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FEATURES NEURO-ENDOCRINE SUPPORT DIVERSITY OF IMMUNE RESPONSES TO CHRONIC STRESS IN MALE RATS

Lyubomyr M Zajats[1], Ilona S Polovynko[1], Walery Zukow[2]

[1]Department of Pathophysiology, National Medical University, Ivano-Frankivs'k, patfisiology@ifnmu.edu.ua Ukraine VLDC@meta.ua
[2]Faculty of Physical Education, Health and Tourism, Kazimierz Wielki University, Bydgoszcz, Poland w.zukow@ukw.edu.pl

Abstract

Background. In the previous report, we showed that the immune response to chronic stress in male rats are characterized by diversity. We assume that a variety of immune responses to chronic stress caused by a variety of reactions neuroendocrine factors. The aim of this study is to test the hypothesis. **Material and methods.** The experiment is at 50 white male rats. Of these 10 animals not subjected to any influences and 40 within 7 days subjected to moderate stress by daily 30-minute immobilization. The day after the completion of stressing neuro-endocrine and immune parameters were determined. **Results.** Found that each immune cluster is characterized by particular constellation of neuroendocrine factors. Interestingly, the most numerous and tangible change occurred in rats with minimal deviations immune status. Moderate inhibition microphage, killer and T-cellular links in combination with a strong activation macrophage link in another cluster is associated with similarly the previous cluster increase the thickness of the reticular and fascicular zones adrenal cortex, but without increasing plasma levels of testosterone and corticosterone, combined with a decrease in the thickness of the glomerular zone and mineralocorticoid activity. More pronounced poststressory changes immune system, first activation of macrophage link in combination with inhibition of microphage and T-link associated with the most elevated sympathetic tone and low vagal tone as well as moderately elevated level of corticosterone, combined with moderately low level of triiodothyronine. **Conclusion.** Variety of immune responses to chronic stress caused by a variety of reactions immunomodulating neuroendocrine factors.

Keywords: chronic stress, HRV, corticosterone, testosterone, triiodothyronine, thymocytogram, splenocytogram, immunocytogram of blood, male rats.

INTRODUCTION

In the previous report [19], we showed that the immune response to chronic stress in male rats are characterized by diversity. Using cluster analysis we retrospectively divided chronic stressed rats into three homogeneous for immunity while different one from the other groups.

We stated that the immune status of 40% of the rats subjected to moderate chronic stress was resistant to its factors. For the immune status of 37,5% rats typical moderate inhibition microphage, killer and T-cellular links in combination with a strong activation macrophage link. Poststressory changes in immunity in 22,5% rats differ from those in last cluster both qualitatively and quantitatively. In particular, the rats in this cluster were found no deviations from the norm neither reaction blast transformation T-cells nor NK-lymphocytes levels. However, other parameters of T-link and microhage link suppressed more and settings macrophage link appeared activated very significantly, and the area of activation, except thymus and blood, spread to the spleen.

We assume that a variety of immune responses to chronic stress caused by a variety of reactions neuro-endocrine factors. The aim of this study is to test the hypothesis.

MATERIAL AND METHODS

The experiment is at 50 white male rats Wistar line weighing 240-280 g. Of these 10 animals not subjected to any influences (intact), accounting for the control group, and the remaining 40 within 7 days subjected to moderate stress by daily 30-minute immobilization. The day after the completion of stressing in rats of both groups took samples of peripheral blood (through a cut tail) to analyze 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]. Then the rats were placed in individual chambers with perforated bottom to collect daily urine, in which determined the concentration of 17-ketosteroids (by method colorimetric reaction with m-dinitrobenzene), followed by calculation of the daily excretion.

The next day, the animals were decapitated, for the purpose of collecting blood plasma, in which was determined concentration of adaptive hormones corticosterone, testosterone, thyroxine and triiodothyronine (by ELISA).

In the same portion of the blood immunological parameters were determined by tests I and II levels of WHO as described in the handbook [15] and the previously developed algorithm [14,22]. 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) [3,6], with the calculation of derivative indices: microbial capacity (number of microbes that are able to absorb phagocytes contained in 1 L of blood) and bactericidal capacity (number of microbes that are able to neutralize neutrophils or monocytes contained in 1 L of blood) [14,22].

