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Immunomodulatory properties of the interferoninducing molecular complex

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Abstract. In *in vitro* experiments the MC was suggested to perfect the activity of monocyte-macrophageal system via the increase of phagocytosis percent (by 2,5 – 3,5 times), phagocyte number (by 2 times); the MC also accelerates the oxygen-dependent cell metabolism. The MC demonstrates also a dose-dependent modulatory effect on indices of cytolytic activity of natural killer cells: low and moderate MC concentrations inhibit this activity, while high concentration stimulates it. The MC was also proved to have influence on peripheral blood lymphocytes at the receptor expression level. So MC can be attributed to a potential immunomodulator with different types of effects on the immune system

Keywords: *yeast RNA, tilorone, immunomodulator, lymphocytic cells, phagocytosis*

Introduction. Many years of experience in clinical use of interferon (IFN) drugs of I type (α, β-IFN), which have antiviral, immunomodulatory and antiproliferative effects [3, 14], revealed their significant efficacy for the prevention and treatment of viral, bacterial and some cancer deseases. The same properties in varying degrees are found in some inducers compounds of IFN synthesis [5, 7, 12], in particular, tilorone [2, 8].

Previously, it was found that a perspective inducer of IFN of I type is a molecular complexes (MC), which are formed by the interaction of yeast RNA and tilorone [4]. Obtainment of complex preparations based on synthetic and natural compounds is a new, promising direction in the pharmaceutical field. Thus, yeast RNA is a natural compound, which the immune system has phylogenetic adaptation to. Artificial hapten (in this case – tilorone) has a targeted immunotropic action [2, 8, 11], being a xenobiotic for the human body against which protective responses are induced. In this paper, we aimed to investigate the effect of MC on immunocompetent cells in *in vitro* experiments.

Objects of research. In *in vivo* experiments the CBA and Balb/c mice were used. In *in vitro* experiments there was used blood of 0 (I) group of healthy volunteer donors. The components of MC were the marketable preparation of RNA yeast and synthetic preparation – 2,7-bis[2-(diethylamine-ethoxy)-fluorene]-9-on dihydrochloride (tilorone). MC is formed by the interaction of single-stranded yeast RNA with tilorone and is considered one of the most promising inducers of IFN-α/β of semi-natural origin due to the presence of ribose within its composition and formation of numerous double-stranded regions within the structure of single-stranded RNA under tilorone. Preparation of MC solutions of desired concentration was performed by direct mixing of appropriate solutions of tilorone and yeast RNA in buffer 0.01 M tris-HCl (pH 6.8) and 0.05 M NaCl at a ratio of 1:10 (M:M).

RNA, pure tilorone and well-known inducer of IFN-α/β of ribonucleic nature – rydostyn (double-stranded RNA of *Saccharomyces cerevisiae* yeast, RPA(Research and production association) "Vector", Russia were used as comparison preparations.

Research methods. To study the effect of MC on the immune system of experimental animals, the humoral immune response of the mice was modeled using a T-dependent antigen (AG) – sheep erythrocytes (SE) and T-independent AG – lipopolysaccharide (LPS *E.coli* 0111). The MC drug was intraperitoneally administered to mature CBA mice in doses of 1.25 and 12.5 mg/kg of body weight of animals. SE was intraperitoneally administered to animals in optimal dose of 4×10^8 in 0.2 ml of normal saline, and LPS was subcutaneously administered in a dose of 0.3 mg. Antigens were injected once. Animals injected with equal volumes of SE and LPS according to their groups served as a control value. Mice were sacrificed by cervical dislocation under light ether anesthesia.

During the research there were determined the values of formation of humoral immune response – the content of antigen-producing cells (APC) in the spleen and IgG titers in spleen blood serum as of the 5th, 7th and 14th day after immunization in 7 animals from each group. Number of APC in the spleen of mice was determined by direct hemolysis by Yerne. Antibody levels in blood serum were determined by the method of passive hemagglutination by Boyden.

Assessment of direct effects of MC on the functional activity of the cells of immune protection was conducted through *in vitro* tests. The functional state of neutrophils and monocytes of blood were characterized by their ability to absorb latex particles (d = 1,0 – 1,3 mm) with calculating percent of phagocytosis (PP) – percentage of phagocytic cells and phagocytic number (PN) – an average of their activity [17] and the intensity of their oxygen-dependent metabolism through NBTR (Nitro Blue Tetrazolium Reduction) test according to the method [9]. The assessments of peroxidase activity was conducted by means of cytochemical coefficient (CCC). Cytotoxic activity of killer cells was determined by non radiometric method based on spectrophotometric count of hemoglobin released from the red blood target cells destroyed by the killers (SE) during their joint incubation [6]. Rosette forming cells (RFC) was defined through the rosette formation method with application of particles coated with monoclonal antibodies [10].

