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Features of Endocrine and Immune Status in Rats with Different State of Autonomous Nervous System

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The presence of interconnections between the parameters of the nervous, endocrine and immune systems within the framework of the triple complex is well known [5,6,9,18,20]. However, data on the nature (synergism or antagonism) of the influence of the sympathetic and vagus link of the autonomic nervous system on the individual parameters of immunity are ambiguous [11-15,21,24-26]. Consequently, research in this area remains relevant. One of the approaches to solving this problem is to compare immunity parameters in individuals with different states of the autonomic nervous system, both constitutional and induced vegetotropic factors. This is what determined the purpose of this study.

Material and methods. The experiment is at 60 female and 50 male white rats Wistar line weighing 210-320 g. Of these for 10 animals of each sex not subjected to any influences and others within 6-7 days were subjected to different manipulations (fixation in the hand of the experimenter, infusion into the stomach through a probe of various liquids, application of ozokerite to the tail with 30-minute immobilization).

The day after the completion of stressing or adaptogenic manipulations in all rats took samples of peripheral blood (through a cut tail) to analyze of leukocytogram. An hour under light ether anesthesia for 15-20 sec recorded ECG in standard lead II (introducing needle electrodes subcutaneously) to determine parameters of heart rate variability (HRV) [1]. The next day, the animals were decapitated, for the purpose of collecting blood. The plasma levels of the hormones of adaptation were determined: corticosterone, triiodothyronine, thyroxine and testosterone (by the ELISA); as well as electrolytes: calcium (by reaction with arsenase III), phosphates (phosphate-molybdate method), sodium and potassium (by flaming photometry).

According to the plasma level of electrolytes hormonal activity was evaluated: parathyrin by coefficient $(\text{Cap/Pp})^{0.5}$, calcitonin by coefficient $(\text{Cap} \cdot \text{Pp})^{-0.5}$ and mineralocorticoid by coefficient $(\text{Nap/Kp})^{0.5}$, based on their classical effects and recommendations by IL Popovych [21].

The analyzes were carried out according to the instructions described in the manual [4,7]. The analyzers “Tecan” (Oesterreich), “Pointe-180” (“Scientific”, USA) and “Reflotron” (Boehringer Mannheim, BRD) were used with appropriate sets and a flaming spectrophotometer “CФ-47”.

Immunological parameters were determined by tests as described in the handbook [16] and the previously developed algorithm [3]. On the state of the phagocytic function of neutrophils (microphages) and monocytes (macrophages) judged by phagocytic index, microbial (phagocytic) number and index of killing regarding museum culture *Staphylococcus aureus* (ATCC N 25423 F49) [3], with the calculation of bactericidal capacity (number of microbes that are able to neutralize neutrophils or monocytes contained in 1 L of blood) [21].

Among the parameters of immunogram determined the relative amount of blood population of T-cells by spontaneous rosette test with sheep erythrocytes by M Jondal et al [8], their theophylline resistant (T-helper) and theophylline sensitive (T-cytotoxic) subpopulations (by test sensitivity rosette to theophylline by S Limatibul et al [17]), the population of B-lymphocytes by test complementary rosette of sheep erythrocytes by C Bianco [2]. Natural killers identified as big containing granules lymphocytes.

After a blood sample was removed spleen, thymus and adrenal glands and weighed them. From the spleen and thymus did smears for counting splenocytogram and thymocytogram [3]. For the latter, as well as immunocytogram and leukocytogram we calculated entropy [21,25]. In addition, the modules of deviation from the norm of monocytes, eosinophils and stubnucleary neutrophils of the leukocytogram were calculated, on the basis of which its disharmony was calculated [15].

In sections of the adrenal glands was measured under a microscope the thickness of glomerular, fascicular, reticular and medullar zones [3].