Among the parameters immunogram determined the relative amount of blood population of T-cells by spontaneous rosette test with sheep erythrocytes by M Jondal et al. [10], their theophylline resistant (T-helpers) and theophylline sensitive (T-cytotoxic) subpopulations (by test sensitivity rosette to theophylline by S Limatibul et al. [16]), the population of B-lymphocytes by test complementary rosette of sheep erythrocytes by C Bianco [2]. Natural killers identified as big containing granules lymphocytes. We set also induced by phytohemagglutinin blast transformation reaction T-Lymphocytes, as described in the handbook [15].

After a blood sample was removed spleen, thymus and adrenal glands and weighed them. Since the spleen and thymus did smears for counting splenocytogram and thymocytogram [3]. For the latter, as well as to leukocytogram and immunocytogram we calculated entropy [22,24,29]. In sections of the adrenal glands was measured under a microscope the thickness of glomerular, fascicular, reticular and medullar zones.

Digital material it is traited using the package of softwares “Statistica 5.5”.
Abstracts of the results published in the materials of conference [17].

RESULTS AND DISCUSSION

From the standpoint of the triune concept of neuro-endocrine-immune complex components which interact closely [14,18,20,21,22,28], follows the assumption that the identified features of immune responses to chronic stress associated with features of reactions to stress autonomic nervous system and classical adaptive glands as adrenal, thyroid and gonads as well as parathyroid. Astonishing that the program discriminant analysis (forward stepwise [12]) were included in the model almost all (except the adrenal mass) registered neuro-endocrine parameters (Table 1), ie, they are to some extent determine the features found post stress immunity in rats three clusters.

Table 1. Discriminant Function Analysis Summary
Step 15, N of vars in model: 15; Grouping: 3 grps
Wilks' Lambda: 0,120; approx. $F_{(30)}$=2,89; $p<10^{-3}$

Variables currently in the model	Control group (10)	Cluster I (9)	Cluster II (15)	Cluster III (16)	Wilks Λ	Par-tial Λ	F-re-move (2,2)	p-le vel	Toler an-cy
Triiodo-thyronine, nM/l	2,50±0,17 1 0	2,17±0,21 0,87±0,08 -0,62±0,40	2,70±0,14 1,08±0,06 +0,39±0,27	2,88±0,13 1,15±0,05 +0,72±0,25	,177	,679	5,44	,012	,295
Fascicular Zone Adrenals Cortex, μM	218±11 1 0	214±16 0,99±0,07 -0,09±0,43	254±13 1,17±0,06 +1,00±0,36	252±12 1,16±0,05 +0,96±0,32	,155	,776	3,33	,054	,312
Glomerular Zone Adrenals Cortex, μM	129±11 1 0	102±10 0,79±0,08 -0,75±0,27	116±5 0,90±0,04 -0,36±0,14	115±5 0,89±0,03 -0,38±0,13	,133	,900	1,28	,296	,371
Reticular Zone Adrenals Cortex, μM	20±2 1 0	20±3 0,97±0,13 -0,10±0,46	25±2 1,24±0,08 +0,84±0,28	24±2 1,20±0,09 +0,70±0,31	,140	,857	1,92	,169	,290
Medullar Zone of Adrenals, μM	87±7 1 0	84±13 0,97±0,15 -0,11±0,56	87±7 1,00±0,09 +0,02±0,32	87±6 1,00±0,07 +0,02±0,26	,138	,871	1,70	,205	,558
Thyroxine, nM/L	60±6 1 0	85±10 1,42±0,16 +1,32±0,51	58±3 0,97±0,05 -0,11±0,16	59±4 0,99±0,06 -0,04±0,19	,148	,811	2,69	,089	,311
$(Ku/Nau)^{0,5}$ as Mineralocorti-coide Activity	0,73±0,07 1 0	0,93±0,10 1,27±0,14 +0,93±0,49	0,70±0,07 0,96±0,09 -0,13±0,32	0,74±0,05 1,02±0,07 +0,06±0,23	,227	,529	10,2	,001	,277
AMo HRV as Sympathotone, %	56±7 1 0	85±7 1,53±0,12 +1,25±0,28	55±5 0,98±0,09 -0,05±0,21	69±5 1,25±0,10 +0,59±0,23	,143	,842	2,16	,139	,009
$(1/Cap•Pp)^{0,5}$ as Calcitonine Activity	0,49±0,02 1 0	0,49±0,02 1,01±0,03 +0,07±0,23	0,48±0,01 0,99±0,03 -0,06±0,18	0,55±0,03 1,12±0,05 +0,80±0,36	,168	,714	4,60	,021	,032
Corticosterone, nM/L	340±45 1 0	417±70 1,23±0,20 +0,55±0,49	342±30 1,01±0,09 +0,02±0,21	472±69 1,39±0,20 +0,94±0,48	,194	,618	7,11	,004	,465
Testosterone, nM/L	34,6±4,6 1 0	33,4±2,6 0,97±0,07 -0,08±0,18	36,5±5,5 1,06±0,16 +0,13±0,38	48,4±4,8 1,40±0,14 +0,96±0,33	,133	,900	1,27	,299	,730
$(Cap/Pp)^{0,5}$ as Parathyrine Activity	1,66±0,06 1 0	1,64±0,05 0,99±0,03 -0,07±0,27	1,66±0,04 1,00±0,02 +0,03±0,21	1,50±0,06 0,90±0,03 -0,79±0,28	,185	,648	6,26	,007	,029
ΔX HRV as Vagotone, msec	42±8 1 0	16±5 0,39±0,13 -1,04±0,22	42±6 1,00±0,15 -0,01±0,26	26±5 0,63±0,12 -0,63±0,20	,135	,892	1,39	,269	,004
Moda HRV, msec	184±11 1 0	154±8 0,84±0,04 -0,88±0,22	181±13 0,98±0,07 -0,10±0,36	159±6 0,87±0,03 -0,72±0,17	,142	,847	2,08	,148	,017
17-Ketostero-ides urine, nM/100 g•day	26±6 1 0	24±7 0,93±0,28 -0,10±0,39	33±7 1,27±0,29 +0,37±0,41	25±4 0,98±0,15 -0,03±0,21	,150	,802	2,85	,079	,432

