ROLE OF THE AUTONOMIC NERVOUS SYSTEM AND LIPOPEROXIDATION IN IMMUNOTROPIC EFFECTS OF NITROGENOUS METABOLITES IN PATIENTS WITH POSTRADIATION ENCEPHALOPATHIA

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Abstract

Background. We have previously shown that nitrogenous metabolites have immunomodulatory effects, both suppressor and enhancing, both in healthy rats and in humans exposed to pathogenic influences. The immunomodulatory effect of bilirubin is probably mediated through aryl hydrocarbon receptors, and uric acid through TL- and adenosine receptors of immune cells. The question of mediators of the immunomodulatory action of urea and creatinine remains open. We hypothesized the mediating role of mediators of the autonomic nervous system. A strong correlation was found between the constellation of nitrogenous metabolites, on the one hand, and the HRV markers of ANS, on the other hand. The **aim** of this study is to analyze the relationships between HRV markers of the parameters of the ANS as well as Lipoperoxidation, on the one hand, and the parameters of Immunity - on the other hand. **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 state of the autonomic nervous system (ANS) was judged by the HRV parameters recorded before and after submaximal bicycle ergometric loading. The state of lipid peroxidation assessed the content in the serum diene conjugates, malonic dyaldehid, activity

of catalase serum and superoxide dismutase erythrocytes. **Results**. The coefficient of canonical correlation between the constellation of HRV markers of ANS and parameters of Immunity was 0,947 ($\chi^2_{(126)}$=178; p=0,002) The inclusion in factor structure parameters of Lipoperoxidation increases R to 0,973 ($\chi^2_{(231)}$=314; p<10^{-6}). **Conclusion**. Previously identified immunomodulatory effects of urea and creatinine as well as uric acid and bilirubin are realized, possibly, through cholinergic and adrenergic mechanisms as well as reactive oxygen species.

Key words: **urea, uric acid, creatinine, bilirubin, HRV, Lipoperoxidation, Immunity, relationships, humans.**

INTRODUCTION

We have previously shown that nitrogenous metabolites have immunomodulatory effects, both suppressor and enhancing, both in rats [16,17,42] and in humans [18,19,24,50]. Analysis of the literature gives reason to believe that immunomodulatory effect of bilirubin is probably mediated through aryl hydrocarbon receptors [2,6,9,34,46,54], and uric acid through TL- and Adenosine receptors [11,12,30,31] of immune cells. The question of mediators of the immunomodulatory action of urea and creatinine remains open. We hypothesized the mediating role of mediators of the autonomic nervous system and adaptation hormones in line with the concepts of neuroendocrine-immune complex [15,20,37,39,40,45] and functional-metabolic continuum [14]. The first step to confirming the hypothesis was detection the relationships between the parameters of nitrogenous metabolites, on the one hand, and HRV markers of the parameters of the autonomic nervous system - on the other hand [23]. The aim of this study is to analyze the relationships between the parameters of ANS and Immunity parameters that are subject to regulatory exposure to nitrogenous metabolites. In addition, the subject of the study were the parameters of lipoperoxidation, the role of which in the regulation of immunity is well known, on the one hand, and which are subject to exposure to at least uric acid [12,30,31] - on the other hand.

MATERIAL AND METHODS

The object of observation in 1997 were 19 men (26÷61 y) and 3 women (38, 40 and 47 y) with 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 [41,47]. 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 [13].

State of lipid peroxidation assessed the content in the serum its products: diene conjugates (spectrophotometry of heptane phase of lipids extract) [11] and malonic dyaldehid (test with tiobarbiture acid) [1], as well as the activity of antioxidant enzymes: catalase serum (by the speed of decomposition hydrogen peroxide) [22] and superoxide dismutase erythrocytes (by the degree of inhibition of nitroblue tetrazolium recovery in the presence of N-methylphenazone metasulfate and NADH) [8,28].

The analyzers "Pointe-180" ("Scientific", USA) and "Reflotron" (Boehringer Mannheim, BRD) were used with appropriate sets.

State of autonomous nervous system was assessed by the method of HRV using the "Cardio" device (Kyiv). The classical parameters of Baevskiy were analyzed: Mode (Mo), Amplitude of the Mode (AMo) and variational swing (MxDMn) as markers of the humoral channel of regulation, sympathetic and vagal tones respectively [3].

A feature of the design was the registration of HRV at rest (basal conditions, B) and immediately after the second bicycle ergometric load (L) [48], which allowed the assessment of autonomic reactivity as L/B ratio [23].

