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SEXUAL DIMORPHISM IN RELATIONSHIPS BETWEEN OF URICEMIA AND SOME PSYCHO-NEURO-ENDOCRINE PARAMETERS

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Abstract

Background. There is a hypothesis that urate is not only the end product of the metabolism of purines like adenosine, but even more a novel target for neuroprotection. The purpose of this study, conducted in line with this hypothesis, is to clarify the relationship between the level of uricemia and EEG/HRV parameters both in men and women. **Materials and Methods**. The object of observation were almost healthy volunteers: 30 females (30÷76; 49±13 y) and 31 males (24÷69; 47±12 y). In basal conditions we estimated the state of the autonomous regulation by the method HRV, recorded EEG, determined level of uric acid and testosterone as well as estimated level of the trait and reactive anxiety. After 4 or 7 days, repeated testing was performed. **Results**. The method of canonical correlation analysis revealed a strong urato-neural relationships in both men (R=0,709; R^2=0,503; Adjusted R^2=0,393) and women (R=0,812; R^2=0,659; Adjusted R^2=0,542). Moreover, in women, the factor structure of the neural root is almost completely different from that in men, and also includes reactive anxiety and HRV parameters, which are absent in the factor structure of men. In addition, significant differences were found between the profiles of urato-neural correlations of women of reproductive age and postmenopausal women. **Conclusion.** The level of uricemia is significantly related to a number of parameters of EEG, HRV and anxiety. The strength and even the direction of the correlations are determined by factors linked to gender.
Keywords: uricemia, EEG, HRV, anxiety, testosteroneemia, men, women.

INTRODUCTION

Uric acid (2,6,8-trioxipurine) is traditionally considered as the final product of human and primate DNA/RNA degradation, devoid of useful physiological activity.

During primate evolution a series of mutations occurred in the urate oxidase gene (*UOx*) likely accounting for the relatively high levels of urate (the physiologically dissociated form of uric acid) in apes and humans compared to other mammals (Oda et al., 2002). In the excellent review of Morelli et al. (2010) hypothesized that urate is not only the end product of the

metabolism of purines like adenosine, but even more a ***novel target for neuroprotection***. To substantiate their hypothesis, the authors cite a number of facts.

First of all, urates possesses antioxidant properties comparable to those of ascorbate (Ames et al., 1981) and accounts for most of the antioxidant capacity in human plasma (Yeum et al., 2004), supporting the hypothesis that our ancestors gained antioxidant benefits from *UOx* mutations and a resulting elevation of urate concentrations (Proctor, 1970). While higher levels of urate may have conferred an evolutionary advantage through bolstered defenses against oxidative damage (Ames et al., 1981) today they are also the core molecular culprit in gout and uric acid kidney stones. Sofaer & Emery (1981) as well as Efroimson (1987) considered hyperuricemia to be one of the factors of increased mental activity (even genius), based on the abnormally high incidence of gout and urolithiasis among prominent individuals.

In addition to its antioxidant actions, urate has also been shown to possess other potentially protective properties *in vitro*. It has been shown to scavenge peroxynitrite as well as oxygen free radicals *in vitro* (Whiteman et al., 2002; Franzoni et al., 2006) and displays potent iron-chelating activity independent of its direct antioxidant action (Davies et al., 1986).

Direct evidence for a neuroprotective effect of urate has come initially from cellular and animal models of multiple sclerosis (Hooper et al., 1997, 1998; Scott et al., 2002), stroke (Yu et al., 1998; Romanos et al., 2007) and spinal cord injury (Scott et al., 2002; Du et al., 2007).

Urate also confers protection in cellular models of Parkinson's disease (PD). In PC12 cells, urate blocked apoptosis and oxidant production induced by dopamine (Jones et al., 2000) or the pesticide rotenone in combination with homocysteine (Duan et al., 2002) and reduced cell death induced by MPP^+ or Fe^{2+} (Haberman et al., 2007). Urate also attenuated toxin-induced loss of primary neurons in culture. A recent study of dopaminergic neurons in primary midbrain culture of rat ventral mesencephalon found that their physiological function and survival were significantly enhanced by urate (Guerriero et al., 2009) at concentrations (≥30-50 μM) corresponding to those in human cerebrospinal fluid, associated with a reduced of clinical decline in PD (Ascherio et al., 2009).

When first considered in case-control studies, lower urate levels were found in serum (Larumbe et al., 2001; Annanmaki et al., 2007; Bogdanov et al., 2008; Johansen et al., 2009; Andreadou et al., 2009), possibly in cerebrospinal fluid (Tohgi et al, 1993), and in post-mortem nigrostriatal tissue samples (Church & Ward, 1994) of PD patients compared to those of controls. These studies suggested that low CNS as well as peripheral levels of urate are associated with PD.

A series of epidemiological investigations of prospectively followed cohorts has more incisively linked higher blood urate with a reduced risk of developing PD (Davis et al., 1996; De Lau et al., 2005; Weisskopf et al. 2007; Chen et al., 2009). For example, in the largest of these cohorts (18000 men were followed for more than 8 years in the HPFS), Weisskopf et al. (2007) found that those in the top quartile of plasma urate concentration had a 2- to 3-fold lower risk of PD than subjects in the bottom quartile ($p<0,02$ for trend across all quartiles). Amongst the subset of cases for whom blood was collected at least four years before the diagnosis of PD, an even greater reduction of PD risk was observed – with those in the highest urate quartile having a 5-fold lower risk of PD compared to the lowest quartile ($p<0,01$ for trend). This further analysis suggests that the low uricemia among individuals with PD precedes the onset of neurological symptoms and is thus unlikely to be a consequence of changes in diet, behavior, or medical treatment early in the course of the disease. This inverse association was independent of age, smoking, caffeine consumption and other aspects of lifestyle that have been related to PD or uricemia.

Similarly, urate-elevating diet was also associated with a lower risk of PD (Gao et al., 2008). The authors found that a higher dietary uricemic index (reflecting dietary patterns linked to higher plasma urate) predicted a reduced risk of developing PD ($p<0,001$ for trend). The

association between the index and PD risk remained strong and significant in models further adjusted for age, smoking and caffeine intake. Their findings suggest that dietary interventions that raise blood urate concentrations might reduce the risk of PD.

In a related set of epidemiological studies of large prospectively followed cohorts, a diagnosis of gout (a form of arthritis due to urate crystallization in joints and associated with hyperuricemia) was linked to a lower risk of later being diagnosed with PD (Alonso et al., 2007; De Vera et al., 2008). Together these epidemiological data establish urate exposure – assessed by laboratory, dietary or pathological indicators – as a robust inverse risk factor for PD.

The emergence of robust epidemiological data linking higher urate levels amongst healthy populations to a reduced risk of developing PD, prompted a corollary hypothesis*:* Amongst people already diagnosed with PD, do higher urate levels predict a slower rate of clinical decline? To test the hypothesis, incidentally measured urate levels in two large completed 'neuroprotection' trials were related to rates of clinical decline over years. Although neither the PRECEPT (Parkinson Study Group, 2007) nor the DATATOP (Parkinson Study Group, 1993) trial had demonstrated efficacy of candidate neuroprotectants, each had collected data for routine safety lab tests -- including serum urate -- at enrollment of some 800 recently diagnosed '*de novo*' PD patients, who were then followed closely for two years. For both trials the primary outcome was time to disability warranting the initiation of levodopa or dopaminergic agonist therapy, with secondary outcomes including rate of UPDRS change and, in the case of the PRECEPT trial, rate of loss of dopamine transporter (DAT) ligand uptake in the striatum.

In the PRECEPT cohort, subjects with higher (but still normal) levels of serum urate at baseline were significantly less likely to develop disability warranting dopaminergic therapy and also retained significantly more striatal DAT binding capacity during the study (Schwarzschild et al., 2008). For example, subjects in the top quintile of serum urate (~7-8 mg/dL with normal value reference ranges typically 3-8 mg/dL) reached the end point at only half the rate of subjects in the lowest quintile (*p* for trend <0,001). In the DATATOP cohort higher baseline urate concentrations in CSF as well as in serum were similarly associated with a slower rate of reaching the primary disability endpoint (Ascherio et al., 2009). In both cohorts higher urate levels were also predictive of a favorable rate of clinical decline measured by the change in UPDRS score. Although several descriptive clinical features of PD have been identified as probable predictors of the rate of clinical decline in PD (Post et al., 2007), urate may be the first molecular factor clearly linked to clinical progression of idiopathic PD.

On the other hand, Morelli et al. (2010) cite the epidemiological evidence that consumption of caffeine (2,6-dioxi-1,3,7-trimethylpurine), a non-specific A_1/A_{2A} receptor antagonist, also is associated with a reduced the risk of developing PD (Ascherio et al., 2001; Schwarzschild et al., 2003b).

Considerable epidemiological and laboratory data have suggested that A_{2A} receptor blockade by caffeine, a nonselective adenosine receptor antagonist, may protect against the underlying neurodegeneration of PD. Drinking caffeinated beverages (coffee and to a lesser extent tea) has emerged as the dietary factor most consistently linked to an altered risk of PD, with greater consumption associated with a reduced risk (Hellenbrand et al., 1996; Fall et al., 1999; Benedetti et al., 2000; Ross et al., 2000; Ascherio et al., 2001; Checkoway et al., 2002; Ragonese et al., 2003; Tan et al., 2003; Hu et al., 2007). In the early 90's case-control studies suggested a reduced risk of developing PD associated with drinking coffee but the reduction either was not statistically significant (Jimenez-Jimenez et al., 1992; Morano et al., 1994), or was significant but partially attributable to the confounding association of smoking in coffee drinkers (Grandinetti et al., 1994) and thus difficult to interpret. Following on from this, larger, case-control studies, using better-matched cohorts demonstrated that even after adjusting for tobacco smoking and other potential confounding factors, the significant inverse relationship between prior coffee drinking exposure and PD remained (Hellenbrand et al., 1996; Fall et al.,

1999; Benedetti et al., 2000). These latter studies also specifically investigated dose-response relationships, with increasing coffee consumption (measured in cups per day) associated with decreasing likelihood of having developed PD. In these retrospective analyses PD patients were 4 to 8 times less likely than control subjects to have reported being heavy coffee drinkers in the past. While case control studies have some advantages, weaknesses of these designs for investigating dietary etiology of chronic diseases are well known (Willett, 1998) and include for example difficulty selecting appropriate control subjects and recall bias. The introduction of large cohort prospective investigations (see below) has overcome many of these limitations through follow-up evaluations to determine disease incidence in subjects from a single population in which the exposure in question (i.e., coffee or caffeine consumption) had been reported years earlier.

Relatively few studies have considered the effect of tea drinking and its association with PD risk. This could be attributed to its low consumption in North America and Europe (Ascherio et al., 2001; Chan et al., 1998). These studies usually (Ho et al., 1989; Hellenbrand et al., 1996; Ayuso-Peralta et al., 1997; Chan et al., 1998; Checkoway et al., 2002; Tan et al., 2003, 2007), although not always (Preux et al., 2000), indicated a reduced risk of developing PD amongst frequent tea drinkers. Interestingly, epidemiological studies from China have observed that the prevalence of PD is much lower than in the Caucasian population (Li et al., 1985; Zhang et al., 1993). Barranco et al. (2009) reviewed observational studies that evaluated tea consumption and the risk of PD (11 case-control and 1 cohort) between 1981 and 2003. The studies represented documented cases from North America, Europe and Asia. Amongst the case-control studies, the pooled OR was 0,8 suggesting that tea consumption is inversely associated with the risk of PD. It is unclear whether the active ingredient(s) mediating this observed protective effect is caffeine or some biologically active substance(s) present in tea but not coffee.

More convincing epidemiological evidence that caffeine as well as coffee consumption are linked to a reduced risk of developing PD has been obtained from the study of prospectively followed, large populations (Ross et al., 2000; Ascherio et al., 2001). Three decades after ~8000 Japanese-American men were enrolled in the Honolulu Heart Program (and provided details of their dietary caffeine consumption), over 100 had gone on to develop PD. Higher initial coffee intake was dose-dependently associated with a reduced incidence of PD, with a 5-fold lower risk amongst those who drank over 24 oz per day (Ross et al., 2000). Confirmation of these findings was provided by two prospective studies of larger, multiethnic populations, namely the Health Professionals Follow-up Study (HPFS) of 50 000 men followed for a period of 10 years, and the Nurses Health Study (NHS) of 90 000 women followed over 16 years (Ascherio et al., 2001). Amongst the men, increased coffee, tea and non-coffee caffeine consumption, as well as total caffeine consumption were all significantly, dose-dependently and negatively correlated with the incidence of subsequent PD. These associations were independent of smoking and other potential confounding factors. By contrast, the rates of consuming *decaffeinated* coffee were unrelated to the risk of PD, implicating caffeine as the component in coffee that is inversely associated with PD risk. Similar findings were observed in 2 separate cohort studies of Finnish men and women free from PD at baseline (Hu et al., 2007; Saaksjarvi et al., 2008). Heavier coffee consumption was associated with a reduced risk of PD even after adjustment for confounding factors. The Finnish population is of particular interest since it exhibits one of the world's highest rates of coffee consumption (Fredholm et al., 1999).

Interestingly, a stark gender difference in how caffeine relates to PD risk emerged from comparison of female and male cohorts within a large protective study of health care workers (Ascherio et al., 2001). Initially, analysis of women in the NHS study revealed no clear relationship between PD and caffeine or coffee intake. This gender difference was consistent with the observations of PD incidence rates in Olmstead County, MN, which were strongly

inversely related to prior coffee drinking in men (with a ~17-fold reduction in risk amongst drinkers vs. non drinkers; p<0,01) but did not vary with coffee exposure in women (with a relative risk of 1.0; Benedetti et al., 2000). Ascherio et al. (2001) gained insight upon stratification of the women by estrogen exposure history. In two separate prospective studies (Ascherio et al., 2003, 2004) they showed 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.

