ВЛИЯНИЕ ЛИМФОЦИТОВ СЕЛЕЗЕНКИ, ОБРАБОТАННЫХ ОРИГИНАЛЬНЫМ АНТИКОНВУЛЬСАНТОМ, НА ГЕМОПОЭЗ ПРИ ДЛИТЕЛЬНОМ УПОТРЕБЛЕНИИ АЛКОГОЛЯ

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Резюме. Излишнее потребление алкоголя оказывает негативное влияние на гемопоэз, что выражается в значительной супрессии как продукции клеток крови, так и в структурных изменениях предшественников, а именно в подавлении их созревания, вплоть до панцитопении. Различают прямой эффект алкоголя (токсический эффект на костный мозг, гемопоэтические предшественники и зрелые клетки крови) и непрямой эффект, обусловленный дефицитом трофических факторов. У алкоголиков зачастую выявляется анемия, как следствие разрушение эритроидных клеток до их созревания. Тромбоцитопения – также один из важнейших показателей гематологических нарушений при алкоголизме – является причиной появления петехий и спонтанных кровотечений. Хроническое употребление алкоголя также оказывает супрессивное воздействие на продукцию и функции клеток белой крови, следствием чего является низкая способность противостоять бактериальной инфекции. Нами ранее выявлены иммуномодулирующие свойства инновационного антиконвульсанта, мета-хлорбензгидрилмочевины, что обуславливает его позитивный эффект при внутрижелудочном введении у длительно алкоголизированных мышей. Показано также, что модулированные *in vitro* указанным антиконвульсантом селезеночные лимфоциты посредством относительно независимых механизмов оказывают позитивное психонейромодулирующее влияние при хронической интоксикации этанолом. В настоящей работе на модели хронического алкоголизма исследовалось влияние трансплантации лимфоцитов селезенки, прекультивированных с мета-хлорбензгидрилмочевиной, на костномозговой гемопоэз и показатели периферической крови. В костном мозге длительно алкоголизированных мышей наблюдалось снижение колониеобразующей активности гемопоэтических предшественников: значительно сократилась популяция эритроидных предшественников, на уровне тенденции также зарегистрировано снижение популяция гранулоцитарно-макрофагальных. Исключение составила популяция ранних предшественников, количество колоний в которой не менялось. В периферической крови наблюдалось снижение количества лимфоцитов, тромбоцитов, эритроци-

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тов, гематокрита (на уровне тенденции) и лейкоцитов при возрастании популяция сегментоядерных нейтрофилов, указывающей на периферическое воспаление. Лимфоциты, прекультивированные с мета-хлорбензгидрилмочевиной, после внутривенного введения сингенным длительно алкоголизированным реципиентам, оказывали корректирующее воздействие на ряд показателей гемопоэза, что проявилось в восстановлении колониеобразующей активности костномозговых гемопоэтических предшественников до показателей, сравнимых с таковыми у интактных мышей соответствующего возраста, в снижении в периферической крови количества сегментоядерных нейтрофилов, восстановлении популяций эритроцитов и лимфоцитов, а также тенденции к повышению количества тромбоцитов. Полученные данные могут свидетельствовать об эффективности трансплантации модулированных мета-хлорбензгидрилмочевиной лимфоцитов в коррекции ряда изменений гемопоэза, спровоцированных длительной интоксикацией этанолом.

Ключевые слова: лимфоциты, оригинальный антиконвульсант, алкоголизм, гемопоэз, костный мозг, клетки периферической крови