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Results and discussion. The sympathetic tone estimated by AMo in intact males is (Mean $\pm$ SD) 53 ± 24 %, in females 56 ± 17 %, and the vagus tone, estimated at MxDMn, is 45 ± 25 msec vs 53 ± 41 msec, respectively, that is, almost the same. Instead, the value of Moda as a marker of the humoral regulation channel was significantly higher in males: 189 ± 36 msec vs 124 ± 16 msec, respectively ($p < 0,001$). The integral state of the autonomic nervous system is usually judged by the Baevsky Stress-index (SI). IL Popovych modified the formula to a more adequate form: $SI = (AMo/2 \cdot Mo \cdot MxDMn)^{1/3}$ [19,26]. The magnitude of the Stress-index was slightly higher in females: $0,165 \pm 0,077$ units vs $0,190 \pm 0,074$ units ($p > 0,5$). Previously, we found sexual dimorphism of a number of parameters of the neuroendocrine-immune complex both in rats [22] and in humans [23]. Therefore, for the correct comparison, the actual values of the variables (V) were listed in Z-scores according to the classical formula: $Z = (V/I - 1)/Cv$, where I is the average value for intact males or females, Cv are coefficients of variation.

At the next stage, three groups were formed according to the integral state of the autonomic nervous system. If we accept the range: $-0,5Z \div +0,5Z$ as the eutonia, then it is confirmed in 25 rats (14 males and 11 females). In 33 rats (12 males and 21 females), vagotonia was confirmed, whereas in 52 rats (24 males and 28 females), sympathicotonia was observed. Such a spectrum is due, obviously, to the stressful influence of the applied factors [15,21].

In order to detect endocrine and immune parameters, the totality of which three states of autonomous regulation differ significantly, a discriminant analysis was carried out using the forward stepwise method [10]. The program is included in the model 17 parameters. In particular, in addition to the three **HRV** parameters, by definition, three **endocrine** parameters, two parameters of **thymocytogram**, five parameters of **splenocytogram** and three immune parameters of **blood** appeared to be characteristic. In addition, worth noting yet another 16 parameters that were out of the model (Tables 1 and 2).

Table 1

Discriminant Function Analysis Summary Step 17, N of vars in model: 17;
Grouping: 3 grps Wilks' Lambda: 0,0833; approx. $F_{(34)}=13$; $p<10^{-4}$

Variables currently in the model	Vagotonia (33)	Eutonia (25)	Sympathicotonia (52)	Wilks' Λ	Partial Λ	F-remove	p-level	Tolerance
MxDMn as Vagal tone	+1,05 ± 0,13	-0,23 ± 0,07	-1,12 ± 0,04	,114	,729	16,9	10 ⁻⁶	,569
Moda as Humoral channel	+0,93 ± 0,10	-0,33 ± 0,11	-1,48 ± 0,10	,103	,813	10,5	10 ⁻⁴	,338
Eosinophils of Blood	+0,23 ± 0,18	+0,04 ± 0,21	-0,35 ± 0,12	,099	,842	8,5	10 ⁻³	,339
Lymphoblastes of Spleen	+0,23 ± 0,20	-0,01 ± 0,23	-0,36 ± 0,12	,089	,942	2,8	,065	,610
Lymphoblastes of Thymus	+0,08 ± 0,24	-0,08 ± 0,20	-0,56 ± 0,18	,088	,951	2,3	,103	,850
Plasmocytes of Spleen	+0,13 ± 0,19	-0,15 ± 0,17	-0,28 ± 0,12	,085	,978	1,0	,358	,706
Lymphocytes of Spleen	+0,06 ± 0,16	-0,10 ± 0,17	-0,33 ± 0,16	,091	,914	4,3	,017	,496
AMo as Sympathetic tone	-0,86 ± 0,12	-0,07 ± 0,11	+1,32 ± 0,10	,100	,834	9,0	10 ⁻³	,408
Corticosterone	-0,47 ± 0,17	+0,13 ± 0,21	+0,53 ± 0,20	,086	,964	1,7	,189	,669
Entropy of Thymocytogram	-0,06 ± 0,23	+0,28 ± 0,20	+0,56 ± 0,14	,085	,978	1,0	,369	,776
(Na/K) ^{0,5} of Plasma	+0,59 ± 0,26	-0,17 ± 0,14	+0,51 ± 0,15	,088	,943	2,8	,069	,806
Natural Killers of Blood	+0,36 ± 0,34	-0,19 ± 0,26	+0,28 ± 0,22	,088	,946	2,6	,081	,641
Entropy of Leukocytogram	+0,04 ± 0,19	-0,41 ± 0,27	-0,08 ± 0,18	,086	,969	1,5	,234	,547
Fibroblastes of Spleen	-0,14 ± 0,18	+0,31 ± 0,27	-0,05 ± 0,14	,091	,915	4,2	,018	,492
Thyroxine	-0,18 ± 0,14	+0,14 ± 0,21	-0,13 ± 0,12	,087	,961	1,8	,164	,658
Eosinophils of Spleen	+0,18 ± 0,17	+0,41 ± 0,26	+0,02 ± 0,13	,086	,966	1,6	,205	,717
Blood Monocytes Deviation	+0,31 ± 0,11	+0,53 ± 0,13	+0,43 ± 0,09	,089	,936	3,1	,049	,813
Variables currently not in the model	Vagotonia (33)	Eutonia (25)	Sympathicotonia (52)	Wilks' Λ	Partial Λ	F to enter	p-level	Tolerance
Macrophages of Spleen	-0,41 ± 0,14	+0,28 ± 0,16	+1,14 ± 0,13	,083	,996	,18	,839	,381
(Ca•P) ^{0,5} of Plasma	-0,18 ± 0,09	-0,09 ± 0,10	0,00 ± 0,08	,082	,989	,52	,596	,859
Macrophages of Thymus	+0,37 ± 0,23	+1,02 ± 0,31	+1,17 ± 0,33	,083	1,000	,01	,991	,634
Testosterone	+0,05 ± 0,26	+0,63 ± 0,23	+0,74 ± 0,26	,082	,984	,75	,475	,870
Adrenals Mass Index	+0,45 ± 0,24	0,00 ± 0,42	-0,24 ± 0,20	,083	,991	,39	,675	,924

