IMMUNOTROPIC EFFECTS OF NITROGENOUS METABOLITES (CREATININE, UREA, URIC ACID AND BILIRUBIN) IN HUMANS EXPOSED TO THE FACTORS OF THE ACCIDENT AT THE CHORNOBYL NUCLEAR POWER PLANT

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Abstract

**Background.** In previous studies, we found that nitrogenous metabolites exhibit significant immunotrophic activity, both suppressor and enhancing, at healthy rats. The **purpose** of this and our subsequent research is to elucidate the links between nitrogenous metabolites and immune parameters in different categories of people, both healthy and sick. **Material and methods.** The object of observation in 1997 were 19 men and 3 women who were exposed to pathogenic factors of the accident at the Chornobyl nuclear power plant during the liquidation of its consequences in 1986-87. The survey was conducted twice - on admission and after two weeks of rehabilitation at the Truskavets’ Spa. The plasma and urinary concentration of the nitrogenous metabolites were determined. Immune status was assessed on tests of I and II levels according to the WHO memorandum. **Results.** Both negative and positive metabolic-immune correlations were revealed. Calculation of multiple correlation coefficients between individual metabolite parameters and constellations of immune parameters revealed the maximum immunotrophic effect of Urea urine (R=0.756). This is followed by Uric acid plasma (R=0.727) and urine (R=0.691), Urea plasma (R=0.622), Creatinine plasma (R=0.588), Bilirubinemia (R=0.546) and Creatinine urine (R=0.510). The canonical correlation between the constellation of nitrogenous metabolites, on the one hand, and the parameters of
immunity, on the other hand, was very strong: $R=0.971; \chi^2_{(15)}=239; p<10^{-5}$. **Conclusion.** Nitrogenous metabolites have immunomodulatory effects, both suppressor and enhancing, both in healthy rats and in humans exposed to pathogenic influences.

**Key words:** urea, uric acid, creatinine, bilirubin, immunity, relationships, humans.

**INTRODUCTION**

In previous studies, we found significant links between nitrogenous metabolites of plasma and urine, on the one hand, and immune parameters, on the other hand, in healthy rats [32]. We also found the immunotropic effect of uric acid both in healthy rats [14,15] and patients of Truskavets’ Spa [16,17,35]. The **purpose** of this and our subsequent research is to elucidate the links between nitrogenous metabolites and immune parameters in different categories of people, both healthy and sick.

**MATERIAL AND METHODS**

The database of the Truskavetsian Scientific School of Balneology [22,31] was used for the research. The object of observation in 1997 were 19 men (26÷61 years) and 3 women (38, 40 and 47 years) with urate urolithiasis and chronic pyelonephritis who were exposed to pathogenic factors of the accident at the Chornobyl nuclear power plant during the liquidation of its consequences in 1986-87. According to the documents, the total effective radiation dose was 10÷25 cGy, which is most typical for this contingent [22,31,34]. The survey was conducted twice: on admission and after two weeks of rehabilitation at the Truskavets’ Spa.

The plasma level of the nitrogenous metabolites determined: creatinine (by Jaffe's color reaction by Popper's method), urea (urease method by reaction with phenolhypochlorite), uric acid (uricase method) and bilirubin (by diazoreaction using the Jedrashik-Kleghorn-Grof method). The same metabolites, with the exception of bilirubin, were also determined in the morning urine. The analyzes were carried out according to the instructions described in the manual [12]. The analyzers “Pointe-180” ("Scientific", USA) and “Reflotron” (Boehringer Mannheim, BRD) were used with appropriate sets.

In portion of capillary blood we counted up Leukocytes level, Leukocytogram and its entropy [30]. In the venous blood, the parameters of immunity were determined as described in the manual [28]. The state of cellular immunity judged by the relative content of the population of T-lymphocytes in a test of spontaneous rosette formation with erythrocytes of sheep by Jondal M et al [21], their theophylline-resistant and theophylline-sensitive subpopulations (by the test of sensitivity of rosette formation to theophylline by Limatibul S et al [23] as well as subpopulation of T cells with receptors high affinity determined by test of “active” rosette formation. Additionally evaluated the transformation of T-lymphocytes into blasts under the influence of phytohemagglutinin. Natural killers were identified as large granules contain lymphocytes.

