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Relationships between plasma levels of main adaptogene hormones and EEG & HRV parameters at human with dysadaptation

Mykhaylo M. Korda[1], Anatoliy I. Gozhenko[2], Oksana A. Fihura[2,3], Dariya V. Popovych[1], Xawery Żukow[4], Igor L. Popovych[2,5]
[1]IY Horbachevs'kyi National Medical University, Ternopil', Ukraine
cordamm@yahoo.com darakoz@yahoo.com
[2]Ukrainian Scientific Research Institute of Medicine of Transport, Odesa, Ukraine
prof.gozhenko@gmail.com
[3]Ivan Franko State Pedagogical University, Drohobych, Ukraine
oksanafigura08@gmail.com
[4]Medical University of Bialystok, Bialystok, Poland xaweryzukow@gmail.com
[5]Bohomolets' Institute of Physiology of National Academy of Sciences, Kyïv, Ukraine
i.popovych@biph.kiev.ua

Abstract

Background. The immunoneuroendocrinology became the foundation of the Truskavetsian Scientific School of Balneology. The focus of research was on the relationships between EEG and HRV parameters, EEG&HRV and leukocytogram, phagocytosis, cellular and humoral immunity as well as between changes in these parameters under the influence of adaptogenic factors Truskavets' spa. The purpose of this study is relationships between plasma levels of major adaptogene hormones and EEG&HRV parameters at human with dysadaptation. **Materials and Methods.** The object of observation were 10 women 33-76 y and 10 men 37-67 y without a clinical diagnosis, but with the deviations from the norm in a number of parameters of the neuro-endocrine-immune complex as a manifestation of dysadaptation. Parameters of EEG and HRV as well as hormones levels before and after a one-week course of drinking of Naftussya bioactive water registered. **Results.** Using the method of canonical correlation analysis, it was found that the level of triiodothyronine is determined by the constellation of 17 EEGs and 4 HRVs parameters by 87,5%. The rate of determination of the cortisol level by 14 EEGs and 3 HRVs parameters is 83,7%, and aldosterone by the other 14 EEGs and 3 HRVs parameters is 80,0%. Neuromodulation of testosterone and calcitonin levels is characterized by sexual dimorphism. With the same coefficients of determination (92,4%), the regression model for testosteroneemia in women included 15 EEGs parameters and no HRV parameters, instead testosteroneemia in men is modulated by other 11 EEGs parameters and one HRV parameter. The level of calcitonin in women is determined by 86,2% by the constellation of 9 EEGs and 2 HRVs parameters, while in men by 83,5% by the other 5 EEGs and 4 HRVs parameters. **Conclusion.** Plasma levels of the main adaptation hormones are accompanied by specific patterns of EEG and HRV parameters.

Keywords: EEG, HRV, Cortisol, Testosterone, Aldosterone, Triiodothyronine, Calcitonin, Male, Female, relationships.

INTRODUCTION

According to the modern paradigm, three regulatory systems are involved in maintaining homeostasis: nervous, endocrine, and immune. It is the close and continuous functional interrelationship of the nervous, hormonal and immune systems, which is based on the existence of common and identical receptor structures, that determines the high adaptability of the organism [1]. Interactions of the nervous and endocrine systems in this process are well studied and became the basis for the selection of an independent field of knowledge - neuroendocrinology [1,7,11,51,52]. Interactions between the neuroendocrine and immune systems are intensively studied and are considered the most intriguing field of modern research - immunoneuroendocrinology [9,10,12,18,23,24,27,34,39,40,46, 57,60-63].

The immunoneuroendocrinology became the foundation of the Truskavetsian Scientific School of Balneology. Experimental and clinical-physiological research of this school, carried out in line with the concept of neuro-endocrine-immune complex [36,37], in 2015 was recognized by an expert as the main trend of the last decade in Ukrainian balneology [48]. The focus of research was on the relationships between EEG and HRV parameters [42,45], EEG&HRV, on the one hand, and leukocytogram [30], phagocytosis [29], cellular and humoral immunity [28], on the other, as well as between changes in these parameters under the influence of adaptogenic factors Truskavets' spa, primarily bioactive Naftussya water [31,43,44]. A side effect of the obtained results was the addition and specification of the hypothesis of the immunological homunculus, according to which certain cortical structures exert a regulatory influence on certain links of immunity [61]. However, neuro-endocrine connections have been investigated only in an experiment on rats, and without EEG recording [36], and in humans, only a single fragmentary study of the acute effect of Naftussya bioactive water on EEG&HRV parameters, and blood levels of adaptation hormones has been conducted so far [27].

Based on the above, with this article we begin a series of studies of neuro-endocrine connections and the influence of adaptogens of various nature on them with the hope of creating an endocrine homunculus by analogy with the generally recognized Penfield's W sensorimotor homunculus and hypothetical Tracey's KI immunological homunculus. The purpose of this study is relationships between plasma levels of major adaptogene hormones and EEG&HRV parameters at human with dysadaptation. Classical (main) hormones of adaptation usually include corticosteroid, sex and thyroid [7,11-15,49,51,52]. Our previous experience gave reason to supplement this list with calcitonin (as well as parathyroid hormone) [27,36,39,67].

MATERIAL AND RESEARCH METHODS

The object of observation were employees of the PrJSC "Truskavets' Spa": 10 women 33-76 years and 10 men 37-67 years. 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 dysadaptation.

In the morning in basal condition we recorded simultaneosly electrocardiogram (ECG) and electroencephalogram (EEG). ECG recorded during 7 min in II lead to assess the parameters of heart rate variability (HRV) (hardware-software complex "CardioLab+HRV" produced by "KhAI-Medica", Kharkiv, Ukraine). For further analysis the following parameters HRV were selected. Baevskiy's parameters: heart rate (HR), the mode (Mo), the amplitude of mode (AMo), variational swing (MxDMn). Temporal parameters (Time Domain Methods): the standart deviation of all NN intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the percent of interval differences of successive NN intervals greater than 50 ms (pNN_{50}), triangular index

(TNN). Spectral parameters (Frequency Domain Methods): power spectral density (PSD) bands of HRV: high-frequency (HF, range 0,40÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,040÷0,015 Hz) and ultralow-frequency (ULF, range 0,015÷0,003 Hz). Calculated classical indexes: LF/HF, LFnu=100%•LF/(LF+HF), Centralization Index (CI)=(VLF+LF)/HF), Baevskiy's Stress Index and Activity of Regulatory Systems Index (BARSI) [6,8,19,55]. EEG recorded during 25 sec a hardware-software complex "NeuroCom Standard" (KhAI Medica, Kharkiv, Ukraine) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10-20 international system, with the reference electrodes A and Ref on the earlobes. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), absolute (μV^2/Hz) and relative (%) PSD of basic rhythms: β (35÷13 Hz), α (13÷8 Hz), θ (8÷4 Hz) and δ (4÷0,5 Hz) in all loci, according to the instructions of the device. In addition, calculated coefficient of Asymmetry (As) and Laterality Index (LI) for PSD each Rhythm using formulas [33]: As, % = 100•(Max – Min)/Min; LI, % = Σ [200•(Right – Left)/(Right + Left)]/8.

We calculated for HRV and each locus EEG the Entropy (h) of normalized PSD using Popovych's IL [18,53] formulas based on classic Shannon's CE [56] formula:

$hHRV= -[SPHF•\log_2SPHF+SPLF•\log_2SPLF+SPVLF•\log_2SPVLF+SPULF•\log_2SPULF]/\log_24$;

$hEEG = - [PSD\alpha•\log_2PSD\alpha+PSD\beta•\log_2PSD\beta+PSD\theta•\log_2PSD\theta+PSD\delta•\log_2PSD\delta]/\log_24$.