Killing Index of Neutrophils	+0,48 ± 0,20	+0,21 ± 0,22	+0,15 ± 0,15	,083	,994	,28	,760	,731
Spleen Mass Index	+0,10 ± 0,14	-0,05 ± 0,19	-0,19 ± 0,11	,083	,992	,36	,697	,714
Leukocytogram Disharmony	+0,39 ± 0,06	+0,70 ± 0,13	+0,53 ± 0,07	,083	,998	,07	,933	,630
Stub Neutrophils Deviation	+0,48 ± 0,14	+1,03 ± 0,28	+0,69 ± 0,16	,083	,994	,27	,763	,759
Stub Neutrophils of Blood	-0,22 ± 0,19	-0,77 ± 0,33	-0,08 ± 0,21	,082	,985	,68	,510	,450
Neutrophils of Spleen	+0,23 ± 0,25	-0,51 ± 0,27	-0,33 ± 0,21	,082	,980	,92	,403	,575
Plasmocytes of Blood	+0,18 ± 0,21	+0,22 ± 0,23	+0,62 ± 0,20	,083	,994	,25	,778	,602
Thymus Mass	+0,12 ± 0,18	+0,22 ± 0,22	+0,43 ± 0,14	,082	,982	,84	,435	,807
Hassal corpuscles of Thymus	+0,05 ± 0,17	+0,42 ± 0,17	+0,46 ± 0,13	,083	,993	,30	,742	,437
Lymphocytes of Thymus	-0,13 ± 0,20	-0,12 ± 0,24	-0,69 ± 0,17	,083	,991	,41	,662	,448
Epitheliocytes of Thymus	+0,11 ± 0,21	+0,01 ± 0,24	+0,46 ± 0,12	,083	1,000	,01	,992	,667

