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SEXUAL DIMORPHISM IN RELATIONSHIPS BETWEEN OF PLASMA URIC ACID AND SOME PSYCHO-NEURO-ENDOCRINE PARAMETERS

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SummaryBackground. Earlier we found that effects of plasma nitrogenous metabolites as urea, creatinine, and bilirubin on neuro-endocrine parameters, as well as anxiety, are significantly different in men and women of different ages. The **purpose** of this study is to analyze the relationships between the plasma uric acid level and some psycho-neuro-endocrine parameters in the same cohort. **Materials and Methods**. The object of observation were almost healthy volunteers: 31 males (24÷69 y) and 30 females, from among them 18 postmenopausal (48÷76 y) and 12 of reproductive age (30÷45 y). In basal conditions we determined plasma levels of uric acid and adaptation hormones, estimated the severity of the trait and reactive anxiety, recorded the ongoing HRV and EEG. After 4 or 7 days, repeated testing was performed. **Results**. By uric acid regression models with stepwise exclusion, it was found that in men plasma uric acid downregulates the PSD of β-rhythm in P4 and δ-rhythm in others 4 loci, but upregulates the Asymmetry of δ-rhythm, variability of α-rhythm, PSD of θ-rhythm in P3 and O1 loci, Entropy of EEG in T4 as well as Testosterone plasma level. The measure of determination is 54,5%. In postmenopausal women, uricemia downregulates the Amplitude of β-rhythm and its PSD in 8 loci as well as sympathetic tone, but upregulates the PSD of HF and VLF bands HRV, Testosterone plasma level, PSD of θ-rhythm in F3 and O2 loci as well as the Laterality of δ-rhythm. The degree of determination of neuro-endocrine parameters is 94,4%. In women of reproductive age uricemia upregulates the Asymmetry and Amplitude of β-rhythm and its PSD in 6 loci, the Amplitude and Laterality of θ-rhythm and its PSD in F8 locus, as well as the PSD of α-rhythm in F8 locus. The degree of positive determination of EEGs parameters is 95,5%. **Conclusion.** Plasma uric acid has a modulating effect on neuro-endocrine parameters, but this effect is significantly different in men and women of different ages, which is due, apparently, to the influence of sex hormones on the expression of adenosine receptors in neurons.
Keywords: plasma uric acid and testosterone, ongoing EEG and HRV, men and women.

INTRODUCTION

Earlier we found that effects of plasma nitrogenous metabolites as urea, creatinine, and bilirubin on neuro-endocrine parameters, as well as anxiety, are significantly different in men and women of different ages [7-12]. The **purpose** of this study is to analyze the relationships between the plasma uric acid level and some psycho-neuro-endocrine parameters in the same cohort.

MATERIAL AND METHODS

The object of observation were employees of the clinical sanatorium "Moldova" and PrJSC “Truskavets’ Spa”: 31 males (24÷69 y) and 30 females, from among them 18 postmenopausal (45÷76 y) and 12 of reproductive age (30÷42 y). The volunteers were considered practically healthy (without a clinical diagnosis), but the initial testing revealed deviations from the norm in a number of parameters of the neuro-endocrine-immune complex as a manifestation of maladaptation [21]. Testing was performed twice with an interval of 4 (in 11 men and 10 women; "Moldova") or 7 (in 10 men and 10 women; “Truskavets’ Spa”) days.

We determined the plasma levels of the Uric acid (by uricase method [15]) as well as main adaptation hormones Cortisol, Aldosterone, Testosterone, Triiodothyronine and Calcitonin (by the ELISA with the use of corresponding sets of reagents from “Алкор Био”, XEMA Co. Ltd, and DRG International Inc). The analyzers “Pointe-180” ("Scientific", USA), “Reflotron” (Boehringer Mannheim, BRD) and “RT-2100C” (PRCh) were used.

The levels of the trait and reactive anxiety estimated by STAI of Spielberger ChD [41] in modification of Khanin YL [33]. The state of the autonomic and central nervous systems was evaluated according to the parameters of heart rate variability [5,6,23] (software-hardware complex "CardioLab+HRV", KhAI-MEDICA, Kharkiv) and QEEG (hardware-software complex “NeuroCom Standard”, KhAI MEDICA, Kharkiv). In addition to routine parameters, Shannon’s CE [39] Entropy of HRV and EEG were calculated [21,30]. See please the previous article for details [11].

Results processed by using the software package "Statistica 6.4".

RESULTS AND DISCUSSION

Screening of correlations of uricemia with psycho-neuro-endocrine parameters in men revealed the strongest positive relationship with testosteroneemia (Fig. 1).

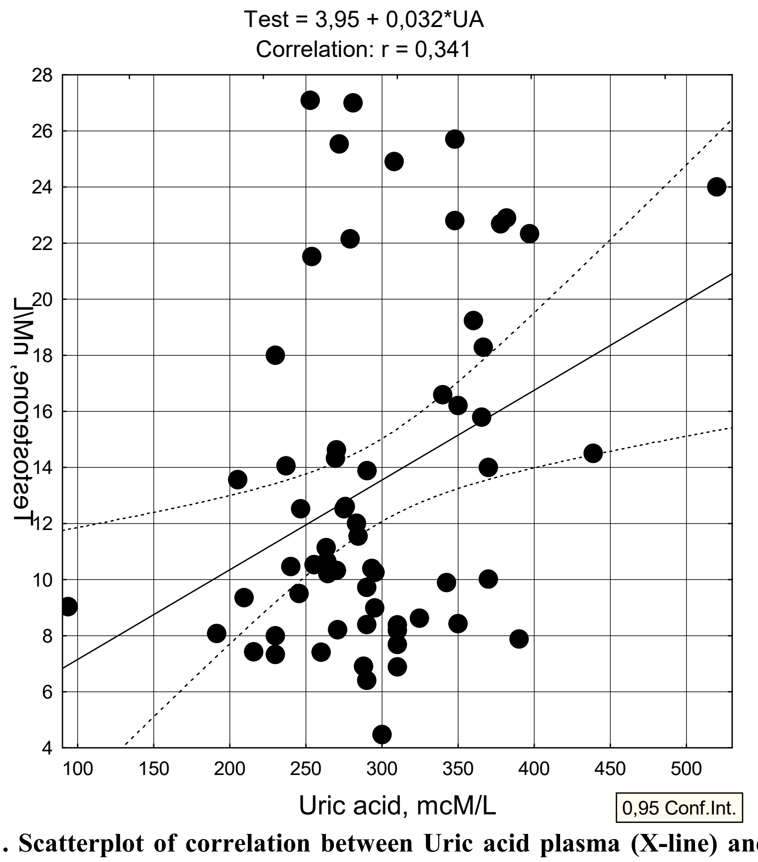


Fig. 1. Scatterplot of correlation between Uric acid plasma (X-line) and Testosterone plasma (Y-line) in Men

The strongest negative relationship was found with PSD of δ-rhythm in O1 locus (Fig. 2). By chance, we would like to draw attention to the fact that an abnormally low level of uricemia accompanies a drastically large PSD. This is about the problem of so-called outliers and the need to remove them from the analysis. In favor of their non-removal, Fig. 3.