Note. In each column the first row: M±SE; second: M/N±SE; third: Z±SE

Identification information is condensed in two canonical roots, the first of which contains 87,1% discriminant capacity, while the second is only 12,9%. After calculating the individual values of both roots using raw coefficients for neuro-endocrine variables and constants given in Table 2, the position of each animal were visualized in two-dimensional information space of the roots (Fig. 1).

Table 2. Standardized and Raw Coefficients and Constants for Canonical Variables

Coefficients	Standardized		Raw		Parameters of Wilks' Statistics				
Variables currently in the model	Root 1	Root 2	Root 1	Root 2	F to enter	p-level	Λ	F-value	p-level
Triiodothyronine	1,103	-,533	1,982	-,957	4,71	,015	,797	4,71	,015
Fascicular Zone Adren Cortex	,860	-,567	,0180	-,0119	3,07	,061	,297	3,70	10^{-3}
Glomerular Zone Adren Cortex	,257	-,755	,0123	-,0362	1,27	,298	,147	3,09	10^{-3}
Reticular Zone Adrenal Cortex	-,754	,302	-,1088	,0436	1,82	,181	,203	3,41	10^{-3}
Medullar Zone of Adrenals	-,528	,128	-,0178	,0043	1,42	,259	,162	3,22	10^{-3}
Thyroxine	-,671	-,804	-,0396	-,0473	2,19	,129	,259	3,62	10^{-3}
$(Ku/Nau)^{0,5}$ as Mineralocort Act	-1,441	-,263	-6,001	-1,097	2,74	,079	,529	4,37	10^{-3}
AMo HRV as Sympathicotone	-4,207	-3,198	-,193	-,147	5,44	,009	,612	5,01	,001
$(1/Cap•Pp)^{0,5}$ as Calcitonine Act	-3,023	-2,010	-39,83	-26,48	2,40	,106	,401	3,82	10^{-3}
Corticosterone	,926	-,586	,0044	-,0028	2,05	,146	,355	3,61	10^{-3}
Testosterone	-,099	-,580	-,0058	-,0340	1,27	,299	,120	2,89	10^{-3}
$(Cap/Pp)^{0,5}$ as Parathyrine Activ	-3,736	-1,463	-20,25	-7,929	2,59	,089	,459	4,04	10^{-3}
ΔX HRV as Vagotone	-5,646	-3,390	-,2545	-,1528	1,24	,307	,133	2,98	10^{-3}
Moda HRV	3,333	,784	,0913	,0215	1,76	,191	,180	3,33	10^{-3}
17-Ketosteroides urine	-,749	,142	-,0335	,0063	1,85	,176	,230	3,50	10^{-3}
Constants			57,33	51,20					
Discriminant Properties, %			87,1	12,9					

Table 3. Correlations Variables-Canonical Roots (Pooled-within-groups correlations). Chi-Square Tests with Successive Roots Removed and Z-scores for Poststressory Clusters

