HEALTH RISK ANALYSIS IN HYGIENE

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ASSESSING RISKS OF ADVERSE CLINICAL COURSE AND OUTCOME OF AN INFECTIOUS DISEASE WITH MATHEMATICAL MODELING OF EXPOSURE TO ENVIRONMENTAL FACTORS ON THE EXAMPLE OF ALUMINUM OXIDE

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Our research goal was to create a mathematical model that described anti-viral immune response regulation taking into account influence exerted by exposure to variable chemical factors. We analyzed a body response to an infection taking into account innate and adaptive immunity mechanisms. This created mathematical model helps to describe spatial distribution of immune and infectious agents in various organs and systems due to allowing for time lags occurring during interactions between different components participating in the process. The mathematical model is a system of ordinary differential equations with a retarded argument; separate addends of the model describe velocity properties of the processes that produce their effects on the development of an infectious disease. We suggest an algorithm for conducting an experiment aimed at identifying certain parameters related to influence exerted by chemical factors on interaction between the neuroendocrine and immune systems. We calculated dynamics in parameters of the immune and neuroendocrine systems when a viral infection occurs under experimental exposure to aluminum oxide. The suggested approach is applied within the concept of a multi-level human body model that takes into account interactions between systems and functional state of organs that are being examined under exposure to adverse factors of variable genesis. The conducted research provides a qualitative conception about causes that explain quantitative changes in a viral agent when an immune response occurs in a body under exposure to variable factors. This approach can be applied to adjust parameters of existing population models, spread and clinical course of different infections, and to draw up a long-term forecast of an epidemiologic situation which is necessary when risks of infectious diseases are analyzed, including those occurring when a body is exposed to adverse environmental factors.

Key words: *mathematical model, dynamic system, viral disease, innate immunity, adaptive immunity, neuroendocrine regulation.*

Introduction. Nowadays an issue of describing interrelations in adaptive systems which modify their functioning in order to preserve their optimal state under changing outer conditions is of great interest to researchers who study neuroendocrine regulation and immune mechanisms [1, 2]. Works published in the field focus on various sings of mutual regulatory influences exerted by the systems being considered on each other [3, 4]. Some

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research dwells on neuroendocrine regulation of the immune system [5, 6] and controlling influence exerted by the immune system, for example, via cytokines production, both on itself and on the neuroendocrine regulatory loop [7, 8]. Most experts in the field believe neuroendocrine and immune regulatory loops are a unified "super"-regulatory metasystem [9, 10] which coordinates a complicated multi-level regulatory process in a human body. The immune system protects a body from multiple threats, including viral infections; losses occurring due to such infectious make a considerable contribution into overall damages done to population by various health disorders and are a great medical and social problem [11].

Technogenic environmental factors can cause pathomorphism and lead to deteriorated clinical course and outcome of infectious diseases [12, 13]. Technogenic processes exert influence on regulatory (immune and neuroendocrine) systems; thus, for example, it was shown [14, 15], that technogenic chemical factors exerted negative impacts on functioning of the said systems.

Observation techniques or an experimental approach with subsequent statistical processing which are conventionally applied to assess functional disorders in the immune and neuroendocrine system, in spite of all their significance, don't fully allow to analyze mechanisms and assess consequences caused by an effect occurring when functional disorders accumulate in body systems. It is due to limitations which exist in choice of representative groups, complications related to identification and detection of basic factors, and substantial material costs which are required for organizing and conducting experiments.

Mathematical modeling seems to be one of the most efficient approaches to finding an optimal strategy for examining as well as predicting clinical course of virus diseases. This approach allows to save time and resources required for solving the abovementioned tasks. Mathematical models make it possible to analyze influence exerted by various factors and their combinations at an individual and population level. An example of such models is mathematical prediction models which describe correlation between human health and environmental factors [16, 17, 18].

Our research goal was to develop approaches to assessing body responses to an infectious disease taking into account interaction between the immune and neuroendocrine system under exposure to aluminum oxide and with functional disorders accumulating in a body.

Data and methods. We worked out an experimental procedure for examining negative influences exerted by chemical agents on interaction between components of the immune and neuroendocrine systems. This procedure allows to determine impacts exerted by various factors on activity of immune cells that protect a body from infections.

We chose aluminum oxide as an influencing factor in this work. Technogenic pollution with metals is a widely spread problem on industrially developed territories; peculiarities related to influences exerted by such contaminants on population health are their ability to change immune cells functioning, either inhibiting or stimulating them as well as controlling proteins produced by such cells. Aluminum compounds produce inhibiting effects on functions performed by immune cells (T- and B-lymphocytes and macrophages) and on controlling proteins production as well as ratio of immune cells quantity.

Our experiment was accomplished on an undivided population of immune cells which included T-helpers (CD3/4), B-cells (CD19/22), NK-cells (CD16/56), and cytotoxic T lymphocytes (CD3/8); the population was extracted from a peripheral blood sample. We examined a combine response given by the immune cells population to impacts, but to assess functionality of each cells type, we chose a specific parameter that reflected functions of only one type of immune cells.