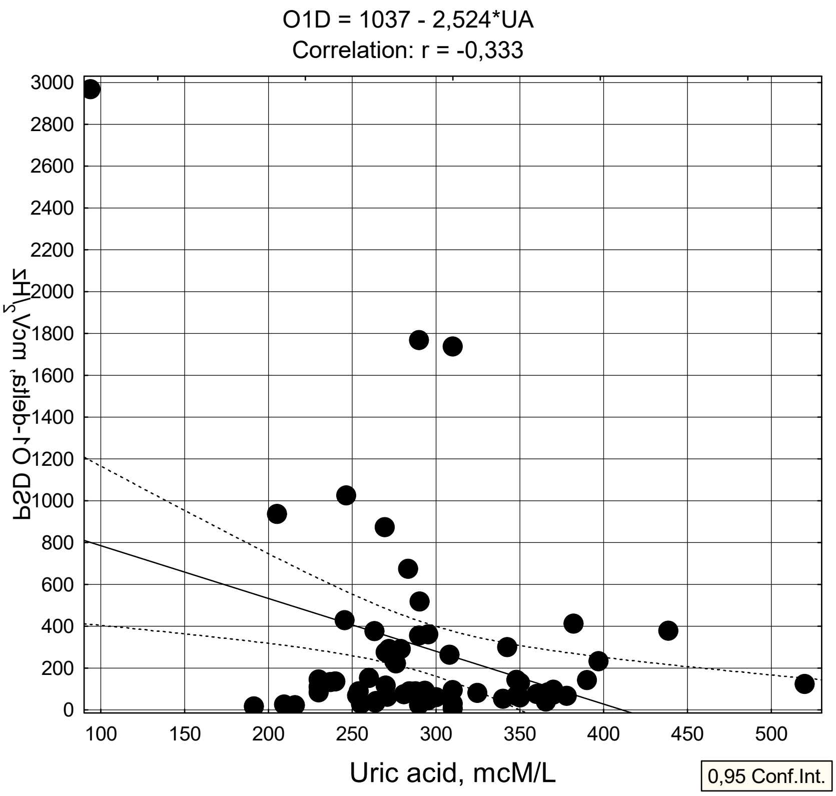


Fig. 2. Scatterplot of correlation between Uric acid plasma (X-line) and absolute PSD of delta-rhythm in O1 locus (Y-line) in Men

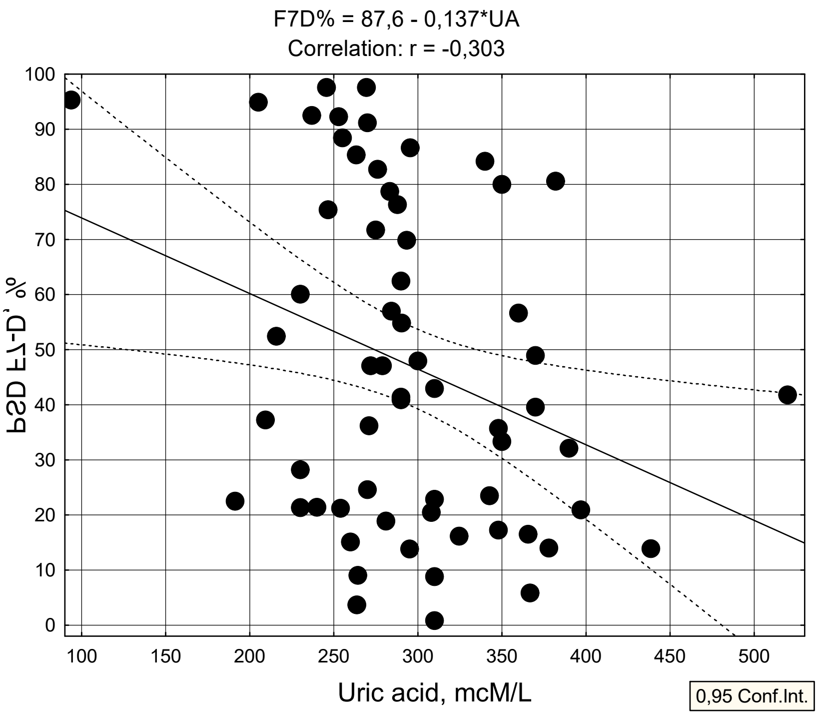


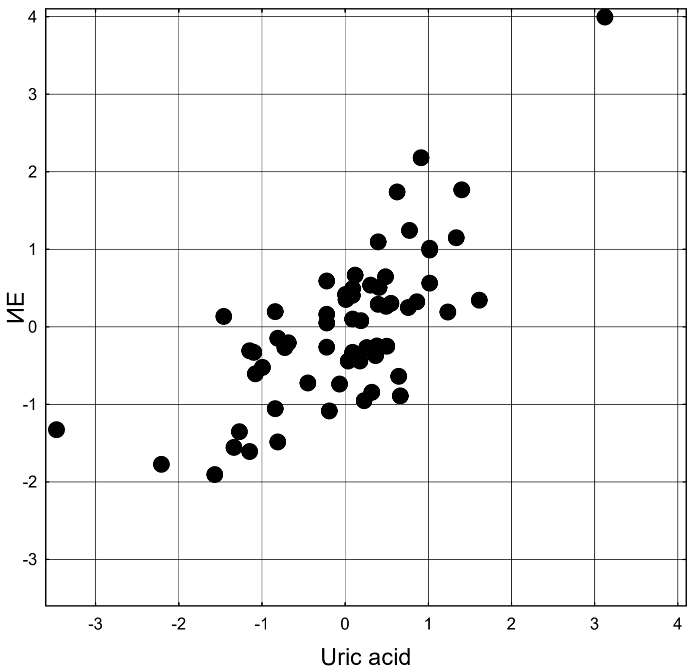
Fig. 3. Scatterplot of correlation between Uric acid plasma (X-line) and relative PSD of delta-rhythm in F7 locus (Y-line) in Men

No significant correlations between uricemia and other hormones, as well as anxiety and HRV parameters, were found.

By uric acid regression models with stepwise exclusion, it was found that in men plasma uric acid downregulates the PSD of β-rhythm in P4 and δ-rhythm in others 4 loci, but upregulates the asymmetry of δ-rhythm, variability of α-rhythm, PSD of θ-rhythm in P3 and O1 loci, Entropy of EEG in T4 as well as Testosterone plasma level. The measure of determination is 54,5% (Table 1 and Fig. 4).