Results and discussions. A characteristical feature of immunomodulator substances is their potential impact on the formation of humoral and cellular immune responses in the body of experimental animals. Therefore, to determine the presence of immunomodulatory activity of MC, at the first stage of our research, we determined its influence on the immune response: humoral immune response to thymus dependent and thymus independent antigens.

Important indicator of the humoral immune system which is changed under the influence of substances with immunomodulatory properties, is the ability of Lph of the spleen to antibody genesis. This is reflected in the increasing number of antibody-producing cells (APC) and antibody production to T-dependent antigen. The results of this determination are shown in Table. 1.

Table 1. Effect of MC on antibody-producing cells content (M ± m; n = 7) in the spleen of CBA mice during immune responses to SE

Administered drug	Number of antibody-producing cells		
	5th day	7 th day	14th day
Control (SE)	112,0 ± 3,3	84,0 ± 2,3	33,0 ± 0,8
MK 12,5 mg / kg	44,6 ± 1,9•	155,0 ± 4,7•	22,0 ± 1,0•
MK 1,25 mg / kg	190,0 ± 4,0•*	137,1 ± 4,1•*	38,6 ± 1,7•*
Yeast RNA	134,2 ± 1,8	98,6 ± 3,5	31,2 ± 1,4
Tilorone	83,0 ± 1,9•*	68,4 ± 2,7•*	29,1 ± 2,1
Rydostyn	92,0 ± 4,1•*	79,0 ± 1,5*	39,0 ± 2,7*

Notes.
1. # –The difference in comparison with the initial figure is accurate (p <0,05).
2. • – The figure difference in comparison with the corresponding figure in the control group (SE) is accurate (p <0,05).
3. * – The figure difference in comparison with the corresponding figure in the group of animals treated with 12.5 mg / kg of MC is accurate (p <0,05).

The analysis of these data revealed the following patterns: MC being administred to animals of the research groups has led to the increase of APC in the spleen, but the use of this drug in doses of 1.25 mg / kg caused an earlier – the 5th day of the study (190,0 ± 4,0, P <0.05), more expressive and longer effect. The RNA drug also increased the content of APC in the spleen on the 5th days of the study, unlike tilorone, which reduced this figure in some extent. Rydostyn's significant effect on the number of APC in comparison with control values has not been revealed.

In general, the obtained results are consistent with the references, since tilorone and yeast RNA as themselves, depending on the dose, can enhance antibody production, while rydostyn practically does not increase the number of APC in the spleen. Therefore, we assume that MC activates processes of APC increase in the spleen due to the presence of the RNA in it.

To determine changes in functional activity of B cells in the dynamics of the immune response to SE and determine the impact of MC drug and comparison preparations on it, the serum hemagglutinin titers were determined. It was found that the MC at a dose of 1.25 mg/kg versus rydostyn exhibits greater ability to induction of antibody synthesis. This may be indicative of its high immunomodulatory activity in these experiments.

To activate the T-independent immune response and study the influence of MC on the formation of the immune response of animals, they were immunized with T-independent antigen – LPS *E. coli*.

To assess the functional activity of APC and quantitative changes in the dynamics of the immune response to LPS there were determined the contents of these cells in the spleen and titers of specific antibodies in blood serum. At that, the maximum content of APC in mice of the control group was observed on 5th day of the study, after which it decreased, and as of 14th day after administration of LPS, this figure has decreased by almost 2.5 times. In mice treated with MC of 12.5 mg/kg, the reduced number of APC in the spleen relative to controls occurred on 5th day of the study, thus as of 7th and 14th day the figure reached control values. In the case of yeast RNA, tilorone and rydostyn, the content of APC was lower than control values, with the lowest figures recorded in animals that were injected with tilorone simultaneously with LPS.

Content analysis of anti-LPS-specific antibodies in experimental animals within the formation of an immune response to LPS has showed reduced titers of anti-LPS antibodies in the blood serum, which is caused by both MC and its components. The only exception is a MC dose of 12.5 mg/kg.

Thus, analysis of APC content changes in the spleen and serum titers of anti-LPS antibodies in experimental animals has showed no significant effect of MC dose of 1.25 mg/kg on the processes of antibody formation in the immune response of CBA mice to thymus dependent antigen, the presence of moderate stimulating effect of this drug if it is administered at a dose of 12.5 mg/kg and the inhibitory effect of the comparison preparations.

An important criterion for assessing the biological impact of any agent in the body's immune system is its expression at the cell level. Therefore, a study of immunomodulatory properties of MC was carried out *in vitro*, using lymphoid blood cells of healthy donors: lymphocytes (Lph), neutrophil granulocytes (NG), monocytes (MN), and natural killer cells (NK cells).

For us it was interesting to investigate the functional activity of phagocytic cells of both NG and Mn under different doses of MC and known interferonogens as a potential immunomodulatory effect on the phagocytic activity of blood cells is one of the necessary tests on the presence of immunomodulatory effect [13].

To investigate the functional activity of phagocytes in the first phase of the research we conducted the study of absorbance ability of NG by means of latex test.