The state of humoral immunity judged by the relative content of the population of B-lymphocytes by the test of complementary rosette formation with erythrocytes of sheep by Bianco C [3], the concentration in serum circulating immune complexes (by polyethylene glycol precipitation method) and Immunoglobulins classes M, G, A (by single radial immunodiffusion method by Mancini G et al [24]) as well as $\gamma$-globulines and C-reactive protein.

About the state of the phagocytic function of neutrophils (microphages) and monocytes (macrophages) judged by the phagocytosis index, the microbial count and the killing index for Staphylococcus aureus (ATCC N25423 F49) [4,8]. In addition, the serum level of Lysozime (by the test of bacteriolysis of Micrococcus lysodeikticus) and Complement (by 50% hemolysis in the complement fixation reaction) was determined.
Digital material is statistically processed on a computer using the software package "Statistica 20".

RESULTS

In presenting the results, we will follow the algorithm used to analyze the experimental data [32].

Screening of linear correlation coefficients between parameters of nitric metabolites, on the one hand, and the recorded parameters of immunity, on the other hand, revealed the following (Table 1). The table does not include registered immunity parameters, which did not reveal any noteworthy correlation coefficient with nitrogenous metabolites.

In the next step of the analysis, a regression model was constructed for each plasma and urine nitrogenous metabolite by stepwise exclusion until the maximum level of adjusted $R^2$ was reached. As a result, it turned out that some regression models included parameters with an insignificant correlation coefficient, while some parameters with a significant correlation were outside the model.

From the regression model it follows that bilirubinemia downregulates the Lysozyme activity (Fig. 1) and relative content in the blood of theophylline-resistant T-lymphocytes, while upregulates the content of Polymorphonuclear Neutrophils and its Phagocytose Index. Judging by adjusted $R^2$, the rate of immunomodulation is 30% (Table 2 and Fig. 2).
Fig. 1. Scatterplot of correlation between Bilirubinemia (X-line) and Lysozyme activity (Y-line)

Table 2. Regression Summary for Bilirubinemia

R=0.546; R²=0.299; Adjusted R²=0.227; F(4,4)=4.2; p=0.007

| Variables                             | Beta | St. Err. of Beta | B   | SE of B | t(39) | p-level |
|---------------------------------------|------|-----------------|-----|---------|-------|---------|
| Intercept                             | 0.887| 5.404           | 0.16|         |       |         |
| Lysozyme, nM/L                        | -0.37| -0.537          | 0.178| -0.058 | 0.019 | -3.01   | 0.005   |
| Theophylline-resistant T-Lymphocytes, %| -0.21| 0.194           | 0.179| 0.104  | 0.096 | 1.08    | 0.287   |
| Polymorphonuclear Neutrophils, %      | 0.23 | 0.293           | 0.138| 0.145  | 0.069 | 2.12    | 0.040   |
| Phagocytosis Index of Neutrophils, %  | 0.23 | 0.312           | 0.138| 0.109  | 0.048 | 2.26    | 0.029   |

R=0.546; R²=0.299; $\chi^2(4)=14.2$; p=0.007; Λ Prime=0.701

Fig. 2. Scatterplot of canonical correlation between Bilirubinemia level (X-line) and parameters of Immunity (Y-line)
Uricemia upregulates the IgM serum level (Fig. 3) and relative content in the blood of theophylline-sensitive T-lymphocytes (Fig. 4) as well as pan-lymphocytes, while downregulates the C-reactive protein level and Microbial Count of Neutrophils. Such constellation of parameters of Immunity is determined by Uricemia by 53% (Table 3 and Fig. 5).

Table 3. Regression Summary for Uricemia, mM/L

| Variables                              | Beta  | St. Err. of Beta | B    | SE of B | t(38) | p-level |
|----------------------------------------|-------|-----------------|------|---------|-------|---------|
| IgM Serum, g/L                         | 0.67  | 0.627           | 0.124| 0.032   | 5.04  | 10^-4   |
| Theophylline-sensitive T-Lymphocytes, %| 0.36  | 0.216           | 0.117| 0.005   | 1.84  | 0.074   |
| Pan-Lymphocytes, 10^9/L                | 0.19  | 0.126           | 0.114| 0.003   | 1.10  | 0.279   |
| C-Reactive Protein, points             | -0.25 | -0.136          | 0.115| 0.012   | -1.18 | 0.244   |
| Microbial Count of Neutrophils, Bac/Phag | -0.18 | 0.153           | 0.124| 0.008   | 1.24  | 0.223   |

