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I.N. Molodovskaya, E.V. Tipisova, A.E. Elfimova, V.A. Alikina, V.N. Zyabisheva

THR RELATIONSHIP OF PARAMETERS OF THE PITUITARY-GONADAL AXIS AND DOPAMINE WITH METEOROLOGICAL FACTORS IN HEALTHY MEN LIVING IN THE SUBARCTIC

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Aim: to evaluate the influence of circannual dynamics of meteorological factors of the temperate continental climate on the levels of sex hormones and dopamine as well as antisperm antibodies in men living in subarctic environmental conditions.

Materials and methods. The concentrations of follicle stimulating hormone, luteinizing hormone, prolactin, progesterone, dopamine, cortisol, total and free testosterone, estradiol, sex hormone-binding globulin, dehydroepiandrosterone sulphate, antisperm antibodies were determined in the blood by the enzyme immunoassay on a quarterly basis (December, March, June, September) for one year in 20 healthy men of Arkhangelsk. The relationships between the hormonal data and the climatic data were assessed by using the Spearman correlation coefficient.

Results. Seasonal fluctuations in the levels of estradiol and antisperm antibodies are comparable to changes in the daylight hours, fluctuations in atmospheric pressure, temperature and relative humidity. Seasonal changes in luteinizing hormone levels are associated with the fluctuations in atmospheric air pressure. Daylight affect annual dopamine dynamics, which also correlated with atmospheric pressure and relative air humidity. Total and free testosterone levels in men are relatively constant throughout the year and do not appear to be influenced by the weather factors.

Conclusion. An increase in day length and air temperature is associated with an increase in estradiol and dopamine levels and a decrease in antisperm antibodies values. We believe that the seasonality of estradiol and antisperm antibodies is a daylight effect mediated by changes in the melatonin levels, just as dopamine seasonality is mediated by changes in vitamin D levels.

Keywords: sex hormones; circannual rhythm; dopamine; estradiol.

MOLODOVSKAYA Irina Nikolaevna – PhD in Biology, senior researcher, N. Laverov Federal Center for Integrated Arctic Research, pushistiy-86@mail.ru; http://orcid.org/0000-0003-3097-9427; **TIPISOVA Elena Vasilievna** – Doctor of Biology, chief researcher, N. Laverov Federal Center for Integrated Arctic Research, tipisova@rambler.ru, +79095555095, http://orcid.org/0000-0003-2097-3806; **ELFIMOVA Alexandra Eduardovna** – PhD in Biology, senior researcher, N. Laverov Federal Center for Integrated Arctic Research, a.elfimova86@mail.ru, http://orcid.org/0000-0003-2519-1600; **ALIKINA Victoria Anatolievna** – PhD in Biology, senior researcher, N. Laverov Federal Center for Integrated Arctic Research, victoria-popcova@yandex.ru, +79216754501, http://orcid.org/0000-0002-0818-7274; **ZYABISHEVA Valentina Nikolaevna** – junior researcher, N. Laverov Federal Center for Integrated Arctic Research, razvalush@yandex.ru, +79965031108, http://orcid.org/0000-0001-6133-8249.

Introduction. The change of the seasons of the year causes an adaptive restructuring of the body in the inhabitants of high latitudes. The physiological characteristics of the body allow most healthy people to adapt to the climate of the northern regions of the Russian Federation without noticeable disorders, and only a decrease in adaptive reserves can lead to various pathological conditions. At the same time, large-scale studies covering a number of populations in different climatic zones [5, 11, 16, 23] have shown a relationship between meteorological factors and the dynamics of sex hormones.

Several studies in recent years have received conflicting results in assessing the environmentally dependent rhythmicity of sex hormone secretion in men.