Figure 1 presents data on the impact of MC on phagocytosis of NG, expressed in percent change in the phagocytes percent (PP) (percentage of cells that have captured the latex particles) (Fig. 1a) and phagocytic number (PN) (average number of particles that were swallowed by the phagocytic cell) (Fig. 1b) compared to the same parameters for the individual components of the MC as well as the standard inducer of IFN of I type – rydostyn.

As shown in Figure 1, none of the drugs in studied concentrations had virtually any effect on the level of PP of studied cells. MC at a concentration of 12.5 mg/ml slightly reduced both the index of PP and PN (26.4% vs. 32.6% and 5.8 c.u. vs. 6.5 c.u. respectively). MC at a concentration of 1.25 mg/ml significantly increased both the index of PP and PN (38.7% vs. 32.6% and 7.5 c.u. vs. 6.5 c.u. USD respectively). RNA and rydostyn also significantly reduced both parameters. Tilorone was the only exception, which in the studied concentration could potentially influence the process of phagocytosis due to its direct action on cellular nucleic acids.

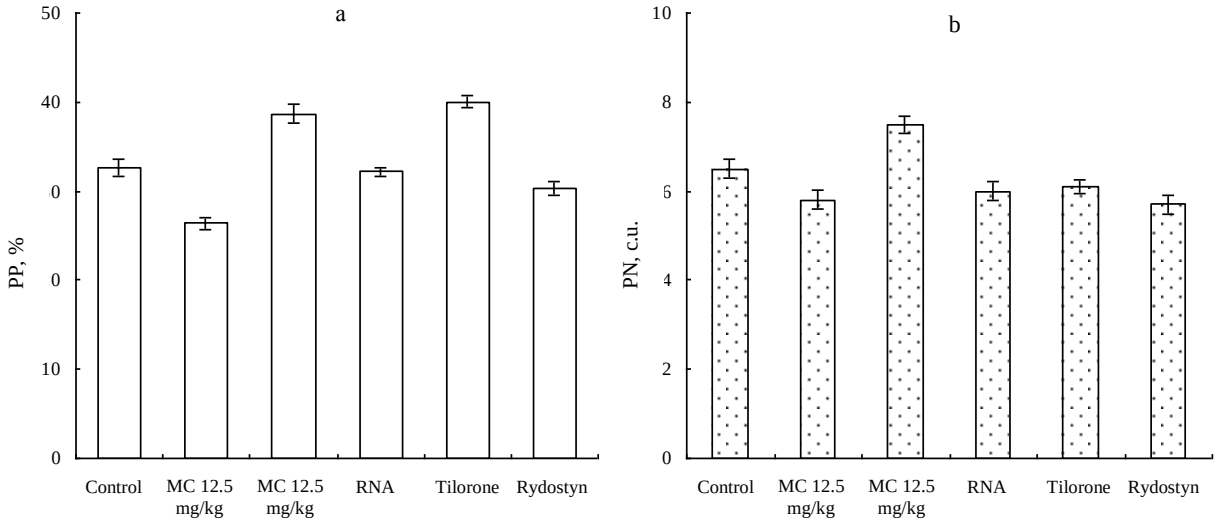

Figure 1. Effect of MC and comparison preparations on the performance of phagocytosis of NG

Thus, during normal phagocytic activity of cells (32,6 ± 0,9%) of NG, PP values before and after incubation with the studied drugs differed a little from each other. As for PN, this figure remained virtually unchanged.

The second stage of this research was to study the digestive capacity of NG in NBTR-test. Results of change in activity of oxygen dependent metabolism after interaction of NG with study drugs and comparison preparations are shown in Figure 2. Definition of oxygen dependent metabolism of NG was performed by evaluating the percentage of NBTR-positive cells (Fig. 2.a) and cytochemical coefficient (CCC) (Fig. 2.b).

Data from this test indicate that all the studied drugs also did not significantly influence both the number of NBTR-positive cells and their functional activity (Fig. 2). The exception is a MC at a concentration of 12.5 mg/ml, which significantly suppressed the number of NBTR-positive cells by 36% and CCC by 31%. This may suggests that the high concentration of MC has a negative impact on functional activity of NG and on the activity of oxygen dependent metabolism of NG.

