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Research Article

Features of metabolic processes in lymphocytes of patients with viral infections

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ABSTRACT

The article provides the results of examination of 63 patients suffering from viral infections (influenza and chicken pox). Assessment of the nature and intensity of the metabolic processes in lymphocytes of patients with viral infections by changes in activity of intracellular enzymes showed that at the height of the disease, there is intensification of glycolysis reactions at a significant increase in the functional load on the cells, there is a significant decrease in the intensity of the reactions of the initial phase of citric acid cycle, which should reduce energy efficiency of the cycle, as well as intense flow of metabolites to supply citric acid cycle with substrates from amino-acid metabolism, providing an increased amino-acid transport to cells.Common trends in the nature of the course of metabolic reactions allows joining individuals with viral infections in general comparable in terms of activity of some enzymes, but differing by etiological factor, by the nature of the clinical course. The use of drugs of succinic acid or its salts provides additional substrate saturation of tricarboxylic acid cycle, increasing energy efficiency of the cycle and higher lymphocyte functional capabilities.

Keywords: Influenza /Chicken pox / Lymphocytes / Metabolic processes / Activity of intracellular enzymes / Substrate

Highlights

- Increased TCA in viral infections provides immune response
- Use of metabolic immune corrections prevents complicating disorders
- Succinic acid provides additional substrate saturation of TCA
- Viral infections have common trends in the clinical course of metabolic reactions

INTRODUCTION

Development, course and outcome of infectious and inflammatory disease depends on the state of the immune system and its response to the microorganism infiltrated. As a result of this response, the pathogen is recognized, inactivated and eliminated from the body. In the first place, It is immune competent cells that are the first to contact the pathogen; their functional state determines the adequacy of the immune response; the most important role among them belongs to the lymphocytes [1–2]. Full manifestation of the functionality of the lymphocytes in the processes of formation of an adequate immune response, including antiviral, is determined by the intracellular metabolism, which is provided by the appropriate level of enzyme activity in cells [3–4]. It hais been proved that the main metabolic pathways of intracellular metabolism are identical, however,while the predominant direction of substrate flows, the rate of substrate processing speed, delivery of metabolites from the outside, the need for them are strictly individual, and may be different and caused by a causative factor and or direct influence of neurohumoral influences ofnthe body causing restructuring in metabolic processes, changed against the background ofin the setting of the disease and causing restructuring in metabolic processes [5–7]. The effect of viral infectious matter agentson the

immune system largely determines the nature, course and outcome of the infection process, but the immune response to infectious aggression is impossible if the lymphocyte is not capable of proliferation, and cytokine and immunoglobulin synthesis. Research rResults of the researches on enzymes of various intracellular lymphocyte metabolism cycles, confirmation of informativeness informational valueof this group of indicators to forcharacterization ofe immunoreactivity and resistance of the body, and determination of their violation mechanisms of their violation allow recommending enzymatic indicators as parameters of estimation and prediction of immunological changes in the body. In our view, cSonducting studies onf activity of enzymes controlling reactions of different intracellular metabolism ways (– citric acid cycle, pentose phosphate cycle, glycolysis),seems to beis necessary for ato more completefully explaination of the pathogenesis of viral infections, which willhelpto choose science-based therapy regimens, predicting results, and monitoring the treatment effectiveness.

*The purpose of the study*was to evaluate the nature and intensity of the metabolic processes in lymphocytes of patients with moderate influenza and chicken pox by changes in the activity of intracellular enzymes.

MATERIALS AND METHODS

To achieve this purpose, enzymatic indicators of lymphocytes were determined in 32 patients with a the diagnosis of “influenza, moderate” and 31 patient with a the diagnosis of “chicken pox, typical, moderate course” who were hospitalized in the infectious department of the Emergency Hospital n.a. N.S. Karpovich in Krasnoyarsk. The patients’ agedwas 18 to 40 years. Genetic material of influenza viruses was identified in nasopharyngeal swabs bypolymerase chain reaction(PCR) technique in 32 patients (100%). The diagnosis of chicken pox was determined in the infectious department by clinical and epidemiological method.

The values of activity of intracellular enzymes of lymphocytes of 37 virtually healthy patients of comparable age, obtained by us earlier, were used as benchmarks [8]. Activity of intracellular enzymes was determined in all patients’ lymphocytes isolated from venous blood by ficoll-verografin density gradient by bioluminescent assay. The following enzymatic indicators of the most important enzymes of the Krebs cycle were determined: activity ofnicotinamide adenine dinucleotide(NAD)-andnicotinamide adenine dinucleotide phosphate(NADPHF)-dependent isocitrate dehydrogenases (NADICDG and NADFNADPHICDG), NAD- and NADFNADPH-dependent glutamate dehydrogenase (NADGDG and NADFNADPHGDG), NAD- and NADFNADPH-dependent malate dehydrogenase (NADMDG and NADFNADPHMDG) [9–11]. Enzyme activity was expressed in mcE per 10000 lymphocytes.