Influences exerted by controlling elements, such as intrleukin-1, interleukin-2, or hydrocortisone, were considered to be contributors that induced (regulated) work performed by immune cells; occurrence of viruses was another contributor (we applied a solution based on hemagglutinin and concanavalin as a viral load simulator due to its ability to induce similar responses from the immune system). Changes that occurred in functional activity of the examined immune cells population were assessed as per production of specific controlling proteins.

Concentration of a viral load simulator (a universal mitogen based on hemagglutinin and concanavalin) applied in experimental research was within 10-1,000 μg/ml range. Operating levels of interleukin-1 were determined as per data on changes in cytokine concentration in a healthy body. Normally, interleukin-1 contents should be within 0-10 pg/ml. Interleukin-2 concentrations were determined as per data obtained for healthy people and existing standards; they amounted to 10 pg/ml and 100 pg/ml respectively. Standard hydrocortisone concentration is 138-635 nmol/l. We analyzed impacts exerted by two aluminum concentrations, 0.01 mg/l and 0.1 mg/l, its maximum permissible concentration in water being equal to 0.2 mg/l.

We determined how many experiments we required judging from the necessity to take into account impacts exerted by all the contributors, namely interleukin-1, interleukin-2, hydrocortisone, aluminum oxide, and viral load. 16 experiments are a half-replicate of a complete factor experiment for 5 factors. Below one can see the overall view of a sought function that describes impacts exerted by the considered factors on marker proteins production by cells:

$$\begin{aligned} y(x_i) = {} & b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_4x_4 + b_5x_5 + \\ & + b_{1,4}x_1x_4 + b_{2,4}x_2x_4 + b_{3,4}x_3x_4 + b_{1,5}x_1x_5 + \\ & + b_{2,5}x_2x_5 + b_{3,5}x_3x_5 + b_{4,5}x_5x_4 + b_{1,4,5}x_1x_5x_4 + \\ & + b_{2,4,5}x_2x_5x_4 + b_{3,4,5}x_3x_5x_4, \end{aligned} \quad (1)$$

where $y(x_i)$ is a concentration of a marker protein that characterizes functional activity of immune cells;

b_j are sought coefficients of the model;

x_1 is a concentration of viral load simulator;

x_2 is interleukin-1 concentration;

x_3 is interleukin-2 concentration;

x_4 is hydrocortisone concentration;

x_5 aluminum oxide concentration.

All the parameters were recalculated as per their maximum value obtained during the experiment; as a result, all the variables in the mathematical model are of the same order. Maximum interferon-gamma concentration amounts to 30.62 [pg/ml] and interleukin, 8 [pg/ml].

We applied a structural scheme shown in Figure 1 to describe interaction between the immune and neuroendocrine systems under exposure to aluminum oxide and with functional disorders accumulating in a body. The scheme is a set of interrelated immune and neuroendocrine system elements which are the most significant components in a body response to a virus invasion. The models takes into account functional state of organs being considered.

As we describe interactions between the immune and endocrine system which are very complicated we introduce certain simplifying assumptions into the design of our model. Cells and viruses populations are assumed to be evenly spread over the epithelial layer of a target organ at any moment. We also assume that speed of changes in any variable in the model is determined by the current values of all the variables. At present we assume that the basic processes which regulate immune protection dynamics take place in three local volumes: brains (hypophysis and hypothalamus), abdominal cavity (adrenals), and a target organ. Interaction between these three local volumes occurs with a time lag.

Protection mechanisms are activated after macrophages have removed cells affected by a virus, simultaneously information molecules of (cytokine) interleukin-1 are synthesized [19].