HEMATOPOIETIC EFFECTS OF SPLEEN LYMPHOCYTES TREATED WITH AN ORIGINAL ANTICONVULSANT DURING LONG-TERM ALCOHOL CONSUMPTION

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Abstract. Excessive alcohol consumption has a negative effect on hematopoiesis, which manifests with significant suppression of both blood cell production, and structural changes in hematopoietic precursors, i.e., by suppression of their maturation, up to pancytopenia. One may distinguish between the direct effect of alcohol (toxicity to bone marrow, hematopoietic precursors and mature blood cells), and the indirect action caused by deficiency of trophic factors. Alcohol addicts often develop anemia, due to premature destruction of erythroid cells. Thrombocytopenia, also being an important feature of hematological disorders in alcoholism, results in spontaneous bleeding and petechiae. Chronic alcohol consumption also has a suppressive effect on production and functioning of white blood cells, resulting in poor resistance to bacterial infections. We have previously identified the immunomodulatory properties of an innovative anticonvulsant, meta-chlorobenzhydrylurea (m-CBHU). Its positive effect was determined upon intragastric administration in long-term alcoholized mice, In a recent study, splenic lymphocytes, being *in vitro* exposed to the mentioned anticonvulsant, have shown a positive psychoneuromodulatory effect during chronic ethanol intoxication. These effects seem to proceed via relatively independent mechanisms. In this study, the effects of intravenous transfusion of m-CBHU-treated spleen lymphocytes on bone marrow hematopoiesis and peripheral blood cells were tested in murine model of chronic alcoholism. In the bone marrow of syngeneic recipients (long-term alcoholized mice), a decreased colony-forming activity of hematopoietic precursors was observed: the population of erythroid precursors was significantly reduced. Decreased counts of granulocyte-macrophage precursors were also detected at a trend level. The only exception was the population of early progenitors, where the number of colonies did not change. In peripheral blood, a decreased number of lymphocytes, platelets, erythrocytes and leukocytes was observed associated with increase in the population of segmented neutrophils, suggesting peripheral inflammation. Lymphocytes pre-cultured with meta-chlorobenzhydryl urea, after intravenous administration to syngeneic long-term alcoholized recipients, had a corrective effect on a number of hematopoietic parameters, which manifested with restoration of the colony-forming activity of bone marrow hematopoietic precursors to the levels comparable to those in intact age-matched mice, along with decrease of segmented neutrophils and restoration of RBC and lymphocyte counts as wells as a tendency for increase in platelet counts in peripheral blood. The data obtained may suggest the efficiency of meta-chlorobenzhydrylurea-modulated lymphocytes in correction of distinct changes in hematopoiesis associated with long-term ethanol intoxication.

Keywords: lymphocytes, anticonvulsant, alcoholism, hematopoiesis, bone marrow, peripheral blood cells

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Introduction

Excessive alcohol consumption leads to a significant suppression of both the production of blood cells and structural changes in precursors including the suppression of their maturation and subsequent pancytopenia. Specifically, it has been reported that alcoholics often develop anemia as a consequence of the destruction of erythroid cells before they mature [1]. Alcohol has a suppressive effect on the production and function of white blood cells, resulting in frequent bacterial infections [3]. Thrombocytopenia is also reported as one of the important indicators of hematological disorders in alcoholics [2, 14] leading to petechiae and spontaneous bleeding. A distinction is made between the direct effect of alcohol (toxic effect on the bone marrow, hematopoietic precursors and mature blood cells) and the indirect effect via inducing a deficiency of trophic factors in bone marrow microenvironment [1, 2, 3, 4].

Expression of GABAA-R subunits in various types of mammalian immune cells and a role of GABAergic signaling pathway in non-neural tissues has been previously reported [5, 8]. We also described earlier the positive immunomodulatory properties of a synthetic GABAA-R ligand, meta-chlorobenzhydrylurea (m-CBU), when it was administered intragastrically to long-term alcoholized (LTA) mice [5, 6, 7, 8]. We demonstrated that by triggering GABAA-R, *in vitro* treatment with m-CBU normalizes functions of lymphocytes obtained from LTA mice subjected to chronic ethanol intoxication. Specifically, the increased lymphocyte proliferation was reduced by m-CBU and reduced sensitivity to T cell mitogen was increased to levels observed in intact mice [10]. It has also been shown that splenic lymphocytes, modulated *in vitro* by m-CBU and administered to LTA recipients, have a positive psychoneuroimmunomodulatory effects as reflected by improved behavioral patterns, stimulation of neuroplasticity and reduction of neuroinflammation, stimulation of humoral immune response, estimated by the relative number of antibody-forming spleen cells [5, 7, 9].