At last in portion of venous blood we determined plasma levels of major hormones of adaptation: Cortisol, Testosterone, Aldosterone, Triiodothyronine and Calcitonin (by the ELISA with the use of analyzer "RT-2100C" and corresponding sets of reagents from "Алкор Био", XEMA Co., Ltd and DRG International Inc.). After the initial testing, seven days course of drinking of Naftussya bioactive water carried out. The next morning after completing the treatment, retesting was performed.

Results processed using the software package "Statistica 64".

RESULTS AND DISCUSSION

It is known that Naftussya **bioactive** water exhibits neurotropic, endocrinotropic, immunotropic, actotropic, cardiotropic, vasotropic [18,26,27,31,35,36,40,43,44,46,54] activity (which, in fact, became the basis for its name), caused by the organic substances and autochthonous microbes present in its composition [20-22,41,47,64]. Therefore, there are grounds for assuming differences in neuro-endocrine relationships before and after balneotherapy, which will be the subject of the next study. Now let's consider the neuro-endocrine relationships regardless of the use of bioactive water.

According to the previously accepted algorithm, at the first stage, correlation coefficients were screened, then a regression model was built from variables with statistically significant or borderline coefficients by stepwise exclusion of variables until the maximum Adjusted R^2 level was reached. At the final stage, in order to visualize the model, the procedure of canonical correlation analysis was carried out. It was found that the level of triiodothyronine positively correlates with 6 parameters of the alpha-rhythm (Fig. 1) and 3 – delta-rhythm of the EEG, as well as 3 HRV-markers of vagal tone (Fig. 2), on the other hand, it is negatively correlated with 6 parameters of the beta-rhythm and one – theta-rhythm, as well as with entropy in the O1 locus (Table 1).

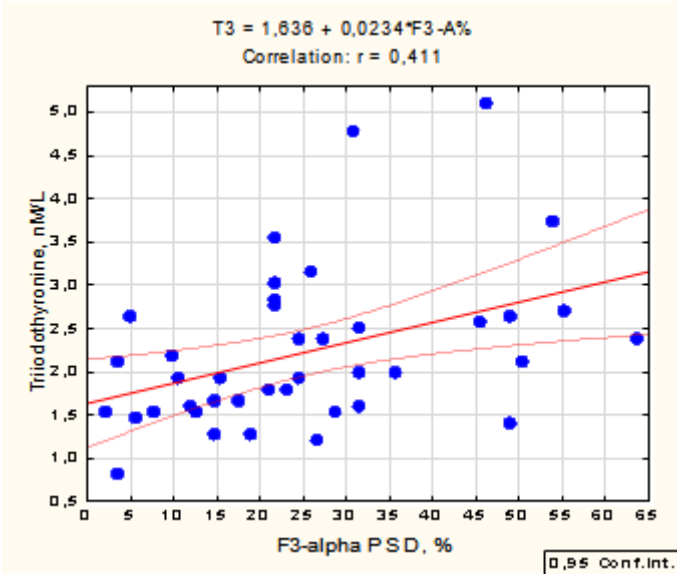


Fig. 1. Scatterplot of correlation between the PSD of α-rhythm in locus F3 (X-line) and Triiodothyronine plasma level (Y-line)

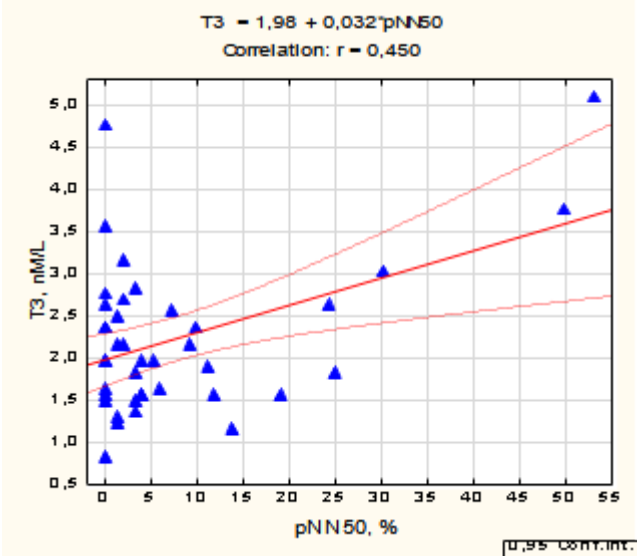


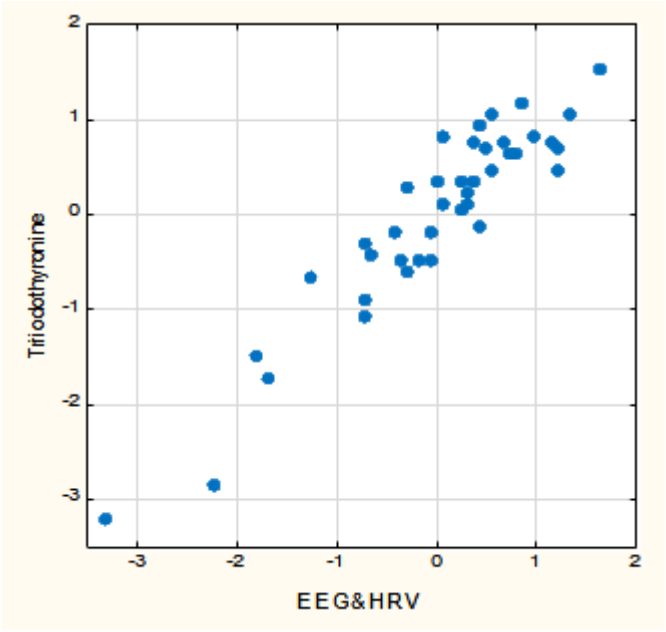
Fig. 2. Scatterplot of correlation between the pNN_{50} HRV (X-line) and Triiodothyronine plasma level (Y-line)

Regarding the VLF band, there are opinions that it directly reflects both vagal and sympathetic tone [2] or vagal tone only [58] as well as saliva testosterone level [59] while inversely - renin-angiotensin-aldosterone system activity [2,58]. Looking ahead, we note that in this study, was also found a direct correlation of the VLF band with the HF band (r=0,65) and plasma testosterone in men (r=0,32), no correlation with LFnu (r=-0,16) as well as also inversely, but insignificantly, with aldosterone (p=-0,19).

Table 1. Regression Summary for Triiodothyronine
R=0,936; R^2=0,875; Adjusted R^2=0,730; $F_{(21,2)}$=6,0; p=0,0002; SE: 0,47 nM/L

N=40		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(18)}$	p-level
Variables	r		Intercpt	-8,647	2,098	-4,12	0,001
F3-α PSD, %	**0,41**	1,149	0,393	0,065	0,022	2,93	0,009
O1-α PSD, %	**0,39**	-1,328	0,374	-0,055	0,016	-3,55	0,002
T4-α PSD, %	**0,35**	0,586	0,362	0,041	0,025	1,62	0,123
C3-α PSD, %	**0,35**	0,551	0,305	0,032	0,018	1,81	0,088
O2-α PSD, μV^2/Hz	**0,31**	0,961	0,305	0,0015	0,0005	3,15	0,006
T5-α PSD, %	**0,30**	-0,799	0,299	-0,042	0,016	-2,67	0,016
Frequency-δ, Hz	**0,45**	0,943	0,163	5,114	0,883	5,79	10^{-4}
C4-δ PSD, μV^2/Hz	**0,30**	0,207	0,139	0,0006	0,0004	1,49	0,155
F8-δ PSD, μV^2/Hz	**0,28**	-0,219	0,158	-0,0007	0,0005	-1,38	0,183
pNN_{50} HRV, %	**0,45**	-0,827	0,689	-0,059	0,049	-1,20	0,245
PSD HF band, $msec^2$	**0,44**	-1,722	0,550	-0,0027	0,0009	-3,13	0,006
RMSSD HRV, msec	**0,38**	2,928	0,671	0,150	0,034	4,36	10^{-3}
PSD VLF band, $msec^2$	**0,30**	0,455	0,196	0,0004	0,0002	2,32	0,032
O1 PSD Entropy	**-0,41**	0,455	0,264	3,140	1,824	1,72	0,102
T3-β PSD, %	**-0,34**	-0,317	0,189	-0,019	0,011	-1,68	0,111
Fp2-β PSD, %	**-0,31**	0,439	0,185	0,026	0,011	2,38	0,029
T4-β PSD, %	**-0,30**	-0,325	0,186	-0,023	0,013	-1,75	0,098
O2-β PSD, %	**-0,29**	-0,679	0,216	-0,054	0,017	-3,15	0,006
T6-β PSD, %	**-0,28**	0,254	0,168	0,016	0,010	1,51	0,147
Asymmetry-β, %	**-0,29**	0,500	0,147	0,032	0,009	3,41	0,003
O2-θ PSD, %	**-0,27**	-0,287	0,160	-0,056	0,031	-1,80	0,089