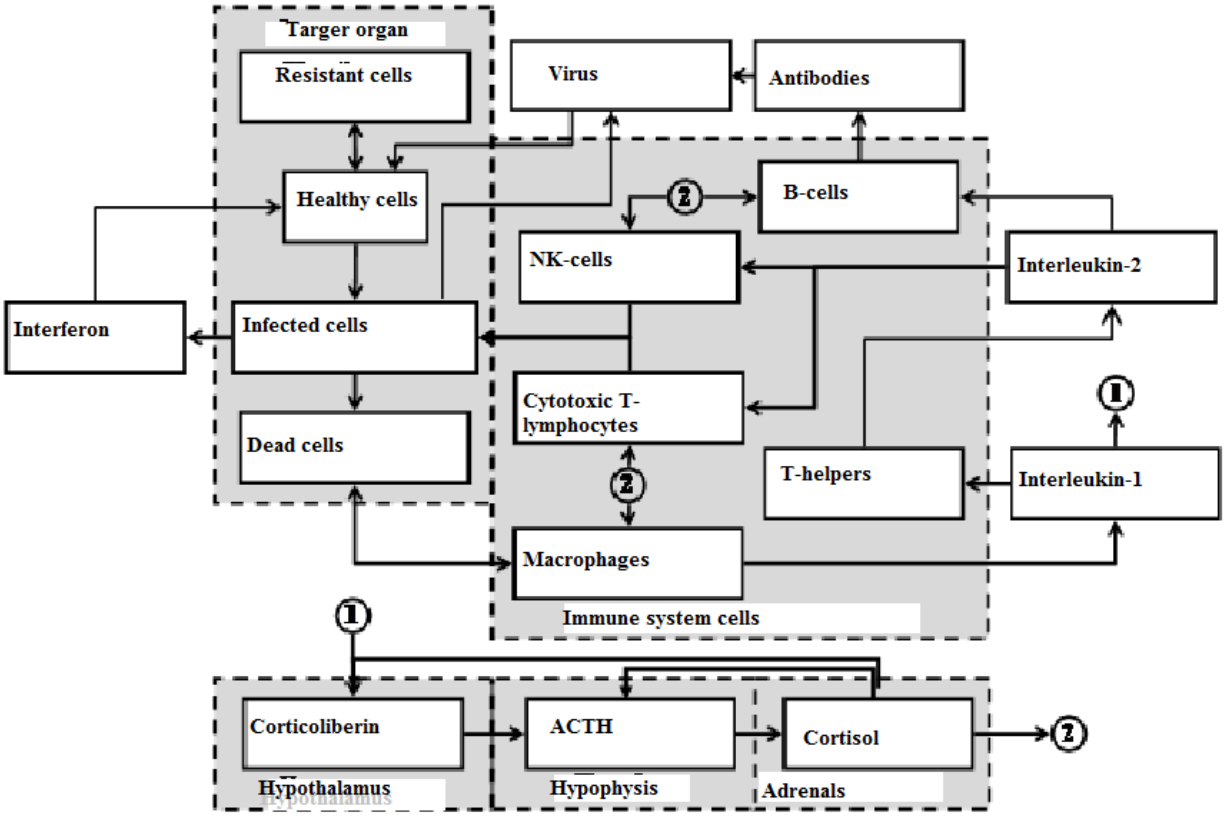


Figure 1. A conceptual scheme showing how the immune and neuroendocrine systems function in case a virus infection occurs

As interleukin-1 concentration in blood increases, it makes for T-helpers producing interleukin-2 and stimulates specific receptors in the hypothalamus to produce corticoliberin, a release hormone. Corticoliberin influences the adenohypophysis and causes adrenocorticotropic hormone (ACTH) secretion [18]. When penetrating blood, ACTH stimulates the adrenals to produce hydrocortisone; increased concentration of this hormone inhibits ACTH secretions and blocks interleukin-1 production as per negative feedback mechanism.

Regulatory impacts exerted by interleukin-2 are aimed at NK-cells [35], cytotoxic T-lymphocytes [15] and B-cells [2]. Basic NK-cells function is related to infected cells elimination at early stages of a body protecting against virus infections. In our work we allow for inhibiting effects exerted on NK-cells by hydrocortisone [23; 24] and stimulating influence by interleukin-2 [25].

Infected cells produce interferon and it is another mechanism of primary anti-virus body protection [26, 27]. There are basic mechanisms of specific acquired immune response: B-cells produce antibodies [28] which bind free viruses, and cytotoxic T-lymphocytes destroy cells infected with viruses [29]. Hydrocortisone inhibits antiviral activity of the examined cells.

Basing on the above-given interaction scheme we can describe a mathematical model for the regulation mechanism comprising elements of the immune and endocrine system with the help of the designed model which is a system consisting of 18 ordinary first-order differential equations with a retarded argument (2):