The purpose of this work was to study bone marrow hematopoiesis and peripheral blood parameters in LTA recipients after transplantation of syngeneic lymphocytes modulated *in vitro* by m-CBU.

Materials and methods

Mice

The study was performed on male (CBAxC57BL/6) F1 mice 10 months of age, obtained at the age of 3 months from the nursery of the Department of Experimental Biological Models of the Research Institute of Pharmacology and Regenerative Medicine. The animals were kept in the laboratory vivarium conditions in cages of 10 animals, on a standard diet, under natural light conditions. Animal studies were conducted in accordance with the legislation of the Russian Federation, the provisions of Directive 2010/63/EU of the European Parliament and Council of the European Union of 22 September 2010 on the protection of animals used for scientific purposes, the requirements and recommendations of the Guidelines for the care and use of laboratory animals and were approved at a meeting of the local ethical committee of Federal State Budgetary Scientific Institution "Research Institute of Fundamental and Clinical Immunology" (minutes of meeting No. 139 dated 30 May 2022).

Considering the presence in the population of male (CBA × C57Bl/6)F1 individuals with active and passive types of behavior that differ in the level of ethanol consumption [5, 6], in order to form homogeneous experimental groups, all mice were preliminarily tested in the "Open field", and only individuals with an average level of behavior were included in the study.

Alcoholization protocol

To model chronic alcohol intoxication, we used the forced drinking method, in which mice were forced to consume a 10% ethanol solution as the only source of liquid for 6 months. Control mice were drinking water under similar experimental conditions.

Preparation and transplantation of lymphocytes

Isolation and preparation of splenic lymphocytes for transplantation have been described in detail previously [9]. Briefly, isolated from LTA mice splenic lymphocytes were incubated *in vitro* with m-CBU at a concentration of 10 μg/mL for 30 minutes. Then, after three times washing from the substance in saline, the cells were resuspended in RPMI-1640 medium. Lymphocytes precultured with m-CBU were injected intravenously (15×10^6 cells per animal) into syngeneic LTA recipients (Recipients 2). LTA mice, which were injected with lymphocytes precultured under similar experimental conditions without m-CBU were used as control group (Recipients 1, negative control #1). LTA mice were used as a negative control #2; intact mice of the corresponding age were used as a positive control. Twenty-four hours after the transplantation, mice from the experimental and control groups were sacrificed by decapitation. Obtained tissues (bone marrow and peripheral blood) were used for this study.

Colony-forming assays

To assess the number of bone marrow hematopoietic progenitors, the bone marrow of animals was washed out from the femur using a syringe with conditioned RPMI-1640 medium containing 10%

FCS. The number of bone marrow cells (BMC) in 1 mL was counted using a PCE-90 hematology analyzer (Erma Inc., Japan). To determine the number of committed precursors, animal BMC at a concentration of 2.0×10^4/mL were incubated in 24-well plates in methylcellulose medium M 3434 (Stem Cell Technology, Canada) containing the cytokines SCF, EPO, IL-3, and IL-6. Granulocyte-macrophage (CFU-GM), erythroid (early BFU-E, late CFU-E) and granulocyte-erythroid-macrophage-megakaryocyte (CFU-GEMM) colonies were counted under an inverted microscope after a 14-day incubation at a temperature of 37 °C, in a humid environment, atmosphere containing 5% CO_2, according to the recommendations of Stem Cell Technologies (Canada). Data are presented as number of CFU/10^5 BMC.

Histology

The cellular composition of the blood of mice was assessed using a PCE-90 hematology analyzer (Erma Inc., Japan). The relative amount of blood cells was counted in smears stained according to Romanovsky–Giemsa.