Interestingly, in contrast to the result from studies by Ascherio et al. (2001), the two prospective cohort studies of Finnish populations (Hu et al., 2007; Saaksjarvi et al., 2008) reported no gender differences in the (inverse) relationship between coffee consumption and PD risk. However as Saaksjarvi and colleagues note in their study, the effect of postmenopausal hormone use could not be examined due to small number of users, which was reported to be ~5% of women and markedly less than in the US cohorts. For example in the NHS, a third of the women were currently taking postmenopausal estrogens and 54% reported ever taking them. Thus, the variability in an overall association between caffeine and PD risk among women between cohorts may be explained by wide variation in their use of postmenopausal estrogen, which appears to complicate the relationship between caffeine and PD.

Recent laboratory experiments have explored the biology that may underlie gender differences in the caffeine-PD link observed in populations with higher rates of estrogen use. Xu et al. (2006) found that the ability of caffeine to attenuate MPTP toxicity in a mouse model of PD was greater in male *versus* female mice, and in ovariectomized *versus* sham-operated female mice. They also demonstrated that chronic estrogen replacement undermined caffeine's protective effect both in male and in ovariectomized female mice, providing direct evidence of a hormonal influence on caffeine's neuroprotective properties in lab animals. The study also implicated a biological basis for the gender difference in the association between caffeine consumption and PD risk. In general, these and other laboratory studies (as reviewed above) support - but do not prove - the hypothesis that the consistent epidemiological association between caffeine and a reduced risk of PD is causal. Recent laboratory experiments have explored the biology that may underlie gender differences in the caffeine-PD link observed in populations with higher rates of estrogen use. Xu et al. (2006) found that the ability of caffeine to attenuate MPTP toxicity in a mouse model of PD was greater in male *versus* female mice, and in ovariectomized *versus* sham-operated female mice. They also demonstrated that chronic estrogen replacement undermined caffeine's protective effect both in male and in ovariectomized female mice, providing direct evidence of a hormonal influence on caffeine's neuroprotective properties in lab animals. The study also implicated a biological basis for the gender difference in the association between caffeine consumption and PD risk. In general, these and other laboratory studies (as reviewed above) support – but do not prove - the hypothesis that the consistent epidemiological association between caffeine and a reduced risk of PD is causal.

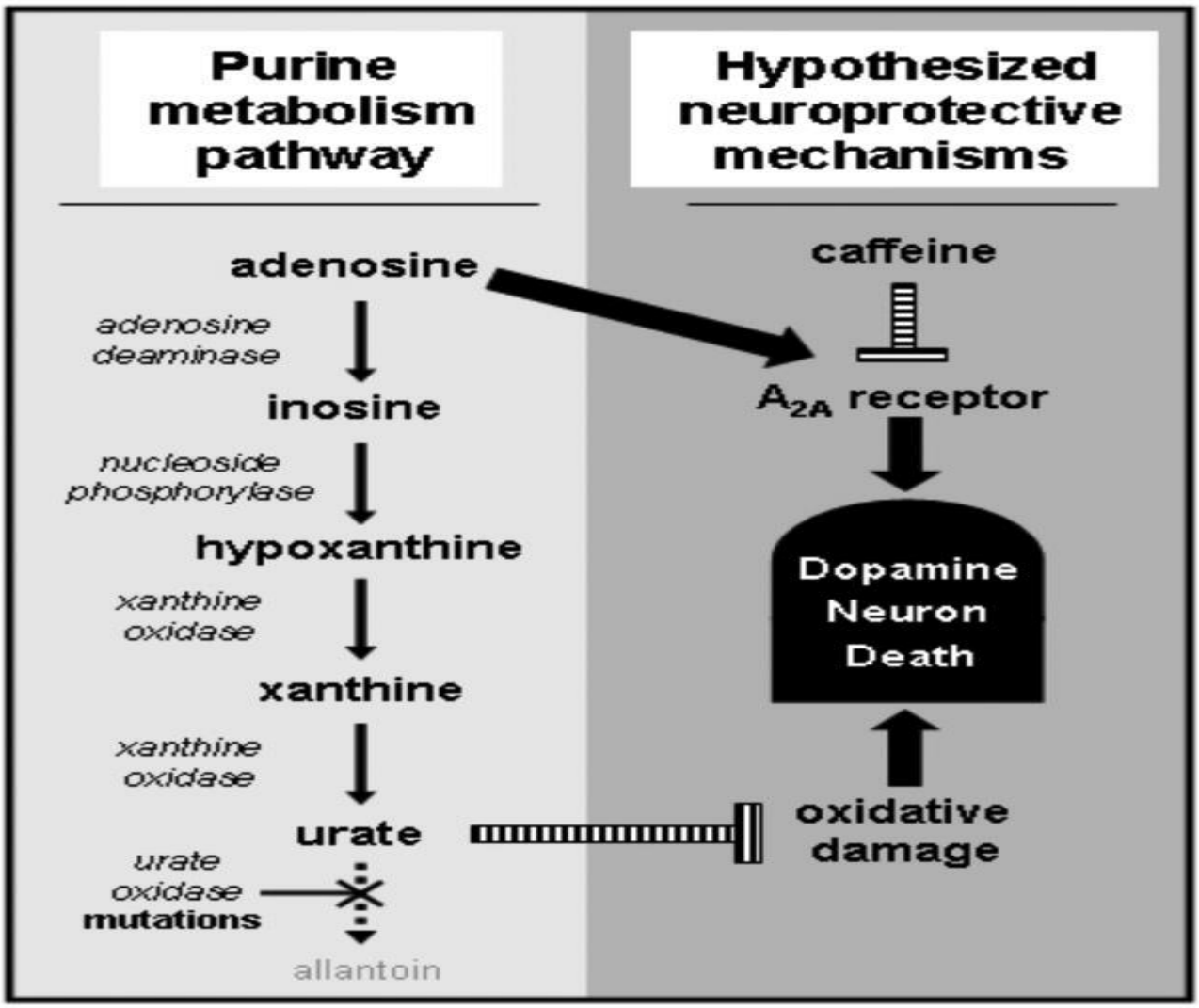
Theophylline, a demethylation metabolite of caffeine as well as an anti-asthmatic agent in common use, is also a non-specific adenosine antagonist. Although small open-label trials of theophylline in PD seemed to suggest antiparkinsonian benefit without exacerbation of dykinesias (Mally & Stone, 1994; Kostic et al., 1999), a subsequent double-blind, placebo-controlled trial of theophylline in PD did not clearly demonstrate relief from symptoms (Kulisevsky et al., 2002). However, the power and design of all these trials like the earlier caffeine studies in PD were not sufficient to rule out clinically useful symptomatic effects, as have been suggested by long-standing preclinical studies of motoric enhancement in PD models (Stromberg & Waldeck, 1973).

Convergent laboratory studies investigating the effect of caffeine and more specific adenosine receptor antagonists suggested that blockade of the A_{2A} receptor subtype prevents nigrostriatal degeneration in several models of PD (Schwarzschild et al., 2006).

An early suggestion of the neuroprotective potential of A_{2A} receptor blockade in PD came with the demonstration that caffeine can attenuate the loss of striatal dopamine induced by acute MPTP administration in mice (Chen et al., 2001). Therefore, blockade of the A_{2A} receptor seems to confer a functional protection of striatal dopamine transmission, as well as to prevent the loss of nigral dopaminergic neurons induced by neurotoxin exposure.

Despite considerable evidence suggesting the neuroprotective potential of A_{2A} receptor blockade in PD, the underlying mechanism is still a matter of debate. In neurons, A_{2A} adenosine receptors have been identified both pre- and post-synaptically, where they control neurotransmitter release and neuronal stimulation, respectively (Schiffman et al., 1991; Rosin et al., 1998; Svenningsson et al., 1999; Rebola et al., 2005). Moreover, cells involved in the neuroinflammatory response such as astroglia, microglia and bone marrow-derived cells all express the A_{2A} receptor (Fiebich et al., 1996; Saura et al., 2005).

Morelli et al. (2010) visualized their hypothesis about the neuroprotective effect of urate and caffeine in the following scheme.



Therapeutic targets along the purine metabolic pathway. Adenosine A_{2A} antagonists (including caffeine) and urate have emerged as realistic candidate neuroprotectants. In humans the enzymatic metabolism of purines such as adenosine ends with urate due to multiple mutations

within the *urate oxidase* gene during primate evolution. The schematic suggests a possible homeostatic mechanism linking an adenosinergic neurodegenerative influence with an offsetting neuroprotective influence of urate (Morelli et al., 2010).

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 (Pousti A et al., 2004) back in 2004 led our group (Ivassivka, Popovych, Aksentiychuk and Flyunt, 2004) 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***.

Observing 66 women and 298 men treated at the Truskavets' spa (Ukraine), authors found a wide range of physiological activity of endogenous uric acid. In particular, they found the connections between balneotherapy-induced changes in the level of uricemia, on the one hand, and the parameters of heart rate variability and hemodynamics, on the other hand. The obtained results allowed authors to assume that the uric acid molecule has physiological activity, which is realized by blocking both A_1 and A_{2A} adenosine receptors, as well as modulating phosphodiesterase, Na, K-ATPase activity and Na/Ca exchanger.

The cited study is not without its limitations. In particular, the neurotropic activity of uric acid was evaluated only by the Baevskiy's parameters of HRV (Mode, AMo, MxDMn), ignoring the CNS (due to the lack of a device for electroencephalography).

Literature data and obtaining long-awaited devices for EEG and HRV registration allows us to offer a topic for future research: "***Neurotropic activity of endogenous uric acid***".

The proposed article is the first swallow of the announced project.

MATERIALS AND METHODS

The object of observation were almost healthy volunteers, employees of the sanatorium "Moldova" and PJSC "Truskavets' SPA": 30 females (30÷76; 49±13 y) and 31 males (24÷69; 47±12 y).

In basal conditions we estimated the state of the autonomous regulation by the method heart rate variability (HRV) (Baevskiy et al, 2001; HRV, 1996; Berntson et al., 1997), using a hardware-programmatic complex "CardioLab+HRV" (KhAI MEDICA, Kharkiv, Ukraine). The following parameters were subject to analysis. Frequency Domain Methods: absolute ($msec^2$) and relative (%) spectral power (SP) of HF (0,4÷0,15 Hz), LF (0,15÷0,04 Hz), VLF (0,04÷0,015 Hz) and ULF (0,015÷0,003 Hz) bands. Time Domain Methods: HR, Mode, Ttiangular Index, SDNN, RMSSD and pNN_{50}. Calculated also LF/HF, (VLF+LF)/HF and LFnu ratio as well as Baevskiy's Activity of Regulatory Systems Index (BARSI).

Simultaneosly with HRV we recorded EEG a hardware-software complex "NeuroCom Standard" (KhAI MEDICA, Kharkiv) 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 tassels on the ears. The duration of the epoch was 25 sec. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), coefficient of asymmetry (%), absolute (μV^2/Hz) and relative (%) power spectral density (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 Laterality Index (LI) for PSD each Rhythm using formula (Newberg et al., 2001):

$LI, \% = \Sigma\ [200 \bullet (Right - Left)/(Right + Left)]/8$

We calculated also for HRV and each locus EEG the Entropy (h) of normalized PSD using Popovych's formulas (Ruzhylo et al., 2015) based on classic Shannon's (1948) formula:

$hHRV=- [SPHF•\log_2 SPHF+SPLF•\log_2 SPLF+SPVLF•\log_2 SPVLF+SPULF•\log_2 SPULF]/\log_2 4$
$hEEG = - [PSD\alpha•\log_2 PSD\alpha+PSD\beta•\log_2 PSD\beta+PSD\theta•\log_2 PSD\theta+PSD\delta•\log_2 PSD\delta]/\log_2 4$

The serum level of the Uric acid by uricase method were determined. The analyzes were carried out according to the instructions described in the manual (Goryachkovskiy, 1996). The analyzer "Pointe-180" ("Scientific", USA) were used with appropriate set.

We determined also plasma level of Testosterone (by the ELISA with the use of analyzer "RT-2100C" and corresponding set of reagents from XEMA Co., Ltd).

At last volunteers filled a questionnaire with the purpose of estimation of level of the trait and reactive anxiety (Practical …, 1998).

After 4 (in 11 men and 10 women) or 7 (in 10 men and 10 women) days, repeated testing was performed.

Results processed by using the software package "Statistica 5.5".

RESULTS AND DISCUSSION

One of the basic approaches for assessing the physiological activity of uric acid is correlation-regression analysis of its relationships with the parameters of interest, in particular EEG, HRV and anxiety.

Given the known sexual dimorphism of these parameters (Abhishekh et al., 2013; Clarke et al., 2001; Nugent et al., 2011; Reznikov et al., 2001; 2004; Sacher et al., 2013; Stevens & Hamann, 2012), men and women were analyzed separately.

At the first stage, correlations of uricemia with registered parameters in men was screened.

According to calculations by the formula:

$|r| = \{\exp[2t/(n - 1,5)^{0,5}] - 1\}/\{\exp[2t/(n - 1,5)^{0,5}] + 1\}$

for a sample of n=62 critical value |r| at $p<0,05$ ($t>2,00$) is 0,252; at $p<0,01$ ($t>2,66$) is 0,329; at $p<0,001$ ($t>3,46$) is 0,418.

As we can see (Table 1), there is no HRV parameter or anxiety in the correlation matrix. At the same time, concomitant correlation coefficients with EEG parameters of age and testosteroneemia were introduced into the matrix.