Fig. 3. Scatterplot of correlation between Uricemia (X-line) and IgM serum level (Y-line)
Instead, the concentration of Uric acid in the urine correlates negatively with the level of IgM. On the other hand, it upregulates the relative content of B-lymphocytes in the blood (Fig. 6), the mitogenic ability of T-lymphocytes and the bactericidal ability of blood
monocytes. Such constellation of parameters of Immunity is determined by Uricosuria by 48% (Table 4 and Fig. 7).

![Fig. 6. Scatterplot of correlation between Uric acid Urine (X-line) and B lymphocytes level (Y-line)](image)

Table 4. Regression Summary for Uric acid Urine, mM/L
R=0,691; R²=0,477; Adjusted R²=0,423; F(4,4)=8,9; p<10^{-4}

| Variables                                      | Beta | St. Err. of Beta | B  | SE of B | t_{399} | p-level |
|------------------------------------------------|------|------------------|----|---------|---------|---------|
| Intercept                                      | 1,455| 0,947            | 1,49| 0,144   |         |         |
| B Lymphocytes, %                               | 0,55 | 0,560            | 0,116| 0,022   | 4,82    | 10^{-4} |
| Blast transformation of T-Lymphocytes, %       | 0,25 | 0,241            | 0,118| 0,009   | 2,04    | 0,048   |
| Bactericidal Capacity of Monocytes, 10^9 B/L.  | 0,22 | 0,259            | 0,117| 0,158   | 2,21    | 0,033   |
| IgM Serum, g/L                                 | -0,23| -0,233           | 0,117| -0,907  | -1,99   | 0,053   |
Urea plasma level downregulates the relative content in the blood of NK-lymphocytes (Fig. 8) and the mitogenic ability of T-lymphocytes (Fig. 8), while upregulates the level of pan-lymphocytes and Microbial Count of Monocytes. Such constellation of parameters of Immunity is determined by Urea plasma by 39% (Table 5 and Fig. 9).

Table 5. Regression Summary for Urea Plasma, mM/L
R=0,622; R²=0,387; Adjusted R²=0,324; F(4,4)=6,2; p=0,0006

| Variables                        | Beta  | St. Err. of Beta | B     | SE of B | t(10) | p-level |
|----------------------------------|-------|-----------------|-------|---------|--------|---------|
| Intercept                        | 5.462 | 1,432           | 1.432 | 3.82    | 0,0005 |
| NK Lymphocytes, %                | -0.38 | -0.282          | 0.134 | -0.131  | -2.11  | 0.0418  |
| Blast transformation of T-Lymphocytes, % | -0.37 | -0.373         | 0.133 | 0.057   | -2.80  | 0.0079  |
| Pan-Lymphocytes, 10⁹/L           | 0.31  | 0.284           | 0.138 | 0.759   | 2.07   | 0.0454  |
| Microbial Count of Monocytes, Bac/Phag | 0.26  | 0.211           | 0.132 | 0.028   | 1.60   | 0.1187  |
Fig. 8. Scatterplot of correlation between Urea Plasma level (X-line) and NK lymphocytes level (Y-line)

Fig. 8. Scatterplot of correlation between Urea Plasma level (X-line) and Blast transformation of T lymphocytes reaction (Y-line)
The most numerous correlations were found for the concentration of Urea in the urine. In particular, it negatively correlates with serum CRP (Fig. 10), Complement and IgA levels, while positively correlates with the relative levels of Eosinophils, B-lymphocytes (Fig. 11) and theophylline-sensitive T-lymphocytes in the blood, as well as the absolute and relative levels of serum γ-globulines. Such constellation of parameters of Immunity is determined by Urea urine by 57% (Table 6 and Fig. 12).
Fig. 11. Scatterplot of correlation between Urea Urine concentration (X-line) and B-Lymphocytes level (Y-line)