Table 1. Regression Summary for Uric acid plasma in Men
$R=0,738$; $R^2=0,545$; Adjusted $R^2=0,433$; $F_{(12,5)}=4,9$; $p<10^{-4}$

N=62		Beta	St. Err. of Beta	B	SE of B	$t_{(49)}$	p-level
Variables	r		Intercpt	182,2	51,5	3,54	0,001
P4-β PSD, %	**-0,30**	-0,228	0,114	-1,328	0,664	-2,00	0,051
O1-δ PSD, μV²/Hz	**-0,33**	-0,431	0,132	-0,057	0,017	-3,28	0,002
F7-δ PSD, %	**-0,30**	-0,386	0,154	-0,851	0,339	-2,51	0,015
Fp1-δ PSD, μV²/Hz	**-0,30**	-0,407	0,166	-0,030	0,012	-2,45	0,018
Fp1-δ PSD, %	**-0,22**	0,446	0,194	1,087	0,473	2,30	0,026
O2-δ PSD, μV²/Hz	**-0,22**	0,324	0,165	0,030	0,015	1,97	0,055
Asymmetry-δ, %	**0,23**	0,415	0,111	0,998	0,268	3,72	0,001
Testosterone, mM/L	**0,34**	0,138	0,108	1,466	1,147	1,28	0,207
Deviation-α, Hz	**0,23**	0,339	0,112	45,31	15,02	3,02	0,004
Entropy PSD T4	**0,23**	0,197	0,149	56,83	42,85	1,33	0,191
P3-θ PSD, μV²/Hz	**0,21**	0,198	0,126	0,357	0,227	1,57	0,122
O1-θ PSD, %	**0,21**	-0,176	0,127	-2,217	1,599	-1,39	0,172



$R=0,738$; $R^2=0,545$; $\chi^2_{(12)}=42$; $p<10^{-4}$; Λ Prime=0,455

Fig. 4. Scatterplot of canonical correlation between Uric acid plasma (X-line) and Neuro-Endocrine parameters (Y-line) in Men

In postmenopausal women, uricemia downregulates the Amplitude of β-rhythm (Fig. 5) and its PSD in 8 loci (Fig. 6 and Table 2) as well as sympathetic tone (Fig. 7 and Table 2), but upregulates the PSD of HF and VLF bands HRV (Table 2), Testosterone plasma level (Fig. 8), PSD of θ-rhythm in F3 (Fig. 9) and O2 loci as well as the Laterality of δ-rhythm (Table 2).

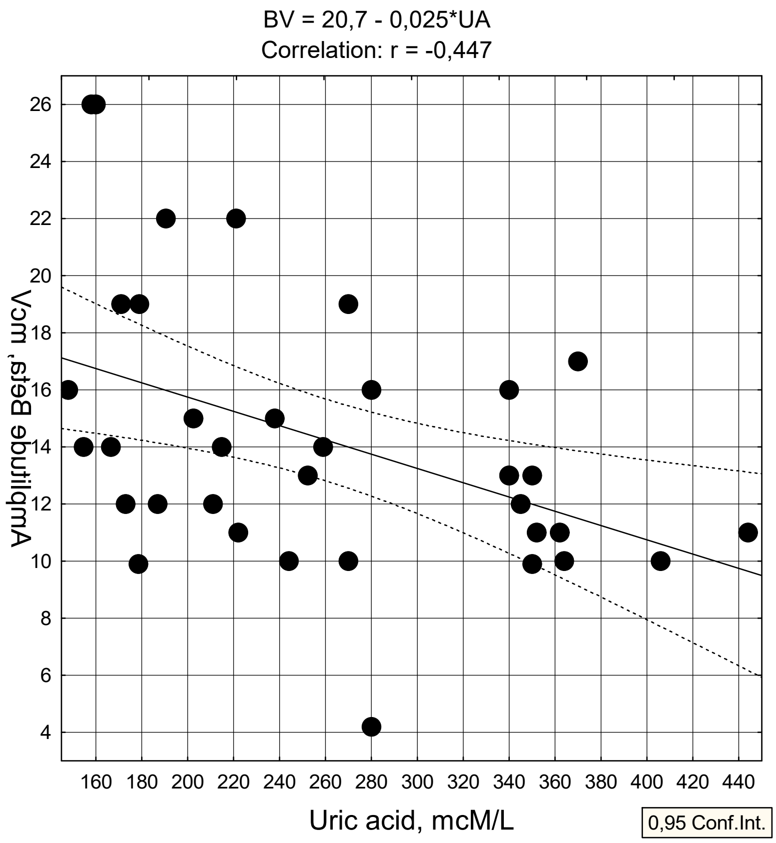


Fig. 5. Scatterplot of correlation between Uric acid plasma (X-line) and Amplitude of beta-rhythm (Y-line) in postmenopausal Women

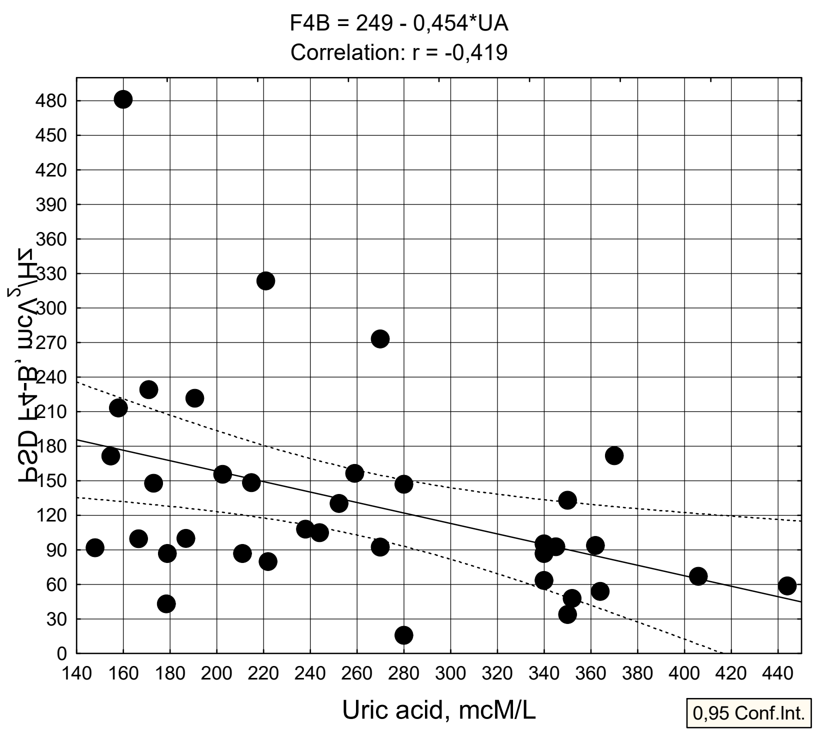


Fig. 6. Scatterplot of correlation between Uric acid plasma (X-line) and absolute PSD of beta-rhythm in F4 locus (Y-line) in postmenopausal Women