The contradictions can be explained by the different geographic location of each study, which affects the length of the seasons, temperature fluctuations, and day/night cycles. In Israel, the highest level of testosterone in men was observed in the summer-autumn season, when the weather is hot without rain, and the lowest - in the winter period with moderately cold and rainy weather [23]. In Italy, peak of testosterone levels in summer correlated with longer daylight duration and higher temperature, LH levels presented 2 peaks of secretion in autumn and spring, independently from environmental parameters, and FSH levels did not show any seasonal distribution [16]. In South Korea, on the contrary, testosterone showed a negative relationship with the length of daylight hours and air temperature, and its maximum levels in the serum of men were recorded in winter [11]. In a cross-sectional study of men living in northern Norway, the lowest testosterone levels were observed in the months with the highest temperatures and longest daylight hours [22]. At the same time, other authors considered cold as one of the stress factors that regulate sexual behavior and testosterone levels in men. The seasonality of testosterone levels in men living in the east of Turkey has been shown, with lower levels in winter [4]. In a longitudinal study of Norwegian men, the concentration of free testosterone during early winter depended on the study area: in Tromsø (69°4′ N) it reached a maximum, and in Oslo (60° N) it reached a minimum [20]. In men living in southern California, there was no seasonal variation in testosterone levels, no association between testosterone and mean air temperature, or testosterone and the hours of sunshine [28]. No seasonal rhythms of testosterone levels were found in 13 Belgian men [3]. Estradiol peaked in May in both a cross-sectional study of Norwegian men [21] and a longitudinal study of Finnish men [2].

Ultraviolet (UV) light is one of several environmental stimuli that can influence the circadian rhythm, playing an important regulatory role in reproduction [23]. Chronic UV light exposure led in male and female mice, to increased pituitary and gonadal hormone levels and to increased sexual responsiveness and attractiveness [27]. Arkhangelsk is located at 64°32′ N, where the difference in length of daylight between mid-summer and mid-winter is more than 18 hours, which allows you to test the hypothesis that seasonal fluctuations in daylight affect the level of sex hormones in the body of men living in high latitudes.

Thus, scientists in many countries recognize that seasonal variations in photoperiod or temperature can affect human reproductive biology. The prevailing part of the ongoing researches are focused on collecting biological material not from the same sample of subjects in dynamics (longitudinal studies), but from different people over a period equivalent to a year (cross-sectional study), for example, as in the works carried out in Israel [23] and Norway [21], which cannot give an objective picture of the true dynamics of the levels of sex hormones and dopamine, so it was preferable to use a longitudinal research of the same participants throughout the year.

Material and methods. The concentrations of follitropin (FSH), lutropin (LH), prolactin, progesterone, dopamine, cortisol, total and free testosterone, estradiol, dehydroepiandrosterone sulphate (DHEA-S), sex hormone-binding globulin, antisperm antibodies (ASAB) were determined in the blood by enzyme immunoassay on a quarterly basis (December, March, June, September) for one year in 20 healthy men from Arkhangelsk (mean age was 33.3±5.3 years). Blood samples were taken between 08:00 and 10:00. Indicators of the cardiovascular system, including heart rate (HR) diastolic (dBP) and systolic Blood Pressure (sBP), were analyzed. This study did not analyze the relationship between blood pressure and hormone levels and geomagnetic activity, since no geomagnetic storms were recorded during the study period according to the site https://www.spaceweatherlive.com: the magnetosphere was calm and no magnetic storms were recorded on the days of the survey of volunteers.

The candidates were recruited through social media platforms. Participants had to be aged 25-45 years and had no history of endocrine disorders. Ten of the men have children, and none of those surveyed had been treated for infertility. Subjects with any factor affecting the hypothalamic-pituitary-gonadal axis were excluded. The study was conducted in accordance with the ethical principles stated in Declaration of Helsinki of 1964 (revised in 2013) and was approved by the Ethics Committee of N. Laverov Federal Center for Integrated Arctic Research of the Ural Branch of the Russian Academy of Sciences (protocol No. 2 dated 04.11.2016, Arkhangelsk).