In portion of capillary blood we counted up Leukocytes level, Leukocytogram and its Entropy [36,38]. In the venous blood, the parameters of immunity were determined as described in the manual [33]. 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 [27] 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 [4], 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 [29]) as well as γ-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) [5,7]. 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.

Results processed by using the software package "Statistica 20".

RESULTS AND DISCUSSION

In the first stage, the connections between the parameters of the autonomic nervous system and those parameters of immunity which, according to preliminary data, are subject to the regulatory influence of nitrogen metabolites, were analyzed. The canonical root directly represents the basal vagal tone and autonomic reactivity, while the inverse - the basal state of vegetative homeostasis and sympathetic tone as well as the reactivity of the vagal tone (Table 1). It was found that most parameters of humoral immunity are subject to enhancing vagal influences and suppressive sympathetic influences, and only complement and neutrophiles are regulated in the opposite way. The integral measure of vagal-sympathetic immunomodulation, judging by the coefficient of determination, is 90% (Fig. 1).
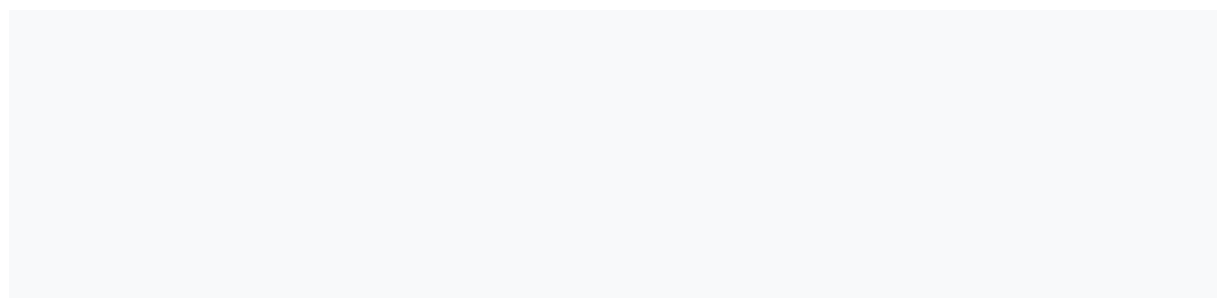
Table 1. Factor load on canonical roots of HRV and Immunity parameters

Left set	Root 1
MxDMn basal	0,913
ANS Reactivity	0,604
Stress Index basal	-0,940
AMo basal	-0,825
(MxDMn) L/(MxDMn) B	-0,718
MxDMn after loading	-0,175
Mode basal	0,034
Right set	**Root 1**
B Lymphocytes, %	0,743
Monocytes, %	0,505
Monocytes, 10^9/L	0,499
Killing Index of Neutrophils, %	0,383
Bactericidal Capacity of Monocytes, 10^9 B/L	0,368
Eosinophils, %	0,330
γ-globulines, g/L	0,319
Lysozyme, nM/L	0,269
γ-globulines, %	0,265
IgM Serum, g/L	0,145
Phagocytose Index of Neutrophils, %	0,106
NK Lymphocytes, %	0,082
IgA Serum, g/L	0,075
Blast transformation of T-Lymphocytes, %	0,002
Complement, CH_{50}	-0,233
Polymorphonucleary Neutrophils, %	-0,227
Pan-Lymphocytes, 10^9/L	-0,060
Phagocytosis Index of Monocytes, %	-0,047
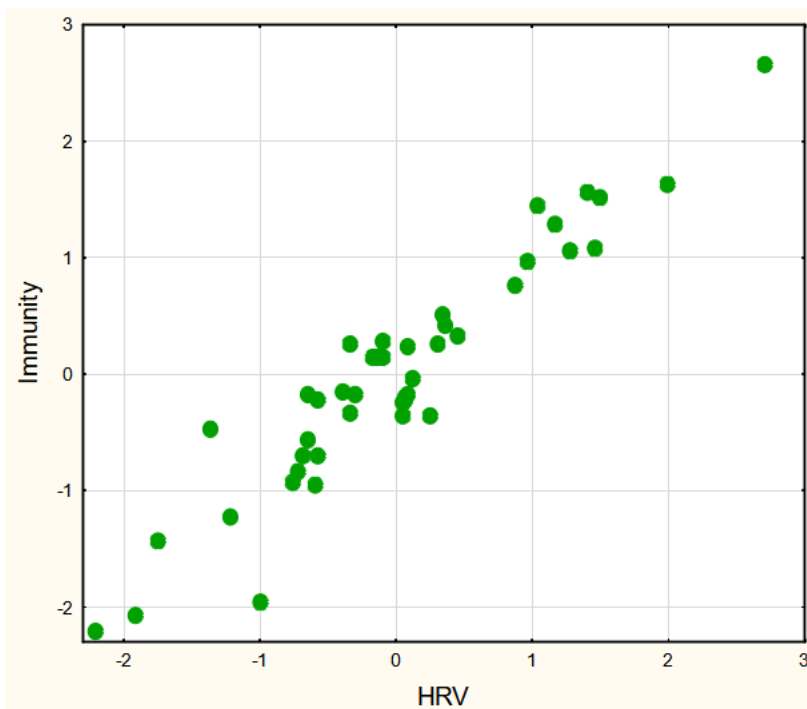
R=0,947; R^2=0,896; $\chi^2_{(126)}$=178; p=0,002; Λ Prime=0,003
Fig. 1. Scatterplot of canonical correlation between parameters of HRV (X-line) and Immunity (Y-line)