$$
\begin{cases}
\frac{dC_{\mathrm{HE}}}{dt} = k_1\left(C_{\mathrm{HE}} + C_R\right)C_D + k_2 C_R - k_3 C_{\mathrm{HE}} C_{IFN} - k_4 C_{\mathrm{HE}} C_V \\
\frac{dC_I}{dt} = k_4 C_{\mathrm{HE}} C_V - k_5 C_{NK} C_I C_{IL2}\left(1 - k_8 \frac{C_K\left(t-T\right)}{k_{47} + C_K\left(t-T\right)}\right) - \\
-k_6 C_{CTL} C_I \left(1 - k_9 \frac{C_K\left(t-T\right)}{k_{47} + C_K\left(t-T\right)}\right) H\left(C_{CTL} - k_{46}\right) - k_7 C_I \\
\frac{dC_R}{dt} = k_3 C_{\mathrm{HE}} C_{IFN} - k_2 C_R \\
\frac{dC_{IFN}}{dt} = k_{10} C_I - k_{11} C_{\mathrm{HE}} C_{IFN} - k_{12} C_{IFN} \\
\frac{dC_D}{dt} = k_7 C_I + k_5 C_{NK} C_I C_{IL2}\left(1 - k_8 \frac{C_K\left(t-T\right)}{k_{47} + C_K\left(t-T_2\right)}\right) + \\
+k_6 C_{CTL} C_I \left(1 - k_9 \frac{C_K\left(t-T\right)}{k_{47} + C_K\left(t-T\right)}\right) H\left(C_{CTL} - k_{46}\right) - k_{13} C_D C_{\mathrm{M}} \\
\frac{dC_V}{dt} = k_{14} C_I - k_{15} C_V C_A - k_{16} C_V C_{\mathrm{HE}} - k_{17} C_V \\
\frac{dC_M}{dt} = k_{18} F_b - k_{19} C_{\mathrm{M}} \\
\frac{dC_{IL1}}{dt} = k_{20} C_{\mathrm{M}} C_D \left(1 - k_{21} \frac{C_K\left(t-T\right)}{k_{47} + C_K\left(t-T\right)}\right) - k_{22} C_{IL1} \\
\frac{dC_{TH}}{dt} = k_{23} F_b - k_{24} C_{TH} \\
\frac{dC_{IL2}}{dt} = k_{25} C_{TH} C_{IL1} - k_{26} C_{IL2} \\
\frac{dC_{NK}}{dt} = k_{27} F_b - k_{28} C_{NK} \\
\frac{dC_{CTL}}{dt} = k_{29} + k_{30} C_{CTL} C_{IL2} - k_{32} C_{CTL} - k_{31} C_{CTL} C_I \left(1 - k_9 \frac{C_K\left(t-T\right)}{k_{47} + C_K\left(t-T\right)}\right) H\left(C_{CTL} - k_{46}\right) \\
\frac{dC_B}{dt} = k_{46} + k_{33} C_B C_{IL2} - k_{34} C_B \\
\frac{dC_A}{dt} = k_{35} C_B \left(1 - k_{36} \frac{C_K\left(t-T\right)}{k_{47} + C_K\left(t-T\right)}\right) H\left(C_B - k_{45}\right) - k_{37} C_V C_A - k_{38} C_A \\
\frac{dC_{CRH}}{dt} = k_{48} F_h \left(1 - k_{39} \frac{C_K\left(t-T\right)}{k_{47} + C_K\left(t-T\right)}\right)\left(1 + k_{40} C_{IL1}\right) - k_{41} C_{CRH} \\
\frac{dC_{ACTH}}{dt} = k_{49} F_p \left(1 - k_{42} \frac{C_K\left(t-T\right)}{k_{47} + C_K\left(t-T\right)}\right) C_{CRH} - k_{43} C_{\mathrm{ACTH}} \\
\frac{dC_K}{dt} = k_{50} F_a C_{\mathrm{ACTH}}\left(t-T\right) - k_{44} C_K,
\end{cases}
\tag{2}
$$

where

C_{HE} is number of healthy non-resistant cells in a target organ, [cells];

k_i are quotients of a model;

C_R is a number of resistant cells in a target organ, [cells];

C_D is a number of dead cells in a target organ, [cells];

C_{IFN} is interferon concentration, [IU/ml];

C_V is viruses concentration, [copies/ml];

C_I is a number of infected cells in a target organ, [cells];

C_{NK} is NK-cells (natural killers) concentration, [cells/ml];

C_{IL2} is interleukin-2 concentration, [pg/ml];

C_K is hydrocortisone concentration, [nanogram/ml];

T is time lag, [minutes];

C_{CTL} is cytotoxic T-lymphocytes concentration, [cells/ml];

C_M is macrophages (monocytes) concentration, [cells/ml];

C_A is antibodies concentration, [mIU/ml];

F_b is marrow functional capacity, synthesizing function, [dimensionless value];

C_{IL1} is interleukin-1 concentration, [pg/ml];

C_{TH} is T-helpers concentration, [cells/ml];

C_B is B-cells concentration, [cells/ml];

C_{CRH} is corticoliberin concentration, [pg/ml];

F_h is hypothalamus functional capacity, synthesizing function, [dimensionless value];

C_{ACTH} is adrenocorticotropic hormone (ACTH) concentration, [picogram/ml (pg/ml)];

F_p is hypophysis functional capacity, synthesizing function, [dimensionless value];

F_a is adrenals functional capacity, synthesizing function, [dimensionless value].

Interactions between cells populations and body information molecules are based on the clonal selection theory (Burnet theory according to which cells clones (B-cells) occur in a body; these cells are specific to different viruses and a virus selectively contacts a corresponding clone thus stimulating it to produce antigens), mass action law (reactions speeds are proportionate to substances concentration product), interaction characteristics and Markov's death and recovery processes.

The model parameters were indentified on the basis of experimental data obtained during research on a process of a body being infected with a flu virus; values for the model parameters are given in Table 1.

As all the equations in the model are complicated and non-linear, it becomes more difficult to obtain analytical solutions with it. To solve the differential equation system, we apply implicit numerical technique by Runge-Kutta of the third order.

Results and discussion. We analyzed the results of our experiment during which we assessed effects produced by various factors on interferon-gamma production and determined that the greatest influence was exerted by a viral load simulator. Average standardized value for interferon-gamma amounted to 0.225±0.058 under low influence exerted by a viral load simulator, but when this influence was significant, it amounted to 0.323±0.086 (there was an authentic discrepancy between the obtained average values, $p<0.05$). We can conclude that interferon-gamma is synthesized due to stimulating effects produced by a viral load simulator and it is well in line with literature data.

