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FEATURES OF THE STATE OF NEURO-ENDOCRINE FACTORS OF ADAPTATION UNDER DIFFERENT OPTIONS OF URIC ACID METABOLISM IN HEALTHY FEMALE RATS

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Abstract

Background. As part of the project "Physiological activity of uric acid", we previously identified 4 variants-clusters of uricemia and uricosuria both in rats and in humans. It was shown that the clusters differ from each other in the constellation of immunity parameters, which to one degree or another correlate with uricemia and uricosuria. The aim of this study was to identify autonomic and endocrine adaptogenic factors, the combination of which differentiates previously formed quantitative and qualitative variants of uric acid metabolism in rats. **Materials and Methods**. Experiment was performed on 58 healthy female Wistar rats 220-300 g. The serum and urine levels of the uric acid, calcium, phosphates, sodium and potassium were determined. The neuro-endocrine status evaluated by the HRV parameters; serum levels of the hormones such as corticosterone, triiodothyronine and testosterone; daily excretion of 17-ketosteroides; electrolytes markers of mineralocorticoid, parathyroid and calcitonin activities as well as by the thickness of glomerular, fascicular, reticular and medullar zones of the adrenals. **Results**. The previously identified four variants-clusters of uric acid metabolism differ from each other by a constellation of 10 neuro-endocrine adaptation factors that reflect the state of glucocorticoid, androgenic and catecholamine functions of the adrenal glands, as well as HRV-marker of vagal tone and electrolyte markers of sympatho-vagal balance as well as calcitonin and parathyroid activities. Classification accuracy is 90%. Uricosuria and uricemia are negatively correlated with HRV-markers of sympathetic tone and circulating catecholamines, the level of corticosterone and the thickness of the fascicular zone of the adrenal cortex secreting them, as well as the level of triiodothyronine and the Ca-P marker of calcitonin activity, on the other hand, they are positively correlated with the HRV marker of vagal tone and urinary excretion of 17-ketosteroids. The rate of determination of neuro-endocrine adaptation factors by uric acid is

62%. **Conclusion.** Uric acid is naturally associated with the state of autonomous and endocrine adaptation factors in healthy female rats.

Keywords: uricemia, uricosuria, HRV, adaptation hormones, relationships, female rats.

INTRODUCTION

As part of the project "Physiological activity of uric acid" [1], we previously identified 4 variants-clusters of uricemia and uricosuria both in rats [2-4] and in humans [5-7]. Using the method of discriminant analysis, it was shown that the clusters differ from each other in the constellation of immunity parameters, which to one degree or another correlate with uricemia and uricosuria. Even earlier in our laboratory, the connection of uricemia with autonomous tone and general adaptive reactions in urological patients was revealed [8]. Therefore, the aim of this study was to identify autonomic and endocrine adaptogenic factors, the combination of which differentiates previously formed quantitative and qualitative variants of uric acid metabolism in rats.

MATERIAL AND METHODS

Experiment was performed on 60 healthy female Wistar rats 220-300 g. Of these, 10 remained intact, while others received drinking water of various compositions during the week. The day after the completion of the drinking course in all rats assessed the state of autonomous regulation. For this purpose, under an easy ether anesthesia, for 15-20 sec ECG was recorded in the lead II, inserting needle electrodes under the skin of the legs, followed by the calculation of the parameters of the HRV: mode (Mo), amplitude of the mode (AMo) and variation scope (MxDMn) as markers of the humoral channel of regulation, sympathetic and vagal tones respectively [9]. Animals were then placed in individual chambers with perforated bottom for collecting daily urine. The experiment was completed by decapitation of rats in order to collect as much blood as possible. The serum and urine levels of the uric acid (uricase method), calcium (by reaction with arsenase III), phosphates (phosphate-molybdate method), sodium and potassium (flamming photometry) were determined. The analyzes were carried out according to the instructions described in the manual [10]. In additional, the serum levels of the hormones of adaptation: corticosterone, triiodothyronine and testosterone (by the ELISA) as well as daily excretion of 17-ketosteroides (by reaction with meta-dinitrobenzene) were determined.