At the same time, a number of other parameters of immunity, judging by factor loadings, are not subject to influences of an autonomic nervous system, that is neither choline-, nor adreno-receptors are involved in their regulation.

In addition to the already mentioned aryl hydrocarbon, TL- and adenosine receptors, mediators of the immunotropic effects of nitrogenous metabolites can be, among many other factors, reactive oxygen species. Correlation screening confirmed the reality of this assumption (Table 2).

Table 2. Matrix of correlations between Nitrogenous metabolites and parameters of Lipoperoxidation

Variable	UreaU	UAU	CrU	UreaP	CrP	UAP	Bilir
SOD	0,11	0,22	-0,12	-0,29	-0,23	-0,15	-0,33
Katalase	0,03	-0,04	0,01	-0,01	0,05	0,29	-0,10
MDA	0,11	0,35	-0,17	-0,42	-0,44	-0,20	-0,07
DC	0,05	-0,05	-0,20	-0,01	-0,07	-0,23	0,31

The constellation of nitrogenous metabolites (primarily plasma urea and creatinine) determines the state of lipoperoxidation by 44% (Table 3 and Fig. 2).

Table 3. Factor load on canonical roots of Nitrogenous metabolites and Lipoperoxidation parameters

Left set	Root 2
Urea Plasma	**0,716**
Creatininemia	**0,686**
Uricemia	**0,379**
Bilirubinemia	**0,331**
Creatinine Urine	**0,310**
Uric acid Urine	**-0,571**
Urea Urine	**-0,217**
Right set	Root 2
Malonic dyaldehid, µM/L	-0,847
Superoxide dismutase, un/mL	-0,705
Diene conjugates, E^{232}/mL	-0,004
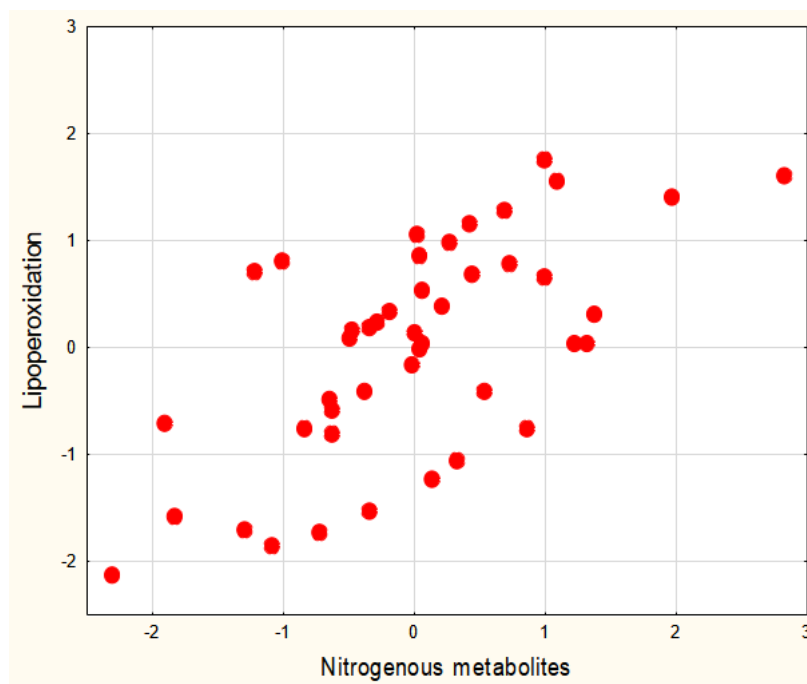
R=0,663; R²=0,440; $\chi^2_{(28)}$=37; p=0,121; Λ Prime=0,369
Fig. 2. Scatterplot of canonical correlation between Nitrogenous metabolites (X-line) and parameters of Lipoperoxidation (Y-line)

At the final stage of the analysis, lipoperoxidation parameters were incorporated into the factor structure of the causal canonical root.