Table 6. Regression Summary for Urea Urine, mM/L
R=0.756; R²=0.571; Adjusted R²=0.473; F(8,4)=5.8; p=0.0001

| Variables                      | Beta  | St. Err. of Beta | B     | SE of B | t_{35} | p-level |
|--------------------------------|-------|-----------------|-------|---------|--------|---------|
| C-Reactive Protein, points    | -0.45 | -0.306          | 0.127 | -34.77  | 14.37  | -2.42   | 0.021   |
| Complement, CH₅₀               | -0.32 | -0.243          | 0.119 | -1.240  | 0.609  | -2.04   | 0.049   |
| IgA Serum, g/L                | -0.28 | -0.315          | 0.130 | -249.0  | 102.9  | -2.42   | 0.021   |
| B Lymphocytes, %              | 0.36  | 0.299           | 0.137 | 7.494   | 3.429  | 2.19    | 0.036   |
| Eosinophils, %                | 0.30  | 0.243           | 0.139 | 11.60   | 6.644  | 1.74    | 0.089   |
| γ-globulines, g/L             | 0.27  | 0.697           | 0.404 | 17.97   | 10.42  | 1.72    | 0.093   |
| γ-globulines, %               | 0.23  | -0.668          | 0.399 | -13.69  | 8.173  | -1.68   | 0.103   |
| Theophylline-sensitive T-Lymphocytes, % | 0.23  | 0.232           | 0.131 | 5.616   | 3.177  | 1.77    | 0.086   |
In contrast, the immunotropic activity of Creatinine was the lowest. In particular, plasma Creatinine downregulates the level of natural killers (Fig. 13) and monocytes, as well as the mitogenic ability of T-lymphocytes, instead upregulates the level of lymphocytes in general. The degree of determination is 35% (Table 7, Fig. 14).
Table 7. Regression Summary for Creatininemia, µM/L

| Variables                             | Beta  | St. Err. of Beta | B     | SE of B | t(38) | p-level |
|---------------------------------------|-------|-----------------|-------|---------|-------|---------|
| NK Lymphocytes, %                     | -0,38 | -0,252          | 0,136 | -0,938  | 0,506 | -1,85   | 0,071   |
| Monocytes, 10⁹/L                      | -0,30 | -0,309          | 0,130 | -25,68  | 10,83 | -2,37   | 0,023   |
| Blast transformation of T-Lymphocytes | -0,29 | -0,307          | 0,136 | -0,375  | 0,166 | -2,25   | 0,030   |
| Pan-Lymphocytes, 10⁹/L                | 0,25  | 0,284           | 0,137 | 6,068   | 2,925 | 2,07    | 0,045   |

R=0,588; R²=0,346; Adjusted R²=0,278; F(4,4)=5,1; p=0,002

Table 8. Regression Summary for Creatinine Urine, mM/L

| Variables                              | Beta  | St. Err. of Beta | B     | SE of B | t(38) | p-level |
|----------------------------------------|-------|-----------------|-------|---------|-------|---------|
| Phagocytose Index of Neutrophils, %    | -0,29 | -0,154          | 0,149 | -0,020  | 0,019 | -1,03   | 0,308   |
| Killing Index of Neutrophils, %       | -0,22 | -0,257          | 0,150 | -0,021  | 0,012 | -1,71   | 0,095   |
| γ-globulines, %                        | 0,28  | 0,237           | 0,148 | 0,059   | 0,037 | 1,60    | 0,118   |
| NK Lymphocytes, %                      | 0,23  | 0,162           | 0,148 | 0,063   | 0,058 | 1,09    | 0,281   |
| Monocytes, %                           | 0,21  | 0,260           | 0,146 | 0,147   | 0,083 | 1,78    | 0,083   |

R=0,588; R²=0,346; χ²(4)=17,0; p=0,002; Λ Prime=0,654

Fig. 14. Scatterplot of canonical correlation between Creatininemia (X-line) and parameters of Immunity (Y-line)

The concentration of Creatinine in the urine is weakly negatively correlated with the activity and completeness of bacterial Phagocytosis by neutrophils and is also weakly positively correlated with the levels of γ-globulins, Natural Killers and Monocytes. Such constellation of parameters of Immunity is determined by Creatinine urine by 26% only (Table 8 and Fig. 15).
At the final stage, following the accepted algorithm, the canonical correlation between the parameters of nitrogen metabolism, on the one hand, and the parameters of immunity - on the other hand, is analyzed.