According to the parameters of electrolyte exchange, hormonal activity was evaluated: parathyroid by coefficients $(Cap/Pp)^{0,5}$ and $(Cap \bullet Pu/Pp \bullet Cau)^{0,25}$, calcitonine by coefficients $(1/Cap \bullet Pp)^{0,5}$ and $(Cau \bullet Pu/Cap \bullet Pp)^{0,25}$ as well as mineralocorticoid by coefficients $(Nap/Kp)^{0,5}$ and $(Nap \bullet Ku/Kp \bullet Nau)^{0,25}$, based on their classical effects and recommendations [11].

The analyzers “Tecan” (Oesterreich), “Pointe-180” ("Scientific", USA) and “Reflotron” (Boehringer Mannheim, BRD) were used with appropriate sets and a flamming spectrophotometer “СФ-47”.

In the adrenal glands after weighing, the thickness of glomerular, fascicular, reticular and medullar zones was measured under a microscope [12].

Digital material is statistically processed on a computer using the software package "Statistica 5.5".

RESULTS AND DISCUSSION

Applying the already described method of discriminant analysis [13], we found 11 variables that are recognizable in relation to the four clusters (Table 1).

Table 1. Summary of the step-by-step analysis of variables ranked by the Λ criterion

Variable Enter	F to enter	p-value	Lambda	F-value	p-value
Uricemia	45,6	0,00000	0,290	45,6	0,000000
Parathyroid Activity	10,2	0,00002	0,187	24,1	0,000000
MxDMn as Vagotone	2,8	0,04599	0,161	16,3	0,000000
Corticosterone	2,1	0,11471	0,144	12,6	0,000000
Medullary Zone Adrenals	2,7	0,05243	0,124	10,8	0,000000
Calcitonin Activity	2,6	0,06466	0,108	9,6	0,000000
17-KS Urine	2,2	0,09718	0,095	8,7	0,000000
Ca/K Plasma	1,8	0,16403	0,086	7,9	0,000000
Fascicular Zone Adrenals	1,7	0,18613	0,078	7,3	0,000000
Reticular Zone Adrenals	1,2	0,30845	0,072	6,7	0,000000
Adrenals Mass Index	1,1	0,36145	0,067	6,2	0,000000

Among them, in addition to **uricemia** by definition, 6 indicators were found that reflect the state of glucocorticoid, androgenic and catechomaminincretory functions of the **adrenal glands**, as well as **HRV**-marker of vagal tone and electrolyte markers of **sympatho-vagal balance** aa well as **calcitonin** and **parathyroid** activity. Instead, **uricosuria**, **HRV-**markers of sympathetic tone and circulating catecholamines, indicators of mineralocorticoid function of the adrenal glands, testosterone (the source of which in females is the reticular zone of their cortex), as well as triiodothyronine were outside the discriminating model (Table 2).

Table 2. Summary of the analysis of discriminant functions for neuro-endocrine variables ranked by structural coefficient

Step 11, N of vars in model: 11; Grouping: 4 grps; Wilks' Λ: 0,0674; approx. $F_{(33)}=6,2$; $p<10^{-6}$