Statistical analysis

Statistical analysis of the data was performed using portfolio Statistica 10.0 for Windows (StatSoft, Tulsa, OK, USA) analytical software. The group data samples did not follow the normal distribution law (according to the Shapiro-Wilk test), so non-parametric tests were used for statistical analysis. For multiple intergroup comparisons, the Kruskal-Wallis test was used for independent variables. If there were statistically significant differences in this test, a posteriori pairwise analysis of intergroup differences in indicators was used using the Mann–Whitney U test. Results are presented as the mean ± SD. Differences were considered significant at $p \le 0.05$.

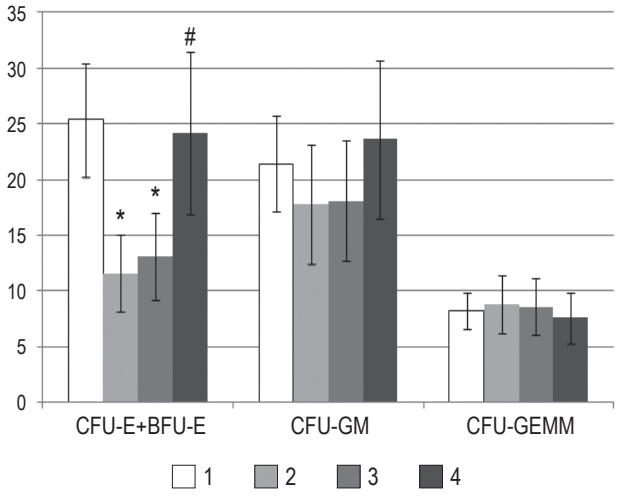

Figure 1. Colony-forming activity of bone marrow hematopoietic precursors of long-term alcoholized males (CBA × C57Bl/6)F1 after transplantation of syngeneic spleen lymphocytes modulated *in vitro* with meta-chlorobenzhydryl urea

Note. 1, intact mice; 2, long-term alcoholized mice; 3, long-term alcoholized recipients after transplantation of syngeneic splenocytes precultured without meta-chlorobenzhydryl urea (Recipients 1); 4, long-term alcoholized recipients after transplantation of syngeneic splenocytes precultured with meta-chlorobenzhydryl urea (Recipients 2). Data are presented as M±SD; n = 8 in each group; *, $p < 0.05$ compared with intact animals; #, $p < 0.05$ compared with long-term alcoholized animals and the "Recipient 1" group (Mann–Whitney test).

Results and discussion

In the bone marrow of LTA mice, a decrease in the colony-forming activity of hematopoietic precursors was observed. The number of erythroid precursors (CFU-E + BFU-E) was decreased from $27.2 \pm 5.9 \times 10^5$ BMC in control mice to $9.2 \pm 3.4 \times 10^5$ BMC in LTA mice ($p = 0.001$, Figure 1). The number of granulocyte-macrophage (CFU-GM) precursors was characterized by a downward trend ($22.8 \pm 4.7 \times 10^5$ BMC in control mice to $17.0 \pm 2.9 \times 10^5$ BMC in LTA mice ($p = 0.0584$, Figure 1). Interestingly, the number of early progenitors (CFU-GEMM) did not change with long-term alcoholization ($8.8 \pm 2.5 \times 10^5$ BMC in LTA mice and $8.2 \pm 2.6 \times 10^5$ BMC in control mice, $p = 0.362$, Figure 1). Our findings are in line with previously reported results that early hematopoietic stem cells (HSC) and multipotent precursors are more resistant to the negative effects of ethanol and acetaldehyde compared to committed precursors [15]. However, other studies report an increased apoptosis of HSC with a reduction in their numbers [1] and a decrease in their functional activity during acute and severe alcohol intoxication was reported [13]. Thus, additional studies are warranted to further clarify the effects of different protocols of alcoholization on bone marrow hematopoiesis.