As a result of canonical analysis, two pairs of canonical roots were formed. Nitrogen root of the first pair (Table 9), judging by the factor loads, represents mainly Urea urine and plasma and Uric acid urine, and to a lesser extent Creatinine urine and plasma. Note the same sign of the factor loads. The immune root of the first pair contains information about the parameters of the Phagocytosis, Cellular and Humoral immunity as well as of the Leukocytogram, which are subject to stimulating or suppressive effects of Urine, Uric acid and Creatinine. The immunomodulatory effect of these nitrogenous metabolites, judging by the coefficient of determination, is 94,3% (Fig. 16).

Table 9. Factor load on canonical roots of nitric metabolites and immunity parameters

| Left set                  | Root 1  | Root 2  |
|---------------------------|---------|---------|
| Urea Urine                | -0.588  | -0.386  |
| Uric acid Urine           | -0.568  | -0.576  |
| Urea Plasma               | -0.505  | 0.299   |
| Creatinine Urine          | -0.305  | 0.267   |
| Creatininemia             | -0.199  | 0.103   |
| Bilirubinemia             | -0.131  | 0.409   |
| Uricemia                  | -0.053  | 0.375   |

| Right set                 | Root 1  | Root 2  |
|---------------------------|---------|---------|
| B Lymphocytes, %          | -0.388  | -0.387  |
| Bactericidal Capacity of Monocytes, 10^7 B/L | -0.303 | -0.082 |
| Phagocytosis Index of Monocytes, % | -0.272 | 0.140 |
| γ-globulines, %           | -0.256  | 0.059   |
| γ-globulines, g/L         | -0.248  | -0.077  |
| Pan-Lymphocytes, 10^9/L    | -0.244  | 0.005   |
| Monocytes, 10^9/L         | -0.192  | 0.033   |
| Monocytes, %        | -0.156 | 0.015 |
|---------------------|--------|-------|
| IgA Serum, g/L      | 0.447  | -0.160|
| Complement, CH50    | 0.252  | 0.240 |
| C-Reactive Protein, points | 0.190  | 0.175 |
| NK Lymphocytes, %   | 0.084  | -0.036|
| IgM Serum, g/L      | -0.044 | 0.375 |
| Polymorphonuclear Neutrophils, % | 0.105  | 0.257 |
| Theophylline-sensitive T-Lymphocytes, % | -0.175 | 0.240 |
| Phagocytosis Index of Neutrophils, %  | -0.060 | 0.081 |
| Eosinophils, %      | -0.134 | -0.347|
| Lysozyme, nM/L      | 0.051  | -0.389|
| Microbial Count of Neutrophils, Bac/Phag | 0.077  | -0.241|
| Blast transformation of T-Lymphocytes, % | 0.054  | -0.235|
| Killing Index of Neutrophils, % | -0.080 | -0.155|
| Theophylline-resistant T-Lymphocytes, % | -0.001 | -0.028|

**Fig. 16. Scatterplot of canonical correlation between Nitrous Metabolites (X-line) and the Immunity (Y-line) in humans. First pair of Roots**

The nitrogen root of the second pair receives a similar in magnitude and sign factor load from Uric acid of urine and less, but also a negative load from Urea of urine, instead of opposite in sign load from Urea of plasma and both Creatinine parameters. The biggest difference in the factor structure is the significant load from Bilirubinemia and Uricemia. Their immunomodulatory effect is directed as a rule to another constellation of immune parameters and is much weaker (Fig. 17). Attention should be paid to identical factor loads on B-lymphocytes, Complement and C-reactive protein.
**CONCLUSION**

The results of clinical and physiological observation, in principle, confirm our previous experimental data [32] on the significant immunotropic activity of nitrogenous metabolites. As we have already noted, the immunomodulatory effect of bilirubin is probably mediated through aryl hydrocarbon receptors [2,6,7,9,29,33,37], and uric acid through TL- and Adenosine receptors [1,5,10,11,19,20,25-27,36] of immune cells. The question of mediators of the immunomodulatory action of urea and creatinine remains open and will be the subject of the next article. And now let's limit ourselves to the announcement of the mediating role of mediators of the autonomic nervous system and adaptation hormones in line with the concepts of neuroendocrine-immune complex and functional-metabolic continuum [13,18].

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**ACCORDANCE TO ETHICS STANDARDS**

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975 and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.
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