The data obtained as a result of the study have been processed by statistical analysis methods used in biology and medicine using Statistica 6.0 software applications. The table shows mean group indicators (M) and the error of mean (m). Due to the fact that distribution of intracellular enzyme activity indicators differed from normal distribution, significance of differences was evaluated using the Mann-Whitney U-test.

Activity of enzymes G6PDH, G3PDH, NADGHDGH, LDH LDGand NADPMDH NADPHMDGin lymphocytes was studied in patients with chronic herpes virus infection [12], and LDH LDG– in patients with cytomegalovirus infectionCMV infection [13]. The indicators of intracellular metabolism were determined, both not onlyof lymphocytes, but also of and neutrophils, erythrocytes,and also in other infectious diseases: in acute intestinal infection, acute and chronic viral hepatitis A and B [14]. The results of the conducted above researches confirmed high informational valueveness of enzyme indicators allowing to clarify the pathogenesis of the pathological processes studied, to assess severity and features specifics of the course, and to predict the outcomes of their development.

The above allowed to suggest that the astudy onf activity of enzymes controlling the reactions of different intracellular metabolism ways – citric acid cycle, pentose phosphate cycle, glycolysis, is necessary to for amore fully completeexplaination of the pathogenesis of

influenza to choose science-based therapy regimens, predicting results, and monitoring the treatment effectiveness. However, no information was found in available publications on similar influenza and chickenpox studies.

RESULTS AND DISCUSSION

Enzymatic indicators determined in the study showed significant differences between intracellular metabolic reactions of lymphocytes in patients with viral infections (Table 1). At that, the attention was drawnit is noticeableto the fact that the indicators of all enzymes significantly changed, and changes had varying degrees of severity, but were unidirectional.

For tricarboxylic acid cycle(TCA) enzymes and associated reactions, [changes]differences were noted in relationas comparedwithto the level of change control. Indicators in lymphocytes NADICDG and NADFNADPHICDG, functioning at the initial stages of the Krebs cycle in patients with influenza and chicken pox, were lower than in healthy patients. NADICDG activity in patients with influenza was 0.15 ± 0.03, whileat the value in the control group it was equal to 1.95 ± 0.25 ($p < 0.001$), and in patients with chicken pox –– 0.47 ± 0.01 (in the control group $–1.95 \pm 0.25$; $p < 0.001$ in the control group). Activity NADFNADPHICDG activity for influenza patients amounted to 0.05 ± 0.02 and 31.02 ± 2.20 ($p < 0.001$), but in patients with chicken pox –it was 0.07 ± 0.01 (control level $–31.02 \pm 2.18$; $p < 0.001$). The first of themformer has a higher activity in case of viral infections. It can be assumed that the effectiveness of TCA in terms of the yield ofadenosine triphosphate(ATP)at the initial stages is lower than capabilities of the cycle in healthy people. As one of the ways to improve the efficiency of the Krebs cycle reactions, we can evaluate activation of NADGDG and NADFNADPHGDG observed in these groups of patients can be considered. These two TCA enzymes, relating the metabolism of amino-acid exchange and TCA –– NADGDG and NADFNADPHGDG –– were significantly more active in patients with viral infections. NADGDG indicators in patients with influenza and in healthy persons amounted to 57.04 ± 8.18 and 0.34 ± 0.06 ($p < 0.001$), and NADFNADPHGDG enzyme –– 1.51 ± 0.35 and 0.11 ± 0.02 ($p < 0.001$). And in patients with chicken pox, NADGDG figure was determined more than 20 times higher than in the control group (73.81 ± 7.10 and 0.34 ± 0.06, respectively; $p < 0.001$), and NADFNADPHGDG –– 10 times higher than in the control group (1.10 ± 0.16 and 0.11 ± 0.02, respectively; $p < 0.001$).

Metabolic reactions of the final phase of TCA, catalyzed by NAD- and NADFNADPH-malate dehydrogenase, were also determined at a higher level in lymphocytes of patients with viral infections. NADMDG activity in patients with influenza was equal to 75.56 ± 22.75 (in the control group – 21.62 ± 1.69; $p < 0.001$ in the control group), and NADFNADPHMDG –– 1.21 ± 0.22 (in the control group – 0.33 ± 0.07; $p < 0.001$ in the control group). In patients with chicken pox, NADMDG was determined equal to 85.94 ± 12.03 (in the control group – 21.62 ± 1.67; $p < 0.001$ in the control group), and the indicator of activity NADFNADPHMDG amounted to 1.83 ± 0.26 (in the control group – 0.33 ± 0.07; $p < 0.001$ in the control group).

