymphocyte count by decreasing the fraction of CD3 + TCRαβ + cells ($p < 0.1$). The ratio of CD4 / CD8 cells, which makes it possible to characterize the state of cellular immunity, did not change during the immunotherapy (before immunotherapy – 1.4 (1.0–1.7), after therapy – 1.4 (1.0–1.7), P = 0.897 The B-lymphocyte content increased after immunotherapy ($p = 0.0003$). A significant general group decrease in the content of T-regulatory cells was revealed after immunotherapy (up to – 4.71 (2.91––6.68)%, after – 2.51 (1.89–3.37)%, $p = 0.0004$), which indicates the lack of development of immunological tolerance.

T-regulatory cells (T-reg.) having the phenotype CD4 + CD25highCD127- / lowFoxP3 + are the main cells of the immunity system with immunosuppressive activity. In the course of the studies, the median values of T-regulatory cells were 0.062 (0.04–0.087) × 106 / ml before immunotherapy and 0.047 (0.037–0.059) × 106 / ml ($p = 0.03$) after DC–IT [10].

To determine the dynamics of the formation of a specific immune response to DC therapy, a determination by flow cytometry of INF-γ-producing CD3 + T cells (antigen-specific cells – ASC) was used after co-cultivation with a complex antigen. The number of ASCs was 0.22 (0.06–0.47)% at the beginning of treatment and 1.11 (0.66–1.58)% after the course of immunotherapy ($p = 0.0001$, Fig. 4).

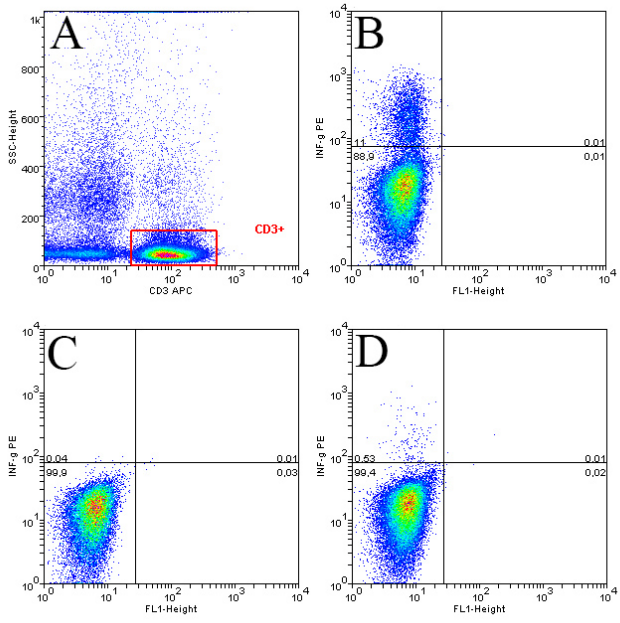

Figure 4. Analysis of antigen-specific CD3 + INF-γ

A – a cytogram in the coordinates of CD3 / SSC, shows the region of CD3 + cells; B – cytogram in FL1 /FL2 coordinates, expression of INF-γ under the action of FMA (positive control); C – T cells

spontaneously producing INF-γ (negative control); D – T cells producing INF-γ in response to stimulation with peptides of mutant p 53.

The increase in ASC during immunotherapy was revealed in 80% of cases [11].

The average number of DCs administered to patients as a single injection was $5.3 \pm 3.1 \times 10^6$. The median amount of DC administered to patients for the entire course of immunotherapy was $27.0\ (21.7–32.3) \times 10^6$. The amount of DC varied, which is due to different levels of monocytes in the blood of patients.

The assessment of tolerability and safety of the applied immunotherapy was carried out based on the examination of patients and the study of laboratory indicators before the start of therapy, during and after it. A thorough control of the parameters of a general analysis of blood, urine and a biochemical blood test was performed to exclude hepato-, nephro- and hematotoxic effects of autovaccine.

After immunotherapy, 8 out of 22 patients (36.4%) noted low and medium intensity skin itching at the site of DC injection, in 5 patients – mild weakness in the healthy mammary gland a day after the injection, which did not require medical care.

Monitoring of clinical and laboratory status of patients testified to the absence of negative effects of multi-stage DC-immunotherapy. There was no need for additional drug therapy and changing the schedule of vaccinations, which confirms the safety of treatment.

Thus, the analysis of clinical observations of patients in conjunction with the results of a dynamic laboratory examination showed satisfactory tolerability and safety of using autologous monocyte DC in patients during the initial complex treatment of aggressive BC early clinical stages.

Analyzing the duration of disease-free postoperative period in patients included in the clinical trials of the developed method, it is taken into account that this group is stratified by the criterion of high biological aggressiveness of cells of distant tumors, as well as the T_2 criterion (tumor size 2.0–5.0 cm), which prognostically has a higher risk of disease progression compared with the retrospective control group with an average degree of histological malignancy ($BC\ T_2\ N0_{-1}\ G_2$).

The duration of the disease free period was monitored for 60 months after initial systemic treatment with the additional application of DC–IT. In this period, two patients recorded a return of the disease 39 and 44 months after the initial treatment, and one patient was diagnosed with BC in the second breast after 41 months after the initial treatment. Analysis of the immunograms in two patients did not detect an increase in ASC, indicating that there was no immune response to DC–IM. This fact indicates that the absence of an immune response in patients after DC–IT (the absence of proliferation of ASC with intracellular cytokine production) can predict the futility of immunotherapy.

At the same time, a comparative analysis of the duration of the disease-free period in the study and control groups showed the effectiveness of the method used [12].

The results indicate a clear trend of prolongation of the disease-free period and, thus, an increase in the overall 3-year and 5-year disease-free survival of patients with active specific DC–IT (3-year disease-free survival in the group with DC–IT – 0.954 +0.003%, in the retrospective group – 0.789 + 0.019%. 5-year disease -free survival (0.840 + 0.021%) in the group with DC–IT [13; 14].

Conclusion. The study allowed to specify the details of the developed method of active antigen-specific DC-autoimmunotherapy for use in clinical practice.

The method is considered as an additional element of an anti-relapse strategy that enhances a specific antitumor immune response in the treatment of patients with biologically aggressive early BC. DC–IT extends the disease-free period in patients at high risk of disease progression.

References:

1. WHO Information Bulletin No. 297 // www.who.int/mediacentre/factsheets/fs297/en/index.html – Date of access: 19.11.2012.
2. Statistics of oncological diseases in the Republic of Belarus (2011–2017): Malignant neoplasms of the breast // Minsk.– 2017.– 67 p.
3. Meeting Highligts: International Expert Consensus on the Rrimery Therapy of Early Breast Cancer – 2005 // Oxford. Univ.Press.– Annals of Oncology.– 2005.– No. 16.– P. 1569–83.
4. Progress and Promise: Highlights of the International Expert Consensus on the Primary Therapy of Early Breast Cancer 2007 // Oxford Univ. Press.– Annals of Oncology.– 2007.– No. 18 (7).– P. 1133–1144.
5. Koshelev S. V. Phenotyping of primary breast cancer for planning of individual schemes of antitumor therapy // Achievements of fundamental sciences in solving urgent problems of medicine.-Astrakhan-Volgograd-Moscow,– 2006.– P. 56–58.
6. Koshelev S. V., Shitikov B. D., Dubrovsky A. C. Clinical significance of testing primary breast cancer by predictive molecular-biological markers // Actual problems of oncology and medradiology.– 2006.– P. 115–123.
7. Shapoval E. V., Prudyvus I. S. Analysis of the survival of patients with breast cancer $T_{1-2}N_{0-1}M_{O}$ in the Republic of Belarus in 2003–2005 // Med. Panorama.– 2010.– No. 4.– P. 79–81.
8. Brossart P. Induction of cytotoxic T-lymphocyte responses in vivo after vaccinations with peptide-pulsed dendritic cells // Blood.– 2000.– V. 96.– P. 3102–3108.
9. Vergati M., Intrivici C., Huen N. Y. et al. Strategies for Cancer Vaccine Development // J. of Biomedicine and Biotechnology.– 2010.– No. 3.– P. 1–13.
10. Goncharov A. E., Koshelev S. V., Romanova I. V., Kvakuho V. A., Titov L. P., Putyrsky L. A. Analysis of the content of antigen-specific lymphocytes and T-regulatory cells in patients with breast cancer in the process of autoimmunotherapy with dendritic cells // Vesti NAN Belarus.– 2012.– No. 1.– P. 276–281.
11. Instruction for Use on "Method for the Evaluation of a Specific Immune Response to Autoimmunotherapy by Dendritic Cells of Patients with Breast Cancer" authors: Goncharov A. E., Titov L. P., Koshelev S. V., Shapoval E. V.: Ministry of Health of Belarus.– 2012.– reg. P. 114–1111.
12. Instruction for Use on "The Method of Anti-relapse Autoimmunotherapy with the Use of Antigen-specific Dendritic Cells in Early Aggressive Breast Cancer" authors: Goncharov A. E., Titov L. P., Koshelev S. V., Shapoval E. V. // Ministry of Health of Belarus.– 2012.– reg. P. 114–1112.
13. Koshelev S. V., Goncharov A. E., Titov L. P., Shapoval E. V., Dubrovsky A. C. Primed Dendritic Cells in the Systemic Treatment of Early Aggressive Breast Cancer // XVII Int.Conf.-Oncology – XXI Century.– Elche(Spain),– 2013.– P. 163–168.
14. Koshelev S. V., Goncharov A. E., Titov L. P., Shapoval E. V., Kolobov A. S. Evaluation of the Effectiveness of Dendritic-Cell Autoimmunotherapy of Early Aggressive Breast Cancer// XVIII Int. Conf.– Oncology-XXI. -Brussels (Belgium),– 2014.– P. 128–133.

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DEVELOPMENT AND EXPERIENCE OF APPLICATION OF THE MAP OF SUBJECTIVE AND OBJECTIVE RESEARCH IN THE DIAGNOSTICS AND AT THE STAGES OF ORTHOPEDIC REHABILITATION OF PATIENTS WITH CRANIOMANDIBULAR DYSFUNCTION (functional disorders of the musculoskeletal system)

Abstract: In this article is investigated a systemization and visualization of complaints and symptoms characteristic of the patients with craniomandibular dysfunction with the aim of making the initial diagnosis, planning additional examination methods and orthopedic treatment of patients with functional disorders of the dentofacial structure.

Keywords: prosthetics, functional disorders, occlusion, occlusion tooth contacts, bruxism, dysfunctional disorder of the masticatory apparatus, deviation or deflection of the mandibular, TMJ area.

Scientific innovation: according to the data provided by domestic and foreign authors, dysfunctional disorders of the dentofacial structure are one the most widely spread illnesses among the patients who come to visit a dentist, and occurs in 31–85% of all patients. According to the European Headache Federation, 80% of the population suffers from occasional tension-type headaches, which occur in the state of general muscle tension, particularly under stress. One of the signs of tension is unconscious teeth clenching, which may lead to pathological teeth clenching, which in turn may provoke the development of bruxism and dysfunctional disorders of the dentofacial structure.

Introduction. Lately, dentistry has been paying more and more attention to the ways the dentofacial structure disorders reflect on the general condition of the patient, his postural status in order to carry out differential diagnostics based on the complaints of the patient with such illnesses as dysfunctions of the muscular-skeletal system, the blood vessels of the brain, the increase or decrease of the intracranial pressure, hypertension, primary headache etc. This group of patients requires an additional consultation and treatment of a neurologist, a vertebrologist, an ENT specialist, a medical psychologist. Quite often patients do not pay attention to certain symptoms and interpret them without relating them to the state of chewing. The majority of them do not suspect that they have some functional or morphological problems, which mask the true clinical picture due to the adaptive properties of a body. Because of this a dentist must analyze the general condition, correlating it with the existing dental issues. Diagnosis of hidden pathologies and in-

forming the patient about them is a primary necessity of the initial dental check up. Because of this, there occurred a need to create a medical card of subjective and objective check up of patients with craniomandibular dysfunction (functional disorders of the dentofacial structure) as the general medical card of a dental patient does not meet all the requirements for reflecting the state of the patient as well as the necessity to prescribe additional check-ups. There are tests for evaluating the presence of dysfunctional disorders, e.g. *the Hamburg Test* (KROGH-POULSENS); according to Ahlers M. O., Jakstat H. A., 2000, the algorithm of this test consists of 6 questions, the positive answer to which may signify a presence of a dysfunction. Using this test, we do not have the possibility to document the complaints, evaluate the clinical pattern in general. There is also a clinical index of dysfunctional disorders of Helkimo (1974) with the help of which a number of received points may be analyzed, but using this method only allows us to evaluate the severity of the dysfunction.

In our opinion, the most informative method in initial diagnosing is questionnaire survey of the complaints and symptoms of a patient. Of the existing content-based questionnaires which reflect the state of a dental patient Gadzhy Dazhaev's 2014–2015 may be singled out. It consists of the dental history, general medical history and the check-up of the patient. Using this questionnaire allows us to gather the maximum amount of medical information from the patient as well as eliminates the necessity to fill in basic medical documentation and additional data for related branches of dentistry. CID\Prof. R. Slavicek's questionnaire of initial diagnosis should be singled out as the most informative one as it allows the evaluation of the general state of the patient and to determine dysfunctional disorders of the condilomuscular complex as well as to evaluate it with the help of the occlusal index and to visualize the chronic toothache and the state of teeth.

We can undoubtedly presuppose that there exists an ideal questioning algorithm for the evaluation of the state of a dental patient with the symptoms of dysfunctional disorders of the dentofacial structure. However, the necessity to not only gather the medical information but also to carry this information to the patient using the terminology that he/she would understand and be able to visually evaluate his/her condition made us develop this questionnaire.

Systemization of the subjective and objective data that signifies the presence of dysfunctional disorders of the masticatory system are the basis of the suggested study. The term craniomandibular dysfunction (CMD) regards the interrelation of the mandible and the scull base, which may be characteristic of patients with functional disorders as well as of healthy patients and those with the asymptomatic TMJ. While filling in the card of a craniomandibular patient, the possibility of visualization of subjective and objective data in the medical card of the patient is taken into account as the graphic demonstrations considerably simplifies the perception of the clinic condition both by the doctor and by the patient. This is important at the stages of diagnosing and orthopedic rehabilitation of the patients with the dysfunctional disorder of the masticatory apparatus. The process itself is influenced by many factors which are crucial for the result of the treatment. Such factors include the psychoemotional state, domestic problems of the patient, other people or circumstances that influence the treatment process, e.g. the tendency of patients to forget the symptoms they had. Thus, documentation of complaints, symptoms and clinical stages of treatment considerably simplifies the dialogue with the patient, as well as the process of medical history taking and allows the doctor to understand the pathologies of the muscular system as well as structural disorders of the TMJ better.

The medical card for the patients with functional disorders of the dentofacial structure consists of two main parts, the subjective and the objective one, and is filled in during the initial consultation as well as at every visit in the course of the treatment process.

The first part (subjective) consists of two tables with questions and a graphic picture. The first table contains the criteria that are based on the complaints and symptoms of dysfunctional disorders. They refer to pain localization, its irradiation, facial numbness, clicking in the TMJ area and complaints regarding earache. The table is systemized in such a way that it minimizes the time spent on collecting the subjective and objective data as the key complaints may be ticked and their intensity evaluated on the 1 to 5 scale.

One of the most important features of the first table are 3 elements:

1) With the graphic image of localization of pain from 4 parts of body and head (Figure 1);

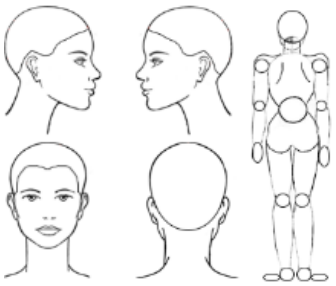


Figure 1.

2) With the graphic image of pain irradiation from the area of TMJ, from right and left part of the body (Figure 2);

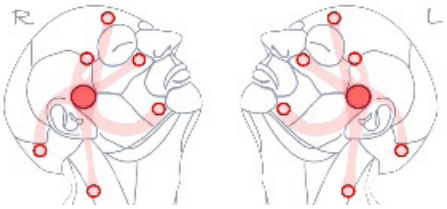


Figure 2.

3) With the graphic image of zones of numbness of face (Figure 3).

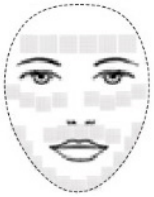


Figure 3.

In the second table you can see 12 questions, that can help you to define reason of origin of complaints, state of a patient and motivation in further treatment are collected:

1) Did you feel a tiredness in the muscles of face, in especially the evening or after the protracted conversation or reception of meal?

– This question concerns the increase of fatigue of mussels with hyperfunction.

2) Did you feel lower jaw stiffness in the morning, after a dream?

– The essence of question consists in presence of reductions of muscels that results in hypertone during within sleeping that testifies the presence of night form of bruxism.

3) Did you notice that, while closing teeth, you try to find a comfort position of your teeth?

– Positive answer can testify the presence of premature contacts, force position of lower jaw.

4) Did you or your nearest ones notice night teeth grinding?

– Positive answer testifies bruxism.