	Clusters of Uric acid Exchange (n)				Parameters of Wilks' Statistics					
Variables currently in the model	S-Un- (15)	SnUn+ (17)	Sn+U± (19)	S+Un+ (9)	Wil-ks' Λ	Parti-al Λ	F-re-move	p-level	Tole-rancy	Norm (10)
Uricemia, µM/L	259	554	865	1379	0,171	0,395	23,5	10^{-6}	0,915	662
MxDMn HRV as Vagal Tone, msec	26	45	39	101	0,095	0,713	6,16	0,001	0,555	53
(Cau•Pu/Pp•Cap)^{0,25} as Calcitonin Activity	1,90	1,57	1,53	1,49	0,082	0,826	3,23	0,031	0,528	1,67
(Cap•Pu/Pp•Cau)^{0,25} as Parathyrin Activity	2,15	1,55	1,71	1,93	0,085	0,790	4,07	0,012	0,677	2,08
(Cap/Kp)^{0,5} as Sympat/Vagal balance	0,92	0,79	0,85	0,91	0,077	0,876	2,18	0,103	0,460	0,89
Fascicular Zone of Adrenals, µM	444	409	374	413	0,075	0,903	1,64	0,193	0,761	402
Corticosterone, nM/L	437	532	422	321	0,082	0,827	3,22	0,031	0,649	482
Medullary Zone of Adrenals, µM	80	78	98	84	0,079	0,851	2,69	0,057	0,703	94
17-Ketosteroides Ex-cretion, nM/100g•24h	55	69	83	62	0,076	0,890	1,89	0,145	0,871	61
Adrenals Mass Index, mg/100g Body Mass	27,7	25,9	27,7	25,7	0,072	0,933	1,09	0,361	0,901	25,2
Reticular Zone of Adrenal Cortex, µM	43,2	47,1	40,5	40,8	0,073	0,927	1,20	0,321	0,867	42,7
Variables currently not in the model	S-Un- (15)	SnUn+ (17)	Sn+U± (19)	S+Un+ (9)	Wil-ks' Λ	Parti-al Λ	F to enter	p-level	Tole-rancy	Norm (10)
Uricosuria, µM/100 g•24h	3,31	5,46	6,63	7,00	0,067	0,997	0,05	0,986	0,398	5,72
AMo HRV as Sympathetic tone, %	70	57	66	42	0,066	0,978	0,34	0,799	0,417	56
Moda HRV as Humo-ral Channel, msec	110	118	111	134	0,067	0,997	0,05	0,984	0,230	124
Testosterone, nM/L	4,19	4,84	5,40	3,65	0,064	0,942	0,93	0,434	0,764	3,93
(Nap•Ku/Kp•Nau)^{0,25} as Mineralocort Activ	3,12	3,09	2,83	3,03	0,064	0,944	0,88	0,457	0,437	2,73
Glomerular Zone of Adrenals, µM	194	187	179	197	0,067	0,986	0,21	0,889	0,757	191
Triiodothyronine, nM/L	2,40	2,28	2,14	2,18	0,067	0,997	0,05	0,986	0,508	2,14

The identifying information contained in the 11 discriminant variables is condensed into three roots. The first root contains 66,4% of the discriminant power (r*=0,879; Wilks' Λ=0,067; $\chi^2_{(33)}=139$; $p<10^{-6}$), second - 21,6% (r*=0,724; Wilks' Λ=0,296; $\chi^2_{(20)}=63$; $p<10^{-5}$), and third - 12,0% (r*=0,615; Wilks' Λ=0,621; $\chi^2_{(9)}=25$; p=0,004).

Having applied the previous algorithm, we calculate the values of the discriminant roots for each animal according to the coefficients and constants given in the table. 3 with the subsequent visualization of each rat in the information space of the roots (Figs. 1 and 2).

Table 3. Standardized and raw coefficients and constants for discriminant neuro-endocrine variables

Variable	Standardized Coefficients		
	Root 1	Root 2	Root 3
Uricemia	0,884	0,319	-0,113
Parathyroid Activity	-0,327	0,614	0,277
MxDMn as Vagotone	0,393	-0,100	1,017
Corticosterone	0,135	-0,487	0,583
Medullary Zone Adrenals	-0,068	-0,058	-0,738
Calcitonin Activity	-0,442	0,582	-0,047
17-KS Urine	0,163	-0,273	-0,418
Ca/K Plasma	-0,287	0,465	-0,497
Fascicular Zone Adrenals	0,157	0,043	0,532
Reticular Zone Adrenals	-0,133	-0,365	0,012
Adrenals Mass Index	-0,133	0,250	-0,269

Variable	Raw Coefficients		
	Root 1	Root 2	Root 3
Uricemia	0,0037	0,0013	-0,0005
Parathyroid Activity	-0,9733	1,8291	0,8254
MxDMn as Vag otone	0,0099	-0,0025	0,0257
Corticosterone	0,0008	-0,0029	0,0035
Medullary Zone Adrenals	-0,0020	-0,0017	-0,0219
Calcitonin Activity	-1,2204	1,6064	-0,1286
17-KS Urine	0,0041	-0,0068	-0,0104
Ca/K Plasma	-1,7617	2,8499	-3,0468
Fascicular Zone Adrenals	0,0020	0,0005	0,0068
Reticular Zone Adrenals	-0,0130	-0,0356	0,0012
Adrenals Mass Index	-0,0307	0,0578	-0,0622
Constant	2,319	-7,507	0,377