Next, we investigated the effects of *ex vivo* m-CBU-modulated lymphocytes on bone marrow hematopoiesis in syngeneic LTA recipients. The number of precursors of different lineages in LTA mice subjected to transplantation of lymphocytes precultured without m-CBU (Recipients 1) did not change significantly compared to LTA (Figure 1). However, in a group of LTA mice that were injected with lymphocytes precultured with m-CBU (Recipients 2), a restoration of the colony-forming activity of erythroid precursors to levels exceeding the control levels was observed ($30.0 \pm 10.1 \times 10^5$ BMC vs $27.2 \pm 5.9 \times 10^5$ BMC, $p = 0.694$); the number of granulocyte-macrophage colonies was also restored to the level of control animals (33.5 ± 13.4 vs 22.8 ± 4.7, $p = 0.162$, Figure 1).

Anemia, leukopenia, lymphocytopenia and thrombocytopenia are commonly observed in alcoholics [2,

3]. Thus, our next objective was to investigate shifts in peripheral blood parameters in LTA mice and the lymphocytes transplantation effect on their dynamics. We found a 1.5-fold decrease in the number of erythrocytes and 1.2-fold decrease in hematocrit in LTA mice compared to control mice (Table 1). This is in line with previously reported findings that alcoholics are characterized by structural disorders of erythroid cells and their destruction, which can lead to the onset of anemia [1]. In this study, we further observed that transplantation of lymphocytes precultured with m-CBU in LTA recipients restored erythrocyte numbers to the level of intact mice (Table 1).

We did not observe a significant decrease in the number of leukocytes in the peripheral blood of LTA mice compared to controls ($p = 0.194$); transplantation of lymphocytes precultured with m-CBU into LTA mice also did not lead to any shifts in this parameter (Table 1).

In line with previously reported observations in human subjects [14], we found a significant decrease in the number of platelets in the peripheral blood of LTA mice comparted to control mice; after transplantation of lymphocytes precultured with m-CBU, an increase in this parameter was recorded (Table 1). The number of blood monocytes in all studied groups did not change (Table 2).

In this study, the population of segmented neutrophils was 1.6-fold increased in peripheral blood of LTA compared to control mice (Table 2). Given a downward trend in the number of myeloid progenitors in bone marrow of LTA mice, the increase in mature cells in peripheral blood is not reflective of increased hematopoietic activity in bone marrow. However, the formation of extramedullary sites of hematopoiesis cannot be excluded at this time. Other published studies report a transient increase in granulocyte counts in the circulation in alcohol abuses, which might be due to the increase in neutrophil release from the bone marrow, rather than increased progenitor proliferation or decreased neutrophil apoptosis [11]. However, there is data on inhibition of granulocyte production in the bone marrow in response to excessive alcoholism [13]. Thus, further research is needed to delineate the mechanisms and dynamics of neutrophil production, migration and functional

TABLE 1. INDICATORS OF ERYTHROCYTES, HEMOGLOBIN, LEUKOCYTES AND PLATELETS IN PERIPHERAL BLOOD OF LONG-TERM ALCOHOLIZED MALES (CBA × C57Bl/6)F1 AFTER TRANSPLANTATION OF SYNGENEIC LYMPHOCYTES MODULATED IN VITRO WITH META-CHLOROBENZHYDRYLUREA.

Groups of animals	Erythrocytes	Hemoglobin	Leukocytes	Platelets
Intact animals	6.7±0.6	11.7±0.6	7.8±2.5	169.0±9.4
Long-term alcoholized animals	4.4±0.9*	9.7±0.8	5.6±2.3	127.6±12.8*
Recipients 1	4.2±1.1*	9.3±1.5	5.5±4.7	119.6±11.8
Recipients 2	5.9±0.4#	10.3±1.3	5.8±3.4	151.6±10.1

Note. Recipients 1, long-term alcoholized recipients after transplantation of syngeneic splenocytes precultured without meta-chlorobenzhydryl urea. Recipients 2, long-term alcoholized recipients after transplantation of syngeneic splenocytes precultured with meta-chlorobenzhydryl urea. The results are presented as M±SD; n = 8 in each group; *, $p < 0.05$ compared with intact animals; #, $p < 0.05$ compared with long-term alcoholized animals and the "Recipient 1" group (Mann–Whitney test).