5) Did you or your nearest ones notice snoring?

– Presence of snoring or sleep apnea gives an opportunity to admit the dislocation asphyxia as the consequence of hypertrophy, hypertone of masticatory mussels or distal position of lower jaw.

6) Do you feel the clench of teeth in the state of calmness?

– Positive answer testifies the presence of daily form of bruxism.

7) Have you ever had tracheal intubation?

– During the placement of endotracheal tube, lots of anesthesiologist try to open widely the mouth of the patient and as the result we can have the stretching of articular jaw, injuries of the ligaments and lateral pterygoid muscle and also dislocation of TMJ.

8) Have you ever extracted "wisdom teeth"? If so, when?

– This question is about the paratherapeutic injuring of area TMJ.

9) Have you ever had orthodontic treatment? When?

– In this question it is important to understand the role of change of occlusion on disfunction abnormalities.

10) Have you ever had the feeling "lump in a throat", or complications in pronunciation?

– Positive answer can testify the presence of hypertone and hypertrophy of muscels.

11) Do you consider your state as serious?

– This question shows patient's interest in further treatment.

12) How often are you in the state of stress?

– It is important to understand that stress provokes the spasm of muscles and it may influence on the process of treatment.

13) How do you see your emotional state?

– This question it is necessary to offer the next possible answers:

1. Anxiety is a normal reaction on a stress factor, but testifies its permanent presence (possible destructive influence on treatment);

2. Fear appears as the result of stress, that can lead to thoughtless decisions (causes destructive influence on treatment);

3. Anger is the directed aggression against someone (causes destructive influence on treatment);

4. Irritation as discrepancy of desirable above the reality, it is necessary to see the threat of discrepancy of imagination of patient to the process or result of treatment (causes destructive influence on treatment);

5. Calmness – ability of patient to get along with the stress even in the armchair of dentist (productive influence on treatment).

The answers on this question are necessary to examine previously in a context, because negative answer foresees the disparity of absence of stress with the presence of abovementioned emotions: anxiety, fear, anger or irritation.

14) Do you need treatment?

– final question that gives an opportunity to estimate patient's perception of the treatment and raise the level of motivation in the future treatment.

NB! You have to follow the abovementioned sequence of questions and their formulation after for expectation of objective answer by a patient.

An obligatory requirement is to observe the order of the questions and their phrasing in order to receive an objective answer from the patient.

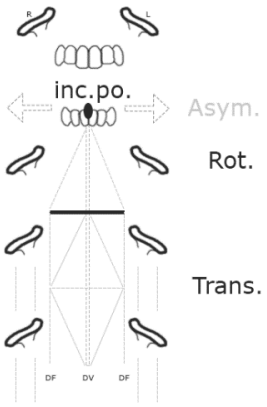


Figure 4.

The second part (objective) contains a table for collecting the objective data, such a palpation of the masticatory muscles as well as the head and neck muscles, palpation of the TMJ in the position of central occlusion and while moving the mandibular, auscultation of the TMJ area, distance between the cutting edges of the maxilla and the mandibular in the position of maximum mouth opening. Moreover, the second part includes a picture of head and neck from the left and right sides (pic. 4) to enable the visualization of hypertension, hypertrophy, muscle segmentation, trigger pain points. The given image allows us to document the localization of trigger muscle points, to determine muscle segmentation. Attention should be drawn to the graphic scheme, which determines the visualization and documentation of mandibular movements while opening and closing the mouth, as it allows us to document either the deviation or deflection of the mandibular, excursion of articular heads of the mandibular while opening and closing the mouth at

the rotation or translation stage. At the beginning of filling in the scheme, the symmetry of the lower third part of the face (pic.5) is visually evaluated, in case of asymmetry the arrow which corresponds to the direction of dislocation of the mandibular is coloured. It will then be necessary to mark the movement of the crossbite from the position of central occlusion to the position of maximum mouth opening (at the stage of mouth opening) either visually or with the help of a clinical clinometer. After that, using palpation, the symmetry of articular heads excursion while opening and closing the mouth is evaluated and either the sequence or the symmetry of the right and the left sides is documented in this very scheme. All the notes in this scheme are taken in the form of arrows the direction of which corresponds to the direction of the shift of either the crossbite or of the articular heads.

Figure 5.

Moreover, the second part contains the card of functional tooth contacts (Figure 6), which consists of five schematic images of the upper and the lower dentitions, each of the five schemes ensures the possibility to determine the existence of contacts in various conditions, monitoring of the contacts is carried out with the help of carbon paper (30 micron), wax occlusiogram: pict.

The centric relation tooth contacts (using the method of muscle deprogrammers (Pankey, Amann, Girrbach), the multi-sheet template etc.), bilateral manipulation (Peter E. Dawson) or the myostimulation apparatus (TENS);

Centric occlusion tooth contacts (centric relation or maximum intercuspidation);

Presence of occlusion blocks and hyper balancing supracontacts during the left-sided mediotrusive movement on the laterotrusive side;

Presence of occlusion blocks and hyper balancing supracontacts during the right-sided mediotrusive movement on the laterotrusive side;

Presence of occlusion blocks and hyper balancing supracontacts during the forward movement (protrusion).

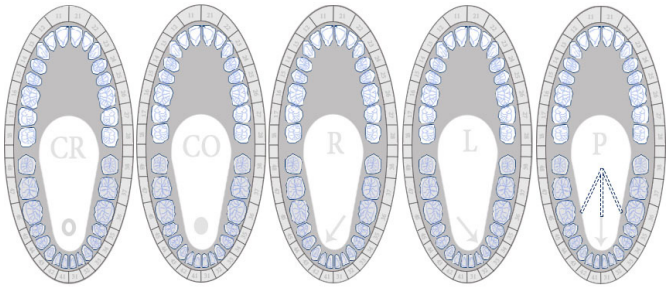


Figure 6.

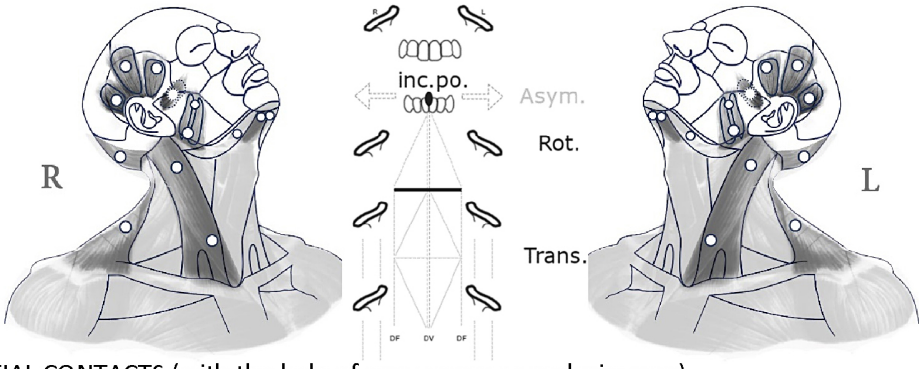
Conclusion: The process of occlusion diagnostics in the articulator and the evaluation of the overall clinical state of the patient are simplified due to documentation of complaints, subjective and objective symptoms, their graphic visualization as well as the analysis of the gathered data, which in turn allows the doctor to give a more accurate initial diagnosis. Using the medical card of a craniomandibular patient allows us to better see and evaluate the clinical picture of the patient; the documentation makes it possible to go back to the discussion of the clinical picture of the patient at any time as well as to compare the current and the initial state of the patient. Visualization considerably simplifies the perception of the clinical picture both for the patient and for the doctor, thus making the treatment process itself also easier. Having all these data available, the doctor can see the necessity of prescribing additional tests and check-ups in order to make the final diagnosis.

№				Main part 1 Palpation of the head	Right Tp* | Sg*	Left Tp* | Sg*
1	Muscles			M.temporalis ant.		
2				M.temporalis med.		
3				M.temporalis post.		
4				M.masseter		
5				M.masseter		
6				M.pterygoideus lateralis		
7				M.pterygoideus lateralis		
8				M.mylohyoideus		
9				M.digastricus		
10				M.sterno-cleido-mastoideus		
11				M.trapezius		
12				M.occipitalis		
13	TMJ	CO		PAIN		
14				Forward position of mandibular head		
15				Back position of mandibular head		
16		Excursion		PAIN		
17				Lig. temporomandibulare		
18				Deflexion		
19				Deviation		
20		Crunch		Rotation		
21				Translation		
22				Right turning		
23				Left turning		
24		Crepitation				
25	Teeth imprints on the tongue					

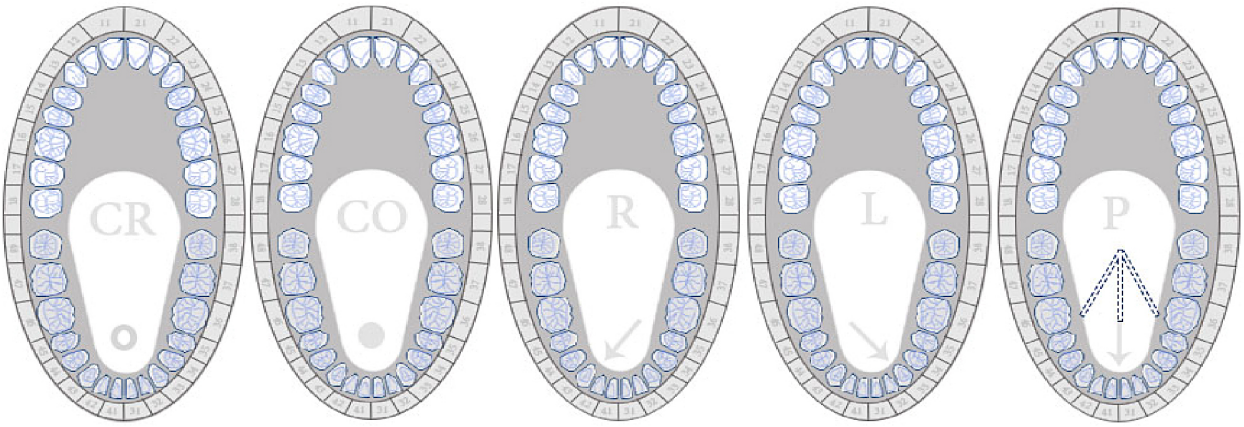
* Tp - trigger point; Sg – segmentation; Gt – hypertonus; Gtr – hypertrophy.

Objective part 2

Mouth opening width
MM.



FUNCTIAL CONTACTS (with the help of copy paper or occlusiogram)

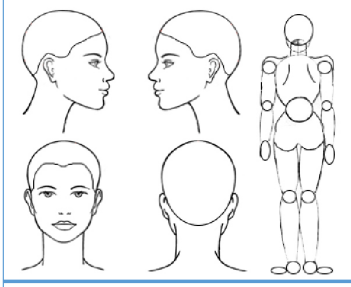


① **NAME, SURNAME** **AGE** **DATE**

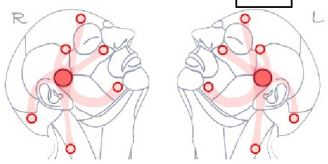
Diagnostic card of craniomandibular patient

№		MAIN PART ❶ Describe the intensive from 1 to 5			V/X	On right 1/5	On left 1/5
1	Localization of pain and irradiation	Headache	Frequency	Medicine			
2		When mouth is opened					
3		When mouth is closed					
4		Pain when the jaw is shifted to the right					
5		Pain when the jaw is shifted to the left					
6		When closing teeth					
7		Pain in the joint					
8		Earache					
9		Neckache					
10		Pain behind the head					
11		Backache					
12	Crunching	Crunch in the joint when opening the mouth					
13		Crunch in the joint when closing the mouth					
14	Ears	Tinnitus when opening the mouth					
15		Tinnitus when closing the mouth					
16		Feeling of fluid in the ears (stuffiness in ear)					
17		Decreased audibility (feeling)					

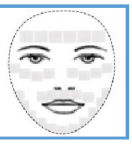
Localization of pain



Irradiation of pain ☐



Numbness on the face ☐



№	MAIN PART ❷	V/X	Answer/Description *
1	Have you ever felt pain in the muscles of the facing the morning or evening?		
2	Have you felt lower jaw contraction in the morning after awakening?		
3	Have you noticed when you closing teeth you are trying to find a comfortable position?		
4	Have you or your closest people noticed night gnashing of teeth?		
5	Have you or your closest people noticed your snore? (troubled sleep, frequent awakening, night uresiesthesia)		
6	Do you feel involuntary closing teeth?		
7	Have you ever had trauma, facial surgery, or general anesthesia (intubation)?		
8	Have your wisdom tooth been removed? How long ago?		
9	Have you been treated by an orthodont? How long ago?		
10	Have you noticed a feeling of having a lump in the throat or difficulties with pronunciation?		
11	Do you think your state of health is serious?		
12	How often you feel stressed?		
13	How do you rate your emotional state recently? Anxiety□; Fear □; Anger □; Irritation □; Calmness □.		
14	Do you feel a need for treatment?		

Signature of consultant physician _____ Signature of patient _____

Section 2. Mediobescience

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SCIENTIFIC SUBSTANTIATION OF THE ORGANIZATION OF THE HEALTH STAGE OF REHABILITATION OF PATIENTS WITH PRIORITY DISEASES OF THE POPULATION OF KYRGYZSTAN

Abstract: Improving the effectiveness of rehabilitation of patients with acute myocardial infarction in medical institutions on the basis of analysis of the quality and effectiveness of its delivery.

Keywords: acute myocardial infarction, rehabilitation, efficiency, sanatorium stage.

Introduction: Diseases of the circulatory system, nowadays, are one of the most important public health problems in the world and in our country, among which an important place is occupied by acute myocardial infarction (AMI). According to the State Statistics Committee of Russia, only for 4 years the mortality rate from AMI increased by 12.5% (Bokeria L. A. 2005). The age-standardized mortality rates for men of working age from AMI are more than 8 times higher than for a similar contingent of the female population of Russia (Bokeria L. A. and others, 2005). In Kyrgyzstan, CVD occupies the 1 st place in the structure of total mortality. The standardized death rate from CVD is 53.7 per 100,000 population. The increase in mortality for the years from 1990 till 2004 in working age was an average of 16.2%. The maximum increase in mortality was observed at the age of 30–39 years and amounted to 19.6% of the CAD.(Mirrahimov V. M.,2012). At the same time, the total economic losses from disability in 2008 amounted to more than 17 billion soms (Kydyralieva R. B., 2012). The increase in the incidence of CAD in our country is more than 21% in the last 15 years. The average mortality rate from CAD in the Central Asian region is 4.2 times higher than the death rate for the European Union. The most common cause of death from cardiovascular disease is acute myocardial infarction (AMI), the overall mortality rate is about 30% (WHO — World Health report., 2005).

In this regard, the desire to organize the most effective medical care for patients with AMI is one of the urgent tasks of modern healthcare. In our country, a stage-by-stage rehabilitation of patients with MI was developed, and among the proposed stages an important role is assigned to the stage of medical rehabilitation, during which the process of physical rehabilitation of patients with myocar-

dial infarction became widespread. There is a sufficient number of published works on the development and organization of rehabilitation of patients after AMI in the second half of the XX century (Kochorova L. V., 1981; Romanov A. I., 1985; Nikolaeva L. F., Aronov D. M., 1998; Chasov E. I., 2010; Gusev A. O., Kovalchuk V. V., 2011, Gusev A. O., 2014.), and foreign authors (Koch M., Blumenthal W., 1981; Cassak D., 1984). However, over the past 20–30 years, both diagnostic (coronaroaortography) and therapeutic (stenting, shunting) methods and possibilities for patients with AMI have changed markedly. The organization of inpatient care for the population (differentiation of bed capacity according to the degree of intensity of treatment and care and the restructuring of the hospital bed facility) and the entire health care system in connection with the introduction of the CMI system have undergone considerable reform. Meanwhile, if clinical aspects of the rehabilitation of patients with AMI are covered in many studies (Barbarash R. L. и oth.., 2001; Povorinskiy A. L., Sokolova L. A., 2008; Aronov D. M. и др., 2009; Arutyunov G. P. and oth., 2003, 2009) and quite extensively are covered in the literature the issues of disability after the disease of the circulatory system (BSC) (Baskakova N. P., 2006; Marusheva L. G., German S. V., 2010; Domanyanko A. A., Nadel R. V., 2010; Samorodskaya I. V., Fufaev E. N., 2011), then the organizational issues of rehabilitation of patients after AMI, with modern methods of diagnosis and intensive treatment of such patients, the need of the population in inpatient beds after AMI in the literature is not enough, which determines the relevance of the chosen research topic.

The aim of the study is to substantiate the need for medical rehabilitation for patients after acute myocardial infarction and to develop proposals for optimizing the work of inpatient departments of medical rehabilitation of the cardiac profile.

Objectives of the study are:

1. To analyze the statistics of the morbidity of the population with cardiovascular diseases

2. To present the features of the medical and statistical characteristics of patients with acute myocardial infarction (AMI) hospitalized in the cardiology department of the Kyrgyzian Scientific Research Institute of Balneology and Rehabilitation.

3. Determine the need of the population in hospital beds for the rehabilitation of patients after AMI and develop proposals for improving the work of cardiac sections in a medium-altitude mountains hospital.