On the plane of the first two roots (Fig. 1), in which 88% of the information is condensed, only two clusters are clearly demarcated. The localization of members of the **S-Un-** cluster in the left (negative) zone of the first root axis reflects (Table 4) a combination of hypouricemia with reduced vagal tone and increased calcitonin activity. Despite not being formally included in the discriminant model (due to duplication/excess of information), hypouricosuria, increased sympathetic tone and circulating catecholamine level (a marker of which is a reduced HRV mode) deserve attention as characteristic signs. The opposite right (positive) zone of the axis is occupied by members of the **S+Un+** cluster, which reflects the combination of hyperuricemia with slightly increased uricosuria and significantly increased vagal tone and reduced calcitonin activity, and thus reduced sympathetic tone and the level of catecholamines in the blood. The members of the remaining two clusters occupy an intermediate position along the axis of the first root and are partially mixed.

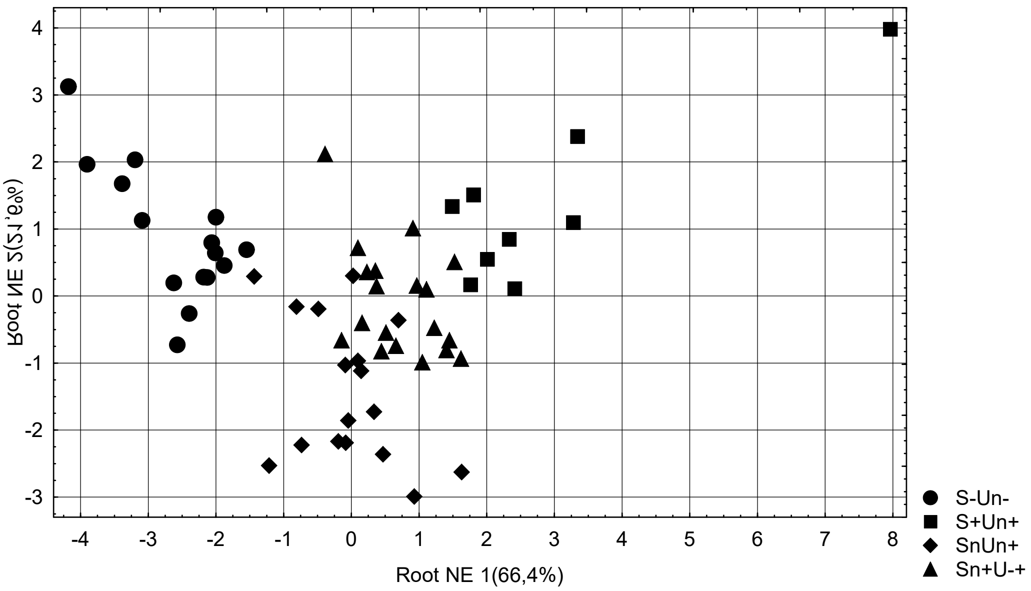


Fig. 1. Scattering of individual values of the first and second discriminant neuro-endocrine roots of rats of different clusters

Table 4. Correlations between neuro-endocrine variables and roots, centroids of clusters and Z-values of clusters

	Correlations Variables-Roots			**S-Un-**	**SnUn+**	**Sn+U-+**	**S+Un+**
Root 1(66,4%)	Root 1	Root 2	Root 3	**-2,61**	-0,05	+0,71	**+2,93**
Uricemia	**,823**	,366	-,0109	**-1,18**	-0,32	+0,59	**+2,10**
Uricosuria	currently not in the model			**-0,45**	-0,05	+0,17	**+0,24**
MxDMn as Vagal tone	**,284**	,175	,374	**-0,63**	-0,18	-0,34	**+1,18**
Moda as Humoral Channel	currently not in the model			**-0,92**	-0,42	-0,89	**+0,71**
Calcitonin Activity	**-,231**	,160	,097	**+0,62**	-0,25	-0,37	**-0,47**
AMo as Sympathetic tone	currently not in the model			**+0,84**	+0,05	+0,60	**-0,77**
Root 2(21,6%)	Root 1	Root 2	Root 3	+0,90	**-1,41**	-0,08	+1,33
Parathyroid Activity	-,175	**,597**	,102	+0,13	**-1,08**	-0,75	-0,31
$(Ca/K)^{0,5}$ Plasma	-,040	**,315**	,033	+0,17	**-0,58**	-0,27	+0,11
Fascicular Zone Adrenals	-,119	**,120**	**,312**	+0,49	**+0,08**	+0,49	+0,13
Corticosterone	-,105	**-,356**	,068	-0,36	**+0,40**	-0,47	-1,28
Root 3(12,0%)	Root 1	Root 2	Root 3	+0,18	+0,59	**-1,06**	+1,83
Medullary Zone Adrenals	,052	,028	**-,295**	-0,43	-0,50	**+0,14**	-0,30
17-Ketosteroides Excretion	,073	-,116	**-,272**	-0,11	+0,14	**+0,40**	+0,02
Adrenals Mass Index	-,063	,072	**-,223**	+0,49	+0,13	**+0,49**	+0,10
Testosterone	currently not in the model			+0,25	+0,85	**+1,38**	-0,26
Reticular Zone Adrenals	-,051	-,185	**,213**	+0,06	+0,58	**-0,29**	-0,25
Glomerular Zone Adrenals	currently not in the model			+0,07	-0,08	**-0,27**	+0,15
Mineralocorticoid Activity	currently not in the model			+0,50	+0,46	**+0,12**	+0,39
Triiodothyronine	currently not in the model			+0,46	+0,24	**0,00**	+0,07