Table 2

Summary of Stepwise Analysis

MxDMn as Vagal tone	F to enter	p-level	Λ	F-value	p-level
AMo as Sympathetic tone	214	10 ⁻⁶	,200	213,8	0,00
Moda as Humoral channel	11,8	10 ⁻⁴	,164	78,0	0,00
Eosinophils of Blood	4,7	,011	,150	55,3	0,00
Blood Monocytes Deviation	3,5	,034	,141	43,3	0,00
Plasmocytes of Spleen	3,6	,030	,131	36,2	0,00
(Na/K) ^{0.5} of Plasma	2,9	,059	,124	31,2	0,00
Corticosterone	2,5	,089	,119	27,5	0,00
Thyroxine	2,5	,084	,113	24,7	0,00
Entropy of Leukocytogram	1,8	,165	,109	22,3	0,00
Lymphoblastes of Thymus	1,9	,157	,105	20,5	0,00
Natural Killers of Blood	1,5	,226	,102	18,8	0,00
Lymphocytes of Spleen	1,3	,272	,099	17,4	0,00
Fibroblastes of Spleen	2,2	,121	,095	16,5	0,00
Lymphoblastes of Spleen	1,9	,152	,091	15,6	0,00
Eosinophils of Spleen	1,6	,217	,088	14,7	0,00
Entropy of Thymocytogram	1,5	,231	,085	14,0	0,00
Entropy of Thymocytogram	1,0	,369	,083	13,2	0,00

Recognition information contained in the listed variables is condensed in two discriminant roots, 92,7 % in the first and 7,38 % in the second. Calculating the values of individual roots by adding products of discriminant variables to their Raw Coefficients plus the Constant (Table 3) makes it possible to visualize each rat in a two-dimensional information space of radicals (Fig. 1).

Table 3

Standardized, Structural and Raw Coefficients
and Constants for Discriminant Variables

Coefficients	Standardized		Structural		Raw	
	Root 1	Root 2	Root 1	Root 2	Root 1	Root 2
Variables currently in the model						
MxDMn as Vagal tone	-,696	,395	-,765	,041	-1,480	,839
Moda as Humoral channel	-,628	,775	-,629	-,110	-,984	1,215
Eosinophils of Blood	,241	-1,092	-,102	-,086	,256	-1,156
Lymphoblastes of Spleen	,040	-,521	-,096	-,058	,039	-,510
Lymphoblastes of Thymus	-,212	-,229	-,084	-,090	-,167	-,181
Plasmocytes of Spleen	-,170	,136	-,073	,026	-,182	,147
Lymphocytes of Spleen	,315	-,500	-,065	-,037	,314	-,497
AMo as Sympathetic tone	,108	1,067	,541	,394	,160	1,573
Corticosterone	,128	,337	,128	-,010	,104	,275
Entropy of Thymocytoqram	,073	-,258	,093	,005	,066	-,234
(Na/K) ^{0.5} of Plasma	-,074	,436	-,008	,360	-,064	,377
Natural Killers of Blood	,293	-,160	-,006	,173	,179	-,097
Entropy of Leukocytoqram	,013	,405	-,013	,172	,010	,329
Fibroblastes of Spleen	,090	-,689	,011	-,205	,081	-,619
Thyroxine	,135	-,353	,007	-,188	,150	-,391
Eosinophils of Spleen	,014	-,370	-,028	-,181	,014	-,356
Blood Monocytes Deviation	,296	-,087	,030	-,142	,469	-,138
Eigenvalues	6,822	,534	Constants		-1,158	,043
Discriminant Properties, %	92,7	7,3				
Canonical R	,934	,590				
Wilks' Lambda	,083	,652				
Chi-Sqr.	246	42				
Degree freedom	34	16				
p-level	10-6	,0003

Fig. 1. Individual Roots values for rats in state of **vagotonia** (V), **eutonia** (E) and **sympathicotonia** (S)

Even at first glance it is possible to state a clear enough difference between clusters. The visual impression is documented by calculating the square of Mahalanobis distance (D^2_M). Between eutonic and sympathicotonic rats $D^2_M = 10$ ($F = 7,9$; $p < 10^{-6}$), between eutonic and vagotonic rats: 15 ($F = 10,6$; $p < 10^{-6}$), while between sympathicotonic and vagotonic rats distance is drastical: 37 ($F = 36,5$; $p < 10^{-6}$).

Extreme left localization vagotonic rats cluster along the axis of the first root (cluster centroid: -3,62) reflect their minimal among cohort size positively correlating with the root not only the Sympathetic tone, but also plasma level of Corticosterone and Entropy of Thymocytogram, while the maximum value negatively correlating with the root not only the Vagal tone and Moda (minimal Heart Rate), but also blood level of Eosinophils as well as level of Lymphoblastes in Thymus and Lymphoblastes, Plasmocytes and Lymphocytes in Spleen (Table 3). Instead, the sympathicotonic rats occupy the rightmost zone of the axis of the first root (centroid: +2,38), which reflects the opposite deviations of the listed parameters. The intermediate position is occupied by eutonic rats (centroid: -0,18).