Subject of the study: patients with myocardial infarction hospitalized for phased rehabilitation in the cardiology department of the Kyrgyzian Scientific Research Institute of Balneology and Rehabilitation.

In the course of the study from 2012 to 2015, 1280 outpatient cards of patients who were on dispensary registration in the Centers of Family Medicine (CFM) Bishkek City, were studied, 148 medical history of patients who received rehabilitation treatment in the department of cardiology of the Kyrgyzian Scientific Research Institute of Balneology and Rehabilitation, as well as 142 questionnaires for doctors of Centers of Family Medicine (CFM) and the Kyrgyzian Scientific Research Institute of Balneology and Rehabilitation.

The program of rehabilitation measures included:

I. **Dietary food**. Lipid-lowering diet

II. **Basis maintenance medication** was conducted in accordance with international recommendations and included: antihypertensive, lipid-lowering and antiplatelet therapy.

III. **Physiotherapy in combination with climatotherapy:**

1. Morning hygienic gymnastics from 5 to 15 minutes

2. Therapeutic gymnastics was prescribed during the day in the form of aerobic exercise at a free pace on the main muscle groups — the neck, back, abdomen, limbs starting at 5, then gradually adjusted to 10–12 repetitions per procedure. Breathing exercises and stretching exercises were necessarily included.

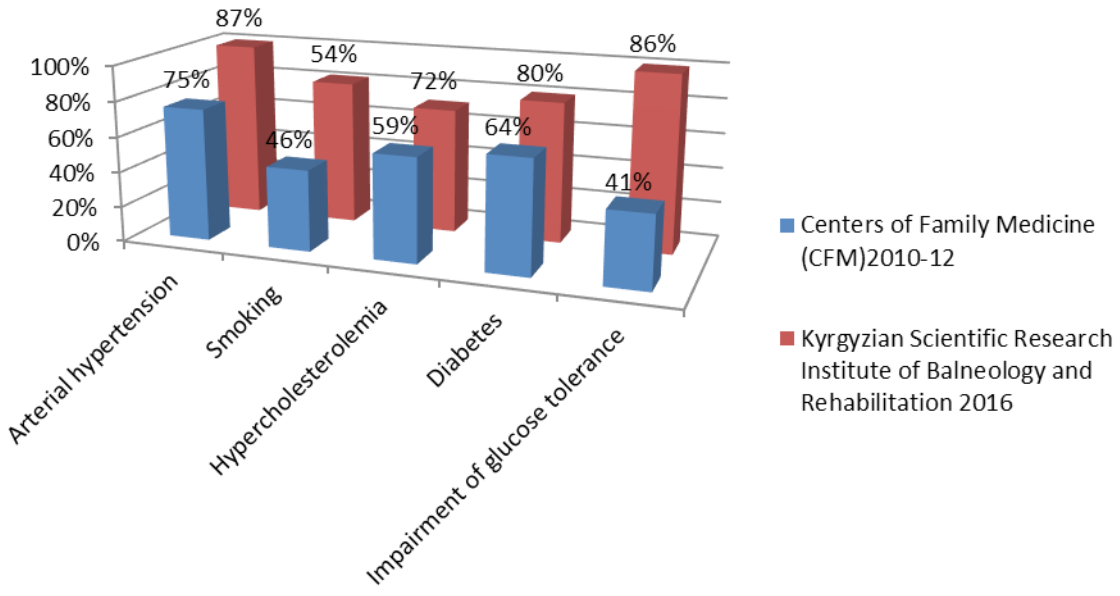
3. Special physical training was conducted on the cardiorespiratory complex, the company "Schiller" with computerized ECG and blood pressure monitoring.

4. Walking was also used as a means of physical training — walking on an even surface from 500 m gradually to 3 km a day, then later as mastering in the form of a terrenkur. Assignments were made in free regime on the territory of the sanatorium and sleep on the open veranda. Classes were conducted individually with a specialist in exercise therapy, taking into account the individual tolerability of physical exertion, the severity of the disease and concomitant pathology.

IV. **Psychological rehabilitation** was carried out by a doctor-psychotherapist and was conducted both individually and in the form of group psychotherapy. If necessary, psychopharmacotherapy was prescribed.

Table 1. – Achieving target levels of risk factors for CAD in patients who underwent AMI, who were on rehabilitation treatment

No.	Risk factors for CAD	Years of observation					
		2014		2015		2016 (6 months)	
		Abs.	%	Abs.	%	Abs.	%
1.	Arterial hypertension	14	65,3	21	90,2	18	87,2
2.	Smoking	7	41,3	5	40,1	2	54,8
3.	Hypercholesterolemia	4	26,7	9	43,8	3	72,5
4.	Overweight	10	14,3	6	18,3	4	29,0
5.	Dyslipidaemia	9	16,1	8	53,3	3	22,5
6.	Impairment of glucose tolerance	6	9,0	11	74,7	6	86,0
7.	Diabetes	4	7,1	13	64,7	5	80,0



Specialized cardiologic rehabilitation of patients with AMI under conditions of mid-range hospital is more effective than rehabilitation in outpatient settings in Bishkek, since it allows reaching the target levels of the main risk factors for CAD to a much greater extent. A phased combination of sanatorium and outpatient rehabilitation is advisable.

Practical recommendations:

1. To use the stage of sanatorium rehabilitation of patients who underwent AMI, in the conditions of an medium-altitude mountains hospital.

2. Conduct regular monitoring of the quality and effectiveness of rehabilitation care for patients with AMI in regions and in the country.

References:

1. Макаридзе, А. О. Анализ некоторых показателей работы отделения восстановительного лечения кардиологического профиля / А. О. Макаридзе, А. О. Гусев // Проблемы городского здравоохранения: Сб. науч. тр. / Под ред. проф. Н. Н. Вишнякова.– Санкт-Петербург, 2011.– Вып. 16.– С. 174–177.
2. Макаридзе, А. О. Развитие восстановительного лечения пациентов после острого инфаркта миокарда в России и за рубежом / А. О. Макаридзе // Проблемы городского здравоохранения: Сб. науч. тр. / Под ред. проф. Н. Н. Вишнякова.– Санкт-Петербург, 2011.– Вып. 16.– С. 171–174.
3. Гусев, О. А. Анализ результатов лечения больных острым инфарктам миокарда в специализированных отделениях / О. А. Гусев, А. О. Макаридзе // Проблемы городского здравоохранения: Сб. науч. тр. / Под ред. проф. Н. Н. Вишнякова.– Санкт-Петербург, 2012.– Вып. 17.– С. 68–71.
4. Гусев, О.А. О выборе больных острым инфарктом миокарда учреждения для восстановительного этапа после интенсивного лечения / О. А. Гусев, А. О. Макаридзе // Проблемы городского здравоохранения: Сб. науч. тр. / Под ред. проф. Н. Н. Вишнякова.– Санкт-Петербург, 2012.– Вып. 17.– С. 212–214.
5. Макаридзе, А. О. Сопутствующие заболевания у больных острым инфарктом миокарда в кардиологическом отделении с интенсивным лечением и в отделении медицинской реабилитации / А. О. Макаридзе // Проблемы городского здравоохранения: сб. научн. трудов / под ред.з.д.н. РФ, д.м.н., проф. Н. И. Вишнякова.– Вып. 19.– Санкт-Петербург: Изд-во «Любавич», 2014.– С. 103108.
6. Oldridge N. B., Guyatt G. N., Fischer M. E. et al. Cardiac rehabilitation after myocardial infarction. JAMA 1988; 260: 945–950.
7. Oldridge N. B., Guyatt G. N., Fischer M. E. et al. Cardiac rehabilitation after myocardial infarction. JAMA 1988; 260: 945–950.
8. Leon A. S. Franklin B. A. Costa F. Cardiac rehabilitation and secondary prevention of coronary heart disease. Circulation 2005; 111: 369–376.
9. Witt B. J., Jacobsen S. J., Weston S. A. Cardiac rehabilitation after myocardial infarction in the community. I Am Coll Cardiol 2004; 44: 988–996.

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CORRECTION OF THE EXPERIMENTAL PATHOLOGY OF CARBOHYDRATE METABOLISM BY THE INTERNAL APPLICATION OF MINERAL WATER WITH AN INCREASED CONTENT OF ORGANIC SUBSTANCES

Abstract: In an experiment on white male rats with a model of the metabolic syndrome (MS), a corrective effect of mineral water (MW) with an increased content of organic substances on metabolic parameters was established. During the influence of MW, the mass of animals was restored (decreased to the level of the control group of healthy animals), the glucose level decreased by 38%, the triglyceride concentration remained elevated, the cholesterol concentration was completely restored. Restoration of the urinary, ion-regulating and excretory functions of the kidneys is determined. The positive effect obtained from the use of MB on individual links of pathogenesis, although not fully implemented, is of a stable nature, which justifies the feasibility of further research. Restoration of the urinary, ion-regulating and excretory functions of the kidneys is determined. The positive effect obtained from the use of MW on some links of pathogenesis, although not fully implemented, but has a stable character, which justifies the feasibility of further research.

Keywords: metabolic syndrome, mineral water with high content of organic substances, corrective effect.

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КОРРЕКЦИЯ ЭКСПЕРИМЕНТАЛЬНОЙ ПАТОЛОГИИ УГЛЕВОДНОГО ОБМЕНА ВНУТРЕННИМ ПРИМЕНЕНИЕМ МИНЕРАЛЬНОЙ ВОДЫ С ПОВЫШЕННЫМ СОДЕРЖАНИЕМ ОРГАНИЧЕСКИХ ВЕЩЕСТВ

Аннотация: В эксперименте на белых крысах самцах с моделью метаболического синдрома (МС) установлено корректирующее влияние минеральной воды (МВ) с повышенным содержанием органических веществ на метаболические параметры. Под воздействием МВ восстанавливалась масса животных (уменьшалась до уровня контрольной группы здоровых животных), уровень глюкозы снизился на 38%, концентрация триглицеридов оставалась повышенной, концентрация холестерина была полностью восстановлена. Определено восстановление мочеобразовательной, ионорегулирующей и выводящей функций почек. Полученный положительный эффект от использования МВ на отдельные звеньях патогенеза, хотя и не реализован полностью, но носит стабильный характер, что обосновывает целесообразность проведения дальнейших исследований.

Ключевые слова: метаболический синдром, минеральная вода с повышенным содержанием органических веществ.

Прогрессирующее распространение метаболического синдрома (МС) в современном обществе вызывает тревогу. В настоящее время это явление можно считать эпидемией. Данным не-

дугом страдает около 25% взрослого населения развитых стран [1; 2]. Следует отметить рост заболеваемости МС среди детей и подростков. Критериями МС считаются абдоминальное ожирение, гипергликемия натощак, гипертензия, гипертриглицеридемия, низкий уровень холестерина липопротеинов высокой плотности [3; 4; 5]. Наиболее распространенная и общепринятая точка зрения – ведущая роль инсулинорезистентности как механизма, запускающего весь каскад метаболически-взаимосвязаных нарушений МС [6]. Учитывая вышеизложенное, поиск терапевтических возможностей восстановления нарушеной чувствительности клеток-мишеней к действию инсулина остается наиболее перспективным в предупреждении и лечении МС [7; 8].

МС является многокомпонентным комплексом патологических изменений, поэтому выбор адекватной экспериментальной модели является основополагающим для изучения данного состояния. В связи с этим особый интерес представляют экспериментальные исследования по моделированию МС у животных, которые позволяют понять причины развития и прогрессирования МС, а также исследовать потенциальные методы его профилактики и лечения.

В связи с этим следует указать на возможность и эффективность восстанавительной медицины, в частности, применения немедикаментозных способов коррекции составляющих МС с помощью природних лечебных ресурсов, к которым относятся минеральные воды (МВ) [9].

Цель: Исследовать влияние МВ «Збручанская» при ее внутреннем применении на показатели метаболизма белых крыс с моделью метаболического синдрома.

Материалы и методы: Эксперимент проведен на 40 белых крысах-самцах линии Вистар аутбредного разведения, в соответствии с правилами и требованиями, установленными Директивой Европейского парламента и Совета Европы [10, 11]. Во время эксперимента животные содержались в стандартных лабораторных условиях экспериментальной биологической клинике (виварии) ГУ «УкрНИИМРиК МОЗ Украины», при свободном доступе к корму и воде.

Длительность эксперимента составляла 72 суток. В начале эксперимента вес животных составлял 230,0–250,0 г. Животные были разделены на три группы:

– I группа – 16 интактных крыс (контроль);

– II группа – 12 крыс, у которых была воспроизведена модель МС;

– III группа – 12 крыс, которым на фоне развития МС (з 60 по 72 сутки исследования) проводили водную нагрузку фасованной и дегазированной МВ «Збручанская». МВ вводили в пищевод животных мягким зондом с оливой, один раз в сутки 12 дней подряд, в дозе 1% от массы тела животного, в вечернее время (приблизительно в 17.00), учитывая особенности суточного биоритма крыс.

Известен ряд экспериментальных моделей МС [12], но нами была выбрана и модифицирована модель без применения в рационе чрезмерного содержания жиров растительного или животного происхождения, а также использования раствора фруктозы меншей концентрации, чем в распространенных моделях (20 или 30% раствор фруктозы). Для воспроизведения модели МС животных содержали в течении 60 суток на стандартном рационе, но при этом крысы дополнительно получали 30 г сухарей из белого хлеба на одно животное и употребляли только 10% раствор фруктозы на дистилированной воде (в качестве питьевой жидкости) в режиме свободного доступа к поилкам. Биохимическими методами в сыровотке крови определяли уровень глюкозы, содержание холестерина, триглицеридов и маркеров эндогенной интоксикации – $МСМ_{254}$ і $МСМ_{280}$, креатинина, мочевины и мочевой кислоты. Функциональное состояние почек оценивали по влиянию на функцию мочеобразования (скорость клубочковой фильтрации, канальцевая реабсорбция, суточный диурез), на выводящую функцию (по экскреции креатинина и мочевины) и ионорегулирующую

функцию (по концентрации и суточной экскреции ионов калия, натрия и хлорид-ионов). Определяли кислотно-щелочную реакцию суточной мочи по показаниям концентрации ионов водовода, а таже наличие в моче глюкозы. На протяжении эксперимента каждые сутки протоколировали вес животных, количество выпитого раствора фруктозы, воды и количество употребляемой пищи.

В исследовании применяли МВ «Збручанская 77», которая является слабоминерализованной (общая минерализация 0,82 g/l) с высоким содержанием органических веществ (0,009–*0*,017 mg/l) гидрокарбонатной магниево-натриевой водой.

Методические приемы и методики, которые были задействованы в исследованиях, опубликованы в сборнике и утверждены приказом МОЗ Украины № 692 от 28.09.2009 [13]. Полученные данные сравнивали с подобными показателями интактных крыс (контрольная группа). Статистическую обработку полученных данных в сериях опытов проводили с использованием программ для медико-биологических исследований Statistica и Exel. Достоверными изменениями считались те, которые находились в пределах вероятности по таблицам Стьюдента P < 0,05 [14].

***Результаты и их обсуждение*:** В (таблице 1.) приведены данные по динамике изменений физиологических параметров животных с МС и животных, которые на фоне развития патологии получали МВ «Збручанская 77». Вес животных с МС достоверно увеличивался на 14% (< 0,01), а под влиянием МВ снизился на 8% и не отличался от контроля (p > 0,5). Количество употребленных белых сухарей (источники углеводов) у животных II группы увеличилось на 90%, а количество комбикорма наоборот, знизилось на 40% на фоне ухудшения аппетита. У животных III группы под влиянием МВ установлены положительные изменения – усилился апетит животных: употребление белах сухарей знизилось на 70%, а употребление комбикорма и смеси овощей повысилось на 30 и 15% по сравнению с показателями II группы. Употребление раствора фруктозы у животных на фоне развития МС превысило данные контроля на 100% (животные за сутки выпивали почти по 30–35 ml раствора фруктозы, и наверняка ощущали жажду), при этом в группе крыс с МС, которые дозировано получали МВ, употребление раствора фруктозы низилось на 50%. Следует подчеркнуть, что животные II группы на 72 сутки опыта имели неухоженный вид, шерсть – тусклая и редкая. Крысы выглядели заторможенными, вялыми (как бы уставшими), но при проведении манипуляций с ними (поение МВ и взвешивание) выглядели перепуганными и раздраженными, привлекало внимание частое мочевыделение (признак того, что животные испытывают страх). У животных III группы, на фоне употребления МВ «Збручанская 77» в конце опыта снижалась вялость и заторможенность, они выглядели более оживленными, исчезла перепуганность и раздраженность, при проведении манипуляций и снижалось мочевыделение.