Additional delimitation of these clusters occurs along the axis of the second root. As can be seen, members of the **SnUn+** cluster occupy the lower zone of the axis (centroid: -1,41), which reflects their reduced parathyroid activity and serum Ca/K ratio in combination with a completely normal thickness of the fascicular zone of the adrenal cortex and a slightly increased level of corticosterone, while in members of the **Sn+U-+** cluster (centroid: -0,08), the first two parameters are reduced to a lesser extent, the fascicular zone is slightly thickened, and the corticosterone level is slightly reduced.

Along the axis of the third root (Fig. 2), members of the **Sn+U-+** cluster occupy the lower zone (centroid: -1,06), which reflects the **maximum** for the sample mass index of the adrenal glands, the thickness of their medullary zone, and the excretion of 17-ketosteroids in combination with the **minimum** for sampling the thickness of the reticular zone of the adrenal glands. It should be noted that the maximum serum level of testosterone (secreted by the adrenal glands) in combination with the minimum for sampling the thickness of the glomerular zone of the adrenal glands and mineralocorticoid activity, as well as serum triiodothyronine, are also not included in the model.

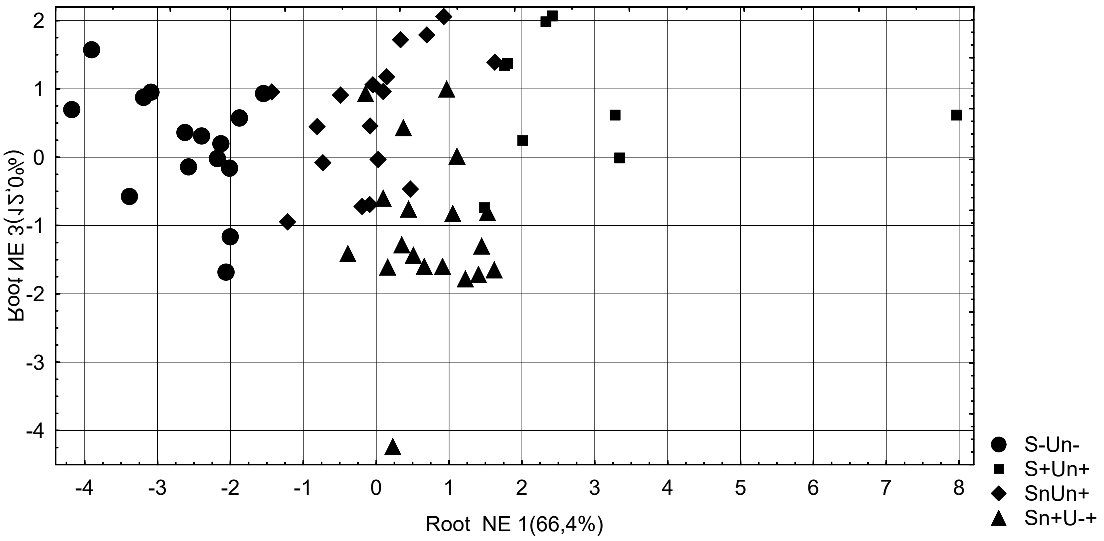


Fig. 2. Scattering of individual values of the first and third discriminant neuro-endocrine roots of rats of different clusters

In general, in the information space of the three discriminant roots, all four clusters are clearly demarcated among themselves, that is, they differ significantly from each other in terms of uricemia and the constellation of 10 neuro-endocrine parameters. This demarcation is documented by calculating the squared Mahalanobis distances between clusters (Table 5).