In the second stage, by stepwise exclusion to reach a maximum of Adjusted R^2, in the regression model for uricemia 11 EEG parameters were included, including 3, despite very low correlation coefficients, while some parameters with significant coefficients were found outside the model. Such constellation of EEG parameters is determined by uricemia on 50,3% (Table 2 and Fig. 1).

In the examined sample of men, no relationship between uricemia and age was found (Fig. 2), instead, a weak but statistically significant direct relationship with testosteroneemia was found (Fig. 3), which, in turn, is inversely related to age at the limit of significance (Table. 1). The complex effect on the level of uricemia of testosterone and age-related factors was found to be very weak, although statistically significant (Fig. 4).

This conclusion is confirmed by the results of the canonical analysis: the additional inclusion in the set of factors of testosterone and age (Table 3) increases the degree of determination of the set of EEG parameters by only 3,6% (Fig. 5).

In women, unlike men, the screening revealed, firstly, significant relationships of uricemia with HRV parameters and the level of reactive (but not trait) anxiety, and secondly, a completely different set of EEG parameters (only relative PSD C4β is a common parameter) (Table 4).

The rate of uricemia determination of the constellation of psycho-neural parameters increased in women to 65,9% (Table 5 and Fig. 3) against 50,3% in men.

In addition, the relationship between uricemia and testosteroneemia was found to be somewhat stronger in women than in men: 0,416 vs 0,341 (Fig. 4), while (at first glance) there is no relationship with age either (Fig. 5).

The complex effect on the level of uricemia of testosterone and age-related factors was found to be very weak too (Fig. 6), barely stronger than in men (R^2 0,211 vs 0,136).

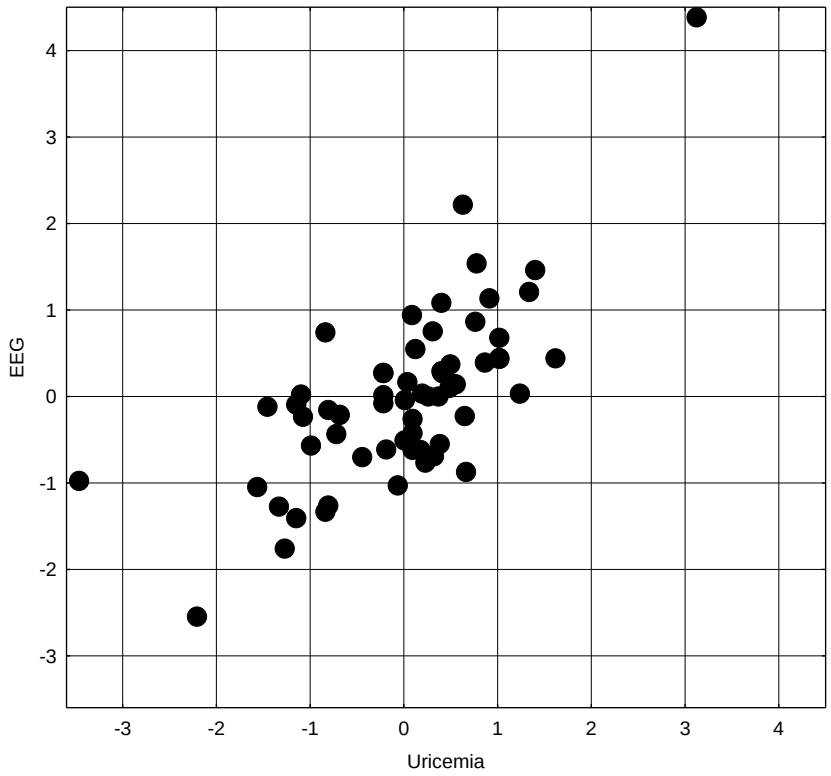
Table 1. Matrix of correlations for Males

Variable	Correlations for men		
	UA	Age	Testost
Uric Acid	1,000	0,050	0,341
Age	0,050	1,000	-0,251
Testosterone	0,341	-0,251	1,000
Deviation A	0,226	0,034	0,142
Asymmetry D	0,229	0,138	0,002
FP1H	0,345	0,115	0,025
FP1D	-0,295	0,115	-0,052
FP2H	0,315	-0,024	0,083
FP2D	-0,263	0,118	-0,069
F7A%	0,256	-0,262	0,209
F7T%	0,289	0,147	0,124
F7D%	-0,303	0,070	-0,045
T3H	0,357	-0,027	0,058
T4T%	0,231	0,043	0,156
C4B%	-0,253	0,201	-0,136
C4T	0,264	-0,059	0,251
T5H	0,232	0,149	-0,090
T6H	0,300	-0,065	0,009
T6A%	0,298	-0,355	0,277
T6D%	-0,331	0,175	-0,068
P4B%	-0,299	0,150	-0,302
O1H	0,296	0,253	0,048
O1D	-0,333	0,169	-0,153
O2D	-0,224	0,064	-0,048

Table 2. Regression Summary for Uricemia at Males

R=0,709; R^2=0,503; Adjusted R^2=0,393; $F_{(11,5)}$=4,6; p=0,00008

N=62		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(50)}$	p-level
Variables	r		Intercpt	187,9	64,2	2,93	0,005
T3 PSD Entropy	**0,357**	0,236	0,182	83,694	64,762	1,29	0,202
O1 PSD Entropy	**0,296**	0,137	0,153	49,117	54,975	0,89	0,376
F7-θ PSD, %	**0,289**	-0,181	0,172	-2,415	2,287	-1,06	0,296
C4-θ PSD, μV^2/Hz	**0,264**	0,136	0,133	0,330	0,323	1,02	0,312
δ-rhythm Asymmetry, %	**0,229**	0,348	0,107	0,838	0,258	3,24	0,002
α-rhythm Deviation, Hz	**0,226**	0,300	0,113	40,146	15,060	2,67	0,010
O1-δ PSD, μV^2/Hz	**-0,333**	-0,226	0,154	-0,030	0,020	-1,47	0,148
F7-δ PSD, %	**-0,303**	-0,273	0,159	-0,602	0,350	-1,72	0,092
P4-β PSD, %	**-0,299**	-0,343	0,117	-1,997	0,678	-2,95	0,005
Fp1-δ PSD, μV^2/Hz	**-0,295**	-0,223	0,172	-0,016	0,013	-1,30	0,199
O2-δ PSD, μV^2/Hz	**-0,224**	0,353	0,175	0,033	0,016	2,02	0,049



R=0,709; R^2=0,503; $\chi^2_{(11)}$=38; $p<10^{-4}$; Λ Prime=0,497

Fig. 1. Scatterplot of canonical correlation between Uricemia (X-line) and EEG parameters (Y-line) at Males

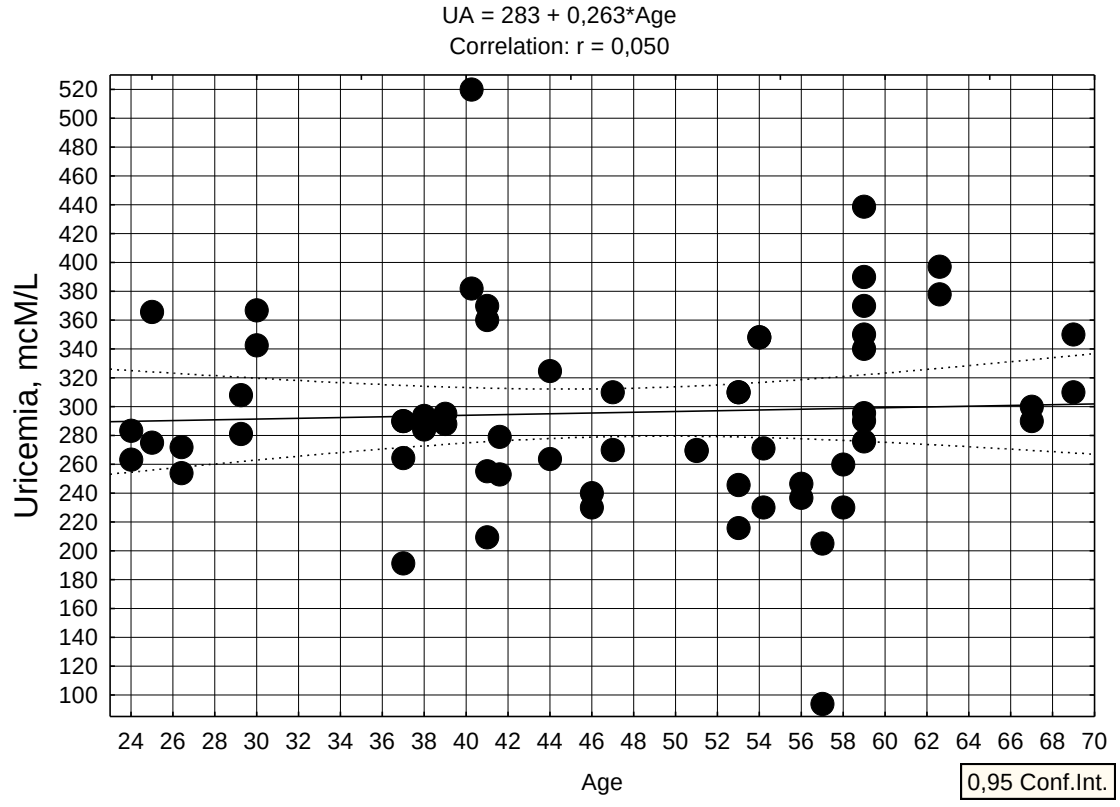


Fig. 2. Scatterplot of correlation between Age (X-line) and Uricemia (Y-line) at Males

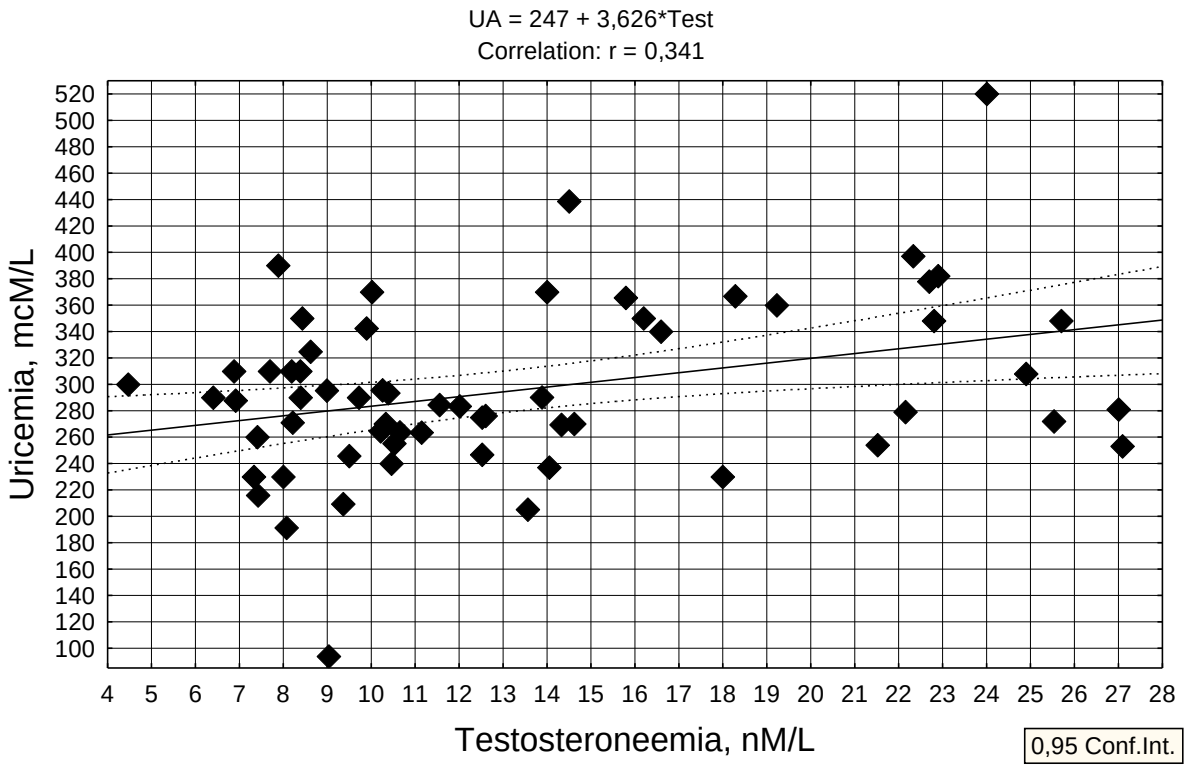
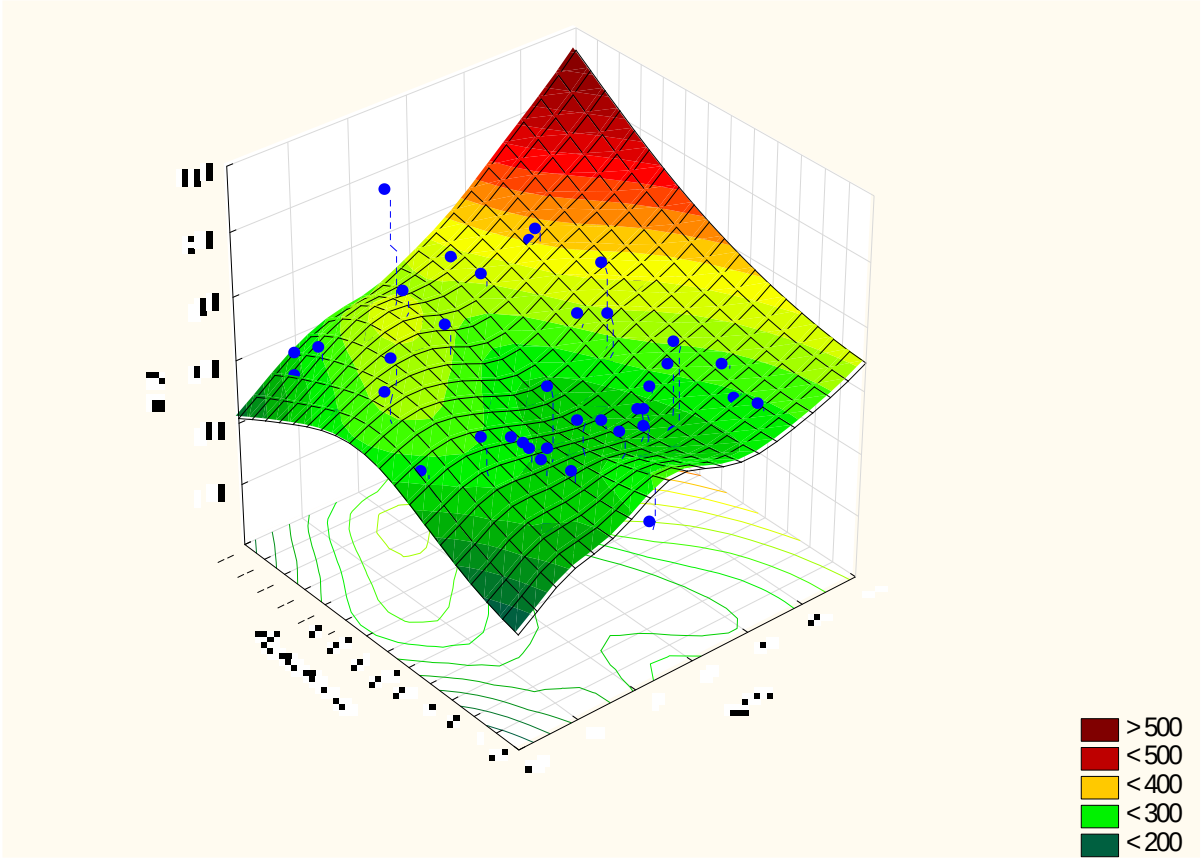