Judging by the coefficient of determination, the constellation of EEG and HRV parameters modulates the level of triiodothyronine by 87,5% (Table 1 and Fig. 3).



R=0,936; R^2=0,875; $\chi^2_{(21)}$=57; p<10^{-4}; Λ Prime=0,125
Fig. 3. Scatterplot of canonical correlation between the EEG&HRV parameters (X-line) and Triiodothyronine plasma level (Y-line)

The plasma cortisol level is upregulated by δ-rhythm generating neurons projecting to the right loci of the scalp (Fig. 4), and θ-rhythm generating neurons projecting to the left loci, as well as β-rhythm asymmetry and entropy of PSD in locus O1 (Table 2).

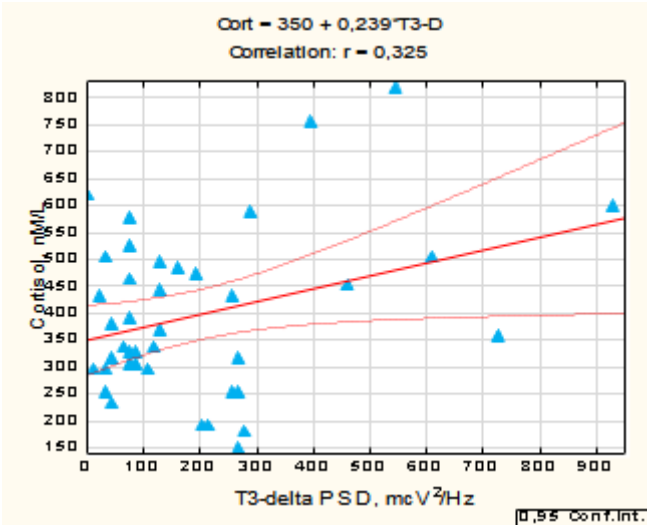


Fig. 4. Scatterplot of correlation between the PSD of δ-rhythm in locus T3 (X-line) and Cortisol plasma level (Y-line)

Instead, entropy of PSD in other loci, β- and α-rhythm generating neurons projecting to F7 and T3 loci respectively as well as HRV-markers of vagal tone (Fig. 5) carry out downregulation.

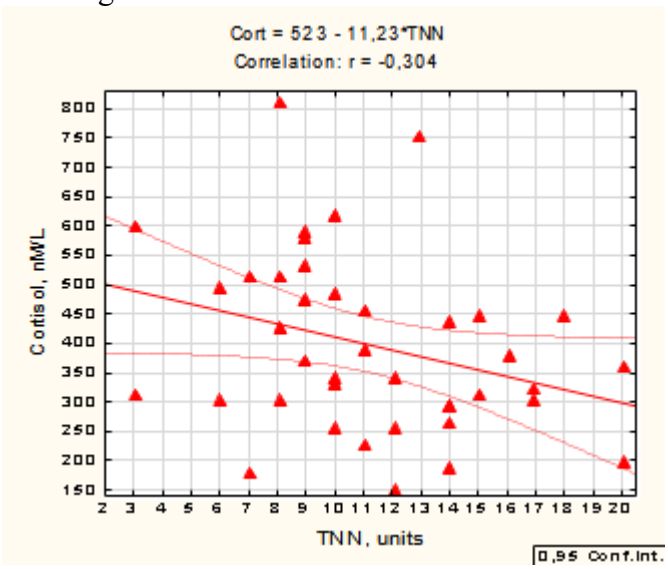
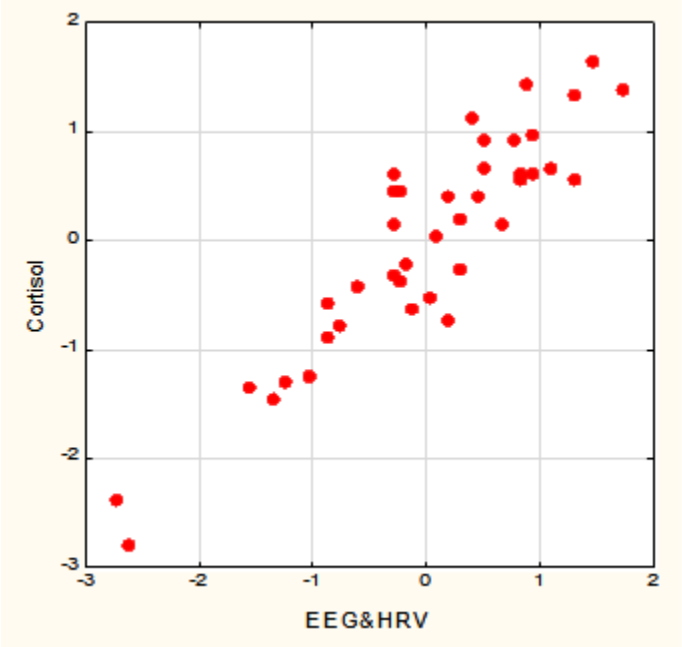


Fig. 5. Scatterplot of correlation between the Triangular index HRV (X-line) and Cortisol plasma level (Y-line)

Table 2. Regression Summary for Cortisol
R=0,915; R^2=0,837; Adjusted R^2=0,712; $F_{(17,2)}$=6,7; p=0,00003; SE: 82 nM/L

N=40		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(22)}$	p-level
Variables	r		Intercpt	311	276	1,13	0,272
T3-δ PSD, μV²/Hz	**0,32**	-1,077	0,315	-0,791	0,232	-3,42	0,002
T5-δ PSD, %	**0,30**	0,549	0,185	3,763	1,265	2,97	0,007
F7-δ PSD, %	**0,27**	-0,503	0,217	-3,631	1,566	-2,32	0,030
F7-δ PSD, μV²/Hz	**0,26**	0,546	0,223	0,369	0,151	2,45	0,023
T3-δ PSD, %	**0,26**	0,813	0,375	6,048	2,793	2,17	0,041
T6-θ PSD, μV2/Hz	**0,33**	0,229	0,162	0,623	0,440	1,41	0,171
F8-θ PSD, μV2/Hz	**0,25**	0,581	0,199	1,446	0,497	2,91	0,008
Asymmetry-β, %	**0,26**	0,664	0,187	7,054	1,989	3,55	0,002
O1 PSD Entropy	**0,35**	0,389	0,146	383,0	143,2	2,68	0,014
T4 PSD Entropy	**-0,27**	0,212	0,138	246,8	160,8	1,53	0,139
T3 PSD Entropy	**-0,26**	-0,963	0,189	-1118,7	219,8	-5,09	10^{-4}
F4 PSD Entropy	**-0,26**	0,487	0,198	404,5	164,2	2,46	0,022
F7-β PSD, μV²/Hz	**-0,25**	-0,646	0,151	-1,577	0,368	-4,28	10^{-3}
T3-α PSD, %	**-0,25**	0,627	0,244	6,427	2,498	2,57	0,017
TNN HRV, units	**-0,30**	-1,120	0,348	-41,34	12,83	-3,22	0,004
SDNN HRV, msec	**-0,28**	0,950	0,397	7,067	2,954	2,39	0,026
PSD VLF band, msec²	**-0,24**	-0,493	0,246	-0,081	0,040	-2,01	0,057

The integral effect of this constellation of EEG and HRV parameters determines the cortisol level by 83,7% (Fig. 6).