Variables currently in the model	Root 1	Root 2	Z-scores for Clusters		
			I (9)	II (15)	III (16)
Triiodothyronine	**,246**	-,079	-0,62	+0,39	+0,72
Fascicular Zone Adren Cortex	**,153**	,086	-0,09	+1,00	+0,96
Glomerular Zone Adren Cortex	**,125**	,075	-0,75	-0,36	-0,38
Reticular Zone Adrenal Cortex	**,118**	,118	-0,10	+0,84	+0,70
Medullar Zone of Adrenals	**,021**	,012	-0,11	+0,02	+0,02
Thyroxine	**-,221**	-,142	+1,32	-0,11	-0,04
$(Ku/Nau)^{0,5}$ as Mineralocort Act	**-,155**	-,148	+0,43	-0,47	-0,09
AMo HRV as Sympathicotone	-,142	**-,435**	+1,25	-0,05	+0,59
$(1/Cap•Pp)^{0,5}$ as Calcitonine Act	,089	**-,412**	+0,07	-0,06	+0,80
Corticosterone	,015	**-,354**	+0,55	+0,02	+0,94
Testosterone	,109	**-,305**	-0,08	+0,13	+0,95
$(Cap/Pp)^{0,5}$ as Parathyrine Activ	-,100	**,431**	-0,07	+0,03	-0,79
ΔX HRV as Vagotone	,100	**,407**	-1,04	-0,01	-0,63
Moda HRV	,054	**,319**	-0,88	-0,10	-0,72
17-Ketosteroides urine	,032	**,204**	-0,10	+0,37	-0,03
Canonical R	,898	,618			
Wilks' Lambda	,120	,618			
Chi-Sqr.	63,6	14,4			
Degree freedom	30	14			
p-level	,0003	,419			

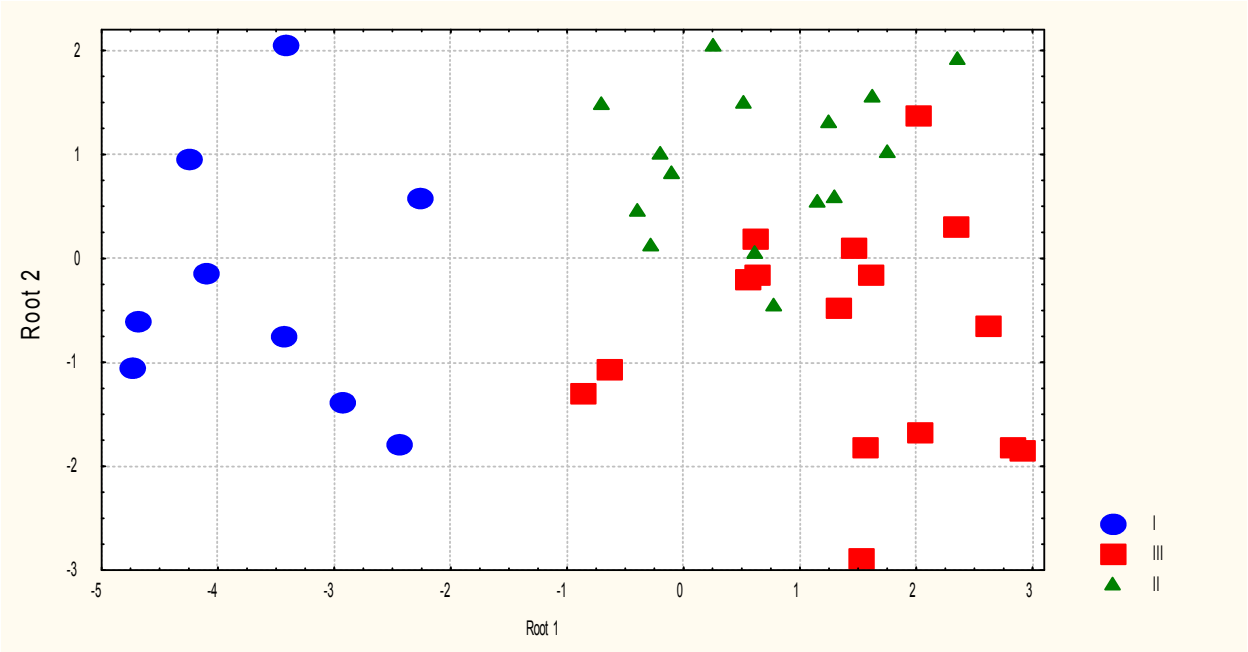

Fig. 1. Individual discriminant value neuroendocrine roots of male rats of different clusters of immune responses to stress

Calculating averages neuro-endocrine roots makes it possible to visualize the localization in two-dimensional information space centroids three clusters immune response to chronic stress (Fig. 2).