Table 5. Squares of Mahalanobis distances between clusters (above the diagonal) and F-criteria (df=11,5) and p-levels (below the diagonal)

Clusters	S-Un-	S+Un+	SnUn+	Sn+U-+
S-Un-	0	31	12	14
S+Un+	13,2 10^{-6}	0	16	11
SnUn+	7,2 10^{-6}	7,2 10^{-6}	0	5
Sn+U-+	8,5 10^{-6}	4,8 10^{-5}	3,4 0,002	0

The selected neuro-endocrine variables were used to identify the belonging of one or another rat to one or another cluster with the help of classification functions (Table 6, see the appendix).

Table 6. Coefficients and constants of classification functions for neuro-endocrine support of uric acid metabolism clusters

Variable	S-Un- p=,250	S+Un+ p=,150	SnUn+ p=,283	Sn+U-+ p=,317
Uricemia	0,003	0,024	0,009	0,015
Parathyroid activity	11,00	6,932	4,621	4,947
Vagal tone	-0,062	0,009	-0,020	-0,059
Corticosterone	-0,001	0,005	0,010	0,001
Medullary Zone Adrenals	0,108	0,081	0,097	0,130
Calcitonine activity	33,39	27,24	26,51	27,92
17-Ketosteroides urine	0,004	0,017	0,026	0,038
Ca/K ratio plasma	72,05	61,53	59,73	67,21
Fascicular Zone Adrenals	0,053	0,069	0,060	0,051
Reticular Zone Adrenals	0,277	0,191	0,326	0,267
Adrenals Mass Index	1,970	1,784	1,733	1,889
Constant	-127,2	-119,6	-101,0	-109,4

The use of classification functions makes it possible to retrospectively identify the **S-Un-** cluster without error, and others - with 1-3 errors (Table 7, see the appendix), as a result, the overall classification accuracy is 90,0%.

Table 7. Classification matrix for uric acid metabolism clusters
Rows: observed classifications; columns: predicted classifications

Clusters	Percent Correct	**S+Un+** p=,150	**Sn+U-+** p=,317	**SnUn+** p=,283	**S-Un-** p=,250
S+Un+	88,9	**8**	**1**	0	0
Sn+U-+	89,5	0	**17**	**2**	0
SnUn+	82,4	0	**2**	**14**	**1**
S-Un-	100	0	0	0	**15**
Total	90,0	8	20	16	16

Now let's analyze the connections between parameters of uric acid metabolism, on the one hand, and neuro-endocrine adaptation factors, on the other. The matrix illustrates (Table 8) that uricosuria has wider and closer connections than uricemia. In particular, uricosuria correlates significantly ($_{0,05}|r|\geq 0,25$) positively with the excretion of 17-ketosteroids and vagal tone, but negatively with the level of triiodothyronine, and the thickness of the fascicular zone of the adrenal cortex. The regression model also included Mode HRV as an inverse measure of the level of circulating catecholamines (Table 9).

Table 8. Matrix of correlations between parameters of uric acid metabolism and neuro-endocrine factors of adaptation

Variable	Uricemia	Uricosuria
Uricemia	1,00	0,48
Uricosuria	0,48	1,00
Calcitonin activity	-0,30	-0,09
Vagal tone	0,42	0,21
Sympathetic tone	-0,29	-0,10
Humoral channel	0,28	0,19
Corticosterone	-0,21	-0,02
Testosterone	-0,05	-0,20
Glomerular ZAC	-0,02	-0,19
Fascicular ZAC	-0,23	-0,45
Triiodothyronine	-0,23	-0,47
17-Ketosteroides	0,09	0,56