R=0,915; R^2=0,837; $\chi^2_{(17)}$=54; p<10^{-4}; Λ Prime=0,163
Fig. 6. Scatterplot of canonical correlation between the EEG&HRV parameters (X-line) and Cortisol plasma level (Y-line)

The plasma aldosterone level is upregulated by α-rhythm generating neurons projecting to the left (Fig. 7) and right loci, and θ-rhythm generating neurons projecting to the T3 locus while downregulated by δ-rhythm generating neurons projecting to the left loci.

It is interesting that the α-rhythm index is positively correlated with aldosteroneemia, while its frequency and laterality are negatively correlated, as are the θ-rhythm index and deviation.

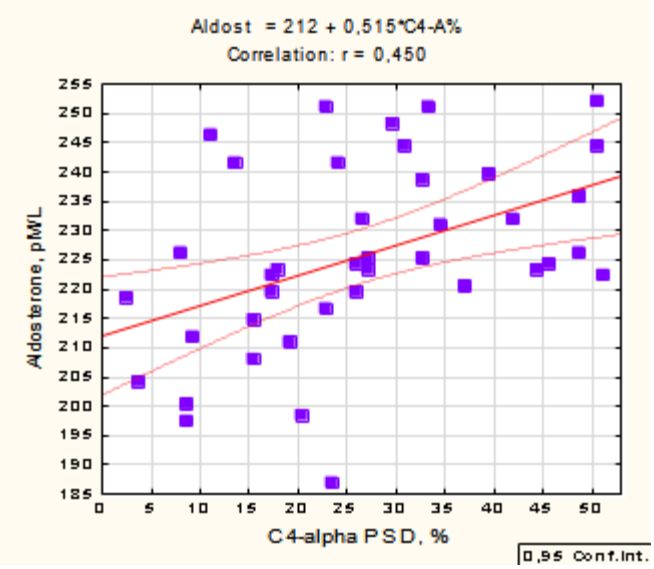


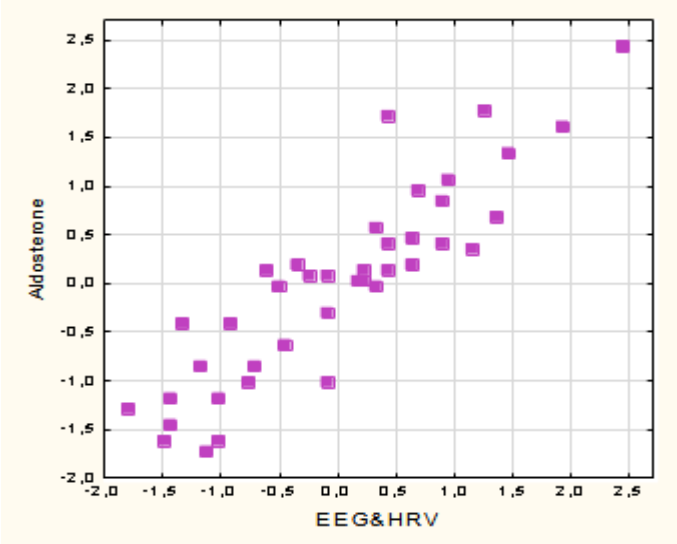
Fig. 7. Scatterplot of correlation between the PSD of α-rhythm in locus C4 (X-line) and Aldosterone plasma level (Y-line)

The physiological interpretation of the HRV parameters included in the regression model is still ambiguous. LF power may be produced by both the vagal and sympathetic, and blood pressure regulation via baroreceptors [55], primarily by the vagal [50] or by baroreflex activity alone [16]. In resting conditions, the LF band reflects baroreflex activity and not cardiac sympathetic innervation [55]. In this study, LF band correlates positively with vagal markers HF (r=0,66) and RMSSD (r=0,25), and the latter, in turn, negatively correlates with aldosteroneemia (r=-0,31), but was outside model. So, in this study, the LF band reflects vagal tone. Baevskiy's Activity of Regulatory Systems Index also reflects both sympathotonia and vagotonia. However, the ULF band continues to be terra incognita.

Table 3. Regression Summary for Aldosterone
R=0,894; R^2=0,800; Adjusted R^2=0,628; $F_{(18,2)}$=4,7; p=0,00054; SE: 9,8 pM/L

N=40		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(21)}$	p-level
Variables	r		Intercpt	267	37	7,27	10^{-6}
C4-α PSD, %	**0,45**	0,492	0,311	0,563	0,356	1,58	0,128
P3-α PSD, %	**0,36**	2,217	0,691	1,935	0,603	3,21	0,004
T5-α PSD, %	**0,33**	-2,308	0,572	-2,155	0,534	-4,03	0,001
T3-α PSD, %	**0,30**	0,281	0,235	0,304	0,254	1,20	0,245
T4-α PSD, %	**0,28**	-0,700	0,290	-0,865	0,358	-2,42	0,025
T3-θ PSD, %	**0,29**	0,285	0,129	0,977	0,441	2,21	0,038
PSD ULF band, %	**0,30**	0,380	0,146	1,266	0,487	2,60	0,017
Index-α, %	**0,31**	0,505	0,271	0,270	0,145	1,86	0,077
Frequency-α, Hz	**-0,40**	-0,439	0,130	-8,651	2,558	-3,38	0,003
Laterality-α, %	**-0,27**	-0,195	0,125	-0,099	0,064	-1,56	0,134
C3-δ PSD, %	**-0,38**	-0,229	0,201	-0,166	0,146	-1,14	0,267
P3-δ PSD, %	**-0,34**	1,880	0,532	1,518	0,429	3,54	0,002
T5-δ PSD, %	**-0,30**	-1,480	0,389	-1,068	0,280	-3,81	0,001
PSD LF band, msec²	**-0,32**	0,296	0,187	0,0045	0,0029	1,58	0,128
Activity RS Index, un.	**-0,26**	-0,266	0,156	-1,547	0,907	-1,71	0,103
Index-θ, %	**-0,29**	-0,248	0,126	-0,177	0,090	-1,97	0,063
Deviation-θ, Hz	**-0,26**	-0,244	0,144	-8,093	4,786	-1,69	0,106

Taken together, the listed EEG and HRV parameters determine the plasma aldosterone level by 80,0% (Fig. 8).



R=0,894; R^2=0,800; $\chi^2_{(18)}$=47; p-0,0002; Λ Prime=0,200
Fig. 8. Scatterplot of canonical correlation between the EEG&HRV parameters (X-line) and Aldosterone plasma level (Y-line)

Unlike the first three hormones, the norms of which for the sexes, according to the kits instructions, are the same, testosteroneemia by definition shows sexual dimorphism. Therefore, the analysis of relationships was conducted separately for women and men.

It was found that the level of testosterone in women is upregulated by β- and θ-rhythm generating neurons (Fig. 9) while downregulated by δ-rhythm generating neurons (Fig. 10).