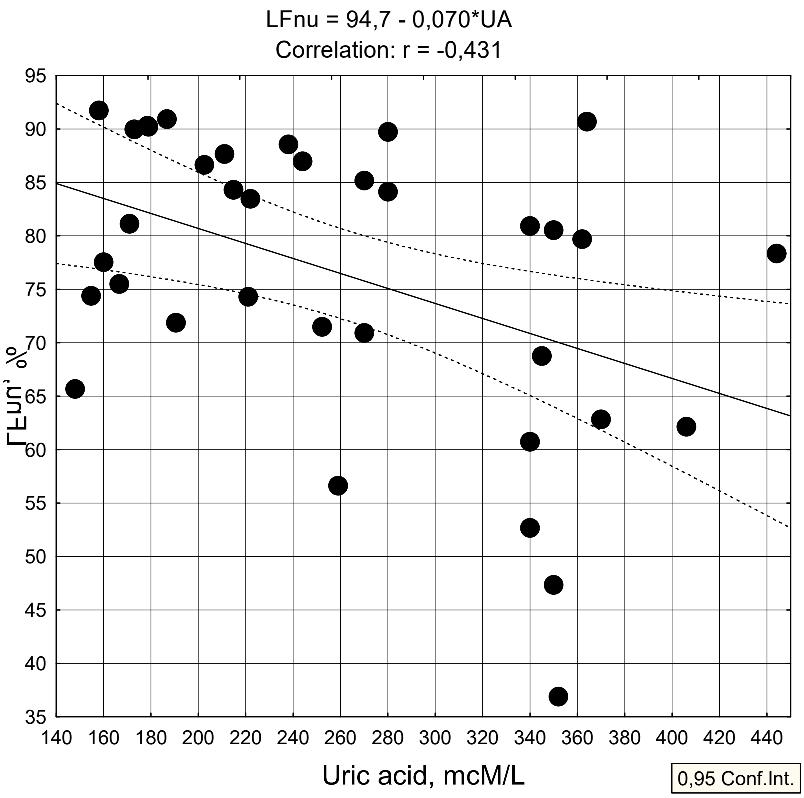


Fig. 7. Scatterplot of correlation between Uric acid plasma (X-line) and LFnu HRV (Y-line) in postmenopausal Women

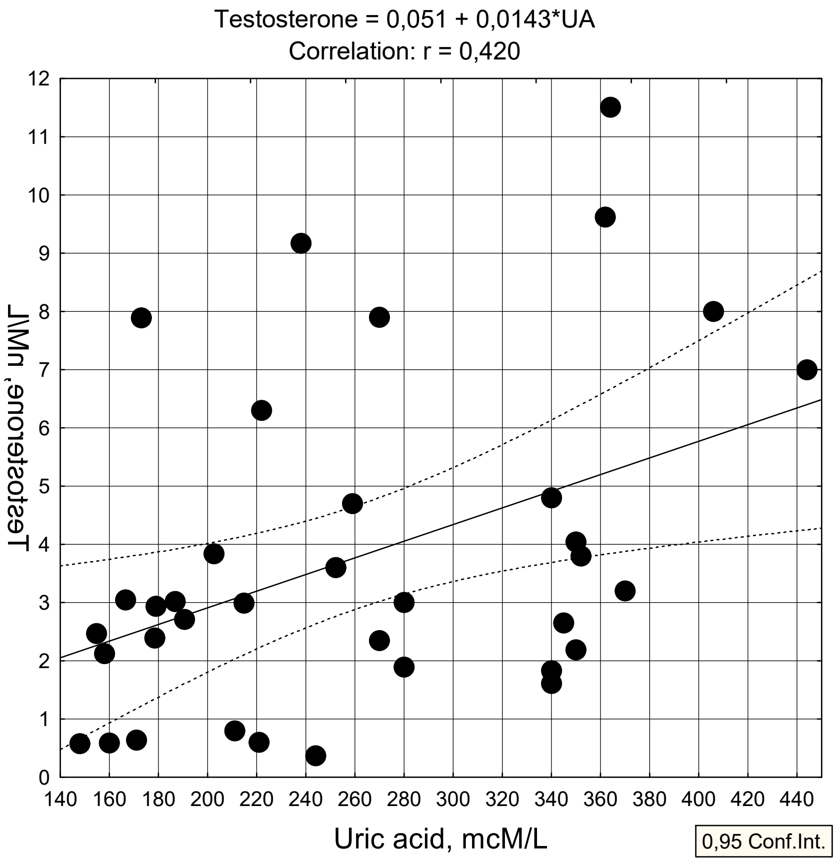


Fig. 8. Scatterplot of correlation between Uric acid plasma (X-line) and Testosterone plasma (Y-line) in postmenopausal Women

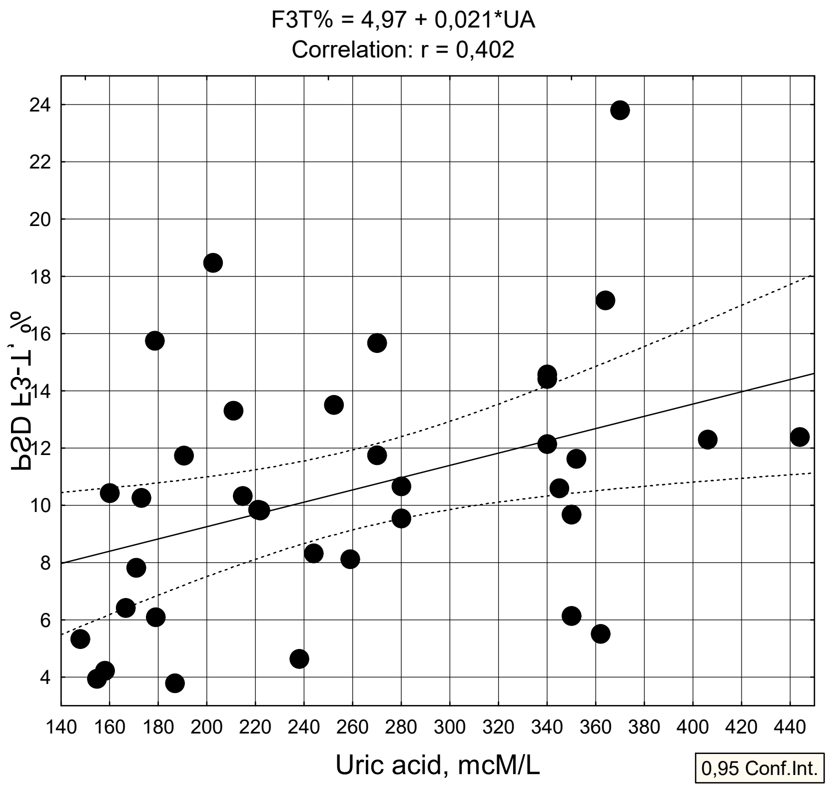


Fig. 9. Scatterplot of correlation between Uric acid plasma (X-line) and relative PSD of theta-rhythm in F3 locus (Y-line) in postmenopausal Women

In addition, significant relationships with Mode HRV (Fig. 10) and Reactive Anxiety (Fig. 11) were found.