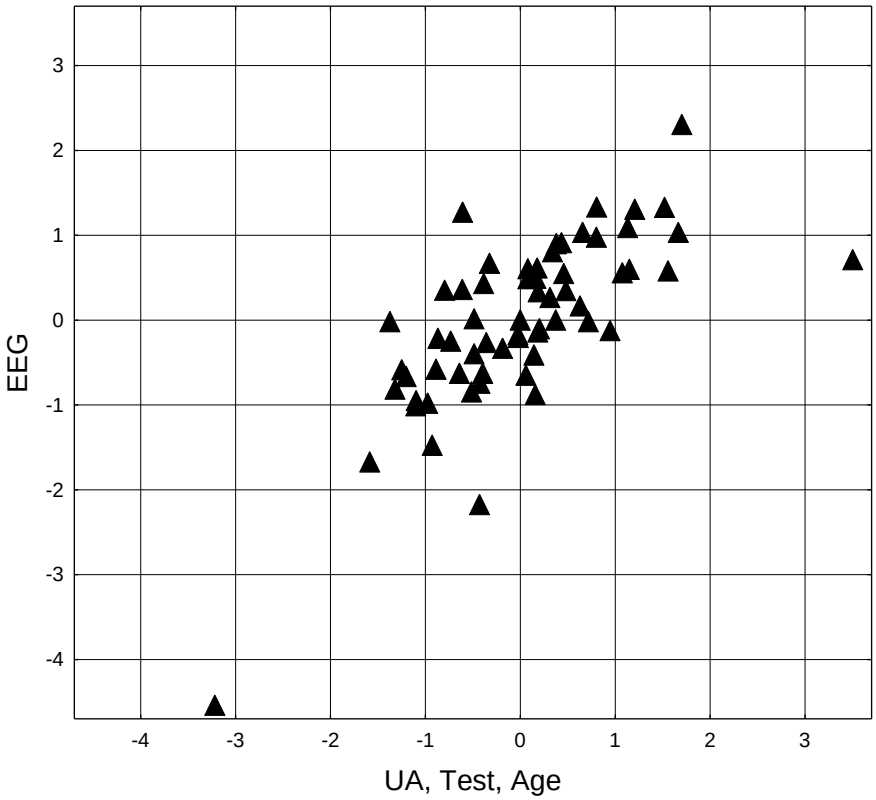
Fig. 3. Scatterplot of correlation between Testosteroneemia (X-line) and Uricemia (Y-line) at Males



UA = 206 + 4,01*Test + 0,758*Age
R=0,368; R^2=0,136; $F_{(2,6)}$=4,6; p=0,014
Fig. 4. Quadratic surface Age (X-line), Testosteroneemia (Y-line), Uricemia (Z-line) at Men

Table 3. Factor load on canonical roots of parameters

Left site	R
Uric Acid, μM/L	0,925
Testosterone, nM/L	0,462
Age, years	-0,329
Right site	R
T3 PSD Entropy	0,467
F7-θ PSD, %	0,301
α-rhythm Deviation, Hz	0,278
O1 PSD Entropy	0,252
δ-rhythm Asymmetry, %	0,220
O1-δ PSD, $\mu V^2/Hz$	-0,514
P4-β PSD, %	-0,473
Fp1-δ PSD, $\mu V^2/Hz$	-0,432
F7-δ PSD, %	-0,419
O2-δ PSD, $\mu V^2/Hz$	-0,318



R=0,734; R^2=0,539; $\chi^2_{(33)}$=65; p=0,0007; Λ Prime=0,297

Fig. 2. Scatterplot of canonical correlation between Uricemia, Testosteroneemia and Age (X-line) and EEG parameters (Y-line) at Males

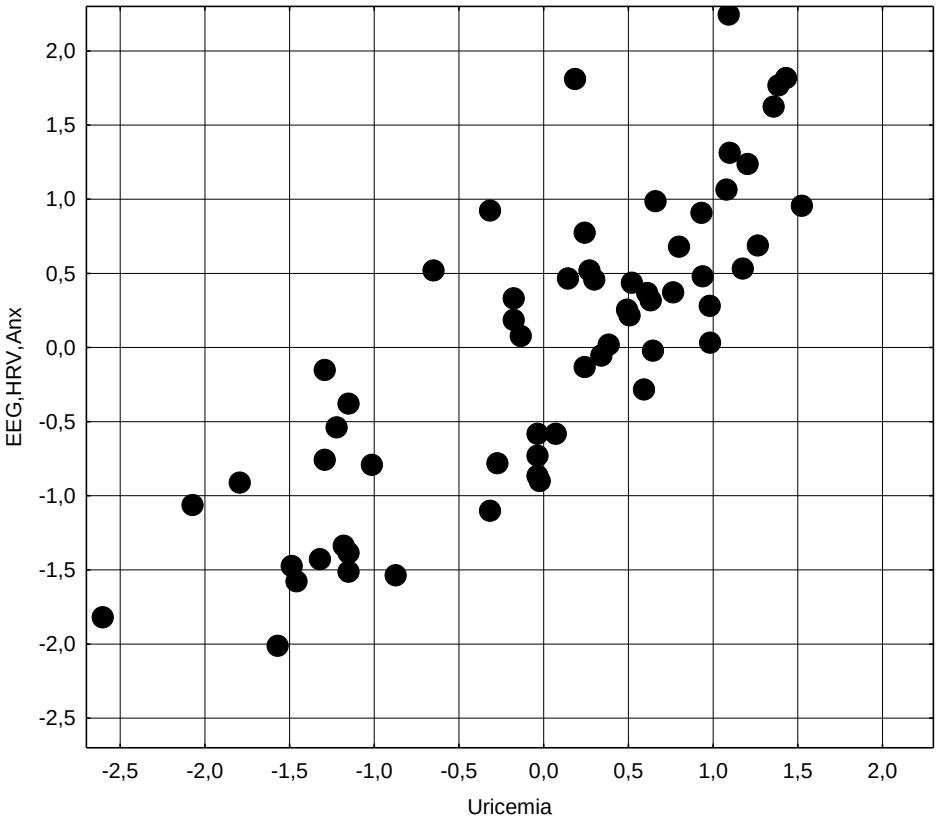
Table 4. Matrix of correlations for Females

Variable	Correlations for women		
	UA	Age	Test act
UA	1,000	0,148	0,416
Age	0,148	1,000	-0,107
Testosterone	0,416	-0,107	1,000
AT	0,252	0,047	0,337
LIB	0,243	-0,085	0,164
LIA	0,284	-0,265	0,167
LIT	0,232	-0,100	0,115
LID	0,329	-0,028	0,285
FP1B	-0,230	0,595	-0,144
F3T%	0,243	-0,077	-0,072
F3B	-0,281	0,521	-0,081
F4B	-0,241	0,507	-0,176
F8T%	0,264	-0,098	-0,006
T3B	-0,223	0,256	-0,164
T4B%	-0,229	0,039	-0,013
C4B%	-0,270	0,132	-0,028
C4D	0,207	0,165	0,234
T5T%	0,233	0,129	-0,007
T5B	-0,306	0,327	-0,171
T6T%	0,264	0,108	-0,136
P3B	-0,223	0,436	-0,208
O1T%	0,278	0,025	-0,009
O2T%	0,270	0,201	-0,057
O2T	0,229	0,428	-0,086
Reac Anxiety	-0,382	0,032	-0,275
BARSI	-0,236	0,037	-0,090
Mode	0,302	0,211	-0,209
HR	-0,319	-0,255	0,180
LF/HF	-0,337	0,009	-0,030
LF%	-0,351	-0,240	-0,018
LFNU	-0,402	-0,003	0,009

Table 5. Regression Summary for Uricemia at Females
R=0,812; R^2=0,659; Adjusted R^2=0,542; $F_{(15,4)}$=5,7; $p<10^{-5}$

N=60		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(44)}$	p-level
Variables	r		Intercpt	479	57	8,33	10^{-6}
LFnu, %	**-0,402**	-0,129	0,109	-0,711	0,603	-1,18	0,244
Reactive Anxiety, points	**-0,382**	-0,365	0,117	-3,644	1,171	-3,11	0,003
LF PSD, %	**-0,351**	-0,326	0,102	-1,534	0,481	-3,19	0,003
Heart Rate, beats/min	**-0,319**	-0,174	0,110	-1,110	0,699	-1,59	0,119
F3-β PSD, μV^2/Hz	**-0,281**	0,327	0,254	0,349	0,271	1,29	0,205
C4-β PSD, %	**-0,270**	0,253	0,178	1,680	1,177	1,43	0,161
Baevski ARS Index, points	**-0,236**	-0,151	0,101	-4,482	3,000	-1,49	0,142
Fp1-β PSD, μV^2/Hz	**-0,230**	-0,262	0,217	-0,302	0,251	-1,20	0,235
T4-β PSD, %	**-0,229**	-0,217	0,157	-1,163	0,839	-1,39	0,173
T3-β PSD, μV^2/Hz	**-0,223**	-0,366	0,157	-0,275	0,118	-2,34	0,024
δ-rhythm Laterality, %	**0,329**	0,143	0,114	0,301	0,240	1,25	0,216

O1-θ PSD, %	**0,278**	0,174	0,124	2,569	1,830	1,40	0,169
F8-θ PSD, %	**0,264**	0,263	0,128	3,514	1,712	2,05	0,046
θ-rhythm Asymmetry, %	**0,252**	0,144	0,107	0,474	0,351	1,35	0,183
C4-δ PSD, $\mu V^2/Hz$	**0,207**	0,141	0,106	0,010	0,008	1,33	0,190



R=0,812; R^2=0,659; $\chi^2_{(15)}$=54; p<10^{-5}; Λ Prime=0,341

Fig. 3. Scatterplot of canonical correlation between Uricemia (X-line) and EEG, HRV and Anxiety parameters (Y-line) at Females

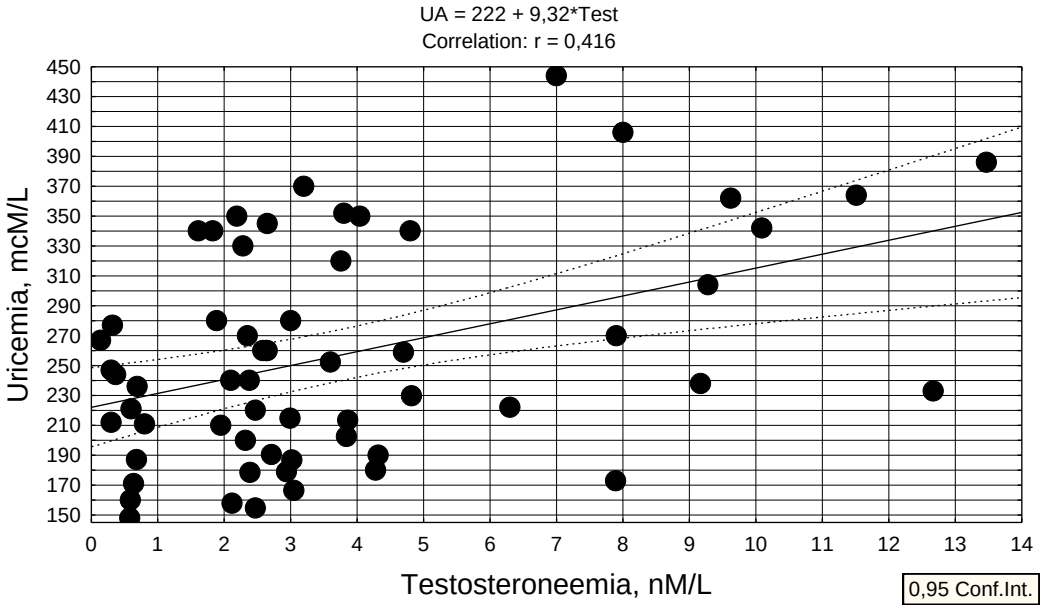


Fig. 4. Scatterplot of correlation between Testosteroneemia (X-line) and Uricemia (Y-line) at Females