Таблица 1.– Динамика изменений веса животных и количество выпитой жидкости крыс с моделью МС и крыс с МС, которые употребляли МВ «Збручанская 77»

Показатели	I группа	II группа	III группа
Масса тела, g	100	114*	106
Употребление10% раствора фруктозы, ml	–	200*	130*
Масса съеденных употребленной еды:			
сухари из белого хлеба, g	100	190*	120*
комбикорм, g	100	60*	90*
смесь овощная, g	100	90	115*

*Примечание: за 100% приняты данные контрольной группы животных; * – достоверные изменения показателей II и III группы расчитаны относительно контроля (p < 0,05).*

У крыс с МС (II группа) установлено достоверное повышение содержания глюкозы в крови на 3 ммоль/л (58%) $p < 0,01$, увеличение содержания холестерина и триглицеридов на 32 и 154% при ($p < 0,01$), (табл. 2). Также увеличилось в крови содержание маркеров эндогенной интоксикации – $МСМ_{280}$ на 41% ($p < 0,01$), креатинина и мочевины на 23% ($p < 0,01$). Содержание мочевой кислоты увеличилось по сравнению с показателем контрольной группы на 66% при ($p < 0,01$). Внутреннее дозированное поение МВ животных с моделью МС вызывало частичную метаболических показателей. превышает контроль на 1 ммоль/л. Полностью восстанавливается содержание холестерина, $МСМ_{280}$ и мочевой кислоты ($p > 0,5$), но содержание триглицеридов остается на уровне крыс с патологической моделью, а содержание креатинина и мочевины превышает соответствующие показатели крыс с МС на 18 и 80% ($p < 0,01$).

Таблица 2. – Биохимические показатели у крыс с моделью МС и крыс с моделью МС и курсом МВ «Збручанская 77», (M ± m)

Показатели крови	I группа	II группа	III группа		
	$(M_1 \pm m_1)$	$(M_2 \pm m_2)$	P_1	$(M_3 \pm m_3)$	P_2
Глюкоза, mmol/l	5,11 ± 0,22	8,06 ± 0,33	< 0,01	6,16 ± 0,13	< 0,05
Холестерин, mmol/l	1,63 ± 0,10	2,15 ± 0,11	< 0,01	1,61 ± 0,06	> 0,5
Триглицериды, mmol/l	1,10 ± 0,06	2,80 ± 0,27	< 0,01	3,08 ± 0,32	< 0,01
$МСМ_{254}$, усл. ед.	0,34 ± 0,02	0,30 ± 0,01	> 0,5	0,30 ± 0,01	> 0,5
$МСМ_{280}$, усл. ед.	0,22 ± 0,01	0,31 ± 0,01	< 0,01	0,30 ± 0,01	> 0,5
Креатинин, mkmol/l	47,80 ± 0,63	59,04 ± 1,78	< 0,05	67,97 ± 1,71	< 0,01
Мочевина, mmol/l	2,80 ± 0,27	3,71 ± 0,21	< 0,05	6,76 ± 0,39	< 0,01
Мочевая кислота, mkmol/l	292,52 ± 6,87	486,17 ± 15,32	< 0,01	260,27 ± 21,71	> 0,5

Примечания: P – достоверные изменения относительно контроля ($p < 0,05$); P_1 – рассчитано между показателями II та I группы; P_2 – рассчитано между показателями III та I группы.

Установлено достоверное снижение уровня глюкозы ($p < 0,05$), но ее уровень все же В соответствии с приведенными в таблице 3 данными, развитие МС у крыс сопровождается нарушением процессов мочеобразования. Объем суточного диуреза снижается на 47% за счет достоверного увеличения процента канальцевой реабсорбции на 0,16% при сохранении скорости клубочковой фильтрации (СКФ) на уровне данных контроля ($p > 0,5$). Установлено снижение суточной экскреции азотистых продуктов обмена: экскреция мочевины снижается на 20%, а экскреция креатинина не отличается от данных контрольной группы. Реакция pH суточной мочи значительно ощелачивается. Концентрация ионов калия и натрия увеличивается на 111 и 134%, а их экскреция на 14 и 38% соответственно. При этом, концентрация хлорид-ионов уменьшается на 12%, а их экскреция на 6%. Можно считать, что организм животных с моделью МС испытывает недостаток воды в связи с повышением уровня глюкозы в крови, и почки компенсаторно выводят гиперосмотическую мочу в небольшом количестве. Следует подчеркнуть, что в суточной моче глюкоза не определялась.

Применение МВ у животных с МС приводит к восстановлению и стимуляции мочеобразовательной и экскреторной функции почек: объем суточного диуреза увеличивается на 50% за счет ускорения СКФ на 66%, увеличивается выведение креатинина и мочевины на 66 и 73%, а калия и натрия на 50 и 320%. Экскреция хлорид-ионов повышается до уровня контроля ($p > 0,5$), pH мочи восстанавливается и не отличается от данных контрольной группы ($p > 0,5$). Экскреция ионов калия и натрия у животных с МС которые употребляли

МВ увеличивается на 50 и 166% по сравнению с группой контроля (у крыс с МС экскреция ионов калия и натрия увеличивается на 14 и 38%). То-есть, установленные эффекты свидетельствуют о значительном коррегирующем влиянии МВ «Збручанская 77» на мочеобразовательную, ионорегулирующую и экскреторную функции почек на фоне развития патологического процесса.

Таблица 3.– Функциональное состояние почек крыс с моделью МС и крыс с моделью МС и курсом МВ «Збручанская 77»

Показатели	**Группа**	**Группа**	**Группа**
Суточный диурез, ml/dm^2 поверхности тела	100	63*	150*
Скорость клубочковой фильтрации, ml/(dm^2×min)	100	100	166*
Канальцевая реабсорбция, процент к фильтрации,%	100	100,16*	100
Выведение креатинина, mmol	100	100	166*
Выведение мочевины, mmol	100	80*	173*
pH суточной мочи, ед. pH	100	133*	99
Концентрация ионов калия в суточной моче,, mmol/l	100	211*	123*
Суточная экскреция ионов калия, mmol	100	114*	150*
Концентрация ионов натрия в суточной моче, mmol/l	100	234*	418*
Суточная экскреция ионов натрия, mmol	100	138*	266*
Концентрация хлорид-ионов в суточной моче, mmol/l	100	88*	64*
Суточная экскреция хлорид-ионов, mmol	100	44*	90

*Примечания: за 100% приняты данные контрольной группы животных; * – достоверные изменения показателей II и III группы расчитаны относительно контроля ($p < 0,05$).*

Выводы. Таким образом, применение МВ «Збручанская 77» на фоне развития МС достоверно снижает уровень глюкозы, полностью восстанавливает содержание холестерина, мочевой кислоты и вес животных; производит значительное восстанавливающее влияние на функции почек. Установленные эффекты можна объяснить влиянием именно органических веществ этой МВ на восстановление управления липидным, углеводным и водно-электролитным обменами. Следует отметить, что метаболический синдром является тяжелой и длительно развивающейся патологией, его развитие вызывает в организме тяжелые осложнения, поэтому установленное корректирующее влияние МВ «Збручанская 77» на отдельные звенья патогенеза хотя и не осуществляется в полном объеме, однако носит стабильный характер.

Список литературы:

1. Ford E. S., Giles WH, Mokdad AH. Increasing Prevalence of the Metabolic Syndrome Among U. S. Adults. Diabetes Care.– 2004; 27: 2444–2449.
2. Nigel U. The metabolic syndrome / Nigel Unwin // J. R. Soc. Med.– 2006; 99 (9): 457–462.
3. Бондар В. М. Чернишова К. С. Особливості кардіоремоделювання у пацієнтів з артеріальною гіпертензією та метаболічним синдромом // J. Clin. Exp. Med. Res.– 2016; 4 (4): 515–522.
4. Simmons R. K., Alberti K. G., Gale E. A. et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO expert consultation // Diabetologia.– 2010; 53 (4): 600–605.
5. Prasad A., Quyyumi A. A. Renin-angiotensin system and angiotensin receptor blockers in the metabolic syndrome // Circulation.– 2004; 110: 1507–1512.

6. Metabolic syndrome / By ed. G. E. Roytberg.– M.: Med-pressinform. 2007.– 224 p.
7. Kolodenko O. V., Gushcha S. G., Zukow W. Possibilities of balneotherapy in patients with coronary heart disease after surgical revascularization of myocardium with concomitant diabetes // Journal of Education, Health and Sport.– 2016; 6 (6): 459–468.
8. Драгомирецкая Н. В., Заболотная И. Б., Гуща С. Г. Пути коррекции инсулинорезистентности. Роль бишофита // Journal of Education, Health and Sport.– 2015; 5 (9): 663–670.
9. Антонюк М. В., Гвозденко Т. А., Юбицкая Н. С., Шатилов И. Н. Санаторно-курортное лечение больных хроническим холециститом в сочетании с метаболическим синдромом // Курортная медицина.– 2016; 3: 40–45.
10. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (Text with EEA relevance). Official Journal.– 2010; 276: 0033–0079.
11. Науково-практичні рекомендації з утримання лабораторних тварин та роботи з ними: монографія / Ю. М. Кожем`якін, О. С. Хромов, Н. Є. Болдирєва [та ін.].– К.: Інтерсервіс,– 2017.– 182 с.
12. Лещенко Д. В., Костюк Н. В., Белякова М. Б. [и др.] Диетически индуцированные животные модели метаболического синдрома (обзор литературы) // Верхневолжский медицинский журнал.– 2015; 14 (2): 34–39.
13. Наказ МОЗ України від 28.09.2009 р. № 692 «Про затвердження методичних рекомендацій з методів досліджень біологічної дії природних лікувальних ресурсів та преформованих лікувальних засобів».– Київ,– 2009.– 117 с.
14. Glants S. Biomedical Statistics / Trans. English.– M.: Praktika,– 1999.– 459 p.

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THE PROCESS OF DEVELOPING AN INNOVATIVE FORM OF FOOD ADDITIVE

Abstract: The article considers the development of the technology of the new innovative form of the food additive in the form of the biologically active substance (BAA) produced at the enterprises of the company ArtLife. The dietary supplement uses an active natural substance – polyprenol, obtained by their needles of fir trees. Also, the structure of the active substance of polyprenol, its formula and functional properties are considered.

The technological process is considered, which includes the following main stages:

- Preparation of raw materials;
- Preparation of a mixture for encapsulation;
- Preparation of gelatin solution;
- Encapsulation and drying;
- Evaluation of the appearance of the intermediate product;
- Packing and packing.

The established technological parameters that are one of the factors shaping the quality and safety of the produced products, along with the formulation composition and the management system, are described.

Organoleptic, physico-chemical, sanitary-hygienic and sanitary-toxicological studies in the production and storage process were conducted, which allowed to determine the regulated quality indicators, terms and modes of sale.

Keywords: Polyprenol, medicine, pharmaceutics, biologically active additive, dietary supplements, nutrients, functional properties, health, nutrition.

The use of natural biologically active substances and their complexes in the correction of nutrition and health is a priority in today's Nutrition. Particular attention in recent years, is given Polyprenols [1–4].

Polyprenols are the most important group of natural bioregulators released from plant raw materials, in particular, greens of Siberian fir and other coniferous plants. Polyprenols are the main secret of biologically active substances contained in the

above objects of nature. For a person polyprenols are the only source of vital molecules – dolichol, responsible for many physiological processes in the body. In Russia, polyprenols are included in the list of essential components for the human body, along with vitamins, minerals and other micronutrients.

Polyprenols are natural long-chain isoprenoid alcohols of general formula H- (C5H8) n-OH, where n is the number of isoprene units. Any prenol with more than 4 isoprene units is polyprenol. Polyprenols occupy key positions in the metabolism, acting as natural bioregulators. Dolicholi, which are found in all living organisms, including humans, are their derivatives – 2,3 – dihydropylenols. Polyprenols and dolichols have a similar chemical structure, since dolicholes are derivatives of polyprenols and differ from them by a single saturated isoprene unit.

Polyprenols are chemical compounds from the group of biopolymers produced in the human liver. These substances are extremely important for the normal functioning of the body, since they are responsible for the processes of interaction between cells and participate in the dolichlorophosphate cycle, during which glycoproteins are formed – receptors, growth hormones, plasma proteins, enzymes and immunoglobulins. Polyprenols restore the structure of the cell and control the process of creating proteins. The lack or lack of polyprenols in the body can lead to the appearance of various diseases. The pharmacological transformation of polyprenols takes place in the liver, where they are metabolized into dolicholes.

Polyprenols are prepared from wood greens coniferous trees botanical family pine (pine, spruce, fir, and others.) By extraction of dried and ground raw materials, followed by purification of the desired product. Contained in the needles of trees, as well as other plants, in the form of acetates – natural mixtures of oligomers (izoprenolov). Content polyprenols in the needles is 0.5–1.5% of the dry weight.

From a chemical standpoint are acyclic terpene alcohols having from 6 to 40 units izoprenodnyh: coniferous trees and the human body – from 10 to 20.

Once in the body through the digestive tract vegetable polyprenols metabolized in the liver dolichols, which also belong to the group, and polyisoprenes have a structural similarity to polyprenols (different one saturated isoprene). Dolichols play a crucial role in the functioning doliholfosfatnogo cycle (DFTS) – defining link in the chain of biosynthesis of glycoproteins and glyukoaminoglyukanov in the cell membranes. The process of glycosylation of membrane proteins occupies a key position in ensuring the vital activity of cells. With dolichols there is a connection glyukoaminoglyukanov and glycoproteins.

It is noted that the emergence of many pathological processes, including diseases of the nervous system associated with impaired development and DFTS dolichols deficit function that determines the relevance of the development of new forms of highly specialized products using polyprenols has scientific and practical importance [5–10].

A new manufacturing technology encapsulated forms of biologically active additives (BAA) "Oleopren Neuro".

The technological process includes the following basic steps.

- Preparation of raw materials. Carry out pregrinding hammer mill glycine MM10, sifted through the SGS-30 vibrating screen with a mesh size of 0.4 mm;
- Preparation of the encapsulation mixture. The components of the formulation are dosed into the reactor-homogenizer in a certain order: refined sunflower oil; antioxidant Grindoks 109; Memree Plus-30h; polyprenols mixture of 75% tocopherol acetate 98%; aerosil (stirred and gomogeneziruyut); glycine (mixed and gomogeneziruyut).

Check compliance with name, number and a series of raw materials routing. Lumps and foreign

matter must be absent. The shelf life of the mixture – no more than 24 hours in a dark place, filled up to the top container;

- Preparation of gelatin solution. Set the parameters in the software mixer Melter MGP: water jacket temperature – 850C; purified water – according to the boot map; speed rpm mixer – 35 rev / min. Charged suspended components in the following order: purified water, glycerin, gelatin.

At least the auxiliary components are added – preservatives and pigments. Preparation time – 2.5 hours per 210 kg of finished gelatin solution. After completing the gelation solution is discharged through a filter (pore size 0.2 mm) in the storage tank, assert 4 hours at a temperature of 600 C and fed to the capsule manufacturing site. Shelf life prepared gelatin is not more than 24 hours;

- Encapsulation and final drying. Soft gelatin capsules are prepared from a solution of a mixture of gelatin and capsule for encapsulating machine SGM1010. Capsules finally dried 30–60 hours in the drying tunnels to cease falling capsules weight;
- Evaluation of the appearance of the precursor. Assess visually average sample is taken and transferred to the production laboratory for testing for compliance with the stated performance requirements of technical documentation. On the container, a label is placed with the name of the precursor, quality, batch number, manufacturing date, operator's signature;
- Packaging and packaging. Implemented in accordance with the technical documentation for the manufactured product. Samples of the finished product (3 pack) are transmitted to the collection of arbitration samples.

All stages of the process are recorded in the route-accompanying sheet.

The established process parameters are one of the factors shaping the quality and safety of products, along with prescription composition and management system.

Carried out the organoleptic, physico-chemical, sanitary-hygienic and sanitary-toxicological studies in the process of production and storage, allowing to determine the regulated quality indicators (Table 1), the terms and modes of implementation.

Table 1.– Regulated indicators of quality dietary supplements "Oleopren Neuro".

Parameter	Contents characteristics
The appearance of	soft gelatin capsules
Color capsule contents	from yellow to orange, It allowed the precipitate inside the capsule
Taste and smell of the contents of the capsule	specific
The average weight of the capsule, mg	790 (от 711 до 869)
Vitamin E content in one capsule, mg	3,75 (от 2,6 до 4,9)
The content of polyprenols in one capsule, mg, not less than	5,0
Contents atsetonrastvorimyh substances (phosphatidylserine and phosphatidic acid) in 1 capsule, mg, not less than	14,5

The developed product is a highly effective natural complex of biologically active substances directed action on the nervous system, having vzaimnopotentsiruyuschimi farmokodinamicheskimi properties obespechivayuschmim prolongation effect after the end of dietetics. Performance and functional orientation BAA "Oleopren Neuro" confirmed by the results of clinical trials in patients.

Displaying hygienic welfare of the product for 27 months after storage (based on the results of microbiological, sanitary-hygienic and sanitary-toxicological tests) possible to determine the shelf life – 2

years at a temperature no higher than 250 °C in a dry, dark place.

Developed and approved technical documentation. BAA "Oleopren Neuro" is produced at the enterprises of the NGO "ArtLife" certificated under the requirements of the international standards of ISO 9000, 22000 and GMP regulations, which ensures the stability of quality and safety of products.