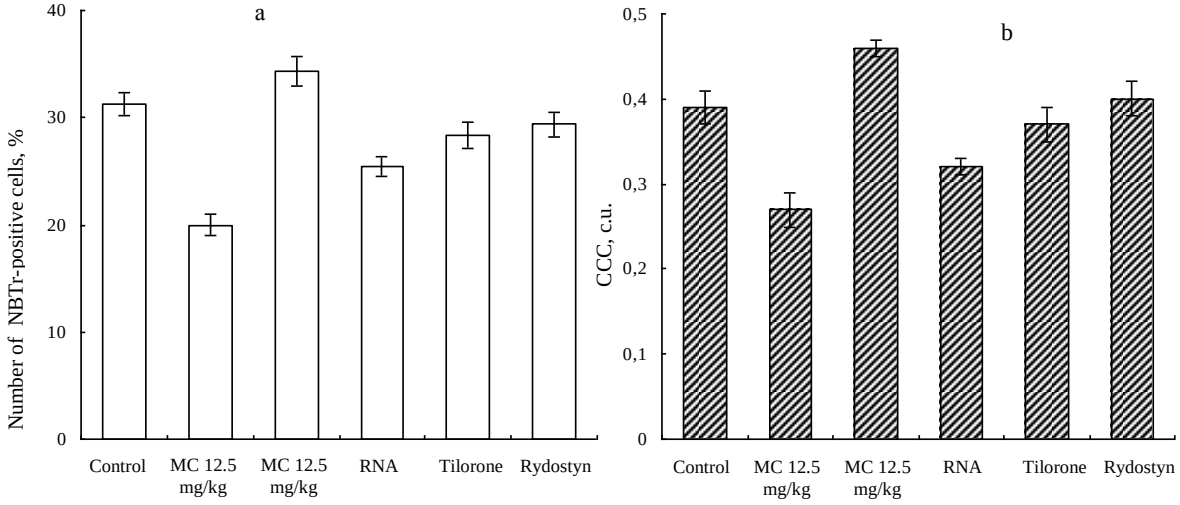

Figure 2. Effect of MC and comparison preparations on the performance of spontaneous NBTR-test of NG

Similar studies on the effect of MC on functional activity of phagocytic cells was performed on a model of MN. First, the absorbance capacity of MN was also studied by means of latex test (Fig. 3).

The data presented in Figure 3a determine absorption activity of MN before and after interaction with the studied drugs and show that MC and rydostyn significantly increase the phagocytic activity of MN both absorption and digesting one, unlike the NG.

Thus, the MC at a concentration of 12.5 mg/ml increased the PP by 3.5 times (Fig. 3a) and PN almost by 2 times (Fig. 3b). When using the MC at a concentration of 1.25 mg/ml, there was an increase of PF by 2.5 times, while SF increased slightly by up to 27%. During the

incubation of target cells with Monocytes with RNA and rydostyn there was also observed a significant increase in PP (2.9 times and 3.2 times, respectively), but PN remained at control values. The least stimulating effect on the number of active cells that absorb latex is observed when adding tilorone (PP increased by 2 times). The average number of particles absorbed by a phagocyting cell (PN) increased by 1.5 times.

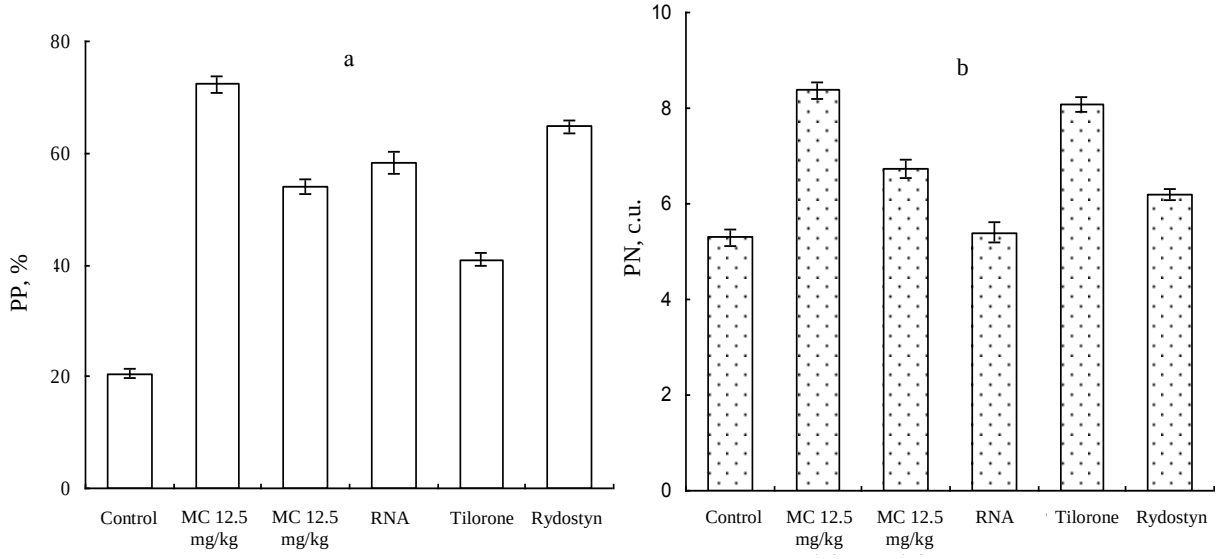

Figure 3. Effect of MC and comparison preparations on the performance of Monocytes phagocytosis

Thus, Monocytes cells were more sensitive to activation by study drug. In this case, based on the results, we can assume that a stimulating effect on Monocytes cell was produced by MC due to the presence of RNA in its structure.

