Heart Rate Variability in Outbred White Rats upon Periodical α-Tocopherol Administration

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Translated from *Byulleten' Experimental'noi Biologii i Meditsiny*, Vol. 147, No 2, pp. 130-133, February, 2009
Original article submitted March 3, 2008

Effect of α-tocopherol (vitamin E) periodical administration on heart rhythm regulation was investigated in outbred white rats. α-Tocopherol administration to males was followed by reduction of sympathetic neural influence on heart rhythm and also by the increase of the number of individuals with high activity of autonomic regulation loop. In female rats α-tocopherol administration modulates the activity of humoral control circuit and promotes heart rate reduction, however upon that the percent of females with high centralization of heart rate regulation was increased.

Key Words: *heart rate variability, α-tocopherol, male and female rats*

Heart rhythm variability analysis is a method of estimation of state of regulatory mechanisms in human and animal body that gain quite a widespread acceptance in experimental and clinical studies [1]. In recent years the studies which demonstrate the close interrelationship of adrenergic and cholinergic regulation with free radical processes intensity and energy metabolism have appeared [3,5]. The role of antioxidant and prooxidant systems components in implementation and modulation of neural and humoral influence on the functions of cardio-vascular system is being investigated [2,6,7]. Thereupon the wide use of antioxidants as part of various vitamin complexes in order to improve the overall vitality of the organism and to prevent age-related changes claims attention as far as the impact of these substances on the state of regulatory mechanisms (also regarding cardiac activity) is practically not studied. To our opinion, experimental simulation of this situation will make it possible to estimate the results of long-term ingestion of vitamins with antioxidant properties not only by changes of free-radical processes intensity in the body but also by the state of regulatory systems.

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The aim of the study was to reveal the distinctive features of cardiac rate variability in outbred white rats which received α-tocopherol from time to time during their lives.

MATERIALS AND METHODS

Experiments were conducted using 165 3.5-month-old outbred white rats of both sexes. Animals were housed in standard vivarium conditions with free access to food and water. During ontogenesis animals (n=84) periodically (on weeks 2-3, 5-6, 10-11 and 14-15 of life) received 10% D,L-α-tocopherol acetate (α-TPh) oil solution in the dose of 10 mg/kg *per os*. The α-TPh dose was selected on the basis of data on optimal antioxidant vitamin E effects upon administration of a single dose of 2 mg/100 g of body weight maximum [8]. The rats which received physiological saline *per os* were used as control.

ECG was recorded in the state of awake rest by means of Varicard hardware-software complex (Ramena) using miniature electrode clamps. Animals were not immobilized or isolated from each other, they were kept in groups of 4-5 in a considerably congested box which facilitated their tranquillization and made ECG recording possible.

0007-4888/09/1472-0173

R-R interval measurement and the primary data processing were performed using ISKIM6 software (Ramena). 300 *R-R* intervals from each record were used for analysis. Further variation pulsometry indices were calculated: average heart rate, *R-R* interval mode, range of variability of *R-R* interval, root mean square successive difference (RMSSD) for adjacent *R-R* intervals, standard deviation of normal-to-normal intervals (SDNN), mode amplitude (AMo 7.8), index of vegetative balance (IVB), and strain index (SI) [1], and also the indices of spectral analysis of heart rate variability in the HF range (0.9-3.5 Hz), LF range (0.32-0.90 Hz) and VLF range (0.18-0.32 Hz). The total spectrum power ($msec^2$) and the normalized spectrum power (HF%, LF%, VLF%) and the centralization index were calculated (IC=(LF+VLF)/HF). Statistical analysis of results was performed by means of Statistica 6.0 software using Student t *t*est and cluster analysis.

RESULTS

Heart rate indices analysis allowed to demonstrate higher heart rate at rest in female rats compared to males ($p<0.001$). These differences were specified by a significantly lower *R-R* interval mode in females ($p<0.001$; $r=-0.980$; Table 1). Mean values of variation pulsometry indices and spectral analysis which reflect activity of extracardial neural regulation circuits in control males and females did not differ, although high variability of these indices inside the group was evident. Therefore, in the state of awake rest heart rate generation in rats is specified predominantly by the activity of humoral regulation circuit characterized by sexual dimorphism.

Administration of α-TPh did not lead to any significant heart rate and *R-R* interval mode alterations in male rats which is in line with data [2], in females the increase of mode and heart rate reduction were noted ($p<0.05$). Changes of extracardial neural influence indices were specific only for males. They had the total cardiac rhythm variability increased: SDNN increased by 23.7% ($p<0.05$). Substantial reduction of mode amplitude (by 19%; $p<0.05$) and SI (by 32.2%; $p<0.05$) afforded a ground for conclusion about the reduction of sympathetic neural influence on the heart of male rats as a result of α-TPh administration. Although the upward changes of mean powers of the main components of heart rate variability spectrum were insignificant, a small trend towards the increase of power of the HF wave in males which received α-TPh, should be noted. Female rats which received α-TPh had

TABLE 1. Indices of Cardiac Rhythm Variability in Outbred White Rats Upon α-TPh Administration (*M±m*)