References:

1. Kochetkova A. A. Theoretical and practical aspects of the development of specializedFood products for diet therapy for cardiovascular diseases / A. A. Kochetkova, V. M. Vorobyova, I. S. Vorob'eva et al. // Food Industry.– 2016.– No. 8.– P. 8–12.
2. Demographic Yearbook of Russia.– 2015. Statistical collection / – M.: Rosstat,– 2015.– 727 p.
3. Pogozheva A. V. Dietotherapy of cardiovascular diseases. General principles. AT.
4. Pogozheva A. R. Bogdanov S. A. Derbeneva // Practical Dietology.– 2015.– No. 4 (16).– P. 36–40.
5. Tutelyan V. A. Biologically active components of cardiac patients nutrition. V. A. Tutelian A. V. Pogozhev A. K. Baturin // – M.: SVR-ARGUS,– 2012.– 380 p.
6. Shevchenko V. P. Clinical Nutrition. P. Shevchenko.– Moscow: GEOTAR-Media,– 2014.– 256 p.
7. Lee J. H. Omega-3 fatty acids for cardioprotection / J. H. Lee, H. O & No. 39; Keefe C. J. Lavie et al. // Mayo Clin. Proc.– 2008.– Vol. 83.– P. 324–332.
8. Kromhout D. Omega-3 fatty acids and cardiovascular events after myocardial infarction / D. Kromhout [et al.] // N. Engl. J. Med.– 2010.– Vol. 363. (21).– P. 2015–2026.
9. Lazarus S. Tomato extract inhibits human platelet aggregation in vitro without increasing basal cAMP levels /S. Lazarus, M. Garg // Int. J. Food Sci. Nutr.– 2004.– Vol. 55.– P. 249–256.
10. Yamamoto J. Tomatoes have natural antithrombotic effects / J. Yamamoto [et al.] // Br. J. Nutr.– 2003.– Vol. 90.– P. 1031–1038.
11. Singh R. B. Effect of coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction / R. B. Singh., N. S. Neki // Mol. Cll. Biochem.– 2003.– Vol. 264 (1–2).– P. 75–82.

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EVIDENCE BASED APPROACH TO SELECTING OF EXTRACTION METHOD FOR OBTAINING OF DRY EXTRACT FROM CORN SILK

Abstract: This article introduces the results of a study for selection of an extraction method and conditions of vitamins from corn silk for obtaining a dry extract. Influence of temperature conditions on the process of extraction of vitamins from corn silk is determined, optimal temperature conditions are selected. By means of HPLC/MS method, the content of vitamins A, B_1, B_2, B_6, C, K in obtained extracts is evaluated. It is pointed out that the extract obtained by vacuum-filtration extraction without ethanol recuperation contains 40% more vitamins, then other studied variations of this extraction method.

Keywords: herbal medicinal products, dry extract, corn silk, vitamins, vacuum-filtration extraction, HPLC/MS.

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НАУЧНО ОБОСНОВАННЫЙ ПОДХОД К ВЫБОРУ МЕТОДА ЭКСТРАГИРОВАНИЯ ДЛЯ ПОЛУЧЕНИЯ СУХОГО ЭКСТРАКТА СТОЛБИКОВ С РЫЛЬЦАМИ КУКУРУЗЫ

Аннотация: В статье приведены результаты исследования по выбору метода и условий экстрагирования витаминов из столбиков с рыльцами кукурузы майской для получения сухого

экстракта. Определено влияние температурного режима на процесс экстракции витаминов из столбиков с рыльцами кукурузы, подобран оптимальный температурный режим. С помощью метода ВЭЖХ/МС определено содержание витаминов А, B_1, B_2, B_6, С, К в полученных вытяжках. Показано, что полученное методом вакуум-фильтрационного экстрагирования без рекуперации этанола извлечение содержит на 40% больше витаминов, чем два других.

Ключевые слова: фитопрепараты, сухой экстракт, кукурузные столбики с рыльцами, витамины, вакуум-фильтрационное экстрагирование, ВЭЖХ/МС

Введение. В настоящее время интерес к фитотерапии во всем мире находится на постоянно высоком уровне (начиная с 2000-х годов). К 2020 году по прогнозам Всемирной организации здравоохранения (ВОЗ) доля фитопрепаратов в общемировом объеме потребления достигнет 60%. Это связано с растущим числом пациентов, страдающих аллергией на синтетические препараты, а также с преимуществами препаратов на основе лекарственного растительного сырья (ЛРС) – безопасностью при длительном применении, меньшим количеством побочных эффектов, широтой терапевтического действия, доступностью сырьевой базы. В рамках реализуемой с 2014 года программы импортозамещения в отечественной фармацевтической науке поддерживается высокий интерес к разработке и созданию новых лекарственных препаратов на основе ЛРС, произрастающего на территории Российской Федерации. Одним из таких видов лекарственного сырья, являющегося перспективным объектом изучения, являются столбики с рыльцами кукурузы майской *(Styli cum stigmatis Zeae maydis),* обладающие выраженным желчегонным и диуретическим действием. Согласно данным Государственного реестра лекарственных средств (ГРЛС) производители ЛРС столбиков с рыльцами кукурузы представлены 15 российскими компаниями.

В официальной медицине применяются жидкий экстракт (1:1) и отвар из кукурузных рылец. В многочисленных клинических исследованиях было показано, что желчегонные препараты кукурузных рылец особенно эффективны при застое желчи: при систематическом применении у больных постепенно исчезало чувство тяжести и боли в области печени, прекращались тошнота, рвота, уменьшались размеры печени. При желчнокаменной болезни препараты не купируют острые печеночные приступы, однако длительное применение кукурузных рылец (до 5 недель) приводит к заметному улучшению состояния [1].

Целью: данной работы является экспериментальное обоснование выбора оптимальной технологии получения сухого экстракта столбиков с рыльцами кукурузы.

Материалы и методы: В исследовании использовано сырьё фирмы ЗАО «Здоровье», определение числовых показателей которого проводили по методикам, описанным в ФС (ФСП Р N003326–01–080909), количественное определение биологически активных соединений в растительном сырье проводили по методикам ГФ XIII. Для определения биологически-активных соединений в ЛРС и продуктах, получаемых на его основе, были модифицированы методики количественного определения витаминов А, B_1, B_2, B_6, D_3, К методом ВЭЖХ/МС и проведена их валидация, согласно требованиям ОФС «Валидация аналитических методик».

***Результаты и обсуждение*:** Классическими способами экстрагирования столбиков с рыльцами кукурузы являются перколяция, реперколяция, ускоренная дробная мацерация [2; 3]. Однако, в исследовании [2] было показано, что эти методы не позволяют максимально экстрагировать биологически активные вещества из ЛРС.

При выборе способа получения жидкого извлечения из ЛРС за основу был взят метод, используемый в исследованиях Никифоровой Е. Б.

и соавт. [2]. Суть метода заключалась в измельчении сырья до среднего размера 0,28 мм и использовании метода вакуум-фильтрационного экстрагирования 70% этанолом для получения жидкого экстракта столбиков с рыльцами кукурузы. Затем спирт отгоняли и получали из шрота сухой экстракт методом ремацерации горячей водой.

Для получения сухого экстракта столбиков с рыльцами кукурузы метод Никифоровой Е. Б. был модифицирован следующим образом: спиртовую вытяжку из ЛРС и водную вытяжку из шрота столбиков с рыльцами кукурузы объединяли и упаривали, получая сухой экстракт.

В качестве метода сравнения был рассмотрен аналогичный метод, в котором была осуществлена экстракция экстрагируемых соединений водой. Третьим методом был традиционный метод, применяемый при производстве жидких экстрактов столбиков с рыльцами кукуруза – перколяция с законченным циклом.

Учитывая содержание термолабильных веществ в ЛРС, представлялось целесообразным не повышать температуру экстрагирования на стадии извлечения водой выше 65 °С [4]. В связи с этим было предварительное изучение влияние температурного режима на выход анализируемых веществ в вытяжку. Исследование по отработке температурного режима в диапазоне от 20 до 65 °С. В начале проводили вакуум-фильтрационную экстракцию, а затем проводили экстракцию из шрота при различных температурах. Результаты представлены в (таблице 1).

Таблица 1.– Зависимость выхода анализируемых витаминов от температуры экстракции

Показатель	**Температура экстракции, °С**				
	20–25	**30–35**	**40–45**	**50–55**	**60–65**
Витамин А	0,00165 ± 0,02	0,00171 ± 0,03	0,00171 ± 0,03	0,00175 ± 0,03	0,00169 ± 0,01
Витамин B_1	0,01012 ± 0,02	0,01015 ± 0,01	0,01020 ± 0,02	0,01038 ± 0,01	0,01020 ± 0,03
Витамин B_2	0,06195 ± 0,03	0,06204 ± 0,01	0,06542 ± 0,03	0,07400 ± 0,02	0,07200 ± 0,03
Витамин B_6	0,00145 ± 0,03	0,00158 ± 0,02	0,00256 ± 0,03	0,00314 ± 0,02	0,00247 ± 0,03
Витамин С	0,60061 ± 0,03	0,62399 ± 0,01	0,63108 ± 0,03	0,70828 ± 0,02	0,64748 ± 0,03
Витамин К	0,00667 ± 0,01	0,00751 ± 0,02	0,00767 ± 0,02	0,00968 ± 0,02	0,00748 ± 0,02

Из данных таблицы следует, что экстракцию из шрота следует проводить в температурном диапазоне 50 °С – 55 °С., так как выход экстрактивных веществ при этом максимален. При повышении температуры происходит уменьшение выхода витаминов [5]. С учетом выбранного оптимального температурного режима были воспроизведены три выбранных, описанных выше методики экстрагирования для получения извлечения из столбиков и рылец кукурузы. Характеристики исследуемых методов экстракции представлены в таблице 2.

Таблица 2.– Характеристика методов экстрагирования

№	**Стадия**	**Вакуумно-фильтрационная экстракция с рекуперацией этанола**	**Вакуумно-фильтрационная экстракция без рекуперации этанола**	**Перколяция с законченным циклом**
1	***2***	***3***	***4***	***5***
1.	Загрузка сырья	Соотношение 1:2	Соотношение 1:2	Батарея из 3-х перколяторов, соотношение сырья и готового продукта 1:1

1	*2*	*3*	*4*	*5*
2.	Экстрагирование 70% спиртом	Метод вакуумно-фильтрационной экстракции	Метод вакуумно-фильтрационной экстракции	Настаивание в течение 24 ч. в каждом из перколяторов
3.	Рекуперация этанола	Рекуперация этанола горячим паром	Отсутствует	Отсутствует
4.	Экстрагирование горячей водой (50–55 ˚С)	Метод ремацерации, первая ступень при соотношении сырья: экстрагента – 1:10, вторая и третья ступень – 1:5, время экстракции 2 ч. на каждой из стадий.	Метод ремацерации, первая ступень при соотношении сырья: экстрагента – 1:10, вторая и третья ступень – 1:5, время экстракции 2 ч. на каждой из стадий.	Отсутствует
5.	Очистка и фильтрование	Отстаивание в течение 24 ч. при t 10 ˚С, фильтрация через фильтровальную бумагу марки Ф.	Отстаивание в течение 24 ч. при t 10 ˚С, фильтрация через фильтровальную бумагу марки Ф.	Отстаивание в течение 24 ч. при t 10 ˚С, фильтрация через фильтровальную бумагу марки Ф.

Полученные извлечения кукурузных рылец представляли собой прозрачную жидкость красно-бурого цвета со своеобразным запахом. Для оценки эффективности сравниваемых методов экстрагирования, проводили сравнительное определение в них экстрагируемых витаминов (табл. 3).

Таблица 3. – Оценка содержания витаминов в полученных извлечениях из ЛРС

Показатель	**Вытяжка, метод 1,%**	**Вытяжка, метод 2,%**	**Вытяжка, метод 3,%**
Витамин А	0,00181	0,00293	0,00154
Витамин B_1	0,01020	0,01053	0,01014
Витамин B_2	0,07692	0,08741	0,06705
Витамин B_6	0,00196	0,00363	0,00192
Витамин С	0,60849	0,73176	0,60197
Витамин К	0,00669	0,01020	0,00854

На основе полученных результатов, было определено, что технология получения сухого экстракта из кукурузных рылец по методу 2 является оптимальной, поскольку увеличивает выход витаминов по сравнению с 1-м методом в среднем на 40%.

При получении сухого экстракта столбиков с рыльцами кукурузы полученную вытяжку упаривали на вакуум-выпарном аппарате BUCHI (Швейцария) при давлении 175 mbar (температура 60 °С, скорость вращения колбы 120–140 об/мин), а затем, после отгона этанола, при 72 mbar для сгущения водной фракции. После упаривания экстракты подвергали заморозке при температуре –25 °С в течение не менее 8 часов. Затем их подвергали лиофильной сушке в течение 24 ч при остаточном давлении 0,03±0,1 мБар и комнатной температуре.

Заключение. В результате проведенных исследований были определены оптимальные условия экстрагирования для получения сухого

экстракта столбиков с рыльцами кукурузы, содержащего максимальное количество экстрактивных веществ. Полученный сухой экстракт, обогащенный витаминами, планируется включить в состав комбинированной лекарственной формы адаптогенного действия.

Список литературы:

1. Гарезина О. В. Особенности клинических проявлений и оптимизации терапии у больных врожденными коагулопатиями, инфицированных вирусами гепатита С и В: дис. … канд. мед. наук: 14.00.29 / Гарезина Ольга Васильевна.– Спб.,– 2004.– 138 с.
2. Никифорова Е. Б. Совершенствование технологии, стандартизации жидкого экстракта и получение водоэкстрагируемого фитокомплекса в условиях малоотходной переработки кукурузных рылец: дис. …канд. фарм. наук: 15.00.01 / Никифорова Елена Борисовна.– Пятигорск,– 2007.– 174 с.
3. Sunnyvale C.A., Gazdik Z., Zitka O., Petrlova J., Adam V., Zehnalek J., Horna A., Reznicek V., Beklova M., Kizek R. Determinatiom of Vitamin C (Ascorbic Acid) Using High Perfomance Liquid Chromatography Coupled with Electrochemical Detection // Sensors.– 2008.– No. 8.– P. 7097–7112.
4. Голубятникова М. В. Система интеллектуальной поддержки при выборе оптимального техноло гического режима: дис. … канд. тех. наук: 05.13.01 / Голубятникова Марина Владиславовна.– Астрахань,– 2011.– 188 с.
5. Ребров В. Г., Громова О. А. Витамины, макро- и микроэлементы – М.: ГЭОТАР-Медиа,– 2008.– 960 с.

Section 4. Physical and chemical life sciences

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WIRKSAMKEIT DES PRÄPARAT REPELLENT AKTION AUF DER GRUNDLAGE DER NATÜRLICHEN BAS ZUM SCHUTZ VOR IXODES ZECKEN

Abstrakt: Zecken sind überträger gefährlicher Infektionskrankheiten. Die Altai-Region und die Republik Altai gehören zu den ärmsten Regionen der Verbreitung von Transmissions-Infektionen. Ein wichtiger Punkt ist die Entwicklung von individuellen Schutzmittel – repellent wirkende Stoffe. Alle sind auf chemischer Basis entwickelt und Ihre Anwendung ist nicht sicher für den Menschen und die Umwelt. Eine neue, umweltfreundliche Droge repellent Aktion gegen ixodes Zecken mit Wirkstoffen-Birke und Jod, als benetzungsmittel flüssige Insektizid-Seife und neionogenes Tensid. Zeitraum der Schutzwirkung des repellent-Präparats auf der Basis von birkenmarmelade, mit 100% Effizienz sind 24 Stunden, das übersteigt das bekannte Analogon- Präparat DETA 6 mal.

Schlüsselwörter: ixodes Zecken, repellent Präparaten, anfängliche Wirksamkeit der Schutzwirkung.

Einführung

Ixodes-Zecken haben sowohl tierärztliche als auch medizinische Bedeutung Estrada Pena et alt. [10]. Sie sind Träger und Reservoire von vielen Naturkatastrophen von Tieren und Menschen, die in einer Gruppe von zeckeninfektionen» Yakimenko et alt [9]; Franke et alt. [12]; Goltz L. Et alt. [12]; Namrata P. et alt. [13]. In Russland beteiligt Sie sich an der Verbreitung von 20 Krankheiten von Tieren und Menschen. In der Region Altai und in der Republik Altai epidemiologische Bedeutung haben die folgenden Arten von ixodovyh Zecken: Ixodes persulatus, Dermocentor Reticulate, Dermocentor Marginatus, dermocentor nuttali und Haemaphysalis concinna Butakov [2; 3]. Die größte Gefahr für Tiere und Menschen sind Zecken der Art ixodedes persulcatus Novikova [5]. Diese Art-überträgt den Menschen das Virus Frühjahr und Sommer (Zecken) Enzephalitis. Die höchste Zahl dieser Art von Zecke registriert in Altai, Ural, und dem Fernen Osten.

Nach der Abschaffung der massiven akarizidalen Behandlungen, in der Republik Altai seit 1978 gab es eine anhaltende Zunahme der Anzahl von Zecken in der Natur und das Wachstum der Häufigkeit von Zecken Enzephalitis Shchuchinova [8]. Die Verwendung von chemischen Pestiziden trägt zur Verschmutzung der Umwelt bei und hat eine Reihe von Einschränkungen hinsichtlich Ihrer Anwendung.