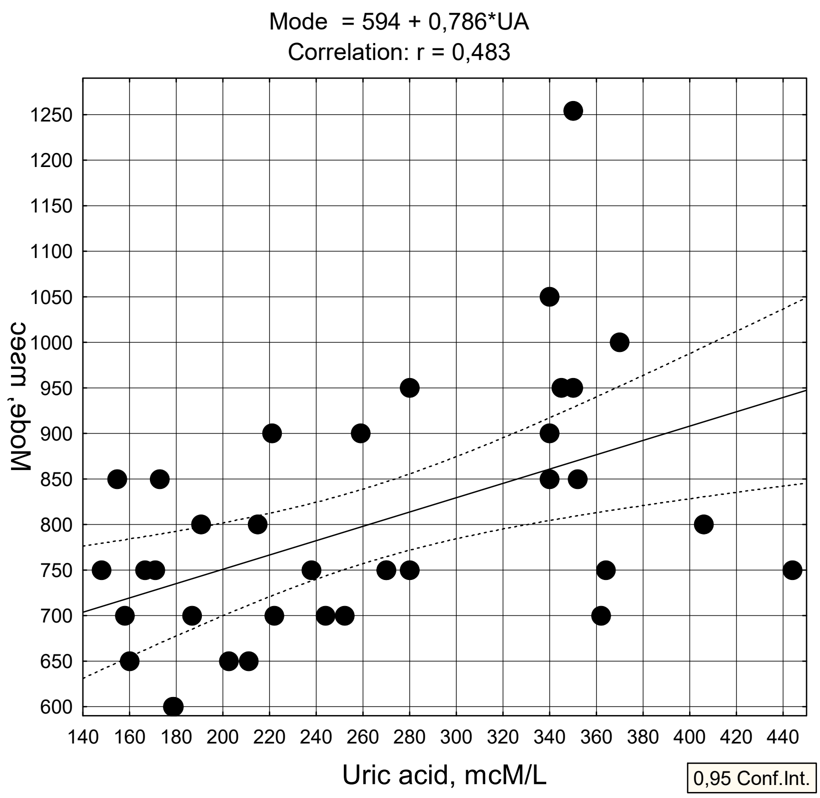


Fig. 10. Scatterplot of correlation between Uric acid plasma (X-line) and Mode HRV (Y-line) in postmenopausal Women

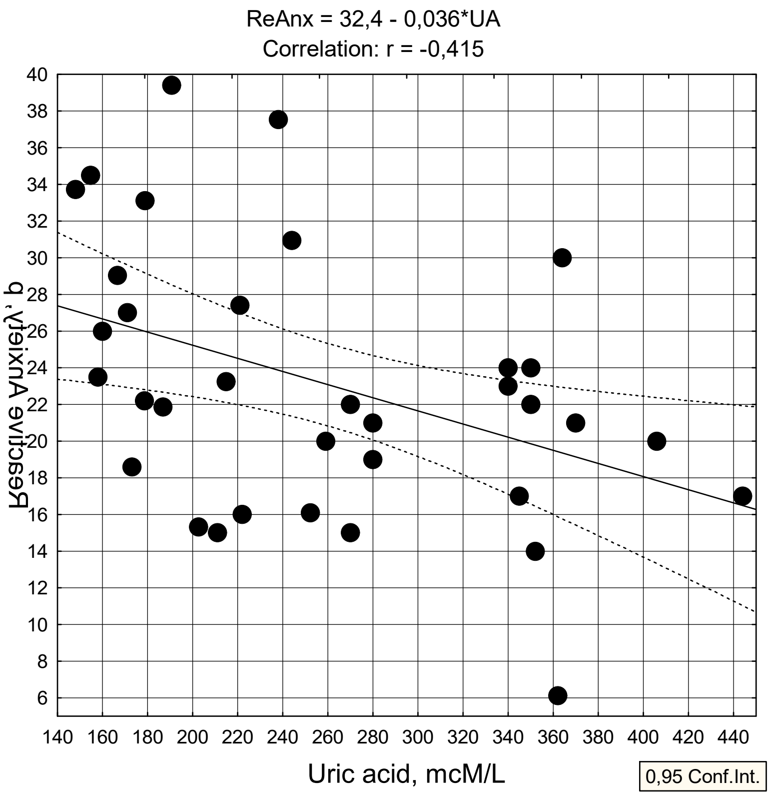


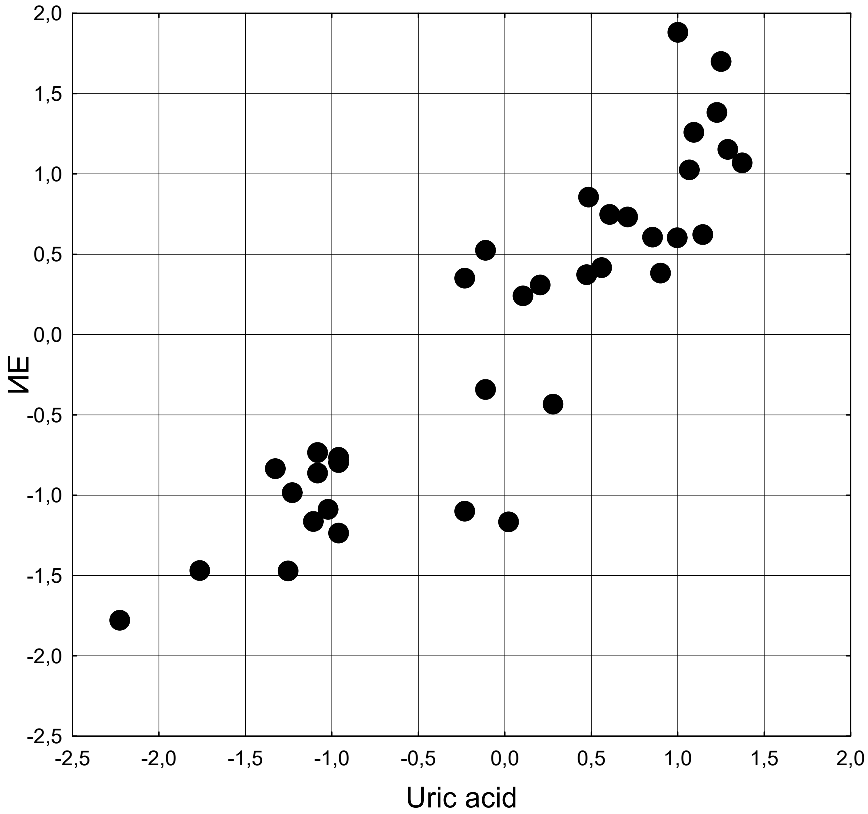
Fig. 11. Scatterplot of correlation between Uric acid plasma (X-line) and Reactive Anxiety (Y-line) in postmenopausal Women

However, the last two parameters were not included by the program in the regression model. But even without them degree of determination of neuro-endocrine parameters is 94,4% (Table 2 and Fig. 13).