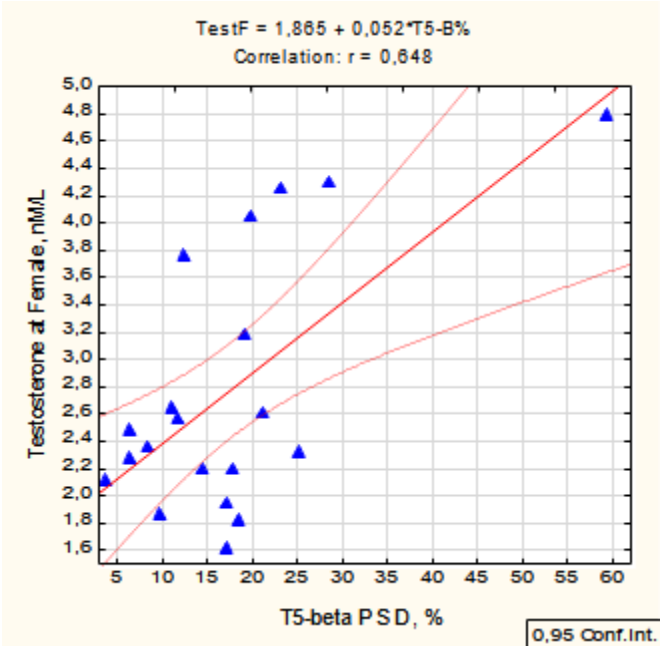


Fig. 9. Scatterplot of correlation between the PSD of β-rhythm in locus T5 (X-line) and Testosterone plasma level (Y-line) at Female

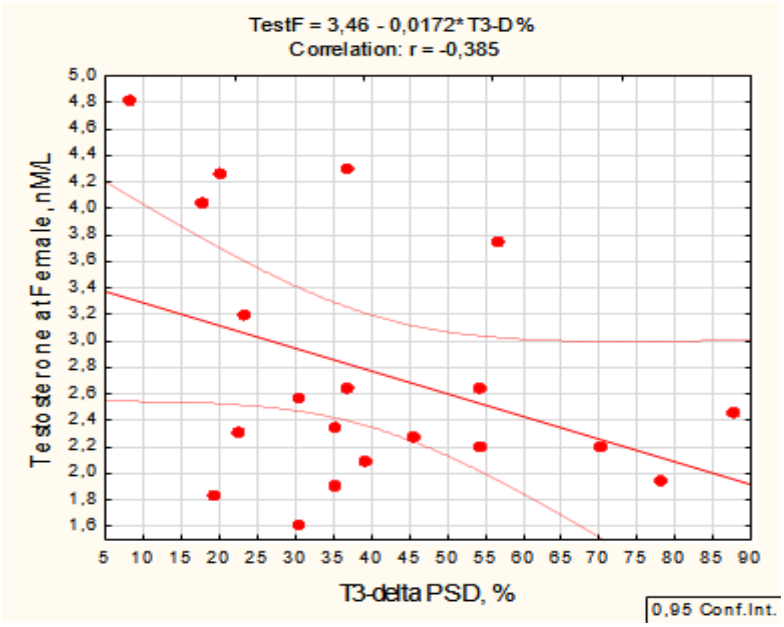
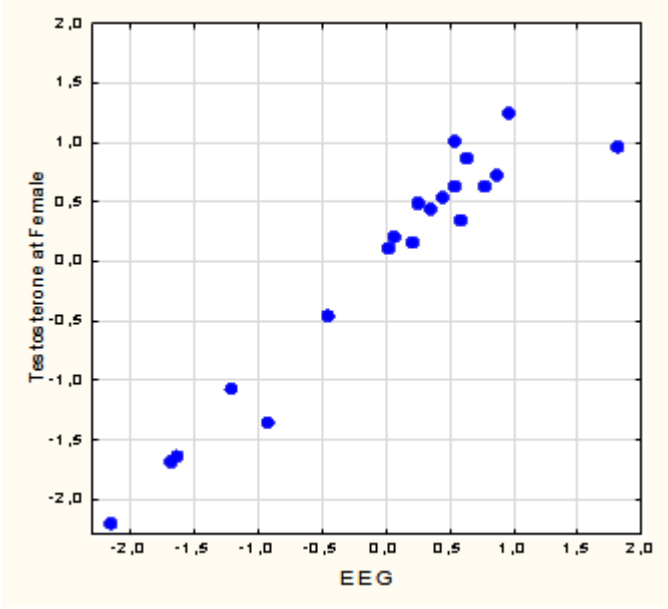


Fig. 10. Scatterplot of correlation between the PSD of δ-rhythm in locus T3 (X-line) and Testosterone plasma level (Y-line) at Female

Taken together, the listed EEG parameters determine the plasma testosterone level by 92,4% (Table 4 and Fig. 11).

Table 4. Regression Summary for Testosterone at women
R=0,961; R^2=0,924; Adjusted R^2=0,637; $F_{(15,4)}$=3,2; p=0,029; SE: 0,57 nM/L

N=20		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(4)}$	p-level
Variables	r		Intercpt	0,255	1,188	0,21	0,840
T5-β PSD, %	**0,65**	0,953	0,499	0,076	0,040	1,91	0,129
F7-β PSD, %	**0,50**	2,368	0,742	0,164	0,051	3,19	0,033
O2-β PSD, %	**0,50**	-1,436	0,613	-0,1208	0,0516	-2,34	0,079
P4-β PSD, %	**0,49**	-3,292	1,186	-0,391	0,141	-2,78	0,050
P3-β PSD, %	**0,48**	1,393	0,561	0,174	0,070	2,48	0,068
T6-β PSD, %	**0,39**	0,708	0,324	0,054	0,025	2,19	0,094
O1-β PSD, %	**0,39**	1,669	0,754	0,1225	0,0554	2,21	0,091
T3-β PSD, %	**0,35**	-2,086	0,592	-0,164	0,047	-3,52	0,024
C3-θ PSD, %	**0,39**	0,310	0,233	0,069	0,052	1,33	0,254
Deviation-θ, Hz	**0,35**	0,970	0,343	1,937	0,686	2,82	0,048
T3-δ PSD, %	**-0,38**	-1,489	0,518	-0,066	0,023	-2,87	0,045
T3-δ PSD, μV²/Hz	**-0,35**	-1,199	0,561	-0,0048	0,0022	-2,14	0,099
O2-δ PSD, μV²/Hz	**-0,36**	-0,985	0,312	-0,0050	0,0016	-3,16	0,034
T5-δ PSD, μV²/Hz	**-0,35**	2,112	0,734	0,0095	0,0033	2,88	0,045
T6-δ PSD, %	**-0,31**	1,599	0,473	0,086	0,025	3,38	0,028



R=0,961; R^2=0,924; $\chi^2_{(15)}$=27; p=0,029; Λ Prime=0,076
Fig. 11. Scatterplot of canonical correlation between the EEG parameters (X-line) and Testosterone plasma level (Y-line) at Female

Although the degree of neurogenic determination of testosterone level was exactly the same (92,4%) in men as well (Fig. 14), the structure of the regression model is completely different (Table 5). And this is quite natural, because the main source of testosterone in women is normally the reticular zone of the adrenal cortex.

With regard to EEG parameters, it was found that downregulation is carried out by entropy (Fig. 12) and θ-rhythm generating neurons projecting to the F7 locus (Table 5), while similar neurons projecting to the T4 locus, as well as scattered δ-rhythm generating neurons, carry out upregulation (Fig. 13).