TABLE 2. RELATIVE AMOUNT OF BLOOD CELLS IN LONG-TERM ALCOHOLIZED MALES (CBA × C57Bl/6)F1 AFTER TRANSPLANTATION OF SYNGENEIC LYMPHOCYTES MODULATED *IN VITRO* WITH META-CHLOROBENZHYDRYLUREA

Animal groups	Monocyte	Segmented neutrophils	Lymphocytes
Intact animals	4.4±2.1	29.0±9.1	66.2±13.8
Long-term alcoholized animals	4.4±1.3	46.2±13.6*	44.8±14.2*
Recipients 1	3.6±1.4	48.1±11.2*	46.1±10.9*
Recipients 2	3.4±1.7	36.0±19.2#	56.2±17.5#

Note. As for Table 1.

activity in response to different doses and protocols of alcohol exposure.

Interestingly, we found that transplantation of the *ex vivo* m-CBU-modulated lymphocytes led to a significant decrease in segmented neutrophil numbers in LTA mice compared to control (Table 2). Multifactorial regulation of the lifespan of neutrophils, chronicity of the pathological process, including chronic low-grade inflammation, characteristic of long-term alcoholism, may be associated with changes in the basal activity of neutrophils and accompanied by a violation of the basic algorithm for the regulation of apoptosis. Many cytokines and growth factors that play an important role in the formation of the inflammatory response can change the lifespan of neutrophils in different directions. It has been shown that IL-1, IL-2, IL-3, IL-6, IL-8, IL-15, IL-18, IL-32γ, TNFα, IFNγ, IFNα, IFNβ, GM-CSF, and G-CSF are able to slow down the apoptosis process, exerting a proinflammatory effect in various pathologies [11]. At the same time, TNFα and IL-6 have bifunctional properties, i.e., can activate apoptosis of these cells under certain conditions. IL-10 also has the property of inducing acceleration of apoptosis. Considering the change in the production of a number of cytokines by peripheral immune cells and brain cells in LTA mice and after transplantation of m-CBU-modulated lymphocytes, which we have previously shown [5, 9], cytokine regulation can be considered in the light of the changes in the number of neutrophils identified during this study.

In our study, LTA mice were also characterized by lymphopenia (1.5-fold decrease in peripheral blood of LTA compared to control mice, Table 2), which supports other reports that chronic alcohol exposure leads to: apoptosis of T cells; reduces the number of peripheral B cells, the interaction of T and B lymphocytes; and disrupts their activation and functional activity [12]. The transplantation of LTA mouse lymphocytes precultured with m-CBU led to a significant increase in the number of blood lymphocytes in syngeneic LTA mice compared to control (Table 2).

Across this study, we observed biological effects *in vivo* induced by transplanted lymphocytes that have been pre-treated by m-CBU *ex vivo*. This finding suggests that the interactions of m-CBU with the GABAA receptor complex expressed on lymphocytes from LTA mice is causing the demonstrated effects through the previously identified modulation of functional activity of cells [10].

Conclusion

Long-term alcoholization in mice led to a decrease in the colony-forming activity of hematopoietic precursors, mainly erythroid, and in the peripheral blood of mice, a significant decrease in the number of erythrocytes, leukocytes, lymphocytes and platelets was recorded, while the population of segmented neutrophils significantly increased. Transplantation of lymphocytes precultured with m-CBU into LTA syngeneic recipients had a corrective effect on a number of hematopoietic parameters including colony-forming activity of erythroid precursors in the bone marrow, the number of erythrocytes, segmented neutrophils and lymphocytes in the peripheral blood. The data obtained may indicate the effectiveness of m-CBU-modulated lymphocytes in correcting changes in hematopoietic homeostasis triggered by long-term ethanol intoxication.

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