Table 2. Regression Summary for Uric acid plasma in postmenopausal Women

R=0,972; R^2=0,944; Adjusted R^2=0,850; $F_{(22,1)}$=10,0; $p<10^{-4}$

N=36		Beta	St. Err. of Beta	B	SE of B	$t_{(13)}$	p-level
Variables	r		Intercpt	-236,8	121,4	-1,95	0,073
Amplitude β, μV	**-0,45**	0,818	0,301	14,62	5,38	2,72	0,018
F4-β PSD, μV²/Hz	**-0,42**	0,773	0,360	0,713	0,333	2,14	0,052
LFnu, %	**-0,43**	0,770	0,227	4,726	1,392	3,40	0,005
LF HRV PSD, %	**-0,43**	-0,361	0,226	-1,805	1,131	-1,60	0,135
LF/HF Ratio	**-0,39**	-1,044	0,214	-28,75	5,91	-4,87	10^{-3}
Kerdö's Veget Ind, un	**-0,32**	-0,265	0,097	-0,825	0,303	-2,72	0,018
C4-β PSD, %	**-0,39**	1,046	0,247	7,431	1,755	4,24	0,001
C4-β PSD, μV²/Hz	**-0,28**	2,297	0,568	1,877	0,464	4,04	0,001
T4-β PSD, μV²/Hz	**-0,38**	-1,341	0,397	-1,017	0,301	-3,37	0,005
T4-β PSD, %	**-0,31**	-0,954	0,209	-5,768	1,266	-4,56	0,001
Fp1-β PSD, μV²/Hz	**-0,38**	-0,687	0,212	-0,816	0,251	-3,25	0,006
P3-β PSD, μV²/Hz	**-0,35**	2,060	0,359	1,580	0,276	5,73	10^{-4}
O1-β PSD, μV²/Hz	**-0,33**	-0,735	0,233	-0,685	0,217	-3,16	0,008
P4-β PSD, μV²/Hz	**-0,30**	-0,686	0,366	-0,673	0,359	-1,88	0,083
C3-β PSD, μV²/Hz	**-0,26**	-4,212	0,827	-3,357	0,660	-5,09	10^{-3}
F3-θ PSD, %	**0,40**	0,647	0,123	12,16	2,32	5,24	10^{-3}
O2-θ PSD, %	**0,35**	0,583	0,148	11,35	2,88	3,94	0,002
Laterality δ, %	**0,36**	-0,814	0,169	-1,860	0,386	-4,82	10^{-3}
Testosterone, mM/L	**0,42**	0,330	0,098	9,687	2,872	3,37	0,005
VLF HRV PSD, msec²	**0,39**	-0,457	0,147	-0,066	0,021	-3,11	0,008
VLF HRV PSD, %	**0,31**	0,623	0,230	2,864	1,056	2,71	0,018
HF HRV PSD, msec²	**0,29**	0,538	0,135	0,149	0,038	3,98	0,002



R=0,972; R^2=0,944; $\chi^2_{(21)}$=41; $p<10^{-4}$; Λ Prime=0,173

Fig. 12. Scatterplot of canonical correlation between Uric acid plasma (X-line) and EEG parameters (Y-line) in premenopausal Women

Let's remember that HF band is an undeniable marker of vagal tone [5,6,23,38] and VLF band directly reflects both vagal and sympathetic tone [1] or vagal tone only [43] as well as saliva testosterone level [44]. In addition to the fact that Mode HRV is an inverse marker of circulating catecholamines [5], there is a clear impression that in this cohort of women, uricemia exerts vagotonic and sympathoinhibitory effects.

In women of reproductive age uricemia upregulates the Asymmetry and Amplitude of β-rhythm and its PSD in F8 (Fig. 13) and other 5 loci (Table 3), the Amplitude and Laterality of θ-rhythm and its PSD in F8 locus, as well as the PSD of α-rhythm in F8 locus (Table 3).

Upregulation of testosterone level (Fig. 14) while downregulation of sympathetic tone (Fig. 15) and reactive anxiety (r=-0,34) were also found for this cohort, but these parameters were outside the regression model. Nevertheless, degree of positive determination of EEGs parameters is 95,5% (Table 3 and Fig. 16).

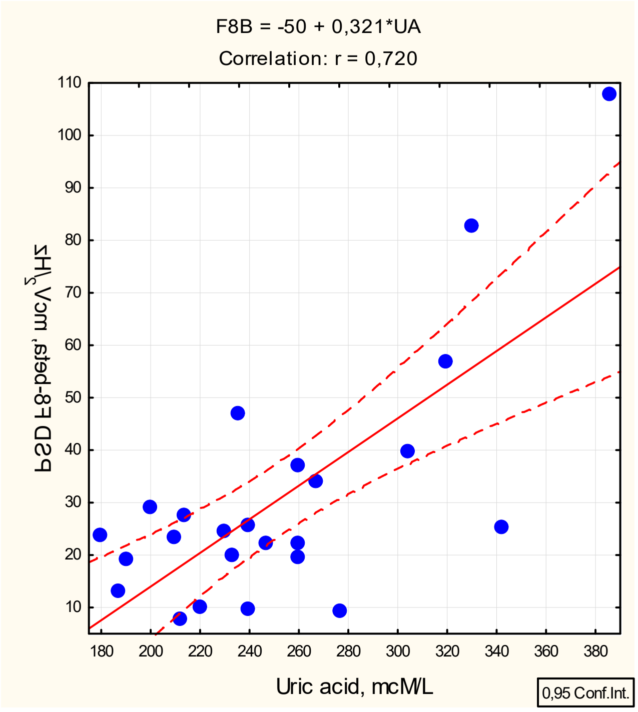


Fig. 13. Scatterplot of correlation between Uric acid plasma (X-line) and absolute PSD of beta-rhythm in F8 locus (Y-line) in premenopausal Women

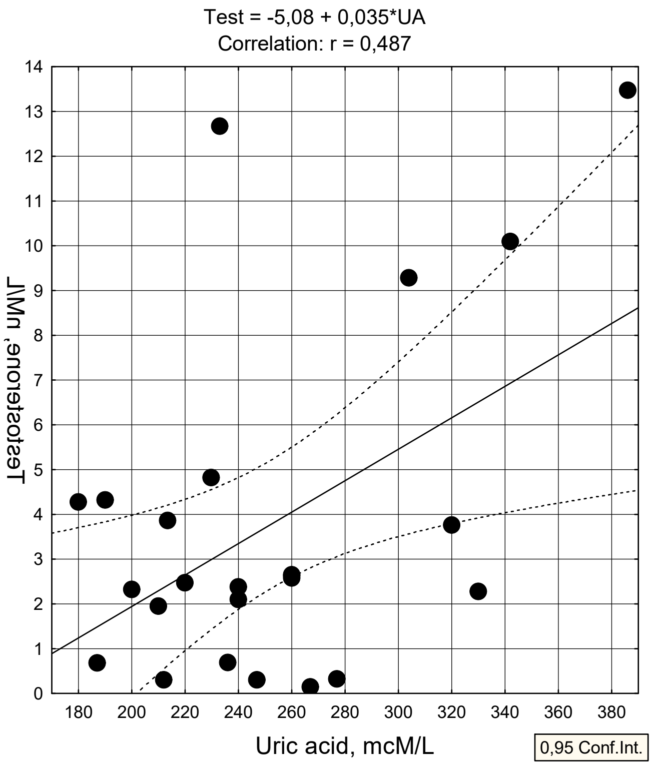


Fig. 14. Scatterplot of correlation between Uric acid plasma (X-line) and Testosterone plasma (Y-line) in premenopausal Women