Table 9. Regressive model for neuro-endocrine adaptation factors and uricosuria

	R=0,780; R^2=0,609; Adjusted R^2=0,573 F(5,5)=16,8; p<10^-5					
N=60	Beta	St. Err. of Beta	B	St. Err. of B	t(54)	p-value
		Intercpt	14,3	3,2	4,54	0,00003
MxDMn	0,339	0,161	0,0239	0,0114	2,10	0,04056
Mode	-0,225	0,161	-0,0356	0,0255	-1,40	0,16775
Fasc ZAC	-0,208	0,111	-0,0083	0,0044	-1,88	0,06615
T3	-0,318	0,112	-2,5152	0,8886	-2,83	0,00651
17-KS	0,595	0,087	0,0471	0,0069	6,85	0,00000

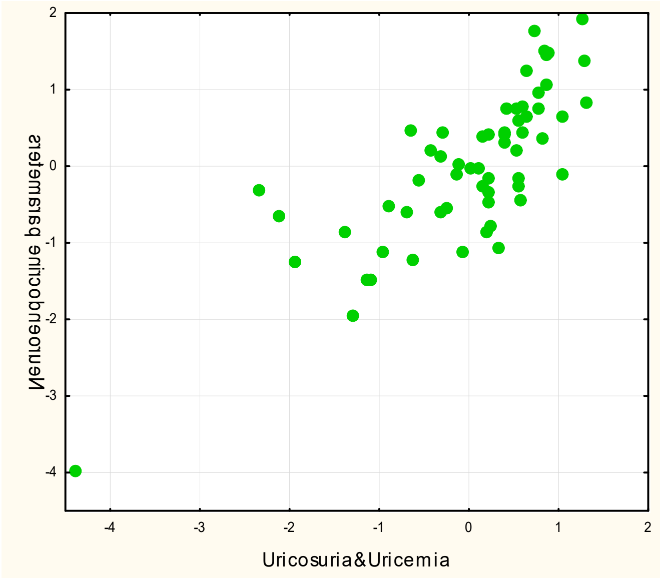
This constellation of neuro-endocrine adaptation factors is determined by uricosuria by 61%.

In the regression model for uricemia, after stepwise exclusion, only three variables remained, determined by uricemia by only 29% (Table 10). However, the sympathetic tone, circulating catecholamines, the fascicular zone and the corticosterone secreted by it are worth attention, which are negatively determined by uricemia.

Table 10. Regressive model for neuro-endocrine adaptation factors and uricemia

	R=0,535; R^2=0,287; Adjusted R^2=0,248; F(3,6)=7,5; p=0,0003					
N=60	Beta	St. Err. of Beta	B	St. Err. of B	t(56)	p-value
		Intercpt	1584,77	407,70	3,89	0,0003
Calcitonin activity	-0,310	0,115	-346,72	129,23	-2,68	0,0096
Vagal tone	0,356	0,117	3,41	1,12	3,04	0,0035
Triiodothyronine	-0,197	0,119	-212,54	127,80	-1,66	0,1019

Canonical correlation analysis shows that the combined determining influence of both parameters of uric acid metabolism exceeds the influence of uricosuria alone by only 1,4% (Fig. 3).



R=0,789; R^2=0,623; $\chi^2_{(12)}$=69; p<10^{-6}; Λ Prime=0,284

Fig. 3. Scatterplot of the canonical correlation between uricosuria and uricemia (X axis) and neuro-endocrine adaptation factors (Y axis) of female rats

Judging by the factor loadings (Table 11), the excretion of 17-ketosteroids was subject to maximum upregulation by uric acid, to a lesser extent to vagal tone, instead, triiodothyronine and the fascicular zone of the adrenal cortex were subject to downregulation, as well as, to a lesser extent, catecholamines and calcitonin.

Table 11. Factor structure of canonical roots of uric acid and neuro-endocrine adaptation factors

Root	left set
Variable	R
Uricosuria	-1,000
Uricemia	-0,450

Root	right set
Variable	R
Calcitonin activity	0,106
Vagal tone	-0,252
Humoral ch annel	-0,227
Fascicular ZAC	0,576
Triiodothyronine	0,594
17-Ketosteroides	-0,721

CONCLUSION

Uric acid is naturally associated with the state of autonomous and endocrine adaptation factors in healthy female rats.

A detailed discussion will be conducted after the publication of the results of a similar study in humans.

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 conduct of experiments was approved by the Ethics Committee of the SR Institute of Medicine of Transport. 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).

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