Index	Males		Females	
	control (*n*=40)	α-TPh (*n*=48)	control (n=41)	α-TPh (n=36)
HR, min^{-1}	328.8±3.3	321.3±5.4	350.9±3.5^{+}	335.80±4.76***
R-R interval mode, msec	183.2±1.8	188.5±3.3	172.3±1.6^{+}	179.90±2.77*
R-R interval range of variability, msec	31.40±1.77	36.40±2.63	31.80±2.01	27.90±2.48^{x}
RMSSD, msec	4.30±0.33	5.3±0.5	4.10±0.27	4.20±0.43
SDNN, msec	5.90±0.28	7.30±0.56*	6.60±0.46	5.50±0.49^{x}
AMo, %	52.90±2.21	42.80±2.34*	47.30±2.19	53.90±3.07^{xx}
SI, rel. units	39.84±5.16	26.98±3.87*	37.25±3.68	52.75±9.34^{xx}
IVB, rel. units	2.23±0.27	1.55±0.21*	1.98±0.19	2.85±0.47^{xx}
Total spectrum power, $msec^2$	15.00±1.37	19.90±2.95	21.26±2.89	16.29±2.54
HF, $msec^2$	5.86±1.02	9.83±2.24	6.89±0.81	6.53±1.66
LF, $msec^2$	4.88±0.48	5.69±1.62	4.86±1.35	4.44±0.96
VLF, $msec^2$	4.24±0.36	4.37±0.85	4.54±0.87	4.27±1.13
HF%	43.90±3.08	49.96±3.64	42.70±2.88	45.18±3.32
LF%	28.27±1.73	24.49±2.25	27.33±1.78	27.74±2.07
VLF%	27.74±2.33	25.54±2.71	29.96±1.84	27.06±1.95
Centralization index, rel. units	1.78±0.18	1.47±0.28	1.97±0.24	1.74±0.24

Note. Significance of effects was calculated using Student test: $^{+}p<0.001$ as compared to males from control group; $^{x}p<0.05$, $^{xx}p<0.01$ as compared to male rats which received α-TPh; ***$p<0.001$ as compared to respective control.

TABLE 2. Indices of cardiac rhythm variability in outbred white rats with high or low activity of autonomous regulation circuit (ARC) in control group and upon α-TPh administration (*M±m*)

Index	Control		α-TPh	
	high ARC activity	low ARC activity	high ARC activity	low ARC activity
Males	*n*=20	*n*=20	*n*=32	*n*=16
R-R interval range of variability, msec	41.30±2.63	21.50±1.21***	44.00±1.92	21.20±1.32***
SDNN, msec	7.70±0.49	4.1±0.2***	8.9±0.4	4.00±0.24***
Total spectrum power, msec^2	52.43±7.81	13.29±1.46***	66.31±5.81	12.65±1.61***
Females	*n*=26	*n*=15	*n*=14	*n*=22
R-R interval range of variability, msec	39.10±2.29	19.10±1.17***	41.60±4.03	19.30±1.11***
SDNN, msec	8.20±0.58	3.90±0.29***	8.10±0.79	3.80±0.23***
Total spectrum power, msec^2	60.42±11.96	13.69±1.83**	57.40±11.12	12.52±1.50***

Note. The null hypothesis about the equality of group (cluster) means for all three variables is rejected upon the significance level of 0.1 and 1%. **p<0.01, ***p<0.001 compared to the high ARC activity.

higher strain of sympathetic regulation loop and lower heart rate variability compared to male rats.

The identify animals with different activity of heart rate regulation loop we performed cluster analysis of the *R-R* intervals range of deviation, SDNN and the total spectrum power in each group using method of k-means clustering into 2 clusters. The clustering demonstrated that the high activity of autonomous regulation loop assessable by high total power and amplitude of regulatory influences (Table 2) is characteristic of 20 control males and 32 males which received α-TPh, respectively, low activity of autonomous regulation loop was also revealed in 20 control males and only in 16 males that received α-TPh. In other words, the distribution of control males over the high and lower activity of autonomous regulation circuit was 50 and 50% respectively, in the α-TPh group — 66 and 33.3% respectively. These data and our previous results [6] enables us to state, according to concept of R. M. Bayevsy *et al.* [1], that periodical α-TPh administration modulates activity of autonomic neural circuits of heart rate regulation, it promotes the increase of percent of animals with high activity of autonomous regulation loop in males.

Cluster analysis of heart rate variability in females revealed a different pattern: 26 control females had high activity of autonomous regulation circuit and only 15 of them had low activity, but among the animals which received α-TPh there were only 14 females with high activity of autonomous regulation circuit and 22 females with low activity. In other words, the percent of females with high strain of sympathetic neural influences in the α-TPh group markedly exceeded this fraction in the control group (61% compared to 37% respectively).

The performed analysis of cardiac rhythm indices suggests that α-TPh administration can influence the activity of regulatory mechanisms not only on the pathological background, as it was demonstrated in [9], but also in usual conditions. We revealed the decrease of sympathetic neural influence on cardiac rhythm in male rats and alteration of activity of humoral circuit of heart rhythm regulation in outbred female rats upon periodical α-TPh administration. Administration of α-TPh obviously has different consequences for regulation of heart chronotropic function animals of both sexes which confirms once more the dependence of α-TPh effects on the hormonal state of the body [8]. α-TPh effects are probably determined by its modulating influence on physical and chemical properties of cardiomiocyte cellular membranes which specify the sensitivity of membrane receptors to relevant ligands, and this requires advanced investigation.

The work was supported by Ministry of Education and Science of the Russian Federation grant within the program "Development of scientific potential of higher school (2006-2008)" for scientific investigations within the bounds of theme schedules, project No. 1.3.08.

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