Influence exerted by low concentrations of a viral load simulator on interferon-gamma production is significantly modified by effects produced by hydrocortisone; this phenomenon corresponds with literature data on qualitative effects produced by hydrocortisone [39]. Average standardized value for interferon-gamma concentration amounts to 0.277±0.098 when influence exerted by a viral load simulator is low and so is hydrocortisone concentration; but when hydrocortisone concentration is high, interferon-gamma concentration is equal to 0.173±0.065 (there was an authentic discrepancy between the obtained average values, $p<0.05$). These values are shown on Figure 2. This observed discrepancy can be an evidence that hydrocortisone has inhibiting effects under low values of a factor that influences immune cells. When a viral load simulator was high, we didn't reveal any significant effects produced by hydrocortisone.

Interferon-gamma is produced in a human body primarily by infected cells in a target organ and NK-cells. The performed experiment revealed that interferon-gamma production by NK-cells was stimulated by a controlling protein, namely interleukin-2. The obtained results are in line with literature data. Average standardized interferon-gamma concentration amounted to 0.193±0.049 under insignificant influence exerted by interleukin-2, but when

Table 1

Parameters of the mathematical model that describes interactions between the immune and endocrine systems under a virus infection

Parameter	Value	Source	Parame-ter	Value	Source
k_1	$2.35*10^{-11}$ [1/cells*day]	[30]	k_{27}	$1.1*10^{14}$ [cells/ml*day]	
k_2	0.98 [1/day]	[31]	k_{28}	0.11 [1/day]	
k_3	$1.1*10^{-17}$ [ml/IU*day]	[32]	k_{29}	$4*10^{15}$ [cells/ml*day]	[31]
k_4	$2*10^{-12}$ [ml/copies*day]	[31]	k_{30}	4.15 [ml/pg*day]	[31]
k_5	$2.5*10^{-17}$ [ml^2/cells*pg*day]		k_{31}	$1.6*10^{-11}$ [1/cells*day]	[32]
k_6	$6.6*10^{-18}$ [ml/cells*day]	[32]	k_{32}	0.4 [1/day]	[31]
k_7	1.5 [1/day]	[33]	k_{33}	5.75 [ml/pg*day]	[31]
k_8	0.5 [dimensionless]		k_{34}	0.4 [1/day]	[31]
k_9	0.5 [dimensionless]		k_{35}	$7.56*10^{12}$[mIU/cells]	[31]
k_{10}	$3.2*10^{6}$ [IU/cells*ml*day]		k_{36}	0.5 [dimensionless]	
k_{11}	$1.01*10^{-10}$ [1/cells*day]	[32]	k_{37}	$8.6*10^{-10}$ [ml/copies*day]	[32]
k_{12}	8 [1/day]	[32]	k_{38}	0.043 [1/day]	[31]
k_{13}	10^{-14} [ml/cells*day]		k_{39}	0.5 [dimensionless]	
k_{14}	510 [copies/ml*cells*day]	[33]	k_{40}	0.002 [ml/pg]	
k_{15}	$8.6*10^{-10}$ [ml/mIU*day]	[43]	k_{41}	3.767 [1/day]	[36]
k_{16}	$6.1*10^{-12}$ [1/cells*day]	[32]	k_{42}	0.5 [dimensionless]	
k_{17}	1.7 [1/day]	[32]	k_{43}	0.7572 [1/day]	[37]
k_{18}	$3*10^{9}$ [cells/ml*day]	[31]	k_{44}	0.1972 [1/day]	[37]
k_{19}	0.03 [1/day]	[31]	k_{45}	$1.8139*10^{20}$ [cells/ml]	
k_{20}	$2.94*10^{-19}$ [pg/$cells^2$*say]	[34]	k_{46}	$0.4*10^{16}$ [cells/ml]	[31]
k_{21}	0.5 {dimensionless]		k_{47}	3.055 [ng/ml]	[38]
k_{22}	0.1245 [1/day]	[35]	k_{48}	7.659 [pg/ml]	[36]
k_{23}	$5.8*10^{3}$[cells/ml*day]		k_{49}	21 [pg/ml]	[37]
k_{24}	0.0058 [1/day]		k_{50}	3.055 [ng/ml]	[38]
k_{25}	$3.28*10^{-7}$ [ml/cells*day]		T	0.0132 [day]	[38]
k_{26}	0.248 [1/day]				