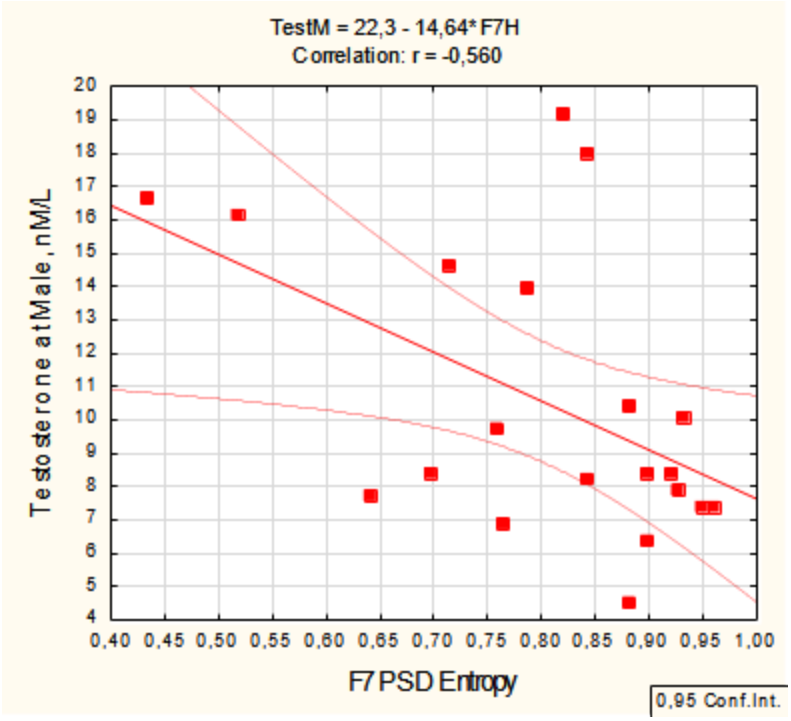


Fig. 12. Scatterplot of correlation between the Entropy of PSD in locus F7 (X-line) and Testosterone plasma level (Y-line) at Male

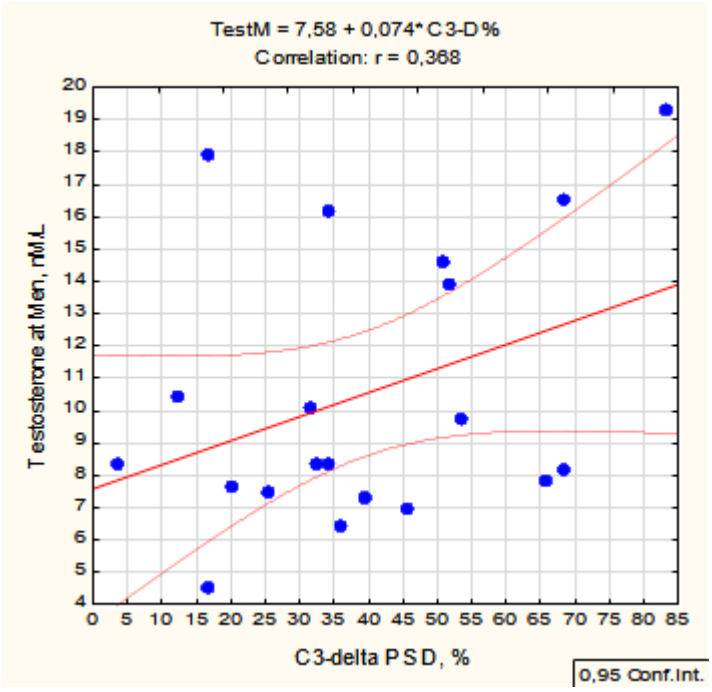
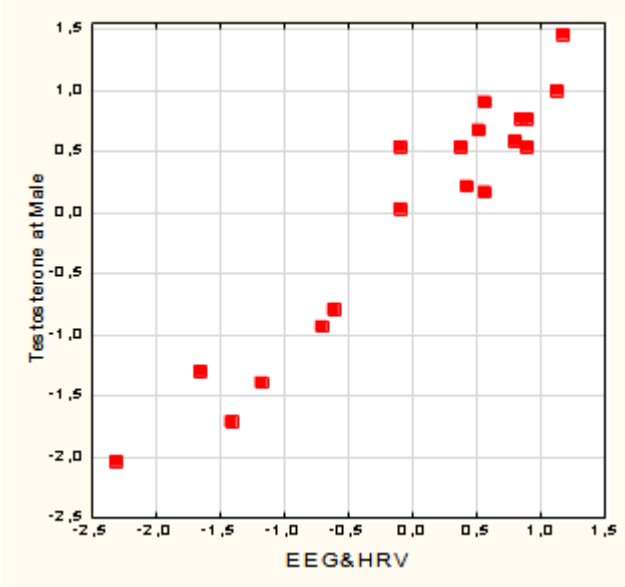


Fig. 13. Scatterplot of correlation between the PSD of δ-rhythm in locus C3 (X-line) and Testosterone plasma level (Y-line) at Male

Additional upregulating factors are the deviation of the β-rhythm and the laterality of the α-rhythm, instead, the sympathetic tone exerts a downregulating effect. By the way, the level of testosterone in women is also negatively correlated with sympathetic tone, but not strongly enough to be included in the regression model (r=-0,29).

Table 5. Regression Summary for Testosterone at men
R=0,961; R^2=0,924; Adjusted R^2=0,771; $F_{(12,6)}$=6,1; p=0,019; SE: 2,09 nM/L

N=20		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(6)}$	p-level
Variables	r		Intercpt	2,51	8,69	0,29	0,782
F7 PSD Entropy	**-0,56**	-0,639	0,195	-19,61	5,974	-3,28	0,017
Fp1 PSD Entropy	**-0,46**	0,833	0,359	26,84	11,57	2,32	0,059
C3 PSD Entropy	**-0,43**	0,420	0,239	14,10	8,02	1,76	0,129
F7-θ PSD, %	**-0,48**	-0,348	0,198	-0,414	0,234	-1,76	0,128
Amplitude Mode, %	**-0,47**	-0,787	0,217	-0,337	0,093	-3,63	0,011
C3-δ PSD, μV²/Hz	**0,43**	0,857	0,452	0,0130	0,0069	1,90	0,107
C4-δ PSD, μV²/Hz	**0,40**	-1,046	0,461	-0,0142	0,0063	-2,27	0,064
F7-δ PSD, %	**0,40**	-0,523	0,285	-0,108	0,059	-1,83	0,117
Fp1-δ PSD, μV²/Hz	**0,38**	0,729	0,348	0,0181	0,0086	2,09	0,081
T4-θ PSD, μV²/Hz	**0,40**	1,280	0,314	0,2172	0,0533	4,07	0,007
Deviation-β, Hz	**0,49**	0,602	0,169	4,158	1,168	3,56	0,012
Laterality-α, %	**0,40**	-0,534	0,202	-0,063	0,024	-2,64	0,039



R=0,961; R^2=0,924; $\chi^2_{(12)}$=28; p=0,005; Λ Prime=0,076
Fig. 14. Scatterplot of canonical correlation between the EEG&HRV parameters (X-line) and Testosterone plasma level (Y-line) at Male

The plasma level of calcitonin also shows sexual dimorphism, although it is less pronounced compared to testosterone. According to the instructions for the DRG International Inc. kit, normal range in women 0,1÷10,0 ng/L, in men 0,2÷27,7 ng/L.

It was found that calcitoninemia in women is upregulated by β-rhythm generating neurons projecting to the T4 (Fig. 15) and Fp2 loci as well as δ-rhythm generating neurons projecting to the O2 and C3 loci. Instead, frequency of δ-rhythm, θ- and α-rhythm generating neurons projecting to F3, C3 and P3 (Fig. 16) loci respectively, as well as entropy of PSD in C3 locus, carry out downregulation (Table 6).