As we can see (Table 4), superoxide dismutase, malonic dyaldehyde and diene conjugates were surrounded by vagal factors that upregulates the parameters of humoral immunity, phagocytosis of macrophages and the level of natural killers. Instead, catalase along with circulating catecholamines and sympathetic tone downregulates the blood levels of two subpopulations of T lymphocytes, complement and C-Reactive protein.

This constellation of ANS and lipoperoxidation parameters determines the constellation of immune parameters by 95% (Fig. 3).

Table 4. Factor load on canonical roots of HRV and Lipoperoxidation (Left set) and Immunity parameters (Right set)

Left set	Root 1
MxDMn basal, sec	-0,711
Superoxide dismutase, un/mL	-0,416
Malonic dyaldehid, µM/L	-0,414
MxDMn after loading, sec	-0,400
Diene conjugates, E^{232}/mL	-0,284
Stress Index basal	0,750
Mode basal, sec	-0,556
AMo basal, %	0,377
Katalase, µM/L•h	0,322
Right set	Root 1
B Lymphocytes, %	-0,503
Monocytes, %	-0,484
Monocytes, 10^9/L	-0,420
Bactericidal Capacity of Monocytes, 10^9 B/L	-0,302
Eosinophils, %	-0,250
NK Lymphocytes, %	-0,237
IgA Serum, g/L	-0,217
γ-globulines, g/L	-0,157
Blast transformation of T-Lymphocytes, %	-0,123
Complement, CH_{50}	0,444
Pan-Lymphocytes, 10^9/L	0,387
Theophylline-resistant T-Lymphocytes, %	0,178
Phagocytosis Index of Monocytes, %	0,174
Theophylline-sensitive T-Lymphocytes, %	0,156
Polymorphonucleary Neutrophils, %	0,156
C-Reactive Protein, points	0,145
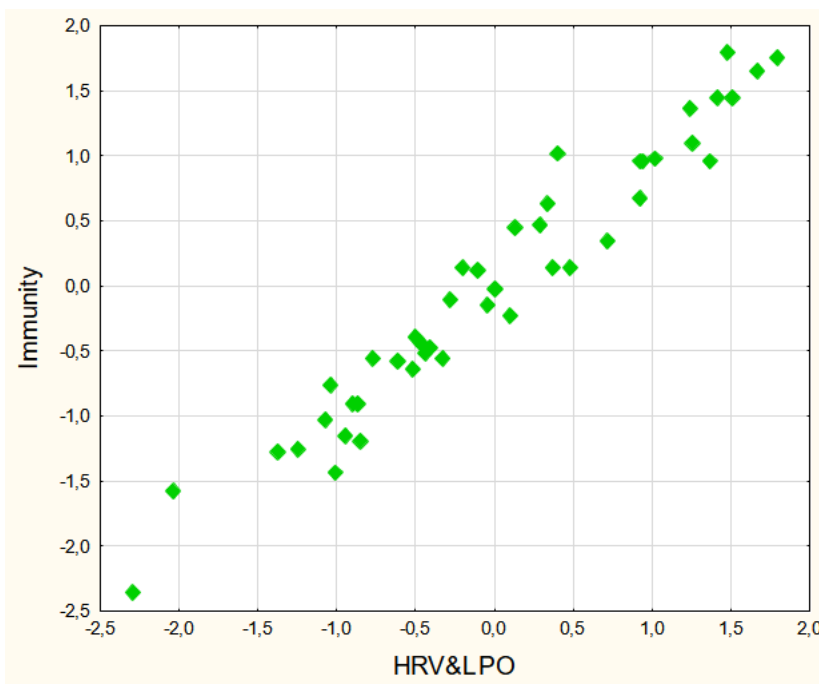
R=0,973; R²=0,946; $\chi^2_{(231)}$=314; p=0,0002; Λ Prime<10^{-5}
Fig. 3. Scatterplot of canonical correlation between parameters of HRV and Lipoperoxydation (X-line) and Immunity (Y-line)

Our data are consistent with numerous data in the literature on the role of the autonomic nervous system and its mediators in the regulation of innate and adaptive immunity [32,35,49,51,52].

Thus, the immunomodulatory effect of nitrogenous metabolites is realized both by their direct effect on aryl hydrocarbon, TL- and adenosine receptors of immune cells, and indirectly through modulation of the activity of the autonomic nervous system, whose mediators, in turn, interact with choline- and adrenoreceptors.

However, we should keep in mind the mediating role of the CNS and endocrine factors [15,20,25,26,35,39,43,44,53,55,56], which will be the subject of our next research.

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