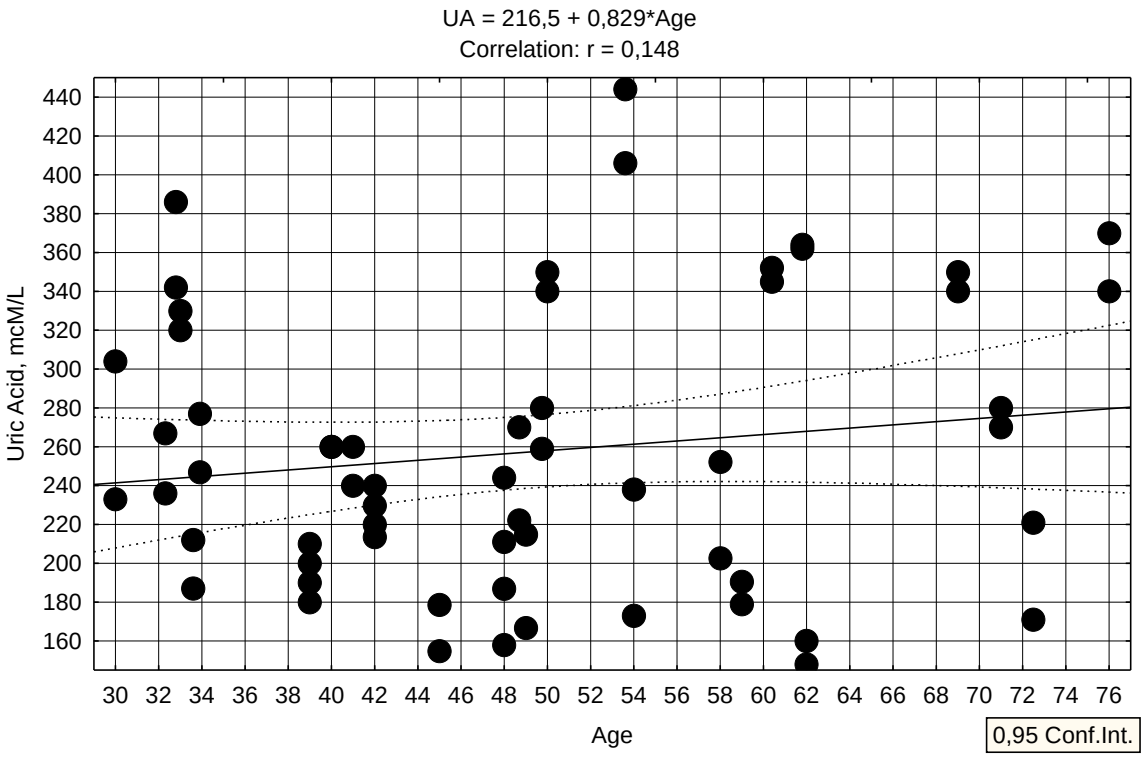
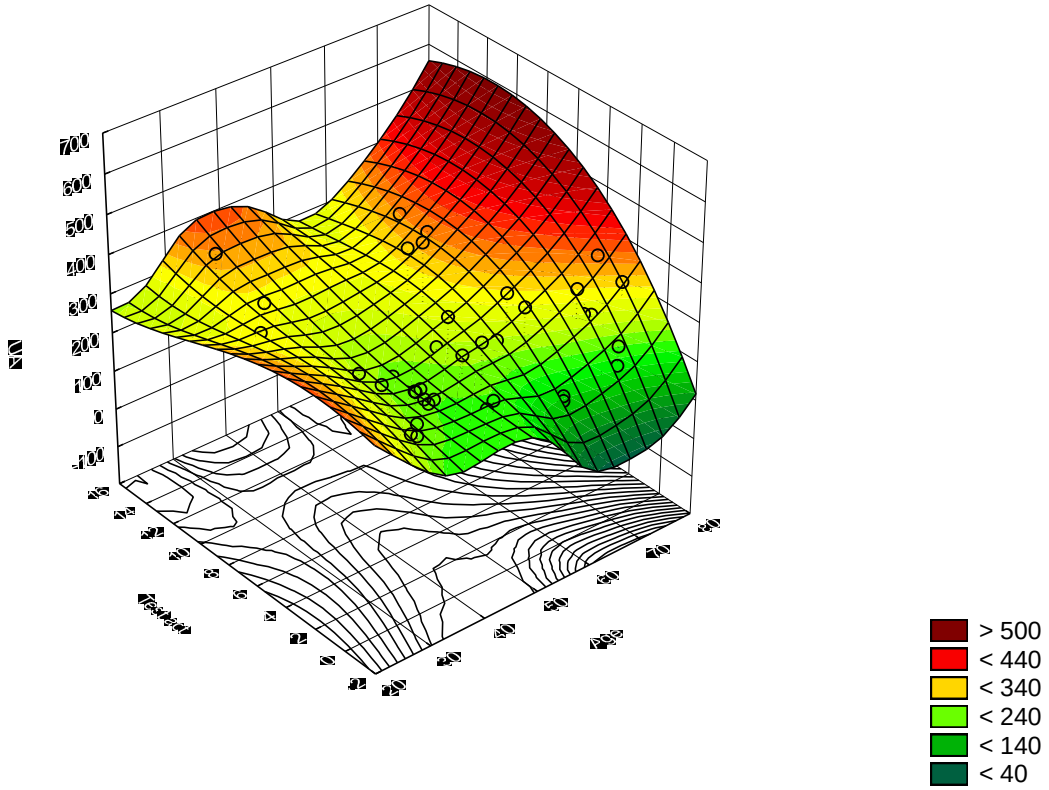


Fig. 5. Scatterplot of correlation between Age (X-line) and Uricemia (Y-line) at Females

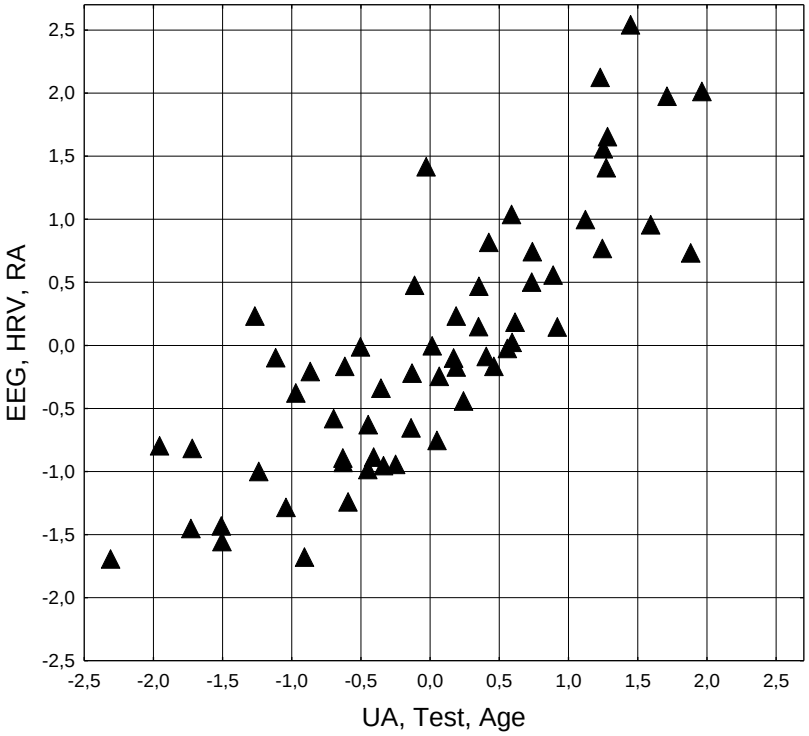


UA = 167 + 9,79*Test + 1,091*Age
R=0,459; R^2=0,211; $F_{(2,6)}$=7,6; p=0,0012
Fig. 6. Quadratic surface Age (X-line), Testosteroneemia (Y-line), Uricemia (Z-line) at Women

Accordingly, the additional increase in the determination of psycho-neural parameters was only 2,3% (68,2 % vs 65,9%) (Table 6 and Fig. 7).

Table 6. Factor load on canonical roots of parameters at Females

Left site	R
Uric Acid, μM/L	-0,876
Testosterone, nM/L	-0,312
Age, years	0,325
Right site	R
F3-β PSD, $μV^2$/Hz	0,641
Fp1-β PSD, $μV^2$/Hz	0,610
LFnu, %	0,495
Reactive Anxiety, points	0,435
C4-β PSD, %	0,406
T3-β PSD, $μV^2$/Hz	0,395
T4-β PSD, %	0,304
Baevski's ARS Index, points	0,295
LF PSD, %	0,285
Heart Rate, beats/min	0,276
F8-θ PSD, %	-0,385
δ-rhythm Laterality, %	-0,366
O1-θ PSD, %	-0,329
θ-rhythm Asymmetry, %	-0,215
C4-δ PSD, $μV^2$/Hz	-0,109



$R=0,826$; $R^2=0,682$; $\chi^2_{(45)}=115$; $p<10^{-5}$; Λ Prime=0,098

Fig. 7. Scatterplot of canonical correlation between Uricemia, Testosteroneemia and Age (X-line) and EEG, HRV and Anxiety parameters (Y-line) at Females

However, a closer analysis of fig. 5 revealed two opposite age trends of uricemia (Fig. 8). It is interesting that the "watershed" is the age of 45, that is, the beginning of menopause.

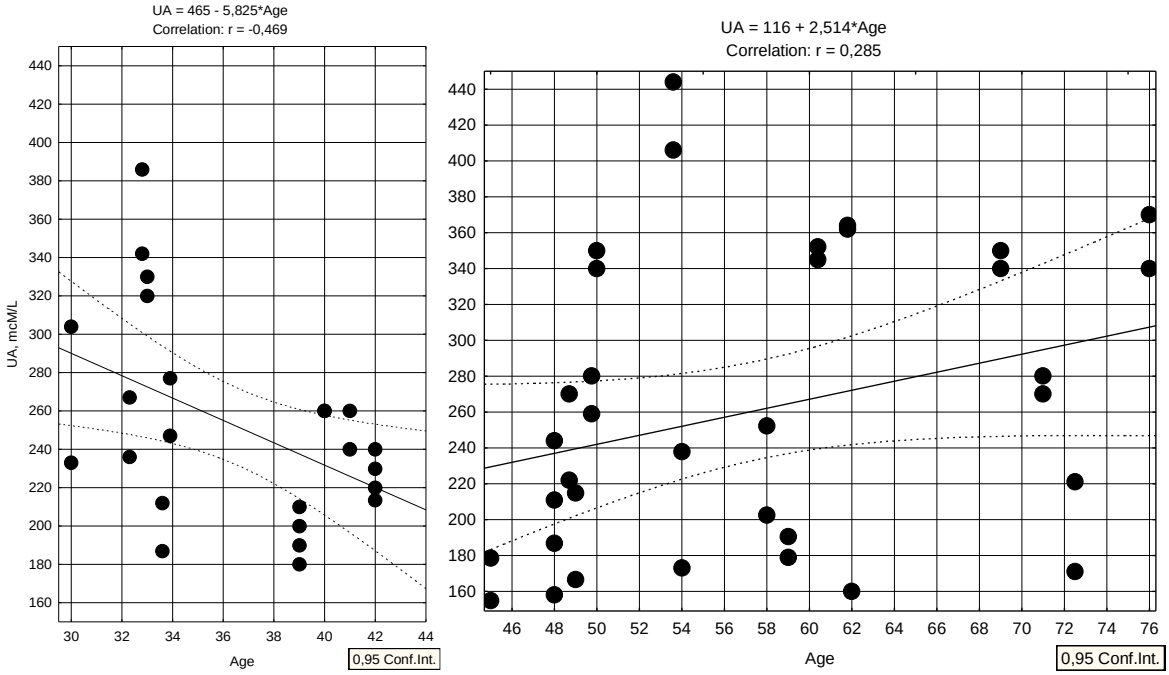


Fig. 8. Differently directed correlations between Age (X-line) and Uricemia (Y-line) at young (r=-0,469) and old (r=0,285) Females

These findings agree satisfactorily with sexual and age norms of uricemia (Fig. 9). As we can see, in men the average level of uricemia fluctuates in the range of only 5%, while in women it increases in the age range of 39-70 years by 20%, which is consistent with our data on a positive correlation with age after 45 years. Admittedly, the previous drop is only 5%, which is not consistent with our data on the inverse correlation with age in younger women.