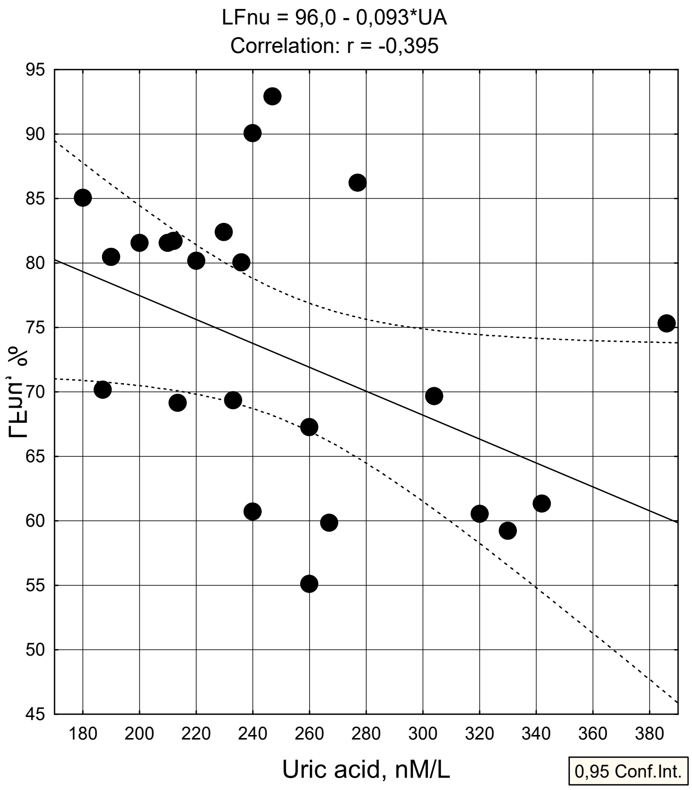
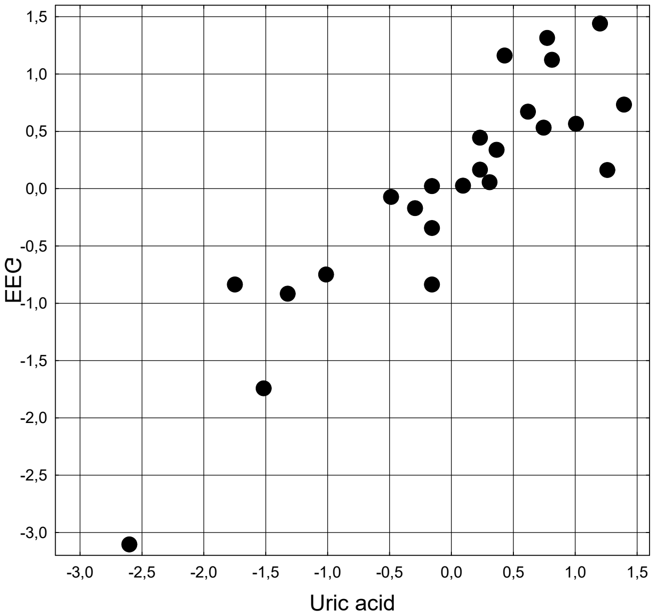


Fig. 15. Scatterplot of correlation between Uric acid plasma (X-line) and LFnu HRV (Y-line) in premenopausal Women

Table 3. Regression Summary for Uric acid plasma in premenopausal Women
R=0,977; R^2=0,955; Adjusted R^2=0,885; $F_{(14,9)}$=13,7; p=0,0002

N=24		Beta	St. Err. of Beta	B	SE of B	$t_{(9)}$	p-level
Variables	r		Intercpt	148,9	47,0	3,17	0,011
Amplitude β, µV	**0,69**	-1,421	0,407	-23,85	6,83	-3,49	0,007
F8-β PSD, µV²/Hz	**0,72**	1,237	0,463	2,776	1,040	2,67	0,026
Fp2-β PSD, %	**0,66**	1,672	0,240	5,471	0,786	6,96	10^{-4}
F4-β PSD, µV²/Hz	**0,65**	-0,278	0,256	-0,680	0,625	-1,09	0,305
T6-β PSD, µV²/Hz	**0,56**	0,900	0,170	1,019	0,192	5,30	10^{-3}
O1-β PSD, µV²/Hz	**0,52**	0,385	0,254	0,401	0,265	1,52	0,164
T3-β PSD, µV²/Hz	**0,45**	-0,516	0,279	-0,540	0,292	-1,85	0,097
Asymmetry β, %	**0,53**	-0,708	0,284	-2,201	0,883	-2,49	0,034
Amplitude θ, µV	**0,44**	1,364	0,198	24,76	3,60	6,88	10^{-4}
F8-θ PSD, µV²/Hz	**0,56**	0,620	0,296	1,031	0,492	2,09	0,066
F8-θ PSD, %	**0,44**	-0,399	0,172	-3,594	1,544	-2,33	0,045
Laterality θ, %	**0,44**	0,212	0,120	0,429	0,244	1,76	0,112
F8-α PSD, µV²/Hz	**0,49**	-0,549	0,239	-1,321	0,575	-2,30	0,047



R=0,977; R^2=0,955; $\chi^2_{(12)}$=42; p=0,0002; Λ Prime=0,455

Fig. 16. Scatterplot of canonical correlation between Uric acid plasma (X-line) and EEG parameters (Y-line) in premenopausal Women

In order to visualize the strength and directionality of the relationships between plasma uric acid levels and psycho-neuro-endocrine parameters at premenopausal and postmenopausal women as well as men, three profiles were created (Fig. 17).

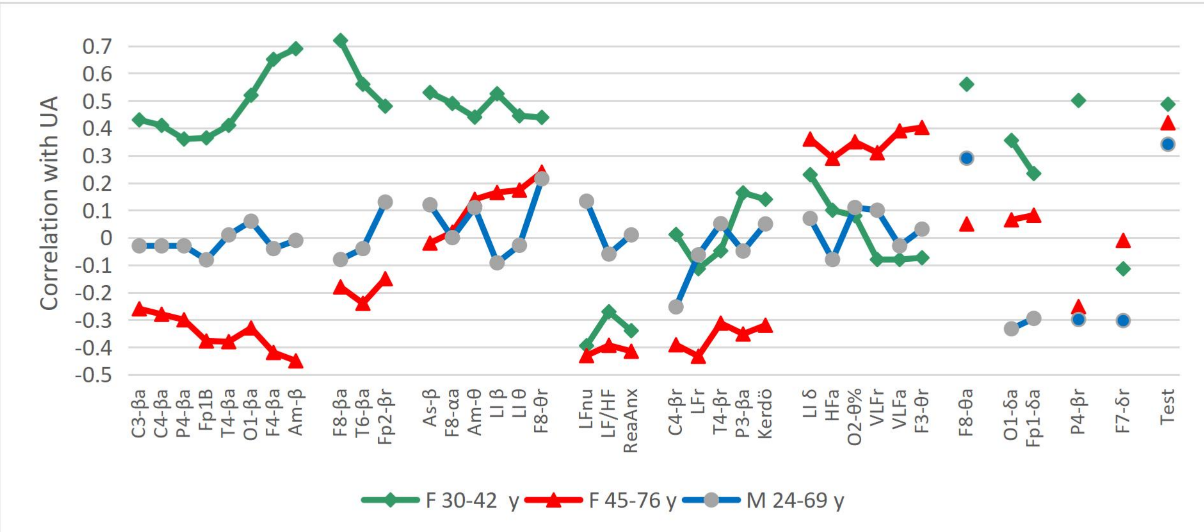


Fig. 17. Profiles of relationships between plasma Uric acid and Psycho-Neuro-Endocrine parameters at premenopausal and postmenopausal Females as well as Males

Next, the parameters were grouped into clusters (Fig. 18).

The first cluster of correlation coefficients, the largest in terms of the number of variables, reflects the enhancing effect of uric acid on neurons that generate β-rhythm specifically in women of reproductive age, while an inhibitory neurotropic effect in postmenopausal women with full areactivity of these nervous structures in men. The next cluster differs from the previous one by a marginally pronounced inhibitory effect on β-rhythm generating neurons.