Das Ziel der Untersuchungen ist das entwickeln repellent Aktionen auf der Grundlage von natürlichen Base zum Schutz vor Ixodes Zecken. **Forschungsziele:** Holen Sie sich die Wirkstoffe für die Entwicklung der Droge repellent Aktion.Finden Sie das optimale Verhältnis der aktiven Komponenten. Verstärken Sie die Wirkung der aktiven Komponenten. Studieren Dauer fumigant Wirkung des Präparat.

Erkenntnis

Die Objekte der Forschung waren Zecken: Dermacentor reticulatus – wiese Zecke und Dermacentor marginatus – Steppen-Milbe. Die Tests wurden durch die abstufung der Konzentrationen durchgeführt Desinfektion [4] Methoden ... (2003). Die Tests wurden in dreifacher Wiederholung durchgeführt, 30 Zecken in jeder Wiederholung. Als Referenz wurde das Präparat DETA getestet. Beseitigen Sie die Nachteile der Verwendung von chemischen repellente Präparaten können durch die Entwicklung von repellent Wirkstoff auf der Basis von natürlichen BAS (biologisch aktive Substanz), mit einem starken resistenten Geruch. Von diesen natürlichen verbindungen sind von großem Interesse Birke Teer und Jod. Die Zusammensetzung der Birke Teer enthalten: Phenol, Xylol, organische Säuren, Toluol, guayaquol, phytoncide, kresol, Benzol, Harz. Dank seiner Zusammensetzung Birke Teer hat antimikrobielle und antiseptische, entzündungshemmende und regenerierende, getrocknet.

Der hohe Gehalt an phytonicid haben wir als Grundlage bei der Entwicklung des Präparat repellent Aktion. Starke spezifische Geruch und Flüchtigkeit hat Jod. In Bezug auf ixodovyh Zecken repellent Wirkung von Jod nicht untersucht. Medizinische (5%), Jod und birkenmehl wurden von uns als Wirkstoffe bei der Entwicklung der Präparat repellent Aktion gegen ixod-milben verwendet. Als zweite aktive Komponente-benetzungsmittel, wurden Liquid Insektizid Seife und unionogenes Tensid getestet. Insektizid-Seife nach der Ursprünglichen Technologie (Patent № 2222572) [6] erhalten, ist ein umweltfreundliches Produkt. Hohe benetzungsaktivität haben nicht-Ionen-Tenside, die wasserlösliche Zusammensetzungen, die fast jede Oberfläche, einschließlich der ausgeprägten hydrophoben Eigenschaften zu benetzen ermöglichen. Nicht-monogene OAS (oberflächlich aktiv Stoffe) sind auf der Grundlage der Trimmer Propylen entwickelt und sind hocheffektive oberflächenaktive Substanzen. Nach dem Grad der Auswirkungen auf den menschlichen Körper, sind Sie zu den risikoreichen Substanzen. Nach Verschlucken haben chwach reizbar Aktion. Rezorbtivnymi und sensibilisierende Eigenschaften haben keine. Neionogene Tenside, die wir bei der Entwicklung von Präparaten repellent Aktion verwendet, in bestimmten Verhältnissen gut mit birkenmarmelade und Jod kombiniert.

In der ersten Stufe der Bestimmung der Schutzwirkung der Präparate Ihre Effektivität haben in verschiedenen Konzentrationen geprüft. Es wurde festgestellt, dass das Präparat auf der Basis von birkenmarmelade bietet 100% anfängliche Wirkung in der Konzentration von 20%. (Abb. 1). Die Dauer der Schutzwirkung des Präparats in dieser Konzentration war 4 Stunden. Nach 8 Stunden sank Sie auf 40%, und nach 10 Stunden die Wirksamkeit der Behandlung war 30% (Abb. 2). Das Präparat auf der Grundlage von JOD zeigte 100% anfängliche Wirksamkeit bei einer Konzentration von 40% (Abb. 3). Jedoch ist die Dauer der Schutzwirkung des Arzneimittels in dieser Konzentration sehr kurz. Bereits nach 2 Stunden seine Wirksamkeit sank auf 80%, 8 Stunden später fiel auf 50%, und 10 Stunden später auf 20% (Abb. 4). Aufgrund der Wirkung von 20% des Arzneimittels auf der Basis von birkenmarmelade

und 40% auf der Grundlage von Jod, weitere Tests wurden unter Verwendung von emulsionskonzentraten dieser Präparate durchgeführt. In dieser Phase als Referenz verwendet repellent Präparat deta.

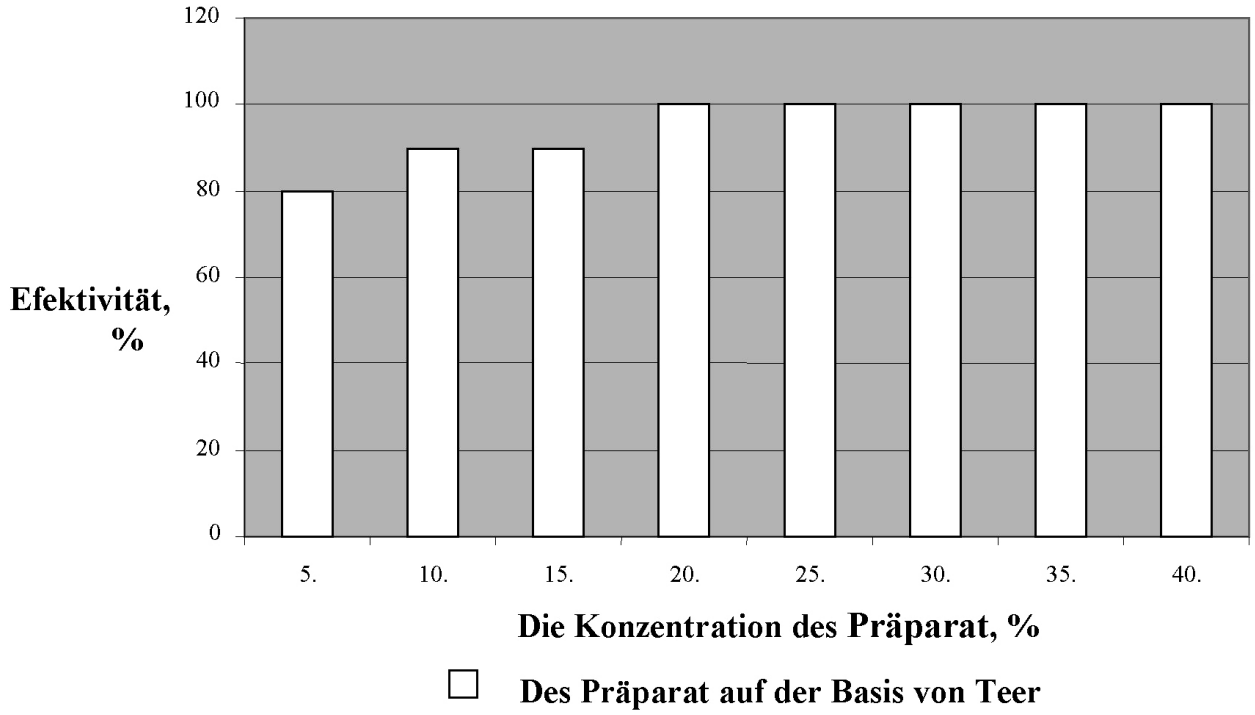

Abbildung 1. Anfängliche Wirksamkeit des repellent-Präparats auf der Basis des birkenmarks

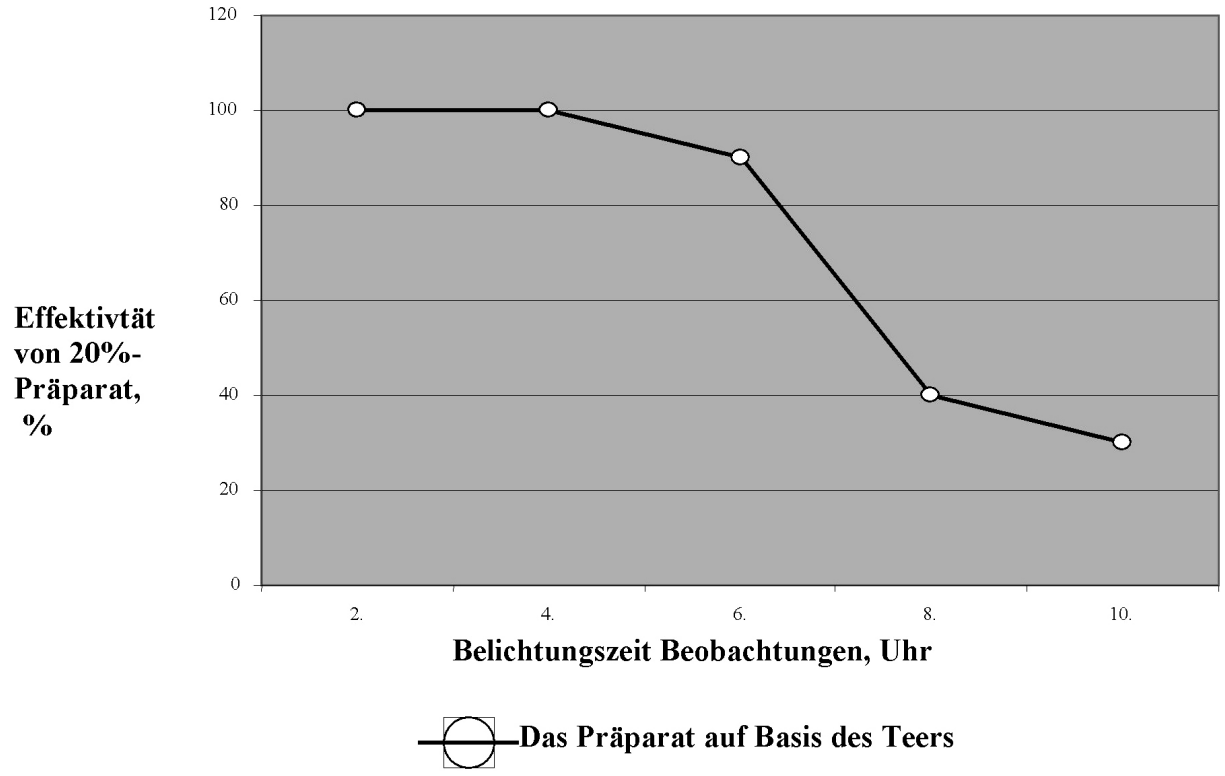

Abbildung 2. Dauer der Schutzwirkung des repellent-Präparats auf der Basis des birkenmarks

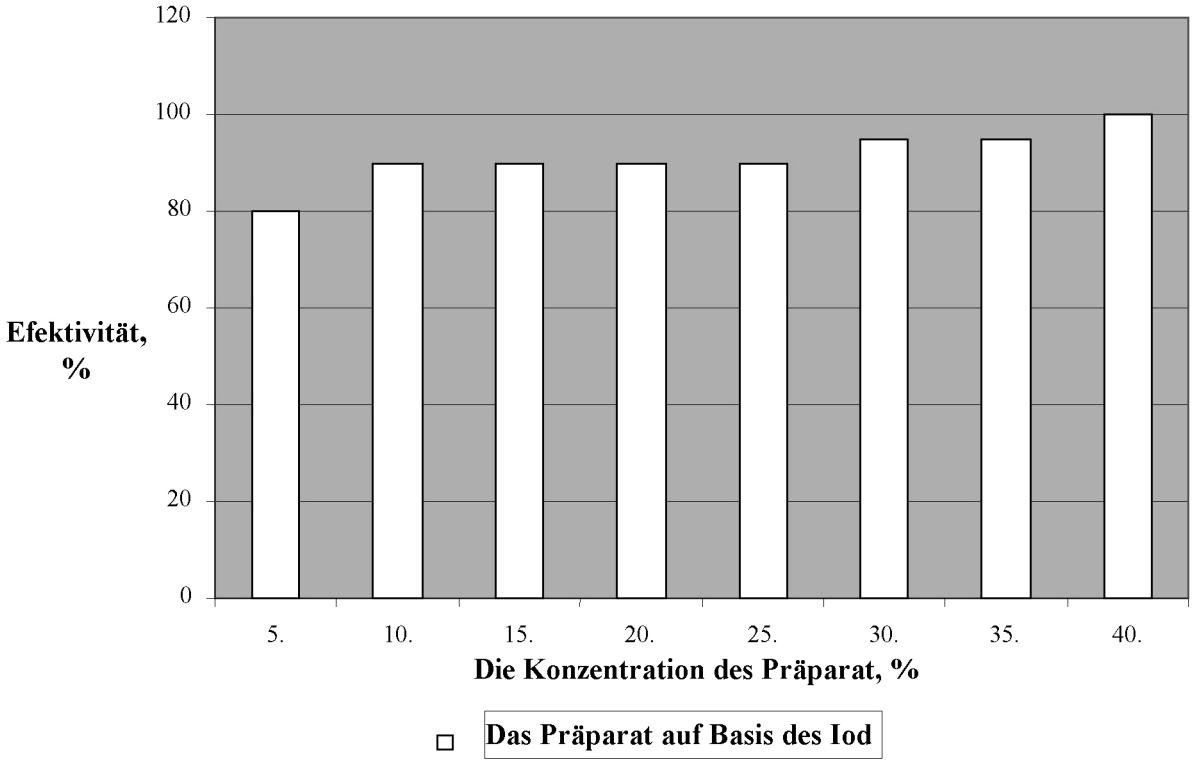

Abbildung 3. Anfängliche Wirksamkeit der repellent- Präparat auf der Grundlage von Jod (№ 2)

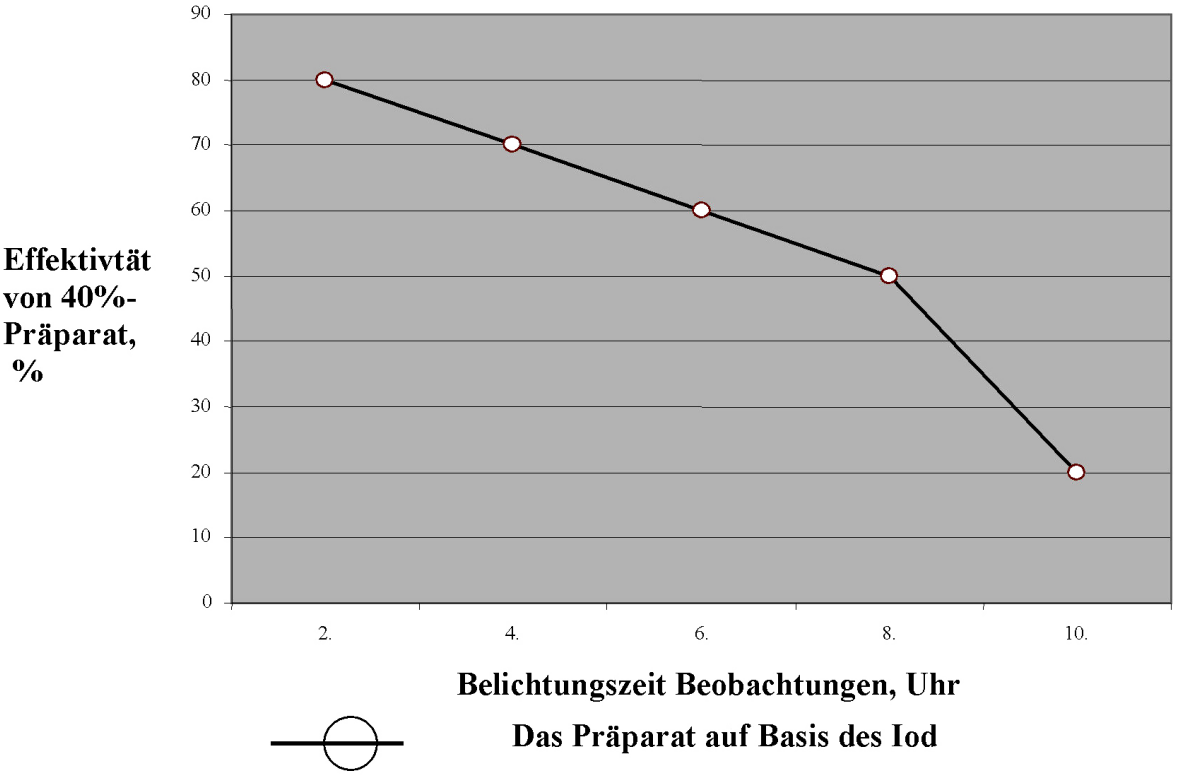

Abbildung 4. Dauer der Schutzwirkung des repellent-Präparats auf der Grundlage von Jod (№ 2)

Überwachung der Wirkung von Präparaten für 264 Stunden durchgeführt. Das Präparat deta, getestet als Standard, hat 100% Schutzwirkung für 4 Stunden. Nach 6 Stunden seine Wirksamkeit sank auf 90%, und 24 Stunden später auf 35% (Abb. 5).