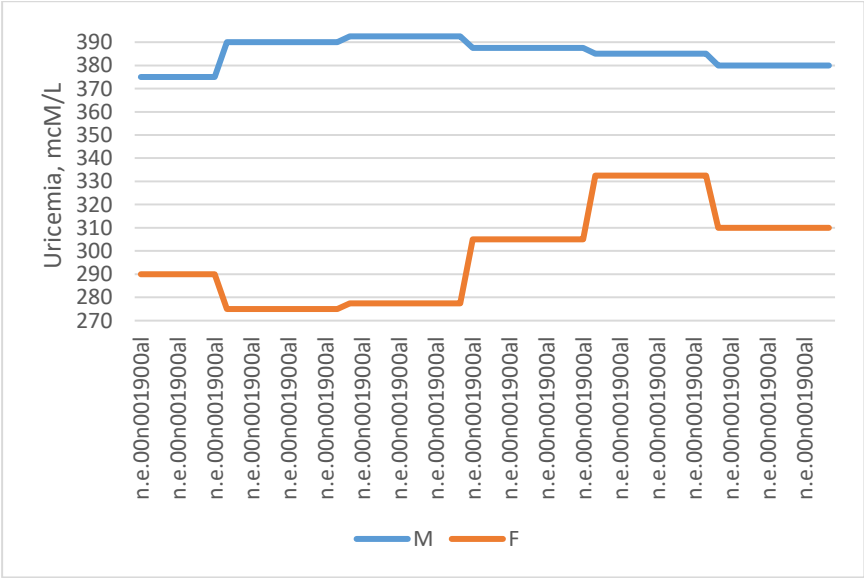


Fig. 9. The average level of uricemia in healthy males and females of different ages (Khmelevskyi & Usatenko, 1987)

The detected inversion of the age trend of uricemia prompted us to recalculate its correlations separately for two age groups of women. The screening results are visualized in the form of profiles of correlation coefficients. Since profiles have both matching and different bands, for the convenience of analysis we will divide them into several patterns.

In fig. 10 displayed profiles of significant urato-neural correlations in men compared with correlations in women of two age categories. First of all, we focus attention on the approximately equal strength of the connections between uricemia and testosterone. Other linked bands are the direct correlation of uricemia with PSD C4-θ and deviation of α-rhythm in men and young women as well as inverse correlation with PSD C4-β, P4-β and Fp2-δ while direct correlation with PSD F7-θ in postmenopausal women.

However, most parameters show opposite correlations in men and young women, while in postmenopausal women urato-neural correlations are quasi-zero. This gives reason to assume that they are affected by estrogens, but not by testosterone.

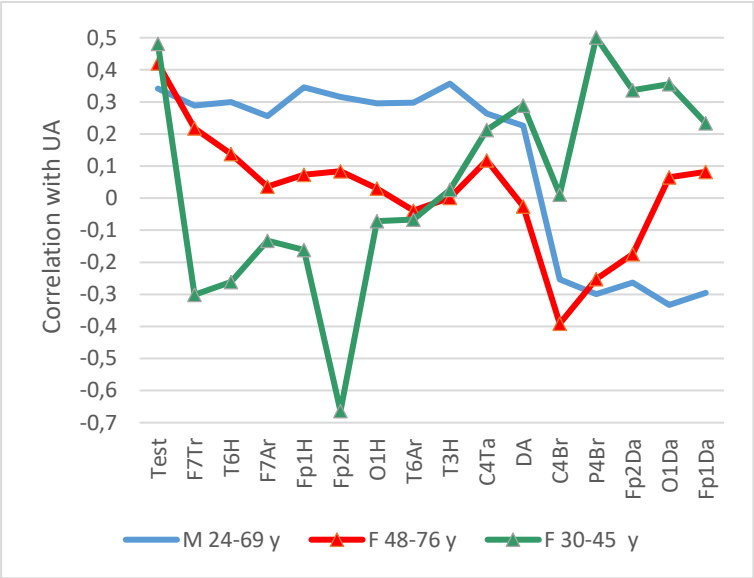


Fig. 10. Profiles of relationships between Uricemia and Neuro-Endocrine parameters at Males as well as young and old Females

In fig. 11 displayed profiles of significant urato-neural correlations in women of two age categories compared with correlations in men.

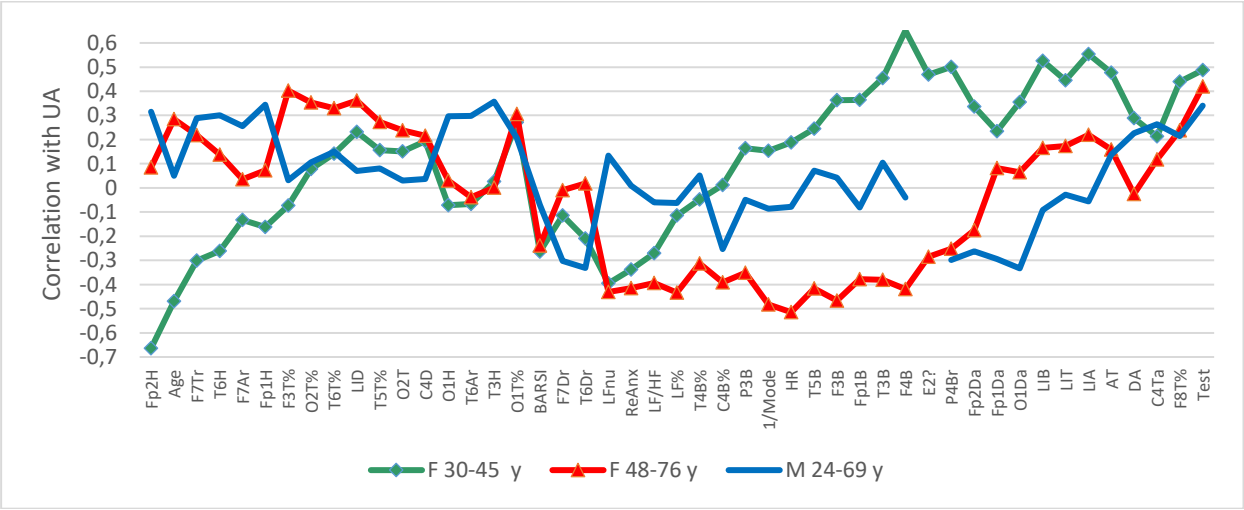


Fig. 11. Profiles of relationships between Uricemia and Psycho-Neuro-Endocrine parameters and Age at young and old Females as well as Males

For the majority of psycho-neural parameters of meni the correlations are quasi-zero or insignificant with a number of exceptions.

The first pattern consists of C4-δ PSDa and O1-θ PSDr, that are upregulated by uricemia regardless of age. While HRV-markers of sympathetic tone BARSI and LFnu as well as reactive anxiety downregulated by uricemia regardless of age.

The other two markers of sympathotonia (LF/HF and LF%) are downregulated by uricemia somewhat more significantly in postmenopausal women than in women of childbearing age. And vice versa, PSD of θ-rhythm in loci O2a, T5r and T6r as well as right-hand shift of δ-rhythm symmetry in postmenopausal women are more significantly upregulated by uricemia.

The next pattern consists of EEG parameters (T4-β PSDr, C4-β PSDr, P3-β PSDa) and HRV-markers of circulating catecholamines (1/Mode and HR) that are downregulated by uricemia in postmenopausal women only. And vice versa, relative PSD of θ-rhythm in loci F3, O2 and T6 are upregulated by uricemia in postmenopausal women only. Instead, in women of reproductive age uricemia upregulate the right-hand shift of α-, β- and θ-rhythm symmetry, θ-rhythm asymmetry as well as F8-θ PSDr, whereas in postmenopausal women the listed EEG parameters are very little or not sensitive to the influence of uricemia.

Especially interesting is the pattern whose members (absolute PSD of β-rhythm in loci T5, F3, Fp1 and F4) are downregulated by uricemia in postmenopausal women while upregulated in women of reproductive age.

Since the postmenopausal women observed by us did not receive estrogen replacement therapy, based on the positive correlation of uricemia with age and the negative correlation of estradiol with it, we assume that the parameter inverse of age (1/Age) may be a marker of estradiol (E2?). It follows from this that the plasma level of estradiol can be included in the composition of this pattern along with the listed parameters of β-rhythm.

It is here that it is appropriate to return to the passage from the introduction regarding a stark gender difference in how caffeine relates to PD risk. Initially, analysis of women in the NHS study revealed no clear relationship between 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 (Ascherio et al., 2001; 2003).

According to the concept of “central autonomic network (CAN)” (Benarroch, 1993; Palma & Benarroch, 2014; Thayer & Lane, 2009) it include following cortical, subcortical, and medullary structures (Fig. 12): the anterior cingulate, insular, orbitofrontal, and ventromedial cortices; the central nucleus of the **amygdala**; the paraventricular and related nuclei of the hypothalamus; the periaqueductal gray matter; the nucleus of the solitary tract; the nucleus ambiguous; the ventrolateral medulla; the ventromedial medulla and the medullary tegmental field. The primary output of the CAN is mediated through the preganglionic sympathetic and parasympathetic neurons, which exert control over the heart via the stellate ganglia and the vagus nerve, respectively. The interplay of sympathetic and parasympathetic influences on sinoatrial node pacemaker activity generates the complex variability that characterizes the healthy heart rate rhythm, which is called HRV. A fundamental principle of the neural control of the heart is its hierarchical organization, with cortical structures providing inhibitory control over limbic and brainstem sympathoexcitatory, cardioacceleratory circuits. The prefrontal, cingulate, and insula cortices form an interconnected network with bi-directional communication with the amygdala. The amygdala is under tonic inhibitory control via prefrontal vagal pathways to intercalated cells in the amygdala. The activation of the central nucleus of the amygdala (CeA) inhibits the nucleus of the solitary tract (NTS) which in turn inhibits inhibitory caudal ventrolateral medullary (CVLM) inputs to the rostral ventrolateral medullary (RVLM) sympathoexcitatory neurons, and simultaneously

inhibits vagal motor neurons in the nucleus ambiguus (NA) and the dorsal vagal motor nucleus (DVN).

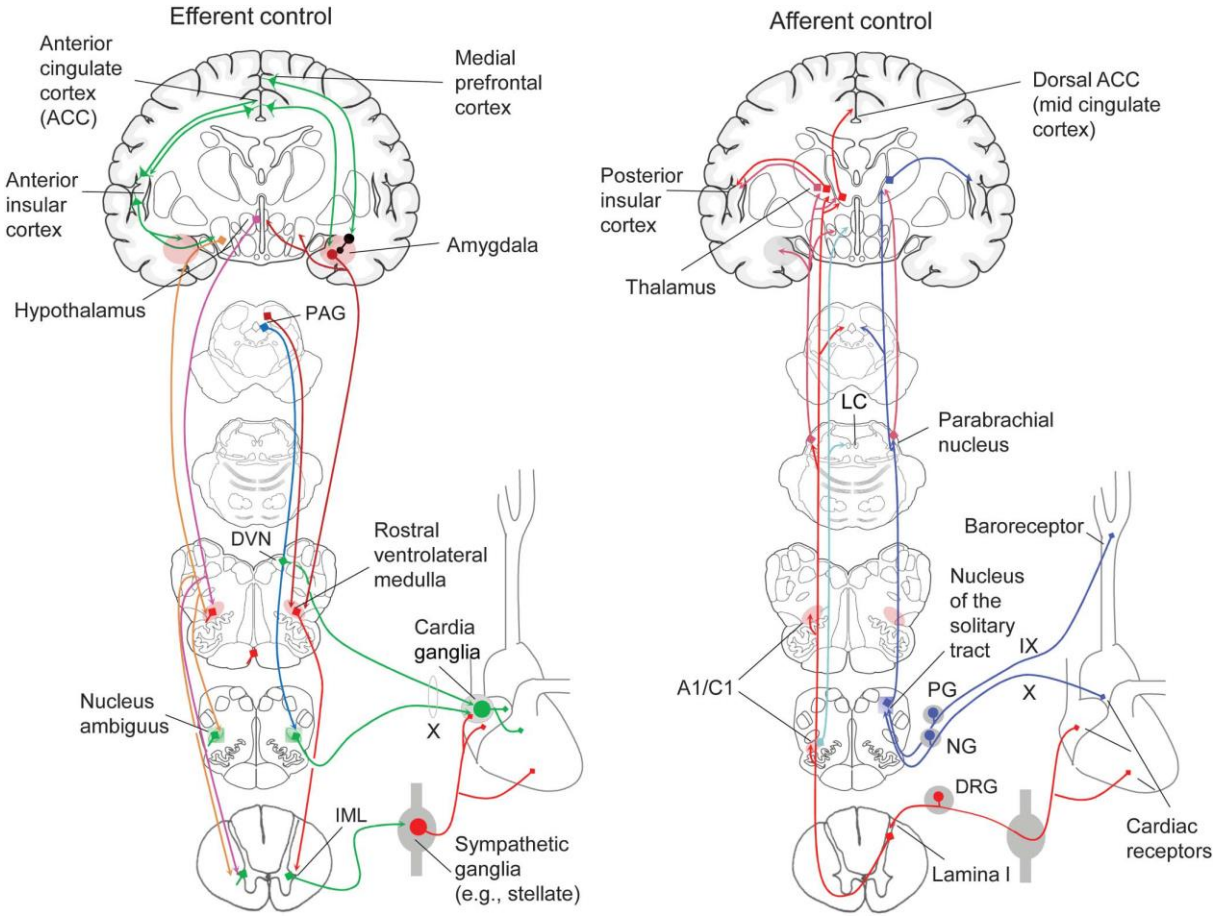


Fig. 12. Efferent and afferent control of cardiac function (Palma & Benarroch, 2014)

In addition, the CeA can directly activate the sympathoexcitatory neurons in the RVLM. Indeed, disruption of prefrontal activity leads to disinhibition of sympathoexcitatory circuits, with a resultant increase in heart rate and decrease in vagally-mediated HRV (Verberne et al., 1996; 1997; Thayer & Lane, 2009). Conversely, let's add from ourselves, activation of prefrontal cortex leads to increase in vagal tone.

Despite the absence of the "Tomography" option in our device, we will still try to identify the nervous structures that are subject to the regulatory influence of uricemia.