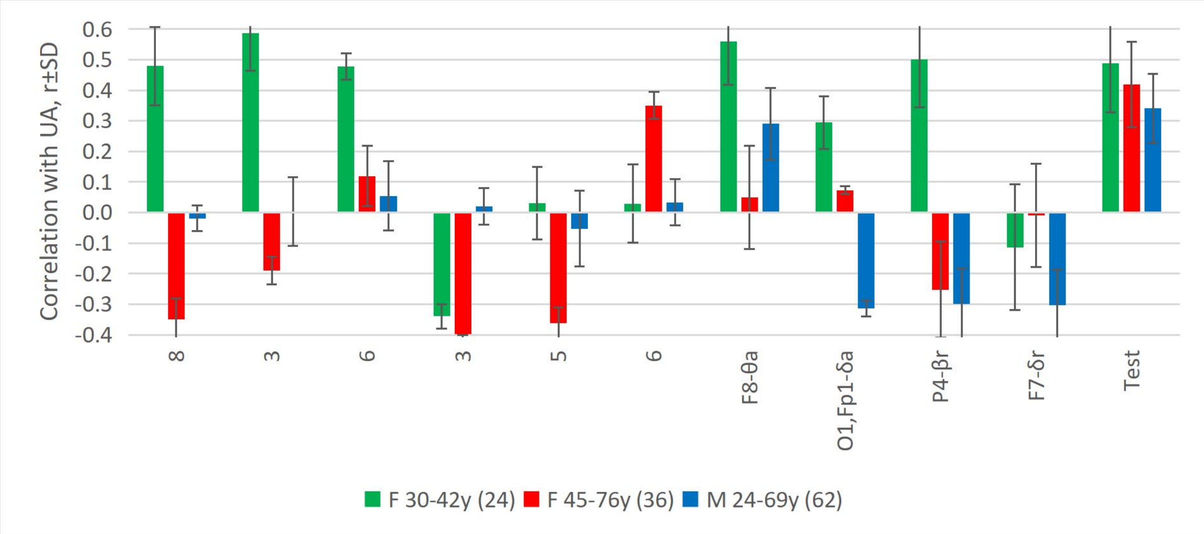


Fig. 18. Clusters of relationships between plasma Uric acid and Psycho-Neuro-Endocrine parameters at premenopausal and postmenopausal Females as well as Males. The number of variables in the cluster is given

The third cluster reflects, first of all, the ability of uric acid to cause a rightward shift of β- and θ-rhythms as well as enhance PSD of α- and θ-rhythms in F8 locus, but only in women of reproductive age. The fourth cluster reflects downregulation by uric acid of sympathetic tone and reactive anxiety in all women, but not in men. The fifth cluster unites the other two markers of sympathetic tone and three β-rhythm parameters, which are subject to downregulation only in postmenopausal women. Instead, three markers of vagal tone and PSD of θ-rhythms in F3 and O2 loci are subject to upregulation by uric acid exclusively in these same women. The following clusters contain only 1-2 parameters. Of greatest interest is the last cluster, which reflects approximately the same upregulation by uric acid of plasma testosterone levels in all three cohorts.

We know that in neurons, A_{2A} adenosine receptors have been identified both pre- and post-synaptically, where they control neurotransmitter release and neuronal stimulation, respectively [34,35,37,42]. Moreover, cells involved in the neuroinflammatory response such as astroglia, microglia and bone marrow-derived cells all express the A_{2A} receptor [13,36].

The similarity of the molecule of uric acid (**2,6,8**-tri**oxipurine**) to the molecules of methylxanthines: caffeine (**2,6**-di**oxi**-1,3,7-trimethyl**purine**) and theophylline (**2,6**-di**oxi**-1,3-dimethyl**purine** or 1,3-dimethyl**xantine**), which in turn are a structural homolog of adenosine [(2R,3R,4R,5R)-2-(6-amino**purine**-il)-5-(hydroximethyl) oxolan-3,4-diol)] and capable of 0,2 mM/L at blocking adenosine A_1- and A_{2A} receptors [32] back in 2004 led our laboratory [22] to hypothesize that uric acid, the level of which in plasma of the same order (normal range: 0,12÷0,58 mM/L), is also an endogenous non-selective adenosine receptor antagonist.

In the excellent review of Morelli M et al [29] hypothesized that urate and caffeine as adenosine A_{2A} antagonists are a novel target for neuroprotection. Initially, analysis of women in the NHS study revealed no clear relationship between Parkinson's disease (PD) and caffeine or coffee intake. However, later it became clear that amongst women who did not use postmenopausal estrogens, caffeine was in fact associated with a reduction in the risk of subsequent PD (just as in men). Conversely, for women who had used estrogen replacement caffeine use did not carry a lower risk of PD, suggesting a hormonal basis for the gender difference in caffeine's association with PD [2-4].

Based on the above, the differences in plasma uric acid relationships with psycho-neuro-endocrine parameters of men and post- and premenopausal women found in this study are somehow due to the effect of estradiol on the expression of A_{2A} adenosine receptors of neurons and/or their sensitivity to uric acid.

At the same time, the hypothesis about the role of cytokines in the neurotropic effects of uric acid has the right to be considered. As part of the single project "Nitrogenous metabolites and the neuro-endocrine-immune complex", our laboratory studied the relationship between plasma uric acid and immunity parameters in the same volunteers [16-20,24-27,31,40].

It turned out that maximal immunotropic activity exhibits exactly uric acid [24-26]. In particular, uric acid upregulates the activity and intensity of phagocytosis of Staph. aureus by blood neutrophils [16]. Our findings are consistent with data from Martínez-Reyes CP et al [28], which showed in vitro that incubation of human macrophages for 12 hours in the presence of increasing concentrations of uric acid (0,23; 0,45 and 0,9 mM/L, ie comparable to its level in plasma) dose-dependently increased their phagocytic activity, which was defined as the percentage of macrophages containing labeled Escherichia coli. This was accompanied by increased expression of TL4-receptors and increased production of TNF-α. A possible mechanism by which uric acid exerts a pro-inflammatory effect on human macrophages affects the anionic transporter of urate URAT1 in a dose-dependent manner. URAT1, in turn, may enhance NF-κB activation and lead to the production of proinflammatory cytokines in ways yet to be elucidated. In addition to TL-receptors, adenosine receptors may mediate the immunotropic effects of uric acid. It is known that the immunotropic effect of adenosine is realized through its receptors (A_1, A_{2A}, A_{2B}, A_3), which express virtually all populations of immunocytes: T, NK, B lymphocytes, macrophages, neutrophils, dendritic and endothelial cells [14].

Given the well-known neurotropic activity of cytokines, it is likely that uric acid affects neurons by regulating the release of cytokines by immunocytes through their TL- and adenosine receptors.

CONCLUSION

Plasma uric acid has a modulating effect on neuro-endocrine parameters, but this effect is significantly different in men and women of different ages, which is due, apparently, to the influence of sex hormones on the expression of adenosine receptors in neurons.

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ACCORDANCE TO ETHICS STANDARDS

Tests in patients are carried out in accordance with positions of Helsinki Declaration 1975 and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.

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