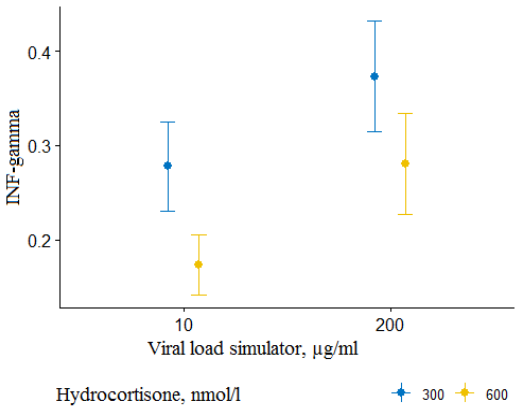


Figure 2. Average standardized interferon-gamma concentrations with error of mean under different concentration of a viral load simulator taking into account effects by hydrocortisone

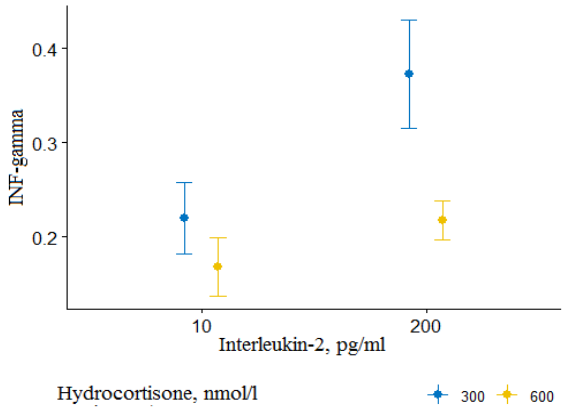


Figure 3. Average standardized interferon-gamma concentrations with error of mean under different concentration of interleukin-2 taking into account effects by hydrocortisone

this influence was high, it was equal to 0.289±0.074 (there was an authentic discrepancy between the obtained average values, $p<0.05$).

As it is not the case with a viral load simulator, hydrocortisone produces significant effects when interleukin-2 concentration is high. This observed discrepancy can be explained by the following: when we consider a viral load simulator, hydrocortisone inhibits immune reaction at the initial stage in the process thus preventing the overall chain of protective reactions in a body from activating as a virus occurs in small quantities and it is not necessary to waste energy accumulated in a body. But if interleukin-2 occurs in high concentrations in a body, it can be a sign that all the protective mechanisms are activated. In this case hydrocortisone controls interferon-gamma production in order to keep a body response to an infection within standardized limits. If the immunity exceeds these limits, interferon-gamma can damage healthy cells thus making a disease even worse and wasting greater amounts of energy.

Average standardized interferon-gamma concentration amounted to 0.372±0.14 under great influence exerted by interleukin-2 and low hydrocortisone concentration; but when hydrocortisone concentration was high, interferon-gamma concentration was equal to 0.217±0.048 (there was an authentic discrepancy between the obtained average values, $p<0.05$); these data are shown on Figure 3. Low hydrocortisone concentrations don't have any significant influence on interferon-gamma production stimulated by interleukin-2.

We applied the least squares method (Statistica 6.0 software) to identify parameters of the model that described effects produced by various factors (1). To test whether the model was relevant to experimental data, we applied dispersion analysis, and the obtained model had the following characteristics: $R^2=0.187$ and $p=0.002$. We simplified the obtained equation by dropping summands which didn't make any authentic contribution into the value for interferon-gamma concentration; this was done basing on Akaike test. We also dropped summands with low influences basing on the assessment of their elasticity coefficient. The equation (1), taking into account the obtained quotients values, can be given as follows:

$$y(x_i) = 0,35 + x_1(0,29x_4 - 0,32) + \\ + x_3x_5(0,72x_4 - 0,56), \quad (3)$$

where $y(x_i)$ is standardized interferon-gamma concentration, and interferon-gamma characterizes functional activities performed by immune cells;

x_1 is standardized concentration of a viral load simulator;

x_3 is standardized interleukin-2 concentration;

x_4 is standardized hydrocortisone concentration;

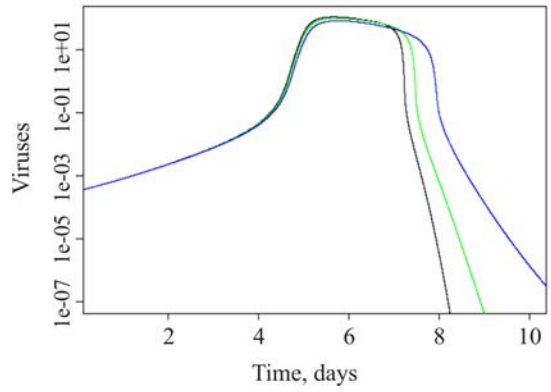
x_5 is standardized aluminum oxide concentration.

The obtained relationship allows to adjust k_{10} quotient in the mathematical model (2). This adjustment allows to take into account influence exerted by aluminum oxide on an infectious process.

Figure 4 shows the results obtained via modeling three different aluminum oxide concentrations. A discrepancy in solutions to the equations systems occurs at the adaptive response stage. The obtained results revealed that exposure to aluminum oxide was at its maximum (concentration was equal to 1 mg/l), a body fought against a virus infection quite intensely but significant damage was done to it in the process. When aluminum oxide concentration was average (0.1 mg/l), dynamics of changes in flu viruses concentration corresponded to a typical average clinical course of the disease. But when exposure to an external factor was minimal (concentration was equal to 0.01 mg/l), the disease lasted longer but lesser damage was done to a body.