It is traditionally believed that loci C3/C4 projected hippocampus, and loci T3/T4 reflect the activity of the **amygdala** (Romodanov, 1993). Montenegro et al. (2011) assessed the effects of anodal direct current stimulation over the T3 scalp position (aims to reach the insular cortex) on measures of cardiac autonomic control. The authors found that the parasympathetic activity (HF(log)) increased and the sympathetic activity (LF(log)) and sympatho-vagal balance (LF/HF(log)) decreased in athletes but not in untrained individuals. No significant changes in HRV indexes were provoked by sham stimulation in both groups. The authors attributed the specific results to neuroanatomical and functional changes in the brain induced by long-term exercise training. Shown that after real HF-trains of transcranial magnetic stimulation over the left dorsolateral prefrontal cortex (which is projected onto the locus F3) the physiological stress response was diminished, as indicated by a significant increase in HRV. No effects were found in the sham or right side (F4) stimulation condition. This is consistent with the provision that

left-sided (dominant hemisphere) forebrain structures appear to be predominantly involved in vagal regulation, whereas homotopic right (non-dominant) forebrain regions seem to primarily control sympathetic tone and responses. Taking together, those studies suggest that stimulation of the left dorsolateral prefrontal or the insular cortex with rTMS or tDCS increase vagal activity. However, the lateralization model of autonomic control of the heart remains controversial (Thayer et al., 2012; Popovych et al., 2013; 2014).

Nugent et al. (2011) by electrophysiology and neuroimaging studies have revealed sex-related differences in autonomic cardiac control, as reflected in measurements of HRV. Imaging studies indicate that the neurobiological correlates of autonomic nervous system (ANS) function can be investigated by measuring indices of HRV during the performance of mildly strenuous motor tasks or mildly stressful cognitive tasks. In this study, young male and female healthy subjects underwent $H_2{}^{15}O$-positron emission tomography (PET) and electrocardiograph (ECG) recording while performing a handgrip motor task and an n-back task. Indices of HRV were calculated and correlated with regional cerebral blood flow (rCBF). Authors hypothesized that sex differences would be evident in brain regions known to participate in autonomic regulation: the anterior insula, the anterior cingulate cortex, the orbitofrontal cortex, and the amygdala. The study found that associations between rCBF and parasympathetic indices differed significantly between female and male subjects in the **amygdala**. Females showed a positive correlation between rCBF and parasympathetic indices while males exhibited negative correlations. This differential correlation of amygdala rCBF and parasympathetic activity between males and females may reflect differences in parasympathetic/sympathetic balance between sexes, consistent with known sexual dimorphism in the amygdala and closely related structures such as the hypothalamus.

How do the literature data agree with the data we obtained in this study?

We found that activation by uricemia of the left dorsolateral prefrontal cortex (F3) is accompanied by a vagotonic shift in the sympatho-vagal balance (as well as a decrease in reactive anxiety), but only in women. We specified that the vagotonic/sympathoinhibitory effect in postmenopausal women is exerted by cortical neurons generating θ-rhythm (r=0,402), while in women of reproductive age – β-rhythm generating neurons (r=0,362). In the latter, an even stronger vagotonic/sympathoinhibitory influence exert β-rhythm generating neurons of the right (F4) dorsolateral prefrontal cortex (r=0,651). On the other hand, the effects of β-rhythm generating neurons in postmenopausal women are opposite (r= -0,467 and -0,419 for F3 and F4 respectively).

If we assume that the T3 locus reflects the activity of the left insular cortex or left amygdala, then it can be argued that the activation of its β-rhythm generating neurons (r=0,454) by uricemia is also accompanied by the vagotonic/sympathoinhibitory effect in young women. While the inhibition of the same neurons in old women (r=-0,380) accompanied by a vagotonic shift in the sympatho-vagal balance too. We confirmed Nugent's et al. (2011) data that in young females take place a positive correlation between activity of the amygdala and parasympathetic indices however, no negative correlation was found in men. However, the last provision is valid for postmenopausal women.

ACKNOWLEDGMENT

We express sincere gratitude to TA Korolyshyn and VV Kikhtan as well as administration PJSC "Truskavets'kurort", "Truskavets' SPA" and clinical sanatorium "Moldova" for help in carrying out this investigation.

ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted 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.

REFERENCES

1. Abhishekh HA, Nisarga P, Kisan R, Meghana A, Chandran S, Raju T, et al. Influence of age and gender on autonomic regulation of heart. J Clin Monit Comput. 2013; 27: 259-264.
2. Alonso A, Rodríguez LA, Logroscino G, Hernán MA. Gout and risk of Parkinson disease: a prospective study. Neurology. 2007; 69: 1696–1700.
3. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A. 1981; 78: 6858–6862.
4. Andreadou E, Nikolaou C, Gournaras F, Rentzos M, Boufidou F, Tsoutsou A, Zournas C, Zissimopoulos V, Vassilopoulos D. Serum uric acid levels in patients with Parkinson's disease: their relationship to treatment and disease duration. Clin Neurol Neurosurg. 2009; 111(9): 724–728.
5. Annanmaki T, Muuronen A, Murros K. Low plasma uric acid level in PD. Mov Disord. 2007; 22: 1133–1137.
6. Ascherio A, Chen H, Schwarschild MA, Zhang SM, Colditz GA, Speizer FE. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. Neurology. 2003; 60: 790–795.]
7. Ascherio A, LeWitt PA, Xu K, Eberly S, Watts A, Matson WR, Marras C, Kieburtz K, Rudolph A, Bogdanov MB, Schwid SR, Tennis M, Tanner CM, Beal MF, Lang AE, Oakes D, Fahn S, Shoulson I, Schwarzschild MA. Urate as a predictor of the rate of clinical decline in Parkinson disease. Arch Neurol. 2009; 66: 1460–1468.
8. Ascherio A, Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Rodriguez C, Thun MJ. Coffee consumption, gender, and Parkinson's disease mortality in the cancer prevention study II cohort : the modifying effects of estrogen. Am J Epidemiol. 2004; 160(1): 977–984.
9. Ascherio A, Zhang SM, Hernán MA, Kawachi I, Colditz GA, Speizer FE, Willett WC. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. Ann Neurol. 2001; 50(1): 56–63.
10. Ayuso-Peralta L, Jiménez-Jiménez FJ, Cabrera-Valdivia F, Molina JA, Javier MR, Almazán, Pedro-Cuesta JD, Tabernero C, Giménez-Roldan S. Premorbid Dietetic Habits and Risk for Parkinson's Disease. Parkinsonism & Related Disorders. 1997; 3: 55–61.
11. Baevskiy RM, Ivanov GG. Heart Rate Variability: theoretical aspects and possibilities of clinical application [in Russian]. Ultrazvukovaya i funktsionalnaya diagnostika. 2001; 3: 106-127.
12. Barranco Quintana JL, Allam MF, Del Castillo AS, Navajas RF. Parkinson's disease and Tea: A quantitative review. J Am Coll Nutr. 2009; 28(1): 1–6.
13. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993; 68(10): 988-1001.
14. Benedetti MD, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, Schaid DJ, Rocca WA. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study. Neurology. 2000 ;55: 1350–1358.
15. Berntson GG, Bigger JT jr, Eckberg DL, Grossman P, Kaufman PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, Van der Molen MW. Heart Rate Variability: Origines, methods, and interpretive caveats. Psychophysiology. 1997; 34: 623-648.
16. Bogdanov M, Matson WR, Wang L, Matson T, Saunders-Pullman R, Bressman SS, Flint Beal M. Metabolomic profiling to develop blood biomarkers for Parkinson's disease. Brain. 2008; 131: 389–396.
17. Chan DK, Woo J, Ho SC, Pang CP, Law LK, Ng PW, Hung WT, Kwok T, Hui E, Orr K, Leung MF, Kay R. Genetic and environmental risk factors for Parkinson's disease in a Chinese population. J Neurol Neurosurg Psychiatry. 1998; 65: 781–784.
18. Checkoway H, Powers K, Smith-Weller T, Franklin GM, Longstreth WT, Jr, Swanson PD. Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake. Am J of Epidemiol. 2002; 155(8): 732–738.
19. Chen H, Mosley TH, Alonso A, Huang X. Plasma urate and Parkinson's disease in the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol. 2009; 169: 1064–1069.
20. Chen JF, Xu K, Petzer JP, Staal R, Xu YH, Beilstein M, Sonsalla PK, Castagnoli K, Castagnoli N, Jr, Schwarzschild MA. Neuroprotection by caffeine and A(2A) adenosine receptor inactivation in a model of Parkinson's disease. J Neurosci. 2001; 21(RC143): 1–6.

21. Church WH, Ward VL. Uric acid is reduced in the substantia nigra in Parkinson's disease: effect on dopamine oxidation. Brain Res Bull. 1994; 33(4): 419–425.
22. Clarke AR, Barry RJ, McCarthy R, Selikowitz M. Age and sex effects in the EEG: development of the normal child. Clin Neurophysiol. 2001; 112(5): 806-814.
23. Davies KJ, Sevanian A, Muakkassah-Kelly SF, Hochstein P. Uric acid-iron ion complexes. A new aspect of the antioxidant functions of uric acid. Biochem J. 1986; 235: 747–754.
24. Davis JW, Grandinetti A, Waslien CI, Ross GW, White LR, Morens DM. Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease. Am J Epidemiol. 1996; 144(5): 480–484.
25. De Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum uric acid levels and the risk of Parkinson disease. Ann Neurol. 2005; 58(5): 797–800.
26. De Vera M, Rahman MM, Rankin J, Kopec J, Gao X, Choi H. Gout and the risk of Parkinson's disease: a cohort study. Arthritis Rheum. 2008; 59: 1549–1554.
27. Du Y, Chen CP, Tseng CY, Eisenberg Y, Firestein BL. Astrogliamediated effects of uric acid to protect spinal cord neurons from glutamate toxicity. Glia. 2007; 55(5): 463–472.
28. Duan W, Ladenheim B, Cutler RG, Kruman II, Cadet JL, Mattson MP. Dietary folate deficiency and elevated homoocysteine levels endanger dopaminergic neurons in models of Parkinson's disease. J Neurochem. 2002; 80(1): 101–110.
29. Efroimson VP. Some biological factors of mental activity [in Russian]. VIET. 1987; 4: 74-84.
30. Fall PA, Fredrikson M, Axelson O, Granerus AK. Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. Mov Disord. 1999; 14: 28–37.
31. Fiebich BL, Biber K, Lieb K, van Calker D, Berger M, Bauer J, Gebicke-Haerter PJ. Cyclooxygenase-2 expression in rat microglia is induced by adenosine A2a receptors. Glia. 1996; 18: 152–60.
32. Franzoni F, Colognato R, Galetta F, Laurenza I, Barsotti M, Di Stefano R, Bocchetti R, Regoli F, Carpi A, Balbarini A, Migliore L, Santoro G. An in vitro study on the free radical scavenging capacity of ergothioneine: comparison with reduced glutathione, and trolox. Biomed Pharmacother. 2006; 60(8): 453–457.
33. Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacological reviews. 1999; 51(1): 83–133.
34. Gao X, Chen H, Choi HK, Curhan G, Schwarzschild MA, Ascherio A. Diet, Urate and PD risk in men. Am Journal of epidemiology. 2008; 167: 831–838.
35. Goryachkovskiy AM. Clinical Biochemistry [in Russian]. Odesa. Astroprint; 1998: 608.
36. Grandinetti A, Morens DM, Reed D, MacEachern D. Prospective study of cigarette smoking and the risk of developing idiopathic Parkinson's disease. Am J Epidemiol. 1994; 139(12): 1129–1138.
37. Guerreiro S, Ponceau A, Toulorge D, Martin E, Alvarez-Fischer D, Hirsch EC, Michel PP. Protection of midbrain dopaminergic neurons by the end-product of purine metabolism uric acid: potentiation by low-level depolarization. J Neurochem. 2009; 109: 1118–1128.
38. Haberman F, Tang SC, Arumugam TV, Hyun DH, Yu QS, Cutler RG, Guo Z, Holloway HW, Greig NH, Mattson MP. Soluble neuroprotective antioxidant uric acid analogs ameliorate ischemic brain injury in mice. Neuromolecular Med. 2007; 9(4): 315–323.
39. Heart Rate Variability. Standards of Measurement, Physiological Interpretation, and Clinical Use. Task Force of ESC and NASPE. Circulation. 1996; 93(5): 1043-1065.
40. Hellenbrand W, Seidler A, Boeing H, Robra HP, Vieregge P, Nischan P, Joerg J, Oertel WH, Schneider E, Ulm G. Diet and Parkinson's disease. II Diet and Parkinson's disease. I: A possible role for the past intake of specific foods and food groups. Results from a self administered food-frequency questionnaire in a case-control study. Neurology. 1996; 47: 636–643.
41. Ho SC, Woo J, Lee CM. Epidemiologic study of Parkinson's disease in Hong Kong. Neurology. 1989; 39: 1314–1318.
42. Hooper CD, Bagasra O, Marini JC, Zborek A, Ohnishi ST, Kean R, Champion JM, Sarker AB, Bobroski L, Farber JL, Akaike T, Maeda H, Koprowski H. Prevention of experimental allergic encephalomyelitis by targeting nitric oxide and peroxynitrite: implications for the treatment of multiple sclerosis. Proc Natl Acad Sci. 1997; 94: 2528–2533.
43. Hooper DC, Spitsin S, Kean RB, Champion JM, Dickson GM, Chudhry I, Koprowski H. Uric acid, a natural scavenger of peroxynitrite in experimental allergic encephalomyelitis and multiple sclerosis. Proc Natl Acad Sci. 1998; 95: 675–680.
44. Hu G, Bidel S, Jousilahti P, Antikainen R, Tuomilehto J. Coffee and tea consumption and the risk of Parkinson's disease. Mov Disord. 2007; 22(15): 2242–2248.
45. Ivassivka SV, Popovych IL, Aksentiychuk BI, Flyunt IS. Physiological Activity of Uric Acid and its Role in the Mechanism of Action of Naftussya Water [in Ukrainian]. Kyiv. Computerpress; 2004: 163.
46. Jimenez-Jimenez FJ, Mateo D, Gimenez-Roldan S. Premorbid smoking, alcohol consumption, and coffee drinking habits in Parkinsons disease: a case control study. Mov Disord. 1992; 7(4): 339–344.