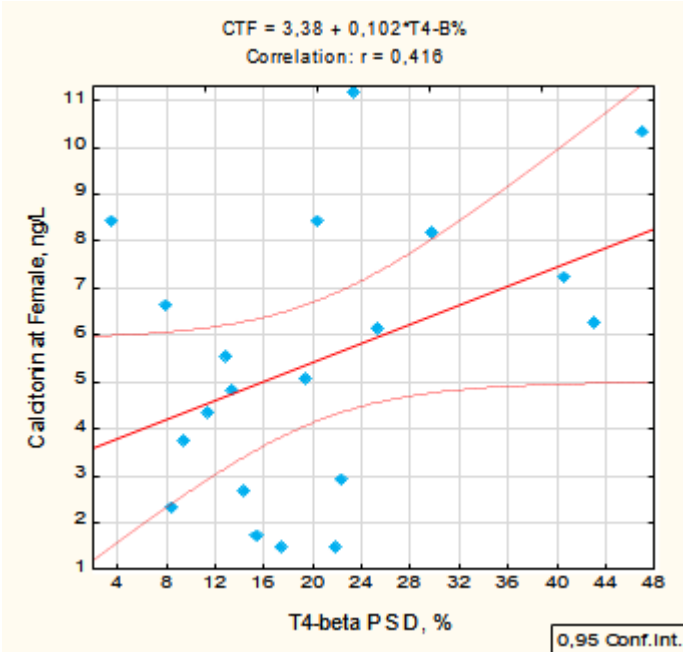


Fig. 15. Scatterplot of correlation between the PSD of β-rhythm in locus T4 (X-line) and Calcitonin plasma level (Y-line) at Female

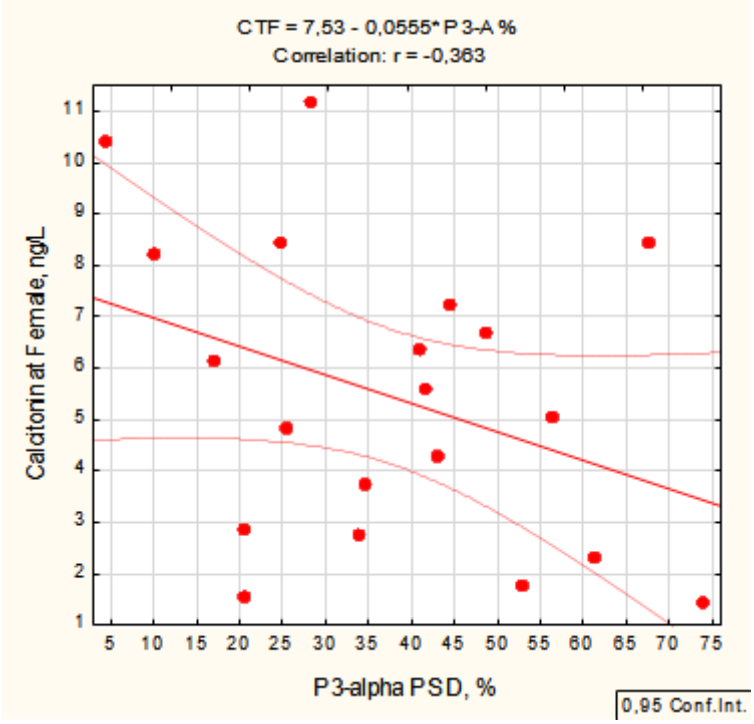


Fig. 16. Scatterplot of correlation between the PSD of α-rhythm in locus P3 (X-line) and Calcitonin plasma level (Y-line) at Female

Additional upregulating factors are the HRV-markers of the sympathetic tone (Fig. 17).

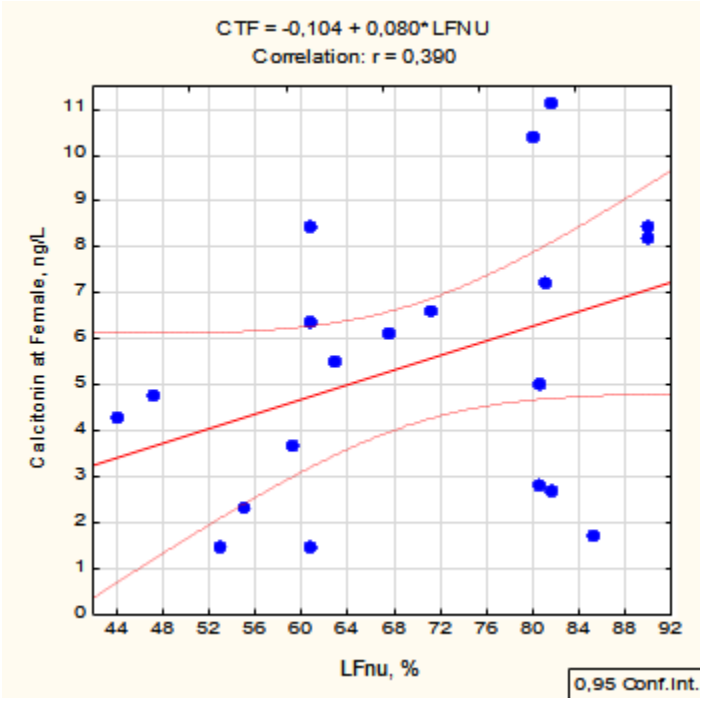
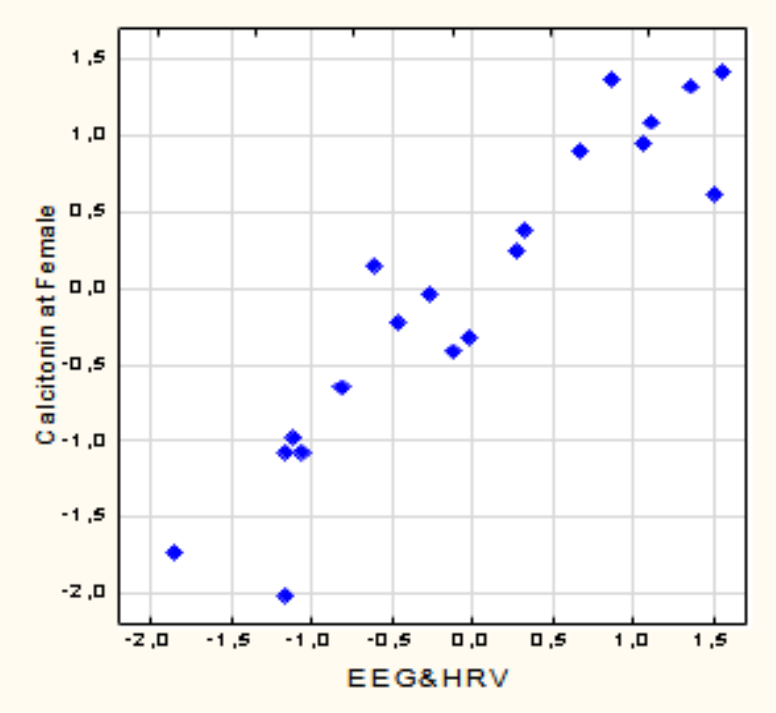


Fig. 17. Scatterplot of correlation between the LFnu HRV (X-line) and Calcitonin plasma level (Y-line) at Female

Taken together, the listed EEG and HRV parameters determine the plasma calcitonin level at women by 86,2% (Table 6 and Fig. 18).

Table 6. Regression Summary for Calcitonin at women
R=0,928; R^2=0,862; Adjusted R^2=0,672; $F_{(11,8)}$=4,5; p=0,021; SE: 1,67 ng/L

N=20		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(8)}$	p-level
Variables	r		Intercpt	70,8	19,3	3,66	0,006
T4-β PSD, %	**0,42**	-1,754	0,528	-0,428	0,129	-3,32	0,011
Fp2-β PSD, %	**0,37**	0,397	0,240	0,112	0,068	1,65	0,137
LFnu HRV, %	**0,39**	0,796	0,400	0,163	0,082	1,99	0,081
LF/HF Ratio HRV	**0,37**	1,130	0,439	1,353	0,526	2,57	0,033
O2-δ PSD, %	**0,38**	-2,011	0,662	-0,269	0,089	-3,04	0,016
C3-δ PSD, %	**0,32**	-1,436	0,654	-0,180	0,082	-2,20	0,059
Frequency-δ, Hz	**-0,38**	-0,599	0,181	-11,36	3,43	-3,31	0,011
P3-α PSD, %	**-0,36**	-2,361	0,675	-0,361	0,103	-3,50	0,008
F3-θ PSD, %	**-0,34**	1,199	0,493	0,741	0,304	2,43	0,041
C3-θ PSD, %	**-0,35**	-1,940	0,536	-1,318	0,364	-3,62	0,007
C3 PSD Entropy	**-0,32**	-1,806	0,579	-33,37	10,69	-3,12	0,014



R=0,928; R^2=0,862; $\chi^2_{(11)}$=25; p=0,010; Λ Prime=0,138
Fig. 18. Scatterplot of canonical correlation between the EEG&HRV parameters (X-line) and Calcitonin plasma level (Y-line) at Female

In men, the upregulation of the calcitonin level is carried out by EEG entropy (Fig. 19) and θ-rhythm generating neurons projecting to the F8 and F4 loci, as well as, apparently, circulating catecholamines, the markers of which are primarily the parameter inverted to Mode HRV, as well as other Baevskiy's RM HRV parameters.