Climatic factors were assessed by 7 indicators, including length of daylight hours and monthly averages and actual data at 9 a.m. on temperature, humidity, atmospheric air pressure. Climatic data were obtained from the weather archive at https://rp5.ru/Archive_weather_in_Arkhangelsk.

Statistical processing was performed using STATISTICA v.10.0. Normality of the data was confirmed by a Shapiro-Wilk test. A nonparametric analysis of variance of Friedman's repeated measures was performed, followed by pairwise comparison using the Wilcoxon rank sum test using a Bonferroni correction, with p values less than 0.05 is considered significant. The relationships between the hormonal data and climatic data were determined by using Spearman's rank correlation test (ρ).

Results and Discussion. The men included in our study showed statistically significant changes in the levels of dopamine, LH, estradiol, and ASAB in different periods of the year. According to our results, no seasonal rhythms were found in the content of total and free testosterone. Similar results were demonstrated in a study of the seasonal fluctuations of certain hormones, including testosterone, in men living in the southwestern United States [11].

Despite the available literature data on the seasonal dynamics of blood pressure [17, 18], the examined men showed no changes in the levels of sBP, dBP, and heart rate (table).

Dopamine levels showed the largest individual seasonal fluctuations, the average difference between the maximum and minimum levels of the hormone was 64.4 ± 23.4%. 65% of men are characterized by the minimum levels of dopamine in the fall, and 60% - the maximum levels in the summer. The levels of estradiol and LH varied on average between the periods of maximum and minimum by 58 ± 18.7 and 45 ± 17.3%, respectively. In winter, the minimum levels of estradiol and LH were established in 45 and 47% of the examined persons, respectively. The maximum values of estradiol were recorded in 45% of the examined in the summer, and the maximum values of LH - in 45% of the persons in the spring.

LH showed a negative correlation with mean monthly atmospheric pressure (ρ=-0.27; p=0.015).

Estradiol showed a positive correlation with the average monthly air temperature (ρ=0.34; p=0.001), with the actual air temperature at the time of blood donation (ρ=0.34; p=0.001), with relative air humidity (ρ=0.23; p=0.04), with length of daylight (ρ=0.24; p=0.033); negative correlation with average monthly atmospheric pressure (ρ=-0.26; p=0.019), average monthly atmospheric air humidity (ρ=-0.25; p=0.023).

Dopamine showed a positive cor-

Levels of SBP, DBP, heart rate in men from Arkhangelsk depending on the photoperiod of the year (results are presented as a median and 10/90 percentiles)

Measure	March	June	September	December	p-level
sBP	127.0 (113.0; 140.5)	121.5 (115.0; 135.0)	122.0 (112.0; 155.5)	127.0 (103.0; 145.0)	p>0.05
dBP	81.0 (65.5; 93.5)	77.5 (70.5; 93.0)	75.0 (64.0; 100.5)	75.0 (69.0; 92.0)	p>0.05
heart rate	66.0 (58.5; 84.0)	66.0 (56.5; 80.5)	71.5 (56.5; 80.0)	71.0 (57.0; 88.0)	p>0.05

relation with length of daylight (ρ=0.28; p=0.012); negative correlation with average monthly atmospheric pressure (ρ=-0.40; p=0.0003), average monthly atmospheric air humidity (ρ=-0.23; p=0.039).

ASAB showed a positive correlation with the average monthly atmospheric air humidity (ρ=0.25; p=0.023); negative correlation with length of daylight (ρ=-0.28; p=0.011), average monthly air temperature (ρ=-0.24; p=0.029), actual air temperature at the time of blood donation (ρ=-0.31; p=0.006).

Seasonal fluctuations in sex hormone levels have been observed in several cross-sectional studies of men around the world [31, 32]. Others, however, did not show such circumannual changes [10, 28]. It is likely that the circannual seasonality of sex hormones in human can't be, evolutionarily, strictly required. In the present study, there was no seasonal rhythm of the levels of total and free testosterone, cortisol, DHEA-S, FSH and progesterone.