47. Johansen KK, Wang L, Aasly JO, White LR, Matson WR, Henchcliffe C, Beal MF, Bogdanov M. Metabolomic profiling in LRRK2-related Parkinson's disease. PLoS One. 2009; 4(10): e7551.
48. Jones DC, Gunasekar PG, Borowitz JL, Isom GE. Dopamine induced apoptosis is mediated by oxidative stess and is enhanced by cyanide in differentiated PC12 cells. J Neurochem. 2000; 74(6): 2296–2304.
49. Khmelevskyi YV, Usatenko OK. Basic Biochemical Constants of Humans at Norm and at Pathology [in Russian]. Kyiv. Zdorovya; 1987: 160.
50. Kostic VS, Svetel M, Sternic N, Dragasevic N, Przedborski S. Theophylline increases "on" time in advanced parkinsonian patients. Neurology. 1999; 52: 1916.
51. Kulisevsky J, Barbanoj M, Gironell A, Antonijoan R, Casas M, Pascual-Sedano B. A double-blind crossover, placebo-controlled study of the adenosine A2A antagonist theophylline in Parkinson's disease. Clin Neuropharmacol. 2002; 25: 25–31.
52. Larumbe Ilundain R, Ferrer Valls JV, Vines Rueda JJ, Guerrero D, Fraile P. Case-control study of markers of oxidative stress and metabolism of blood iron in Parkinson's disease. Rev Esp Salud Publica. 2001; 75(1): 43–53.
53. Li SC, Schoenberg BS, Wang CC, Cheng XM, Rui DY, Bolis CL, Schoenberg D. A prevalence of survey PD and other movement disorders in the People's Republic of China. Arch of Neurol. 1985; 42: 655–657.
54. Mally J, Stone TW. The effect of theophylline on parkinsonian symptoms. J Pharm Pharmacol. 1994; 46: 515–517.
55. Montenegro RA, Farinatti P de TV, Fontes EB, Soares PP da S, Cunha da FA, Gurgel JL et al. Transcranial direct current stimulation influences the cardiac autonomic nervous control. Neurosci Lett. 2011; 497(1): 32-36.
56. Morano A, Jimenez-Jimenez FJ, Molina JA, Antolin MA. Risk Factors for Parkinson's disease: case-control study in the province of Caceres, Spain. Acta Neurol Scand. 1994; 89(3): 164–170.
57. Morelli M, Carta AR, Kachroo A, Schwarzschild A. Pathophysiological roles for purines: adenosine, caffeine and urate. Prog Brain Res. 2010; 183: 183-208.
58. Newberg AB, Alavi A, Baime M, Pourdehnad M, Santanna J, d'Aquili E. The measurement of regional cerebral blood flow during the complex cognitive task of meditation: a preliminary SPECT study. Psychiatry Research: Neuroimaging Section. 2001; 106: 113-122.
59. Nugent AC, Bain EE, Thayer JF, Sollers JJ, Drevets WC. Sex differences in the neural correlates of autonomic arousal: a pilot PET study. Int J Psychophysiol. 2011; 80(3): 182-91.
60. Oda M, Satta Y, Takenaka O, Takahata N. Loss of urate oxidase activity in hominoids and its evolutionary implications. Mol Biol Evol. 2002; 19(5): 640–653.
61. Palma JA, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. Neurology. 2014; 83: 261-271.
62. Parkinson Study Group PRECEPT Investigators. Mixed lineage kinase inhibitor CEP-1347 fails to delay disability in early Parkinson's disease. Neurology. 2007; 69: 1480–1490.
63. Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med. 1993; 328: 176–183.
64. Popovych IL, Kozyavkina OV, Kozyavkina NV, Korolyshyn TA, Lukovych YuS, Barylyak LG. Correlation between Indices of the Heart Rate Variability and Parameters of Ongoing EEG in Patients Suffering from Chronic Renal Pathology. Neurophysiology. 2014; 46(2): 139-148.
65. Popovych IL, Lukovych YuS, Korolyshyn TA, Barylyak LG, Kovalska LB, Zukow W. Relationship between the parameters heart rate variability and background EEG activity in healthy men. Journal of Health Sciences. 2013; 3(4): 217-240.
66. Post B, Merkus MP, de Haan RJ, Speelman JD CARPA Study Group. Prognostic factors for the progression of Parkinson's disease: a systematic review. Mov Disord. 2007; 22: 1839–1851.
67. Practical psychodiagnostics. Techniques and tests [in Russian]. Samara. Bakhrakh; 1998: 59-64.
68. Preux PM, Condet A, Anglade C, Druet-Cabanac M, Debrock C, Macharia W, Couratier P, Boutros-Toni F, Dumas M. Parkinsons's disease and environmental factors. Matched case-control study in the Limousin region, France. Neuroepidemiology. 2000; 19(6):333–337.
69. Proctor P. Similar functions of uric acid and ascorbate in man? Nature. 1970; 228(5274): 868.
70. Ragonese P, Salemi G, Morgante L, Aridon P, Epifanio A, Buffa D, Scoppa F, Savettieri G. A case-control study on cigarette, alcohol, and coffee consumption preceeding parkinson's disease. Neuroepidemiology. 2003; 22(5): 297–304.
71. Rebola N, Canas PM, Oliveira CR, Cunha RA. Different synaptic and subsynaptic localization of adenosine A2A receptors in the hippocampus and striatum of the rat. Neuroscience. 2005; 132: 893–903.
72. Reznikov AG, Nosenko ND, Tarasenko LV, Sinitsyn PV, Polyakova LI. Early and Long-Term Neuroendocrine Effects of Prenatal Stress in Male and Female Rats. Neuroscience and Behavioral Physiology. 2001; 31(1): 1–5.

73. Reznikov AG, Pishak VP, Nosenko ND, Tkachuk SS, Myslyts'kyi VF. Prenatal stress and neuroendocrine pathology [in Russian]. Chernivtsi. Medakademiya; 2004: 351.
74. Reznikov AG, Sinitsyn PV, Tarasenko LV. Age and sexual characteristics of noradrenergic reactivity of the hypothalamic-pituitary-adrenocortical system in prenatal stressed rats [in Ukrainian]. Reports of NAS of Ukraine. 2001; 1: 177-180.
75. Romanos E, Planas AM, Amaro S, Chamorro A. Uric acid reduces brain damage and improves the benefits of rt-PA in a rat model of thromboembolic stroke. J Cereb Blood Flow Metab. 2007; 27(1): 14–20.
76. Romodanov AP (editor). Postradiation Encephalopathy. Experimental Researches and Clinical Observations [in Ukrainian and Russian]. Kyiv. USRI of Neurosurgery; 1993: 224.
77. Rosin DL, Robeva A, Woodard RL, Guyenet PG, Linden J. Immunohistochemical localization of adenosine A2A receptors in the rat central nervous system. J Comp Neurol. 1998; 401: 163–186.
78. Ross GW, Abbott RD, Petrovitch H, Morens DM, Grandinetti A, Tung KH, Tanner CM, Masaki KH, Blanchette PL, Curb JD, Popper JS, White L. Association of coffee and caffeine intake with the risk of Parkinson disease. 2000; 283: 2674–2679.
79. Ruzhylo SV, Fihura OA, Zukow W, Popovych IL. Immediate neurotropic effects of Ukrainian phytocomposition. Journal of Education, Health and Sport. 2015; 5(4): 415-427.
80. Saaksjarvi K, Knekt P, Rissanen H, Laaksonen MA, Reunanen A, Mannisto S. Prospective study of coffee consumption and risk of Parkinson's disease. European Journal of Clinical Nutrition. 2008; 62: 908–915.
81. Sacher J, Neumann J, Okon-Singer H, Gotowiec S, Villringer A. Sexual dimorphism in the human brain: evidence from neuroimaging. Magn Reson Imaging. 2013; 31(3): 366-375.
82. Saura J, Angulo E, Ejarque A, Casadó V, Tusell JM, Moratalla R, Chen JF, Schwarzschild MA, Lluis C, Franco R, Serratosa J. Adenosine A2A receptor stimulation potentiates nitric oxide release by activated microglia. J Neurochem. 2005; 95: 919–929.
83. Schiffmann SN, Jacobs O, Vanderhaeghen JJ. Striatal restricted adenosine A2 receptor (RDC8) is expressed by enkephalin but not by substance P neurons: an in situ hybridization histochemistry study. J Neurochem. 1991; 57: 1062–1067.
84. Schwarzschild MA, Agnati L, Fuxe K, Chen JF, Morelli M. Targeting adenosine A2A receptors in Parkinson's disease. Trends Neurosci. 2006; 29(11): 647–54.
85. Schwarzschild MA, Schwid SR, Marek K, Watts A, Lang AE, Oakes D, Shoulson I, Ascherio A the Parkinson Study Group PRECEPT Investigators. Serum urate as a predictor of clinical and radiographic progression in Parkinson's disease. Arch Neurol. 2008; 65: 716–723.
86. Schwarzschild MA, Xu K, Oztas E, Petzer JP, Castagnoli K, Castagnoli N, Jr, Chen JF. Neuroprotection by caffeine and more specific A2A receptor antagonists in animal models of Parkinson's disease. Neurology. 2003; 61(11 Suppl 6): S55–S61.
87. Scott GS, Spitsin SV, Kean RB, Mikheeva T, Koprowski H, Hooper DC. Therapeutic intervention in experimental allergic encephalomyelitis by administration of uric acid precursors. Proc Natl Acad Sci. 2002; 99(2): 16303–16308.
88. Shannon CE. A mathematical theory of information. Bell Syst Tech J. 1948; 27: 379-423.
89. Sofaer JA, Emery AF. Genes for super-intelligence? J Med Genet. 1981; 18: 410-413.
90. Stevens JS, Hamann S. Sex differences in brain activation to emotional stimuli: a meta-analysis of neuroimaging studies. Neuropsychologia. 2012; 50(7): 1578-1593.
91. Stromberg U, Waldeck B. Behavioural and biochemical interaction between caffeine and L-dopa. J Pharm Pharmacol. 1973; 25: 302–308.
92. Svenningsson P, Fourreau L, Bloch B, Fredholm BB, Gonon F, Le Moine C. Opposite tonic modulation of dopamine and adenosine on c-fos gene expression in striatopallidal neurons. Neuroscience. 1999; 89: 827–837.]
93. Tan EK, Tan C, Fook-Chong SM, Lum SY, Chai A, Chung H, Shen H, Zhao Y, Teoh ML, Yih Y, Pavanni R, Chandran VR, Wong MC. Dosedependent protective effect of coffee, tea and smoking in Parkinson's disease: a study in ethnic Chinese. J Neurol Sci. 2003; 216(1): 163–167.
94. Tan LC, Koh WP, Yuan JM, Wang R, Au WL, Tan JH, Tan EK, Yu MC. Differential effects of black versus green tea on risk of PD in the Singapore Chinese health study. Am J Epidemiol. 2007; 167: 553–560.
95. Thayer JF, Åhs F, Fredrikson M, Sollers JJ 3rd, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev. 2012; 36(2): 747-756.
96. Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev. 2009; 33(2): 81-88.
97. Tohgi H, Abe T, Takahashi S, Kikuchi T. The urate and xanthine concentrations in the cerebrospinal fluid in patients with vascular dementia of the Binswanger type, Alzheimer type dementia, and Parkinson's disease. J Neural Transm Park Dis Demet Sect. 1993; 6(2): 119–126.

98. Verberne AJ, Lam W, Owens NC, Sartor D. Supramedullary modulation of sympathetic vasomotor function. Clin Exp Pharmacol Physiol. 1997; 24(9-10): 748-754.
99. Verberne AJ. Medullary sympathoexcitatory neurons are inhibited by activation of the medial prefrontal cortex in the rat. Am J Physiol. 1996; 270(4Pt2): R713-R719.
100. Weisskopf MG, O'Reilly E, Chen H, Schwarzschild MA, Ascherio A. Plasma urate and risk of Parkinson's disease. Am J Epidemiol. 2007; 166: 561–567.
101. Willett WC. Nutritional Epidemiology. 2nd. New York: Oxford Univ Press; 1998.
102. Xu K, Xu Y, Brown-Jermyn D, Chen JF, Ascherio A, Dluzen DE, Schwarzschild MA. Estrogen prevents neuroprotection by caffeine in the mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. J Neurosci. 2006; 26(2): 535–541.
103. Yeum KJ, Russell RM, Krinsky NI, Aldini G. Biomarkers of antioxidant capacity in the hydrophilic and lipophilic compartments of human plasma. Arch Biochem Biophys. 2004; 430: 97–103.
104. Yu L, Shen HY, Coelho JE, Araujo IM, Huang QY, Day YJ, Rebola N, Canas PM, Rapp EK, Ferrara J, Taylor D, Muller CE, Linden J, Cunha RA, Chen JF. Adenosine A2A receptor antagonists exert motor and neuroprotective effects by distinct cellular mechanisms. Ann Neurol. 2008; 63(3): 338–346.
105. Yu ZF, Bruce-Keller AJ, Goodman Y, Mattson MP. Uric acid protects neurons against excitotoxic and metabolic insults in cell culture and against focal ischemic brain injury in vivo. J Neurosci Res. 1998; 53(5): 613–625.
106. Zhang ZX, Roman GC. Worldwide occurrence of PD: an updated review. Neuroepidemiology. 1993; 12: 195–208.