Definition of oxygen dependent metabolism of Monocytes was performed by evaluating percent of NBTR-positive cells and cytochemical coefficient (CCC). The results reflecting the impact of the studied drugs on the metabolic activity of oxygen dependent Monocytes are shown in Figure 4. Their analysis showed that the percentage of NBTR-positive MN as well as an indicator of CCC, under CC has increased in some extent. At the same time, these figures decreased slightly under tilorone and rydostyn. The latter may indicate that the MC due to its specific physical and chemical properties, can act as an activator of certain redox reactions in MN cells.

Thus, *in vitro* experiments have shown the immunomodulatory effects of MC on functional activity of NG and MN of peripheral blood of healthy donors. Our study also showed that MC has a distinct effect on the physiology of these phagocyting cells, causing intensification of monocyte-macrophage system function. Since hydrogen peroxide and oxygen radicals are the most effective bactericidal phagocytes system, it allows us to consider MC as a very effective factor of increase (MN) and inhibition (NG) of phagocytic immunity activity.

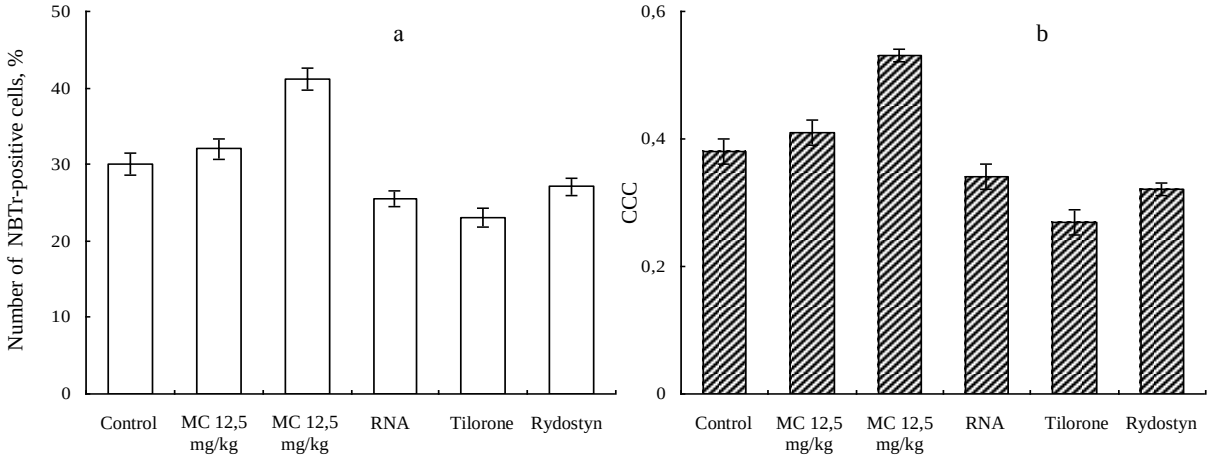

Figure 4. Effect of MC and comparison preparations on the performance of spontaneous NBTR-test of Monocytes

One of the important characteristics that occur under the influence of potential immunomodulators on nonspecific immunity is the cytotoxic activity of NK cells. Given that, we examined the effects of MC on NK cells and possible change of their cytotoxic and antibody-mediated cytotoxicity that occurs in this case. In this regard, the parameters such as spontaneous cytotoxicity (SC) and antibody-cell cytotoxicity (ABCC) of NK cells under MC have been determined. The results of these studies are shown in Figure 5.

As can be seen from the data (Fig. 5), cytotoxic activity of NK cells and cells responsible for antibody-dependent cytotoxic activity increases proportionally with increasing concentrations of MC. Thus, at low concentrations of MC, there is a decrease in the activity of NK cells by 5 times, but at a concentration of MC of 1.25 mg/ml the SC and ABCC values reach control values, while at a concentration of 12.5 mg/ml there is an increase in the activity of NK cells by 2 times.

Since it is known that the manifestation of NK cells activity in the microorganism is usually preceded by infection with viruses, the formation of inflammatory and tumor-forming process, and in experimental conditions – the introduction of interferons and their inducers (and, in particular, s-RNA), NKC activation occurs due to the production of IFN-α/β, and IL(Interleukin)-12, and can increase the activity of NKC by almost 100 times [18]. Therefore, our experimental data are consistent with the references, since it is known that IFN of I type inducers such as poly I:C and tilorone increase NKC cell activity and responses to target cells by inducing perforyn and TRAIL-dependent cytotoxicity [16], but without changing the specificity of target cells [1, 15].