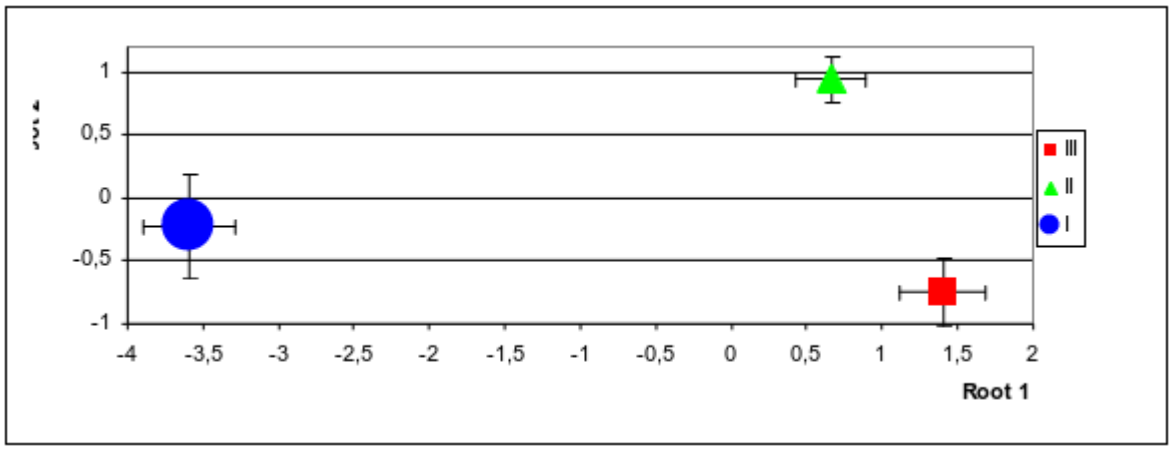

Fig. 2. Averages (Mean±SE) of discriminant neuroendocrine roots of male rats of different clusters of immune responses to stress

Extreme localization members I cluster along the axis of the first root reflect their minimal among stressed cohort size positively correlating with the root plasma level of triiodothyronine and thickness of all four zones of the adrenal glands, and the maximum value negatively correlating with the root plasma level of thyroxine and mineralocorticoid activity (Table 3) . In animals II and III cluster size these endocrine parameters overlap.

Instead, along the axis of the second root overlap values other endocrine parameters and parameters of the autonomic nervous system in rats clusters I and III, while cluster II animals occupy the extreme upper zone axis. This reflects their minimum value among a cohort of sympathetic tone, calcitonine activity as well as levels of corticosterone and testosterone

which associated with the root inverted, while the maximum value directly related to the root parathyrine activity, vagal tone markers and daily excretion of 17-ketosteroids.

Before the next analysis recall the previously described [19] features poststressory abnormalities integral indicator of immune status (Fig. 3).

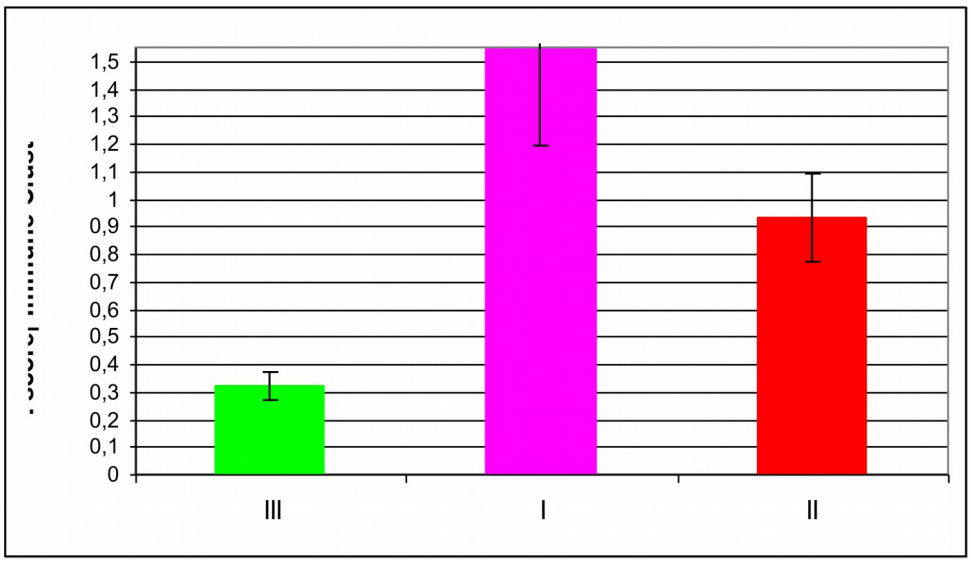

Fig. 3. Modules by chronic stress caused abnormalities of immunity in rats of different clusters