In case aluminum oxide significantly stimulates interferon-gamma production by NK-cells, it allows a greater number of cells in a target organ to simultaneously become resistant. It leads to a decrease in a number of healthy cells which are used by viruses for infecting. This fact makes the disease shorter but

doesn't change maximum damage done to a target organ; we chose a virus for our model identification for which the upper respiratory tracts were such an organ.



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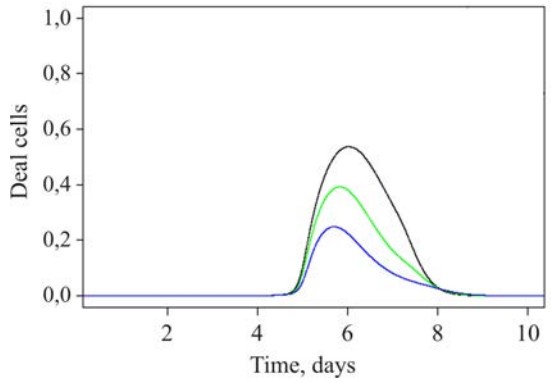


b

Figure 4. a) Relationship between viruses concentrations in a body and time under different aluminum concentrations b) relationship between damage to a target organ and time under different aluminum concentrations (blue line corresponds to aluminum oxide concentration equal to 0.01 ml/l; green line, 0,1 ml/l; black line, 1 mg/l)

We assessed discrepancies in average interleukin-8 concentrations under different levels of influencing factors and revealed that interleukin-1 exerted the most significant influence. Average standardized interleukin-8 concentration amounted to 0.414±0.046 under insignificant influence exerted by interleukin-1; but if this influence was great, it was equal to 0.493±0.047 (there was an authentic discrepancy between the obtained average values, $p<0.05$). We can conclude that interleukin-8 synthesis that characterizes NK-cells functional capabilities is stimulated by interleukin-1 and it is in line with literature data [40]. Influence exerted by low interleukin-1 concentrations on interleukin-8 production is significantly modified by effects produced by hydrocortisone. This phenomenon corresponds to literature data on qualitative influence exerted by hydrocortisone on NK-cells functionality [41]. Average standardized interleukin-8 concentration amounted to 0.448±0.08 under insignificant influence exerted by interleukin-1 and low hydrocortisone concentration; but if hydrocortisone concentration was high, interleukin-8 concentration amounted to 0.38±0.049 (there was an authentic discrepancy between the obtained average values, $p<0.05$). These values are given on Figure 5. This observed discrepancy can be an evidence that hydrocortisone produces inhibiting effects on immune cells when an influencing factor occurs in low concentrations. We didn't reveal any significant influence exerted by hydrocortisone under high interleukin-1 concentration.

This observed discrepancy in produced effects can be explained by the following: hydrocortisone inhibits immune reaction at the initial stage in the process thus preventing the overall chain of protective reactions in a body from activating as a virus occurs in small quantities and it is not necessary to waste energy accumulated in a body.

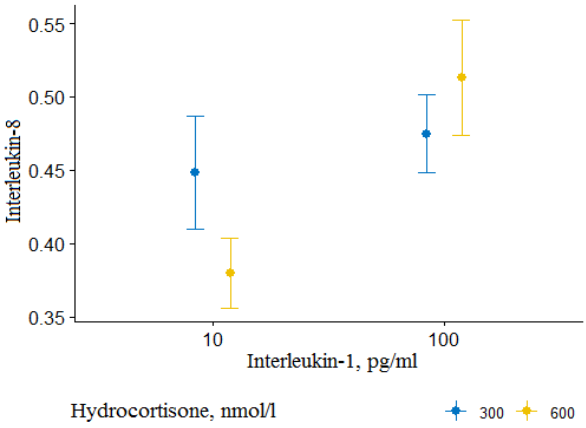


Figure 5. Average standardized interleukin-8 concentrations with error of mean under different concentration of interleukin-1 taking into account effects by hydrocortisone

Aluminum oxide exerts similar influence on interleukin-8 production under exposure to interleukin-1. Average standardized interleukin-8 concentration amounted to 0.453±0.082 under low interleukin-1 influence and low aluminum oxide concentration; but if aluminum oxide concentration was high, interleukin-8 concentration was equal to 0.374±0.042 (there was an authentic discrepancy between the obtained average values, $p<0.05$). These values are shown on Figure 6.