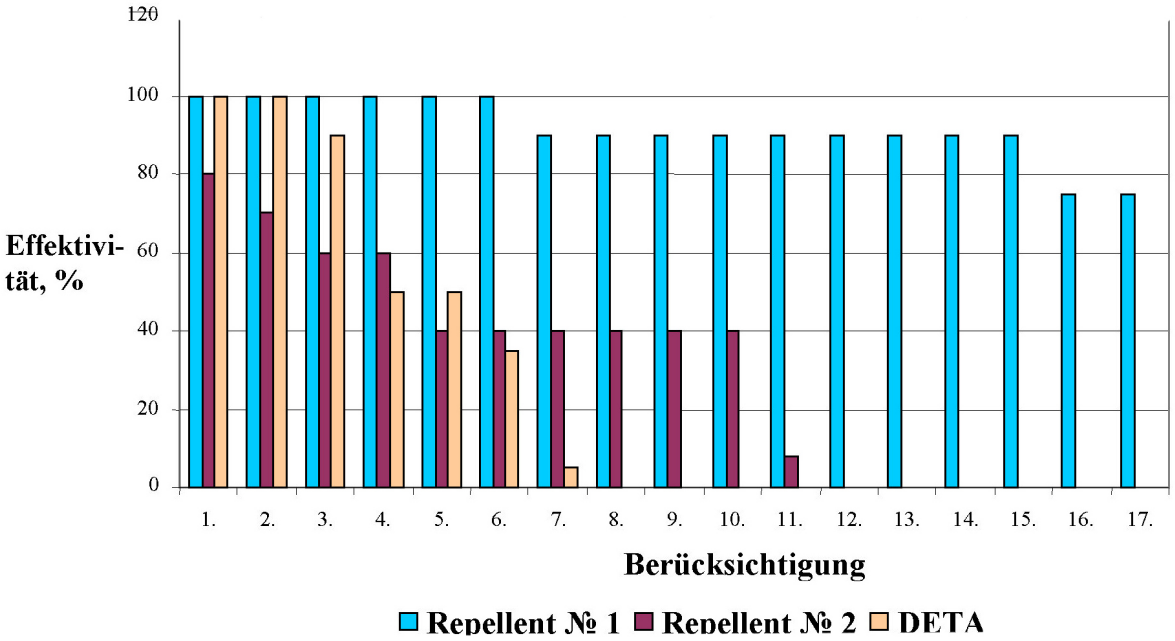

Abbildung 5. Wirksamkeit repellent Präparate gegen Ixodes Zecken

Das Präparat auf der Grundlage von Jod in 2 Stunden Beobachtungen zeigte Wirksamkeit bei 80%, und 24 Stunden – 40%. Dies ist aufgrund der hohen flüchtigen Jod und seine schnelle Verdampfung. Hohe Effizienz vor dem hintergrund dieser beiden Präparate zeigte repellent Nummer 1 auf der Basis von birkenmarmelade. Er hat innerhalb von 24 Stunden absolute (100%) Schutzwirkung gewährleistet. Später, im Laufe von 184 Stunden (von 32 bis 216) seine Effektivität hielt bei 90%. Stärkung der Fumigation Wirkung des Wirkstoffs-Birken-Teer als Teil der Droge repellent Aktion bietet flüssige Konsistenz, durch die Verwendung von neionogen Tenside gewonnen.

Die Dauer der Schutzwirkung des Arzneimittels auf der Grundlage der Birke teere überschreitet den Indikator im Vergleich data 6 mal. Zufriedenstellende Wirkung des Arzneimittels auf der Basis von birkenmehl bleibt für 32–216 Stunden (7,7 Tage), das übersteigt das bekannte Analogon von DETA 30,6 mal. Innovation der Forschung – zum ersten mal auf der Grundlage der natürlichen BAS entwickelt umweltfreundliche Präparat repellent Aktion, die eine langfristige Schutzwirkung gegen ixodes Zecken bietet.

Konsequenzen:

1. Entwickelt ein umweltfreundliches Präparat auf der Basis von natürlichen BAS repellent Aktion gegen ixod-milben;

2. Zeitraum der Schutzwirkung des Arzneimittels mit absoluter (100%) Wirksamkeit ist 24 Stunden, das übersteigt die bekannte Analogon – data-Präparat 6 mal. In den nächsten 7,7 Tage zeigt das Präparat eine Schutzwirkung von 90%, das übersteigt die bekannte Analogon- Präparat deta 30,6 mal;

3. Die Wirksamkeit der neuen repellentnogo Präparat bei hohen Temperaturen nicht reduziert wird, und steigt aufgrund der erhöhten Fumigation Aktivität des Wirkstoffs;

4. Das Präparat der repellent-Aktion kann nicht nur zum Schutz des Menschen verwendet werden, sondern auch Tiere.

Referencez:

1. Badalov E. T. Prävention von piroplazmidozov Rinder / E. T. Badalov // Veterinary,– 1989.– Nummer 6.– S. 37–40.
2. Butakov E. I. Wirksamkeit von insektoacarizid-Präparaten auf der Basis von natürlichen biologisch aktiven Substanzen gegen die häufigsten Ektoparasiten von Nutztieren / E.I. butakov: Autogramm. Diss … kande. Biol. Science 03.02.11 – Parasitologie.– Moskau,– 2016.– 21 s.
3. Butakov Ei instruktiv – methodische Brief über die Organisation der Sammlung von ixodnye Zecken in den Bereichen der Altairegion. Für die dienstliche Nutzung. Die Ausgabe der Altai krajsdravotdela. Barnaul.– 1991.– 3 s.
4. Desinfektion: Methoden zur Bestimmung der Wirksamkeit von Insektiziden, akariziden, Reglern der Entwicklung und repellent in der medizinischen Desinfektion verwendet – M.,– 2003.– 87 s.
5. Novikov T. W. Ökologie der Zecken und эпизоотология übertragenen Krankheiten / T. V. T. V. Novikov, N. In. Molotow, N. Und. Rybakov // Veterinärmedizin,– 2004.– Nummer 11.– S. 32–34.
6. Patent 2222572 RF, IPC C11D13 / 00 Verfahren zur Herstellung von flüssiger wirtschaftlicher insektizidseife aus neutralen Pflanzenölen /Schamanen L.D., Chabarow S.N., Schukowski A.V.; Antragsteller und Patentinhaber: NIISS Ihnen. M. A. Lisawenko.– No. 2000104190/13; Appl. 02.21.2000; publ. 27.01.2004.– Bul. Nummer 3.
7. Patent 2423112 RF. Das prparat FR den Kampf mit puhoperoedami der Vögel / Schamanisch LD, Butakow E. I., Usenko W. I.– die erklrung. 08.04.2010; publ. 10.07.2011; bul. Die Nummer 19.
8. Shchuchinova L. D. epidemiologische überwachung und Kontrolle von Infektionen, die Zecken in der Republik Altai / L. D. Shchuchinova übertragen: 14.00.30 autoref. Diss … kande. Honig. Wissenschaft.– Omsk,– 2009.– 22 s.
9. Yakimenko V. Zecken Westsibirien. Fauna. Ökologie, Grundlegende Methoden der Forschung / v. Yakimenko.– Omsk, 2013.– 239 s.
10. Estrada-Pena A. Association of environmental traits with the geographic ranges of ticks (Acari: Ixodidae) of medical and veterinary importance in the western Palearctic / A. Estrada-Pena, R. Farkas, T.G.T. Jaenson, F. Koenen, M. Madder, I. Pascucci // A digital data set. Exp. Appl. Acarol.– No. 59.– 2013.– P. 351–366.
11. Franke J. Exploring gaps in our knowledge on Lyme borreliosis spirochaetes-updates on complex heterogeneity, ecology, and pathogenicity /J. Franke, A. Hildebrandt, W. Dorn // Ticks Tick Borne Dis. 4,– 2012.– P. 11–25.
12. Goltz Lauren Survey of adult Ixodes scapularis Say for disease agents in Mississippi. / Lauren Goltz, Andrea Varela-Stokes, Jerome Goddard // The Society for Vector Ecology. DOI: 10.1111 / j. – 1948–7134. 12056. Vector Ecology – Volume 38. D. 11,– Nov.– 2013.– P. 401–403.
13. Namrata Pabbati Filarial Nematode Infection in Ixodes scapularis Ticks Collected from Southern Connecticut / Pabbati Namrata, Jamie M. Miller, Madar Sh., Patlolla Raghavend Reddy, Cheryl Bandoski, Michael J. Rossi, Eva Sapi // Department of Biology and Environmental Science. University of New Haven. West Haven. CT 06516. USA. Vet. Sci.– No. 1 (1),– 2014.– P. 5–15.

Section 5. Physiology

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INFLUENCE OF PHENAZEPAMUM ON ACTIVITY AND TOPOGRAPHY OF ENTERAL ENZYMES AT RATS OF NONAGGRESSIVE GROUP IN THE CONDITIONS OF AN IMMOBILIZED STRESS

Abstract: The digestive organs are almost always involved in the stress reaction of the body. Aggressiveness is an important form of zoosocial behavior in animals of different species, which has adaptive significance and is manifested by a species-specific set of behavioral responses (2,4). But the peculiarities of the functioning of the digestive organs, depending on the behavioral characteristics of the organism, have been studied insufficiently neither in norm, nor under stress.

Keywords: synergy, antagonism, somatotropic hormone, insulin, adrenocorticotropic hormone.

Relevance of work: was clarification of the functional condition of a small bowel at rats from nonaggressive group at a stress under the influence of Phenazepamum tranquilizer.

Purpose of work: studying of influence of Phenazepamum on activity and a topography of enteral enzymes at rats from nonaggressive group in the conditions of an immobilized stress.

Materials and methods: Experiments were made on adult not purebred rats with the body weight of 180–200 g. Three groups of rats – mixed (animals were not checked for aggression), nonaggressive and aggressive groups were used.

Animals were checked for aggression by a technique A. L. Rylova (1983); an irritant were electric impulses, each of which was shown to animals quadruple. Aggression size, the bound to pain, was estimated on an index of "an average score of the fights" which arose in response to a series from 88 impulses and the number of fights from 88 possible. Aggressive rats are those who have "the average score of fights" from 45,6 to 39,7. At rats with average aggression this index fluctuates from 38,8 to 33,4. At nonaggressive individuals it makes 32,6–0. The immobilized stress was caused in rats by the forced immobilization within 24 clocks. Phenazepamumwas administeredorally with

the preventive purpose in 30 minutes prior to a stress in a dose 2mg/kg. As monitoring rats are used with the corresponding typological characteristic to whom orally entered the equivalent amount of distilled water. Weight mucous was determined by routine weighing. The activity of digestive enzymes was determined by the following techniques: monoglitseridlipaza – method of A. M. Ugolev and M. Yu. Chernyakhovskaya (1969), glycyl-1-Leucinum-dipeptidgidrolaza – method of A. M. Ugolev and N. M. Timofeeva (1969), amylase – method Smith – the Swarm in A. M. Ugolev's modification (1969); saccharase– the Heleon method in modification of A. M. Ugolev and N. N. Iyezuitova (1969), lactase – the Dalhqvist (1968) method. The activity of enzymes was calculated on 1 g of mass of crude fabric of a mucosa of a small bowel and was expressed in mg/min/g for an amylase and in μmol/min/g for other enzymes. Statistical data processing was carried out by Student-Fisher's method.

***Results of researches*:** In this series of experiments as monitoring served intact rats from nonaggressive group. Nonaggressive ratsbore well a 24-hour immobilization. There were not lethal outcomes. The mass of a mucosa decreased in 6 h after an immobilization along all gut approximately by 1,5 times, in 24 h and further an index came back to monitoring level. In a homogenate of the mucosa removed along all small bowel, the activity of a monoglitseridlipaza was inhibited in 1,5; 2,2; 2,2 times in 6, 24, 48 h after a stress (tab. 1) The activity of a dipeptidgidrolaza increased through 6, 24, 48, h in 1,5; 1,6 and 2, 2 times. The activity of an amylase decreased throughout all experiment: in 6 h by 2,2 times, 24 h – by 2,4 times, 48 h – in the 1, 7 time. Thesaccharase activity was defined raised in 2, 3; 2,5; 2,7 times in 6, 24, 48 h after an immobilization. The activity of a lactase was inhibited by 2,2 times in 6 h, further did not differ from monitoring.

Table 1.– Activity of a monoglitseridlipaza (μmol/min/g) in a mucosa homogenate, removed along all small bowel at an immobilized stress and at a stress against the Phenazepamum at rats from nonaggressive group (M + m, n = 6)

Experimental conditions	Time in hours after a stress		
	6 hours	**24 hour**	**48 hours**
Intact rats (monitoring)	5,7 ± 0,2	5,7 ± 0,2	5,8 ± 0, 2
Immobilized stress	3,7 ± 0,2 < 0.05	2.6 ± 0.2 < 0.01	2.4 ± 0.1 < 0.01
Immobilized stress against the Phenazepamum	2.7 ± 0.2 < 0.01	4.1 ± 0.3 < 0.05	6.0 ± 0.3 < 0.1

The topography of enzymes at adult rats from nonaggressive group after an immobilization is changed, at the same time the expressed tendency to the shift of peaks of activity of enzymes in the caudal direction was traced.

The Monoglitseridlipaza activity in 6 h and 24 h went down in a duodenum and proximal intestine remained at the level of monitoring in medial department therefore its gradient changed. In 48 h, the indicator was normalized in three top departments, and increased in distal. The activity of a dipeptidgidrolaza through 6, 24,48ch went down in a duodenum, remained at the level of monitoring in proximal and medial departments and increased in distal department that also led to gradient shift in the caudal direction (fig). The amylolytic activity decreased in 6 h and 24 h in a duodenum and proximal intestine, remained within norm in medial department and increased in distal. In 48 h after an immobilization, the topography of activity of enzyme did not differ from monitoring. The saccharasa activity was induced throughout all experience on all sites of a gut, but is especially strong in distal intestine therefore the shift of a maximum of its ac-

tivity in the distal direction took place. The activity of a lactase in all terms after a stress did not differ from monitoring on all sites of a gut and its topography did not change. Preventive introduction of Phenazepamum to a stress rendered to animals of this group approximately the same leveling effect on the studied indicators, as well as in the mixed group of animals, i.e. against the background of a tranquilizer the functional condition of a small intestine was almost completely normalized in 48 h. It concerned activity of enzymes in a homogenate mucous, removed along all small bowel (tab.), a topography of enzymatic activities (fig). The mass of a mucosa did not differ from monitoring.

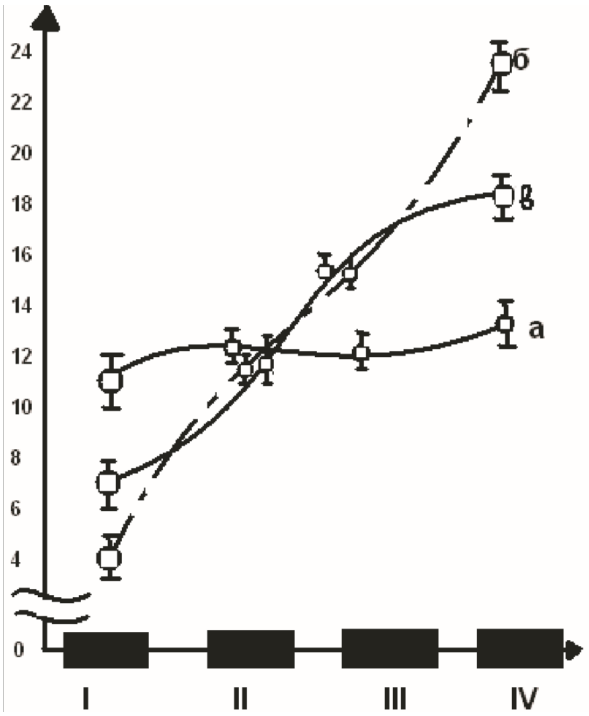

Figure 1. Distribution of activity of a dipeptidgidrolaza along a small bowel in 24 hours after an immobilized stress and after a stress against the Phenazepamum

Axis of ordinates:

a – intact rats (monitoring);

b – an immobilization;

c – an immobilization against the Phenazepamum

Abscissa axis:

I – duodenum;

II – proximal intestine;

II – medial intestine;

IV – distal intestine.

Conclusions

1. The immobilized stress differently influences functional and morphological indicators of a small bowel depending on behavioral features of rats.

2. The stress does not cause death of individuals from the mixed

3. The topography of all enzymatic activities changes, generally at the expense of the shift of their maximum in a distal segment.

4. Decrease in mass of a mucosa on all sites of a small bowel is characteristic.

References:

1. Cox, T. Stress, coping and problem solving // Work and stress.– No. 1 – P. 5–14.

2. Palmour R. M. Genetic models for study of aggressive behavior || Progr. Neuropsychopharmacol and boil. Psychiatr – 2002.– V. 7.– P. 573–576.
3. Ugolev A. M. Physiology and pathology of parietal (contact) digestion. S. Pb. Science.– 2001.– 230 p.
4. Phurduy Ph. I. The modern ideas of physiological mechanisms of development of a stress. Kishinev,– 2001.– P. 8–33.
5. In Methods in Enzymology,– Vol. 1.– 435 p. Ed. by Colowick, S. P. & Kaplan, N. 0. New York: Academic Press Inc.
6. In Advances in Enzyme Regulation,– Vol. 1.– 121 p. Ed. by Weber, G. London: Pergamon Press Ltd.