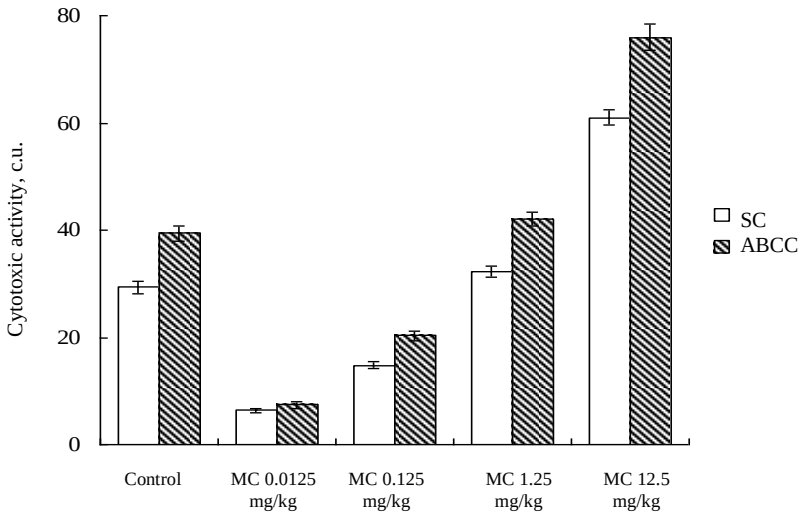

Figure 5. Effect of MC on spontaneous and antibody-dependent cytotoxicity of NK cells

One of the current methods for assessing the impact of a potential immunomodulator for cellular immunity status is to determine the ratio of Lph subpopulations of peripheral blood and phenotypic markers that characterize the change in the functional state of the cell. The presence of monoclonal antibodies virtually to all receptors that provide differentiation and maturation of Lph, allows them to reveal the mechanisms of various pathological conditions of the human body. Therefore, it was considered logical to study the effect of MC on the level of receptor expression on Lph of peripheral blood: on T-Lph (CD3 +), B-Lph (CD22+), as well as their individual subpopulations (CD4+ and CD8+). For this purpose, the method of rosetting of Lph with particles covered with monoclonal antibodies against CD3+ (T-Lph), CD4+ (T-helper) and CD8+ (T-cytotoxic / effector Lph) was used. To determine the density of receptors on B-Lph there were used erythrocytes coated with mAb (monoclonal antibodies) against CD22+ after treatment of Lph with various concentrations of MC. The results of these studies are shown in Figure 6.

In the study on the impact of MC on cell responses, we had found a dose-dependent effect of MC on the reaction of T-rosetting. As seen in Figure 6a, when added MC at a concentration of 0.0125, 0.125 and 12.5 mg/ml, the number of receptors for CD3+ cells remained at the same level, slightly below the control level of cells (by 17%, 13% and 21 %, $p < 0,05$). When Lph were incubated with MC at a concentration of 1.25 mg/ml, the number of receptors for CD+ cells increased by 19%. In the case of the analysis of receptors for CD22+ cells there was observed a slight significant increase in the number of receptors when Lph were incubated with MC at concentrations of 0.0125, 0.125 and 12.5 mg/ml (by 26%, 11% and 19%). When using the MC at a concentration of 1.25 mg/ml, the number of receptors for CD22+ is reduced by 44%. This suggests that MC affects the ability of rosetting both of T-Lph and B-Lph and effectiveness of receptor expression depends on the concentration of MC.

Due to the fact that in this case the expression of receptors both for T-Lph and B-Lph increases, we can assume that MC's immunomodulatory effect on Lph, which we have found, is associated with the effect of this complex both on the T- and B-chain of the immune system of the body. Therefore, in our further research, we aimed to investigate the subpopulation of T-Lph, namely CD4+ (T-helper) and CD8+ (T- cytotoxic / effector Lph), which have different functions.

Performing their helper function, CD4+ Lph help, at first, B-Lph to turn into antibody-producing plasma cells, CD8+ Lph – into mature cytotoxic T cell, and thirdly, help macrophages to perform delayed-type hypersensitivity effects. These functions of T-Lph-helpers are realized due to the fact that they, in their turn, are divided into two subpopulations that perform various helper functions through the production of various cytokines. CD8+ Lph implement specific cellular immune responses – that is the main effector cell of cell-mediated immunity, which carries lysis of targets, providing genetic constancy of internal environment.

Results receptor's expression changes to SE, coated with monoclonal antibodies up to CD4+ and CD8+ after incubation of Lph with MC solutions of different concentrations are shown in Figure 6b. In our experiments, under the influence of MC on the process of rosetting of subpopulation of T-Lph, there is observed a possible reduction of subpopulation of CD4+ when administering cells with low concentrations of MC, namely 0.0125 and 0.125 mg/ml (14% and 27%, respectively, P <0.05) and increase of their number by 23% and 14%, respectively, at higher concentrations of 1.25 and 12.5 mg/ml (P <0.5).