Like most enzymes that we studied, higher activity for glutathione reductase(GR) is also found in the group of patients with viral infections. In patients with influenza, it was determined at the level of 4.92 ± 0.42, whileat the value of this indicators in healthy peoplet the value of this indicators wasequal to 1.28 ± 0.30 ($p < 0.001$). Iin patients with chicken pox, this indicator was also more active than in lymphocytes of healthy people in the control group –– 2.17 ± 0.11 compared to 1.28 ± 0.30 ($p < 0.001$).

Table 1 Activity of metabolic enzymes in lymphocytes (mcE/10000 cells) in patients with chicken pox in the course of the disease ($M \pm m$)

Enzymes	Control group n = 37	Influenza n = 32	Chicken pox n = 31
NADICDG	1.95 ± 0.25	0.15 ± 0.03;$p_1 < 0.001$	0.47 ± 0.01;$p_2 < 0.001$
NADFNADPHICDG	31.02 ± 2.18	0.05 ± 0.02;$p_1 < 0.001$	0.07 ± 0.01;$p_2 < 0.001$
NADGDG	0.34 ± 0.06	57.04 ± 8.18;$p_1 < 0.001$	73.81 ± 7.10;$p_2 < 0.001$

NADFNADPHGDG	0.11 ± 0.02	1.51 ± 0.35; $p_1 < 0.001$	1.10 ± 0.16;$p_2 < 0.001$
NADMDG	21.62 ± 1.67	75.56 ± 22.75;$p_1 < 0.001$	85.94 ± 12.03;$p_2 < 0.001$
NADFNADPHMDG	0.33 ± 0.07	1.21 ± 0.22;$p_1 < 0.001$	1.83 ± 0.26;$p_2 < 0.001$
GR	1.28 ± 0.30	4.92 ± 0.42;$p_1 < 0.001$	2.17 ± 0.11;$p_2 < 0.001$

p_1 <; p_2 <— reliability of differences with the value of the corresponding column in the table

CONCLUSIONS

TCA is the main source of energy production of lymphocytes, several times exceeding glycolysis in its productivity. Therefore, under functional stress that accompanies formation of an immune response to the infectious agent, adaptive mechanisms of the cells are intended to primarily support its activity on ATP production.

Features identified in moderate influenza and chicken pox include very low intensity of reactions at the initial stages of TCA, which reduces energy efficiency of the cycle reflected by NADICDG and NADFNADPHICDG indicators. These enzymatic indicators reflect the reduced amount of the substrate transferred to the reaction catalyzed by NADICDG enzyme from the final stage of the cycle. To the higher extent, aAdditional substrate provision of TCA from cytosol, which is carried out over the control of NADFNADPH-dependent isocitrate dehydrogenaseICDG, is reduced to even greater extent. In patients with viral infections (influenza and chicken pox), a way of additional supply of substrates to TCA is determined,. It consists in representing very intensive supply of metabolites to it from in amino-acid exchange and is confirmed by a very significant increase in the activity of two enzymes carrying these metabolites —— NADGDG and NADFNADPHGDG. GR enzyme activation can be explained by this mechanism, which provides an increased transport of amino acids to lymphocytes. The results of the work of the mechanism of additional substrate supply of TCA to increase production of energy equivalents are reflected by the fact that the reactions of the final stage of this cycle become more intense. This , which is confirmed by several times increase in the activity of the corresponding NADMDG and NADFNADPHMDG enzymes.

The mechanism of enhancing TCA efficiency in viral infections due to the enhanced use of substrates of amino-acid exchange in it cannot be considered optimal, since in its work metabolites are used inefficiently, intended not for energy production in immunocompetent cells, but to ensure synthetic and plastic processes in it, required to implement the an adequate immune response, are used inefficiently. Therefore, taking into account the development of complications in chicken pox and influenza, the results of the study given can be regarded as a theoretical justification for the possibility of using the metabolic immune correction in order to develop optimal conditions for lymphocyte functioning and provide full immune response, preventing complications of the disease. Means used for this purpose may beinclude, for example, preparformulations containing succinic acid or salts thereof: reamberin, mexidol, cytoflavin. As a TCA metabolite, succinic acid can be included directly in the cycle at the stage following the reactions associating it with the amino-acid exchange. As a result, there is an additional TCA substrate saturation, energy efficiency of the cycle improves, providing higher functionality of lymphocytes, but at the same time, there is no need for supply of metabolites to TCA from amino-acid exchange, which can be more efficiently used by cells. Common trends in the nature of theflow course of metabolic reactions allows joining individuals with viral infections in general comparable in terms of activity of some enzymes, but differing by etiological factor, by the nature of the clinical course.

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Competing interests

None declared.

Ethical approval

Not required

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