Fig. 4 illustrates that the lack of poststressory abnormalities indicators of immune status in rats III cluster associated with normal poststressory levels mineralocorticoid activity, thyroxine plasma and daily urinary excretion of 17-ketosteroids, instead with reduced parathyrine activity, tone of vagus and thickness of glomerular zone of the adrenal cortex, on the one hand, and higher levels of sympathetic tone, heart rate, calcitonine activity, thickness reticular and fascicular zones of adrenal cortex, plasma levels of testosterone, corticosterone and triiodothyronine, on the other hand.

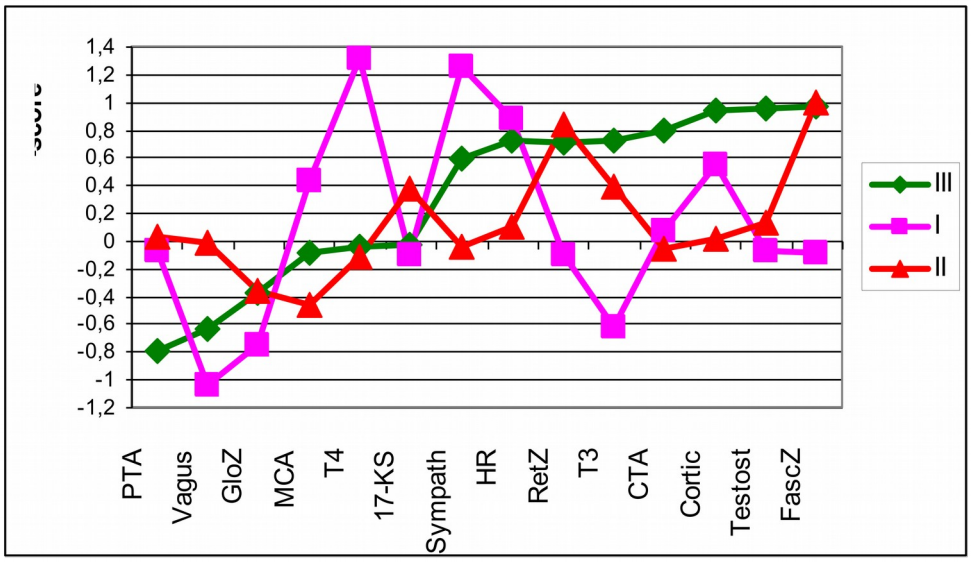

Fig. 4. Neuro-endocrine profiles of rats of different immune clusters

It seems that it is this poststressory constellation neuro-endocrine factors, caused by the individual reactivity, promotes resistance of immune status to stress-induced abnormalities.

Moderate inhibition microphage, killer and T-cellular links in combination with a strong activation macrophage link in rats II cluster is associated with a similar increase in the thickness of the reticular and fascicular zones adrenal cortex, but without increased levels of plasma testosterone and corticosterone, combined with a decrease in the thickness of the glomerular zone and mineralocorticoid activity.

More pronounced poststressory changes in immunity in rats I cluster, first enhancing macrophage link combined with inhibition microphage and T-link, associated with the most elevated sympathetic tone and reciprocal low vagal tone, moderately elevated levels of corticosterone, combined with moderately low plasma level of triiodothyronine, perhaps, due to its inhibition of the formation from prohormone thyroxine, plasma level of which is significantly increased. In addition, there is a dissociation between the decrease in the thickness of glomerular zone of the adrenal cortex and increased mineralocorticoid activity, assessed by K/Na ratio of daily urine.

The literature on the state of the autonomic nervous, endocrine and immune systems in chronic stress as numerous as contradictory [reviews: 4,5,8,9,11,13,14,20-28]. There is even a concept that in response to stimuli of different strengths are developing, in addition to the stress reaction, reaction training, calm and increased activation and superactivation associated with different states of immunity [7]. We hope that the results of our research [17-19] will make a modest contribution to resolving existing contradictions.

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