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SEROTONIN AND HEART FAILURE

Abstract: A various mechanisms of vegetotrophic drugs influence on heart failure development were discussed. Current information about the physiological effects of serotonin in relation to cardiac function was summarized. The features of a possible adrenergic and serotonergic drugs in a treatment of heart failure were shown.

Keywords: Heart failure, serotonin, 5-HT-receptors.

Chronic heart failure is a pathophysiological syndrome as a result of the cardiovascular diseases and reflects a decrease in the pumping function of the heart, which leads to an imbalance between the metabolic requirements of an organism and heart capabilities [1]. Heart failure may develop as a result of myocardial contractility disturbances [2] and metabolic violations in cardiomyocytes [3] or a disturbances of myocardial remodeling [4]. Adaptive response of the heart to the increased workload is hypertrophy. Cardiac hypertrophy is usually characterized by an increase in cardiomyocyte size and thickening of ventricular walls. Initially, this growth is an adaptive response to maintain the function of the heart; however, eventually, under conditions of prolonged stress, these changes become inadequate [5]. Many growth factors and key regulators such as gp130 [6], c-Jun NH(2)-terminal kinase/ p38 kinase (JNK/p38) [7], calcineurin/NFAT, CaMKII/ HDAC [8] promote hypertrophic reaction.

Specific regulators of hypertrophy include additional c GMP, natriuretic peptides, histone deacetylase, interleukin-6 cytokine family, PI3K, MARK pathways, Na/H exchanger, polypeptide growth factors, ANP, NO, TNF-alpha, PPAR, miRNA and gene mutation in the adult heart [9]. It is assumed that the initial phase of the cardiac hypertrophy processes under the influence of paracrine and autocrine factors such as endothelin-1, norepinephrine or angiotensin II [10], whose receptors are linked to

G-proteins associated families Gq/11, G12/13 and Gi/o. An over expression of βl-adrenergic and angiotensin receptors by cardiomyocytes, as well as Gq β-subunit, results in myocardial hypertrophy.

It is proved that regular application of adrenergic blockers for the treatment of cardiovascular diseases leads to a compensatory increase in the amount of 5-HT4 receptors on the membrane of cardiomyocytes. The authors observed a two-time rate increase and power of contraction in response to serotonin reaction of isolated cardiomyocytes derived from patients treated blockers long time [11]. In this context serotonin can be regarded as a competent circulatory hormonal factor that acts either directly on the properties of cardiomyocytes or stimulates chemoreceptor's of the nerve endings in a heart.

Serotonin has a pronounced effect on the myocardium and enhances vagal inhibitory effect [12] and participate in the development of cardiac hypertrophy, cardiac insufficiency [13] and fibrosis [13; 14]. It is noteworthy that the first contraction of embryo's heart due to the action of serotonin [15]. Serotonin receptors are the most common species of receptors in the central nervous system and effector organs. About 40% of serotonin G-protein associated receptors found clinical application, including in the heart failure correction [16].

The structure of the serotonergic system with 5-HT1, 5-HT2, 5-HT3 and 5-HT4 as a receptors of the autonomic nervous system is shown in Fig. 1. According to published scientific data the role of serotonin receptors of activation in the healthy organism and during the heart failure formation was established.

5-HT1A receptors. Activation of this receptor results in a lowering of blood pressure and heart rate. These receptors are involved in the mechanisms of vascular tone regulation.

5-HT2A receptors. The positive inotropic response to serotonin is mediated by 5-HT2A and 5-HT4 receptors, observed in rats with post-infarction ventricular congestive heart failure and pressure overload-induced hypertrophy [17; 18].

5-HT2A receptors mediate the development of hypertrophy in response to endogenous serotonin. Selective blockade of 5-HT2A receptors has beneficial effects in the development of cardiac hypertrophy through inhibition of the calmodulin kinase/ histone deacetylase 4 (CamKII/HDAC4) pathway [13].

5-HT2B receptors. Myocardiocytes also expresses 5-HT2B receptor [19]. Chronic heart failure is accompanied by increased expression of mRNA for 5-HT(2B) and 5-HT(4) receptors [17]. 5-HT2B receptor of nerve cell by stimulation through nicotinamide-adenine dinucleotide phosphate (NAD(P)H) oxidase is associated with the synthesis of reactive oxygen species and a cardiac hypertrophy caused by angiotensin II and isoproterenol [20]. The blockade of 5-HT2B receptor prevents the isoproterenol-induced cardiac hypertrophy; however, activation of 5-HT(2B) receptor causes hypertrophy by direct action on cardiomyocytes [21].

The significant role of serotonin in the development and progression of cardiac hypertrophy of the ventricles has been shown in models of pulmonary hypertension in mice [13; 14; 22]. Terguride (5-HT2A and 5-HT2B receptor antagonist) and SB204741 (5-HT2B receptor antagonist) reduce collagen deposition, thereby inhibiting right ventricular fibrosis [23; 24]. Antagonists of 5-HT2B receptors reduce collagen deposition, thereby inhibiting the fibrosis of the right ventricle. Long-term therapy by drugs with this effect prevents the development and progression of pressure due to overload caused by right ventricular failure in mice. Thus, the 5-HT2B receptor antagonists represent a valuable new treatment of right heart failure [23]. A cross-narrowing of the aorta rapidly increased the expression of 5-HT2 receptor in the left ventricle, and selective receptor blockade prevented the development of cardiac hypertrophy was demonstrated [14; 23].

5-HT4 receptor is a metabotropic agent when increases the amount of cAMP in the cell, which in turn initiates a cascade of neurochemical reactions. Earlier, this receptor seemed as the cardiac specific

receptor due to its discovery in the highest concentrations in parts of the atrial cardiac conduction system [25]·Later, however, the 5-HT4 receptors were found in other tissues and organs: gastrointestinal tract, urinary bladder, adrenal glands [26]. Blockers of 5-HT4 receptors are used in the treatment of atrial fibrillation, incontinence and irritable bowel syndrome combined with diarrhea. Perceptivity of application of these receptors in the treatment of heart failure has been shown [27]. Our analysis of the literature has revealed a wealth of evidence that 5-HT4 receptor agonists have clinical efficacy in the treatment of gastrointestinal disorders and no evidence of cardiovascular safety concerns with selective 5-HT4 receptor agonists [28]. 5-HT4 receptors mediate positive chronotropic and inotropic effects of serotonin in the myocardium of an atrium and a ventricle [11]. In chronic heart failure the positive inotropic effect, implemented through 5-HT4 receptors, have been enhanced [17]. In addition, the contractile response of the left ventricle of the human tissue to activate the 5-HT4 receptors in heart failure is magnified with the prior administration of prostaglandin E1 (PGE-1) [29]. According to J. Tack et al. selective activation of the 5-HT4 receptor does not cause negative cardiotropic effects. These effects are due to non-selective interaction of cisapride with sodium hERG channels, and / or activation of 5-HT1B receptors by tegaserod [28]. Specifically, there was no evidence of an increase in the incidence of prolongation of QT corrected interval of electrocardiogram in the prucalopride treatment [30].

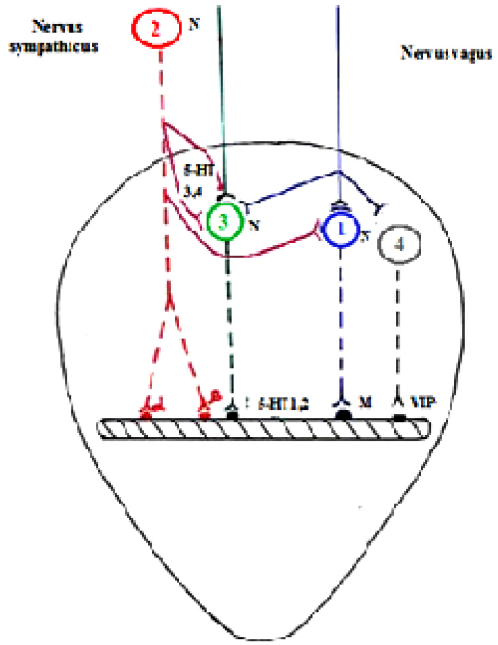

Figure 1. The Scheme of efferent innervation of the heart. Designations: Numbers in the circles denoted neurons:1 – cholinergic, 2 – sympathetic, 3 – serotonergic,4 – VIP-ergic. Receptors: α – alpha-adrenergic receptor; β – beta-adrenergic receptor; M – muscarinic acetylcholine receptor; N – nicotinic acetylcholine receptor, 5-HT – 5 – hydroxytryptamine receptor 1,2,3 and 4 subtypes; VIP – vasoactive intestinal peptide

Thus, serotonin is an important cardiotropic agent ensuring the maintenance of vascular tone and the contractile potential of cardiomyocytes. The review presents information about the physiological role of serotonin and would help to use effective personal strategy of heart failure treatment.

We declare that all authors have seen and approved the final version of the manuscript being

submitted. It is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Conflict of interest

Author has no conflict of interest to disclose. No financial support was provided.

References:

1. Dickstein K., Cohen-Solal A., Filippatos G., McMurray J.J., Ponikowski P., Poole-Wilson P.A., Strömberg A., vanVeldhuisen D.J., Atar D., Hoes A.W., Keren A., Mebazaa A., Nieminen M., Priori S.G., Swedberg K.; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure – 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure – 2008 of the European Society of Cardiology. Eur Heart J. – 2008; 29: 2388–4426.
2. Später D., Hansson E.M., Zangi L., Chien K.R. How to make a cardiomyocyte. Development – 2014; 141:4418–31.
3. Garnier A., Zoll J., Fortin D., N'Guessan B., Lefebvre F., Geny B., Mettauer B., Veksler V., Ventura-Clapier R. Control by circulating factors of mitochondrial function and transcription cascade in heart failure: a role for endothelin-1 and angiotensin II. Circ Heart Fail – 2009; 2: 342–50.
4. Nigmatullina R.R., Kirillova V.V., Jourjikiya R.K., Mukhamedyarov M.A., Kudrin V.S., Klodt P.M., Palotás A. Disrupted serotonergic and sympathoadrenal systems in patients with chronic heart failure may serve as new therapeutic targets and novel biomarkers to assess severity, progression and response to treatment. Cardiology.– 2009; 113: 277–86.
5. Tham Y.K., Bernardo B.C., Ooi J.Y., Weeks K.L., McMullen J.R. Pathophysiology of cardiac hypertrophy and heart failure: signaling pathways and novel therapeutic targets. Arch Toxicol – 2015; 89:1401–38.
6. Askevold E.T, Gullestad L., Dahl C.P., Yndestad A., Ueland T., Aukrust P. Interleukin-6 signaling, soluble glycoprotein 130, and inflammation in heart failure. Curr Heart Fail Rep – 2014; 11: 146–55.
7. Tang K., Li X., Zheng M.Q., Rozanski G.J. Role of apoptosis signal-regulating kinase-1-c-Jun NH2-terminal kinase-p 38 signaling in voltage-gated K+ channel remodeling of the failing heart: regulation by thioredoxin. Antioxid Redox Signal – 2011; 14: 25–35.
8. Oliveira R.S., Ferreira J.C., Gomes E.R., Paixão N.A., Rolim N.P., Medeiros A., Guatimosim S., Brum P.C. Cardiac anti-remodelling effect of aerobic training isassociated with a reduction in the calcineurin / NFAT signalling pathway in heartfailure mice. J Physiol – 2009; 587: 3899–910.
9. Rohini A., Agrawal N., Koyani C.N., Singh R. Molecular targets and regulators of cardiac hypertrophy. Pharmacol Res – 2010; 61: 269–80.
10. Itoh H., Mukoyama M., Pratt R.E., Gibbons G.H., Dzau V.J. Multiple autocrine growth factors modulate vascular smooth muscle cell growth response to angiotensin II. J Clin Invest – 1993; 91: 2268–74.
11. Akhmetzyanov V.F., Yakupov A.F., Nigmatullina R.R. Age features inotropic effect of serotonin in the rat myocardium. Kazan Med J – 2010; 91: 467–471.
12. Lychkova A.E. [Mechanisms of synergism of the autonomic nervous system compartments]. Usp Fiziol Nauk.– 2006; 37: 50–67. Review. Russian.
13. Lairez O., Cognet T., Schaak S., et al. Role of serotonin 5-HT2A receptors in the development of cardiac hypertrophy in response to aortic constriction in mice. Journal of Neural Transmission.– 2013; 120: 927–935. doi: 10.1007/s00702–013–1011–3.
14. Mann D.A., Oakley F. Serotonin paracrine signaling in tissue fibrosis. Biochim Biophys Acta: Mor Basis Dis.– 2013; 1832: 905–910.

15. Shur V. Y., Samotrueva M. A., Mazhitova M. V., Trizno N. N., Fayziev R. M., Petrenko L. V., Shur Y. V. Serotonin: biological properties and prospects of clinical application. Fund Res (Russian).– 2014; 3: 621–629.
16. McCorvy J.D., Roth B. L. Structure and function of serotonin G protein-coupled receptors. Pharmacol Ther – 2015; 150: 129–42.
17. Brattelid T., Qvigstad E., Moltzau L.R, Bekkevold S. V., Sandnes D. L., Birkeland J. A., Skomedal T., Osnes J. B., Sjaastad I., Levy F. O. The cardiac ventricular 5-HT4 receptor is functional in late foetal development and is reactivated in heart failure. PLoS One – 2012; 7: e45489.
18. Maroteaux L., Ayme-Dietrich E., Aubertin-Kirch G., Banas S., Quentin E., Lawson R., Monassier L. New therapeutic opportunities for 5-HT(2) receptor ligands. Pharm Ther.–2017; 170: 14–36.
19. Fonfara S., Hetzel U., Oyama M. A., Kipar A. The potential role of myocardial serotonin receptor 2B expression in canine dilated cardiomyopathy. Vet J – 2014; 199: 406–12.
20. Monassier L., Laplante M. A., Jaffré F., Bousquet P., Maroteaux L., de Champlain J. Serotonin 5-HT(2B) receptor blockade prevents reactive oxygen species-induced cardiac hypertrophy in mice. Hypertension – 2008; 52: 301–7.
21. Ayme-Dietrich E., Marzak H., Lawson R., Mokni W., Wendling O., Combe R., Becker J., El Fertak L., Champy M. F., Matz R., Andriantsitohaina R., Doly S., Boutourlinsky K., Maroteaux L., Monassier L. Contribution of serotonin to cardiac remodeling associated with hypertensive diastolic ventricular dysfunction in rats. J Hypertens – 2015; 33: 2310–21.
22. Shyu K.-G. Serotonin 5-HT_{2B} receptor in cardiac fibroblast contributes to cardiac hypertrophy: a new therapeutic target for heart failure? Circulation Research.– 2009; 104: 1–3.
23. Janssen W., Schymura Y., Novoyatleva T., et al. 5-HT2B receptor antagonists inhibit fibrosis and protect from RV heart failure. BioMed Res Internat.– 2015; 438403.
24. Adegunsoye A., Levy M., Oyenuga O. Novel Therapeutic Strategies for Reducing Right Heart Failure Associated Mortality in Fibrotic Lung Diseases. Biomed Res Internat. – 2015; 2015: 929170.
25. Blondel O., Vandecasteele G., Gastineau M., Leclerc S., Dahmoune Y., Langlois M., Fischmeister R. Molecular and functional characterization of a 5-HT(4) receptor cloned from human atrium. FEBS Lett – 1997; 412: 465–474.
26. Breidert M., Wördehoff S., Hansen A., Eftekhari P. Autoantibodies against serotoninergic 5-HT(4) receptor in patients with heart failure. Horm Metab Res – 2012; 44: 70–4.
27. Brudeli B., Moltzau L. R., Nguyen C. H., Andressen K. W., Nilsen N. O., Levy F. O., Klaveness J. Synthesis and pharmacological properties of a new hydrophilic and orally bioavailable 5-HT4 antagonist. Eur J Med Chem – 2013; 64: 629–37.
28. Tack J., Camilleri M., Chang L., Chey W. D., Galligan J. J., Lacy B. E., Müller-Lissner S, Quigley E. M., Schuurkes J., De Maeyer J. H., Stanghellini V. Systematic review: cardiovascular safety profile of 5-HT(4) agonists developed for gastrointestinal disorders. Aliment Pharm Ther.– 2012; 35: 745–67.
29. RiiseJ Ørstavik Ø., Qvigstad E., Dahl C. P., Osnes J. B., Skomedal T., Levy F. O., Krobert K. A. Prostaglandin E1 facilitates inotropic effects of 5-HT4 serotonin receptors and β-adrenoceptors in failing human heart. Basic Res Cardiol.– 2012; 107: 295. PubMed PMID: 22923058.
30. Camilleri M., Beyens G., Kerstens R., Robinson P., Vandeplassche L. Safety assessment of prucalopride in elderly patients with constipation: a double-blind, placebo-controlled study. Neurogastroenterol Motil.– 2009; 21: e1256–e117.

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