Instead, along the axis of the second root eutonic rats occupy the extreme lower zone (centroid: -1,33) that reflects their minimum value among a cohort of Mineralocorticoid Activity, blood level of Natural Killers and Entropy of Leukocytogram which associated with the root directly, while the maximum value inverted related to the root plasma level of Thyroxine and Blood Monocytes Deviation as well as level of Fibroblastes and Eosinophils in Spleen. The listed parameters are almost identical in both vagotonic and sympathicotonic rats (centroids: +0,43 and +0,37 respectively).

Conclusion. Qualitatively different states of the autonomic nervous system of rats are accompanied by a characteristic constellation of endocrine and immune parameters, one set of which is subordinate to the opposite effects of the sympathetic and vagus link, whereas the other set contains parameters that are not significantly different in sympathicotonic and vagotonic animals and are characteristic of the eutonia.

CONFORMITY TO ETHICAL STANDARDS

Experiments on animals have been carried out in accordance with the provisions of the Helsinki Declaration of 1975, revised and supplemented in 2002 by the Directives of the National Committees for Ethics in Scientific Research.

The conducting of experiments was approved by the Ethics Committee of the Danylo Halyts'kyi National Medical University. The modern rules for the maintenance and use of laboratory animals complying with the principles of the European Convention for the Protection of Vertebrate Animals used for scientific experiments and needs are observed (Strasbourg, 1985).

Рекомендовано до друку комісією з біоетики

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RESEARCH ARTICLE

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The presence of interconnections between the parameters of the nervous, endocrine and immune systems within the framework of the triple complex is well known. However, data on the nature (synergism or antagonism) of the influence of the sympathetic and vagus link of the autonomic nervous system on the individual parameters of immunity are ambiguous. One of the approaches to solving this problem is to compare immunity parameters in individuals with different states of the autonomic nervous system. This is what determined the purpose of this study.

The experiment is at 60 female and 50 male white rats Wistar line weighing 210-320 g. Of these for 10 animals of each sex not subjected to any influences and others within 6-7 days were subjected to different stressing or adaptogenic manipulations. The day after the completion of manipulations in all rats determined parameters of heart rate variability and leukocytogram. The next day, the animals were decapitated, for the purpose of collecting blood. The plasma levels of the hormones of adaptation were determined: corticosterone, triiodothyronine, thyroxine and testosterone; as well as electrolytes: calcium, phosphates, sodium and potassium for evaluation parathyrin, calcitonin and mineralocorticoid activities. On the state of the phagocytic function of microphages and macrophages judged by phagocytic index, microbial number and index of killing regarding museum culture *Staphylococcus aureus*. Among the parameters of immunogram determined the relative amount of blood population of T-cells, their theophylline resistant and sensitive subpopulations as well as the population of B-lymphocytes and Natural killers. From the spleen and thymus did smears for counting splenocytogram and thymocytogram. For the latter, as well as immunocytogram and leukocytogram we calculated entropy.

Three groups were formed according to the integral state of the autonomic nervous system evaluated by Baevskiy Stress-index. The eutonia was confirmed in 25 rats (14 males and 11 females). In 33 rats (12 males and 21 females) vagotonia was confirmed, whereas in 52 rats (24 males and 28 females) sympathicotonia was observed. Discriminant analysis detected 17 parameters, the totality of which three states of autonomous regulation differ significantly. In particular, in addition to the three HRV parameters, by definition, three endocrine parameters, two parameters of thymocytogram, five parameters of splenocytogram and three immune parameters of blood appeared to be characteristic.

Qualitatively different states of the autonomic nervous system of rats are accompanied by a characteristic constellation of endocrine and immune parameters, one set of which is subordinate to the opposite effects of the sympathetic and vagus link, whereas the other set contains parameters that are not significantly different in sympathicotonic and vagotonic animals and are characteristic of the eutonia.

Key words: heart rate variability, corticosterone, triiodothyronine, thyroxine, testosterone, phagocytosis, cellular and humoral immunity, female and male rats.