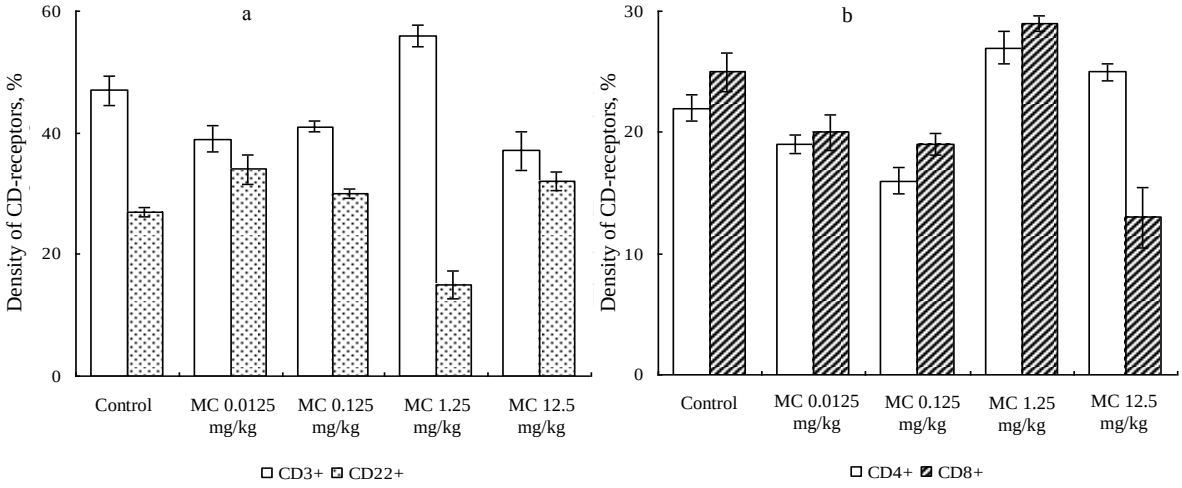

Figure. 6. Effect of MC on the expression of CD-receptor for blood lymphocytes

While determining CD8+ (T-cytotoxic / effector Lph) we noted depressing effect of MC when applied at low concentrations (0.0125 mg/ml and 0.125 mg/ml) by 20% and 24%, and at a concentration of 12.5 mg/ml even by 48% (P <0,05). Only when administering MC into Lph at a concentration of 1.25 mg/ml, an increase in expression of the receptor CD8+ Lph by 16% (P <0.5) was observed. Immunoregulatory index, however, remains within the normal range of 0.9 to 2.0.

Consequently, MC had distinct accurate effects on the expression of receptors both for CD4+ and CD8+ Lph, and the effectiveness of its application depended on the concentration.

Conclusion. Summarizing the results obtained, we can state that a direct effect of MC on cell phagocytes and Lph has been proved. This is confirmed by the increasing number of phagocyting cells of monocyte-macrophage population, increased cytotoxic activity of NK cells and cells responsible for antibody-dependent cytotoxic activity and changing the expression of receptors for Lph under the influence of different concentrations of MC. So MC shows *in vitro* its immunomodulatory properties. It shows the prospectivity of further studies of its effects on the level of macroorganism.

REFERENCES (TRANSLATED AND TRASLITERATED)

1. Fernandez N.C., Treiner E., Vance R.E., Jamieson A.M., Lemieux S., Raulet D.H. A subset of natural killer cells achieves self-tolerance without expressing inhibitory receptors specific for celf-MHC molecules // Blood – 2005. – Vol. 105. – P. 4416-4423.

2. Gaforio J.J., Ortega, E., Algarra I., Serrano M.J., Alvarez de Cienfuegos G. NK cells mediate increase of phagocytic activity but not of proinflammatory cytokine (interleukin-6 [IL-6], tumor necrosis factor alpha, and IL-12) production elicited in splenic macrophages by tilorone treatment of mice during acute systemic candidiasis // Clin. Diagn. Lab. Immunol. – 2002. – Vol. 9. – P. 1282-1294.

3. Goodbourn S., Didcock L., Randall R.E. Interferons: Cell signaling, immune modulation, antiviral responses and virus countermeasures // J. Gen.Virol. – 2000. – Vol.81, №10. – P. 2341-2364.

4. Карпов А.В., Жолобак Н.М. Изучение интерфероногенных свойств комплексов дрожжевая РНК – тилорон в культуре клеток // Антибиотики и химиотерапия. – 1995. – Т.40, № 5. – С. 20-23.

Karpov A.V., Zholobak N.M. The study of the properties of complexes interferonogenic yeast RNA – tilorone in cell culture // Antibiotics and chemotherapy. – 1995. – Vol.40, № 5. – P. 20-23.

5. Хаитов Р.М., Пинегин Б.В. Иммуномодуляторы: механизм действия и клиническое применение // Иммунол. – 2003. – № 4. – С. 196 – 203.

Khaitov R.M., Pinegin B.V. Immunomodulators: mechanism of action and clinical application // Immunol. - 2003. - № 4. – P. 196 – 203.

6. Круглова И.Ф. Естественные киллеры и методы их исследования Лабораторная диагностика. – 1998. – № 2 (4). – С. 32-35.