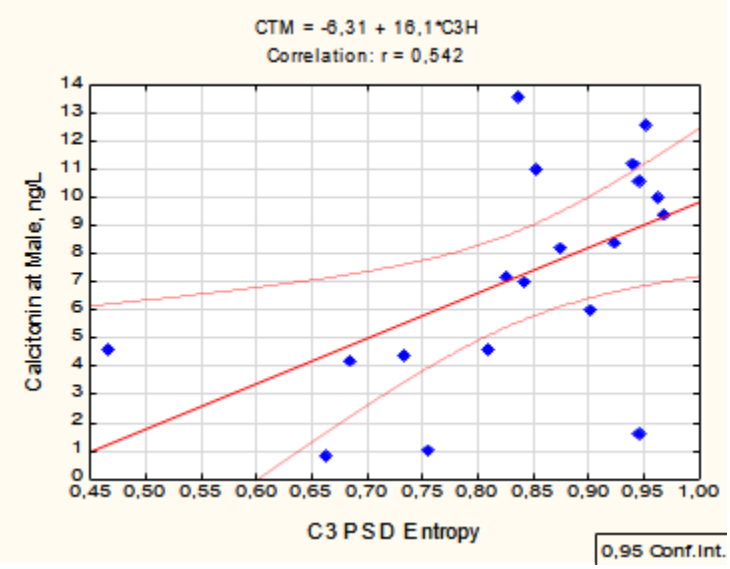


Fig. 19. Scatterplot of correlation between the Entropy of PSD in locus C3 (X-line) and Calcitonin plasma level (Y-line) at Male

Recall that in women, unlike men, θ-rhythm-generating neurons (although with a different localization) negatively regulate the level of calcitonin. An even more striking contrast is shown by β-rhythm generating neurons projecting to the T4 locus: upregulation at women

versus downregulation at men (Fig. 20). Here it is appropriate to note the opposite of cortisol-testosterone correlations: -0,42 at women versus +0,36 at men.

Taken together, the listed EEG and HRV parameters determine the plasma calcitonin level at men by 83,5% (Table 7 and Fig. 21).

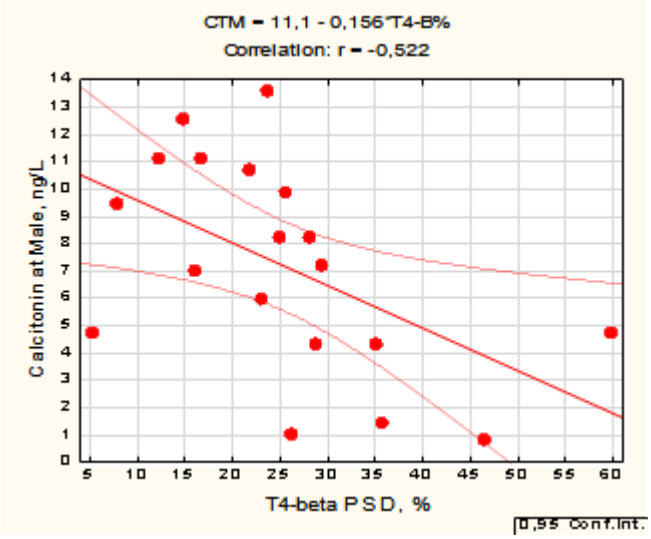
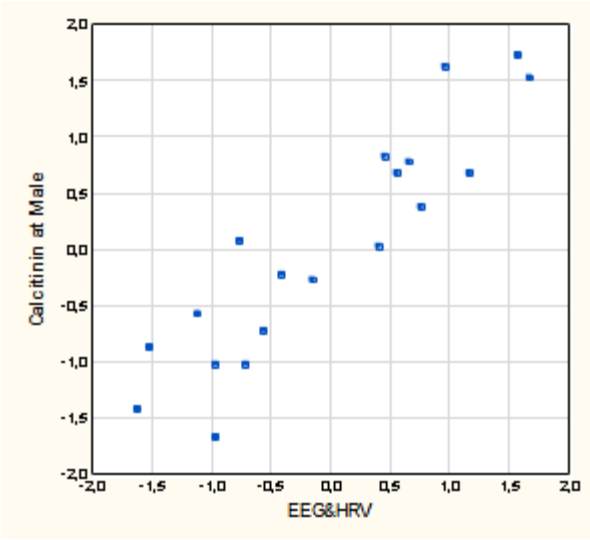


Fig. 20. Scatterplot of correlation between the PSD of β-rhythm in locus T4 (X-line) and Calcitonin plasma level (Y-line) at Male

Table 7. Regression Summary for Calcitonin at men
R=0,914; R^2=0,835; Adjusted R^2=0,670; $F_{(9,9)}$=5,1; p=0,012; SE: 2,22 ng/L

N=19		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(9)}$	p-level
Variables	r		Intercpt	-92,3	51,9	-1,78	0,109
C3 PSD Entropy	**0,54**	0,943	0,235	28,07	7,00	4,01	0,003
C4 PSD Entropy	**0,38**	-0,819	0,271	-18,79	6,23	-3,02	0,015
HR, beats/min	**0,47**	2,113	0,996	0,840	0,396	2,12	0,063
1/Mode HRV, msec^{-1}	**0,44**	1,324	0,971	0,041	0,030	1,36	0,206
Activity RS Index, un.	**0,43**	1,167	0,377	1,993	0,644	3,09	0,013
Stress Index HRV, un.	**0,35**	-0,650	0,305	-0,0215	0,0101	-2,13	0,062
F8-θ PSD, %	**0,40**	0,330	0,177	0,387	0,207	1,87	0,095
F4-θ PSD, μV^2/Hz	**0,35**	-0,903	0,309	-0,169	0,058	-2,92	0,017
T4-β PSD, %	**-0,52**	-0,272	0,180	-0,034	0,022	-1,52	0,164



R=0,914; R^2=0,835; $\chi^2_{(9)}$=22,5; p=0,007; Λ Prime=0,165
Fig. 21. Scatterplot of canonical correlation between the EEG&HRV parameters (X-line) and Calcitonin plasma level (Y-line) at Male

CONCLUSION

We hope that the results obtained in this study will supplement and specify the existing information about neuro-endocrine modulation and its sexual dimorphism normally and in a state of stress [32,39] in adults, perinatal programming of disorders of endocrine functions and behavior [51], the physiological essence of entropy [18] as well as relationships between neuro-endocrine parameters and parameters of acupuncture points and biophotonics [3-5,25,38].

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We express sincere gratitude to administration of clinical sanatorium “Moldova”, “Truskavets’ Spa” and “Truskavets’kurort” as well as Korolyshyn TA and Kikhtan VV for help in recording tests. Special thanks to the volunteers.

ACCORDANCE TO ETHICS STANDARDS

Tests in patients are carried out in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, 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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