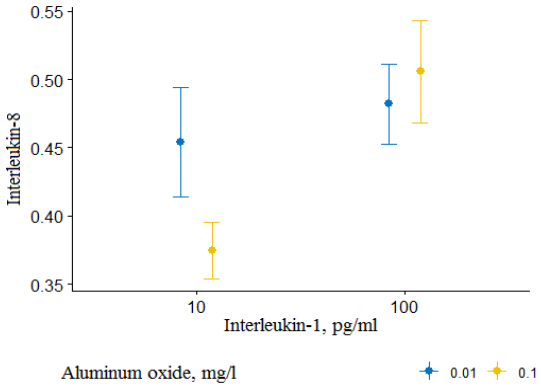


Figure 6. Average standardized interleukin-8 concentrations with error of mean under different concentration of interleukin-1 taking into account effects by aluminum oxide

We applied the least squares method (Statistica 6.0 software) to identify parameters of the model (1). The obtained equation, taking into account new quotients values, can be given as follows:

$$y(x_i) = 0{,}35 + x_2\left(0{,}11 - 0{,}13x_4 - 0{,}11x_5\right), \quad (4)$$

where $y(x_i)$ is standardized interleukin-8 concentration, and interleukin-8 characterizes functional capabilities of immune cells;

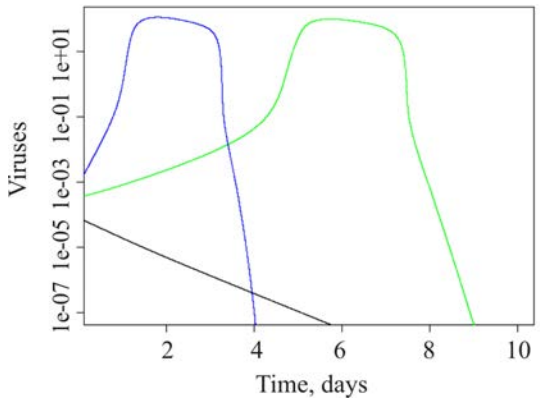
x_2 is standardized interleukin-1 concentration;

x_4 is standardized hydrocortisone concentration;

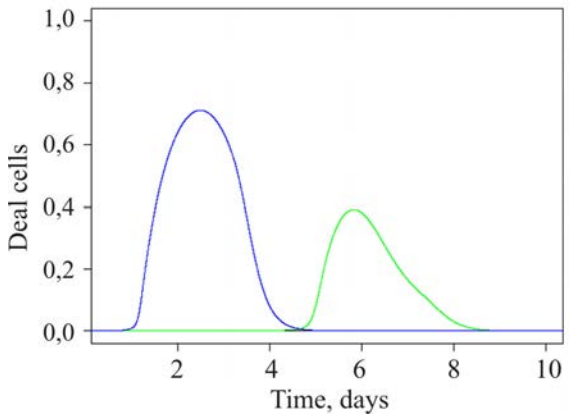
x_5 is standardized aluminum oxide concentration.

The obtained relationship allows to adjust parameters of changes in infected cells quantity under an immune response in the system of equations (2). The summand $k_5 C_{NK} C_I C_{IL2}$ in the equation (2.2) describes destruction of infected cells in a target organ by NK-cells without new viruses occurrence.

To assess what influence was produced on solutions to the system of equations by effects produced by aluminum oxide on NK-cells functional capabilities, we applied a function with an adjusted quotient k_5 together with the previously obtained relationship (4). Figure 7 shows results of modeling for three different aluminum oxide concentrations.



a



b

Figure 7. a) the relationship between viruses concentration in a body and time under different aluminum concentrations, b) the relationship between damage done to a target organ and time under different aluminum concentrations (the black line corresponds to aluminum oxide concentration equal to 0.01 mg/l; the green line, 0.1 mg/l; the blue line, 1 mg/l)

The obtained results revealed that when aluminum concentration was minimal (0.01 mg/l), a body recovered quickly, without any apparent symptoms of the disease. Under average exposure to aluminum (0.01 mg/l) and the same initial conditions, dynamics of changes in flu viruses quantities corresponded to a typical average clinical course of the disease. But if influence exerted by an external factor was high (1 mg/l), viruses swiftly reproduced themselves and it resulted in almost fatal damage to a target organ. There are the following gradations for damages to a target organ tissue corresponding to a clinical form of a disease: damage to less than 8-10% of a tissue corresponds to a mild disease; 10-20%, an average disease; 20-25%, a grave disease; when more than 25-30% of a target organ tissue is damaged, lethal outcome is rather probable [39].

Conclusions. So, we developed a predictive mathematical model that describes functioning of the regulatory systems under exposure to a virus infection; this model allows to take into account influence exerted by exposure to chemical factors on key components in the immunity. We suggested an algorithm for conducting an experiment on identifying some parameters of influence exerted by chemical factors on interaction between the neuroendocrine and immune systems.

We examined immune regulation peculiarities via experimental research and its results revealed that there were interrelations in the system of immune evolution-controlling proteins under combined exposure to hydrocortisone (a neuroendocrine factor) and aluminum (a chemical factor). The developed mathematical model showed that detected regularities related to influences exerted by chemical and physiological factors of various genesis on functions performed by immune cells were nonlinear. These detected relationships can be applied to efficiently predict disorders in an immune response and to assess interactions between the neuroendocrine and immune systems as such interactions determine adaptation reserves of a body under technogenic exposure.

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