Kruglova I.F. Natural killer cells and methods for their research laboratory diagnosis. – 1998. – № 2 (4). – P. 32-35.
7. Leyssen P., Drosten C., Paning M., Charlier N., Paeshuyse J., De Clercq E., Neyts J. Interferons, interferon inducers, and interferon-ribavirin in treatment of flavivirus-induced encephalitis in mice // Antimicrob. Agents Chemother. – 2003. – Vol. 47. – P. 777-782.
8. Mayer G.D., Krueger R.F. Tilorone hydrochloride and related molecules. In D.A. Stringfellow (ed.) Interferon and interferon inducers: clinical applications. Marcel Deccer, New York, N.Y. – 1980. – P. 187-221.
9. Нагоев Б.С. Модификация цитохимического метода восстановления нитросинего тетразолия // Лаб. дело. – 1986. – № 8. – С. 7-11.
Nagoev B.S. Modification cytochemical method nitroblue tetrazolium // Lab. business. – 1986. – № 8. – P. 7-11.
10. Новиков Д.К., Новиков П.Д. Метод определения Т- и В-лимфоцитов диагностикумами на основе моноклональных антител // Иммунол. – 2000. – № 2. – С. 31-33.
Novikov D.K., Novikov P.D. Method for determination of T- and B-lymphocytes diagnosticums based on monoclonal antibodies // Immunol. – 2000. – № 2. – P. 31-33.
11. Ortega E., Algarra I., Serrano M.J., de Pablo M.A., Alvarez de Cienfuegos G., Gaforio J.J. Enhanced resistance to experimental systemic candidiasis in tilorone-treated mice // FEMS Immunol. Med. Microbiol. – 2000. – Vol. 28. – P. 283-289.
12. Padalko E., Nuyens D., De Palma A., Verbeken E., Aerts J.L., De Clrrcq E., Carmeliet P., Neyts J. The interferoninducer ampligen [poly(I)-poly(C_{12}U)] markedly protects mice against coxsackie B3 virus-induced myocarditis // Antimicrob. Agents Chemother. – 2004. – Vol. 48. – P. 267-274.
13. Доклінічні дослідження лікарських засобів: Метод. рекомендації / За ред. О.В. Стефанова. Вивчення імунотоксичної дії лікарських засобів. – К.: МОЗ України, 2001. − С. 102-113.
Preclinical studies of drugs: Method. recommendations / Ed. Stefanova A.V. Study immunotoxic action of drugs. – K.: Ministry of Health of Ukraine, 2001 – P. 102-113.
14. Randall R.E., Goodbourn S. Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures // J.Gen.Virol. – 2008. – Vol. 89. – P. 1-47.
15. Salcedo M., Andersson M., Lemieux S., Van Kaer L., Chambers B.J., Ljunggren H.C. Fine tuning of natural killer cell specificity and maintenance in MHC class I-deficient mice // Eur. J. Immunol. – 1998. – Vol. 28 – P. 1315-1321.
16. Sato K., Hida S., Takayanagi H. Antiviral response by natural killer cells through TRAIL gene induction by IFN-alpha/beta // Eur. J. Immunol. – 2001. – Vol. 31. – P. 3138-3146.
17. Унифицированные иммунологические методы обследования больных на стационарном и амбулаторном этапах лечения: Метод. рекомендации / Киевский НИИ фтизиатрии и пульмонологии. – К., 1998. – 18 с.
Unified immunological methods of examination of patients on inpatient and outpatient treatment stages: Method. recommendations / Kyiv Research Institute of Tuberculosis and Pulmonology. – K., 1998 – 18 p.
18. Ярилин АА. Система цитокинов и принципы ее функционирования в норме и при патологии // Иммунол. – 1997. – № 5. – С. 7-14.
Yarilin A.A. System cytokines and principles of its functioning in normal and pathological conditions // Immunol. – 1997. – № 5. – P. 7-14.

Лыч И.В., Волошина И.Н. Иммуномодулирующие свойства интерферониндуцирующего молекулярного комплекса
Аннотация. В экспериментах *in vitro* доказано непосредственное стимурирующее влияние молекулярного комплекса на моноцитарно-макрофагальную популяцию клеток через увеличение процента фагоцитоза (в 2,5–3,0 раза) и фагоцитарного числа (в 2 раза); МК также влияет на окислительно-востановительный метаболизм клеток. Комплекс демонстрирует дозозависимое модулирующее влияние на показатели цитотоксической активности натуральных киллеров: низкие и средние концентрации МК влияют угнетающе, а высокие концентрации имеют стимулирующее действие их активности. Также показано, что МК имеет непосредственное влияние на уровень экспрессии рецепторов на лимфоцитах переферической крови. Таким образом МК можно отнести к потенциальным иммуномодуляторам с разным характером влияния на иммунную систему.
Ключевые слова:*дрожжевая РНК, тилорон, иммуномодулятор, лимфатические клетки, фагоцитоз*