Monthly mean barometric pressure was the only climate parameter tested that appears to be contributing to seasonal fluctuations in LH levels. Correlation analysis showed that lower atmospheric pressure is associated with higher levels of LH, estradiol and dopamine, lower atmospheric humidity is associated with higher levels of estradiol and dopamine, and the longer the daylight hours – the higher the levels of estradiol and dopamine.

Atmospheric pressure probably affects the levels of the pituitary hormone LH not directly, by proxy, due to changes in the level of melatonin. Low barometric pressure is synonymous with low light levels. Low levels of natural light can cause our body to produce more melatonin. Thus, in men from northern Finland, the melatonin peak in May was associated with a significant increase in serum LH level [2].

In inhabitants of the Arctic territories, a short length of daylight in winter causes an increase in melatonin secretion [20]. Melatonin could act as a naturally occurring antiestrogen as demonstrated on *in vivo* models of animal mammary tumors [8] as well as *in vitro* human breast cancer cells [12]. This melatonin hypothesis may explain the lower level of estradiol in men in the darkest season in Arkhangelsk. This is confirmed by the fact that estradiol has the positive correlation with the length of daylight.

A decrease in the level of estradiol, which has cardioprotective effects, in the winter period correlates with an increase in the complications of cardiovascular diseases, often associated with an increase in blood pressure due to cold vasoconstriction [1]. An increase in blood pressure values during the winter period has been observed in many studies, but most often in elderly people or with chronic diseases, such as arterial hypertension or type 2 diabetes [13, 19, 26]. However, in our study of clinically healthy men, no seasonal dynamics and correlation with climatic factors were found in the values of sBP, dBP, and heart rate. While other studies have demonstrated a significant increase in sBP and dBP in winter compared to summer [17, 18]. These differences may be due to seasonal fluctuations in sunlight exposure. Recent studies show that ultraviolet A (UVA) and ultraviolet B (UVB) have been linearly and inversely associated with sBP. Due to the mobilization of reserve forms in the skin, ultraviolet radiation increases the availability of nitric oxide, the tonic production of which is associated with vasorelaxation and antiatherogenic and antiplatelet effects, thereby contributing to a decrease in blood pressure [6]. In addition, large observational studies have shown that low vitamin D levels are a risk factor for hypertension [7].

The absence of significant seasonal differences in blood pressure may be due to different approaches to the analysis of the seasonality of data, namely, 24-hour monitoring of sBP and dBP levels in work of Goyal A. et al. [17] and, on the contrary, a single measurement of blood pressure before blood sampling in our study.

At the same time, such an indicator of the activity of the sympathoadrenal system as dopamine showed significant seasonal changes and relationships with such climatic indicators as atmospheric pressure, humidity, and daylight hours, but not with air temperature.

The seasonality of the dynamics of dopamine levels with a maximum in summer has been established, which can be associated with both climatic factor (high intensity of ultraviolet radiation) and the connected increase in vitamin D synthesis [30]. Vitamin D modulates the hypothalamic-pituitary-adrenal system by regulating adrenaline, norepinephrine and dopamine production through vitamin D receptors in the adrenal cortex, and also increases expression of the tyrosine hydroxylase gene in adrenal medullary cells [25, 29, 33, 34]. Most vitamin D in the body is obtained by skin synthesis (80–100%), and the body's ability to synthesize vitamin D depends on the amount of sunlight that the skin receives [24]. If a person does not take a vitamin supplement, which was typical for the studied volunteers according to their personal data, then sun exposure is the most important source of vitamin D. In high northern latitudes (above 40°N), even with sufficient sun exposure, skin production vitamin D is low or absent in winter, which increases the need for food ration [9]. Because very few foods naturally contain vitamin D in amounts to meet this increased demand in winter, this leads to marked seasonal fluctuations in vitamin D levels and, as a result, to dynamic levels of biogenic amines.

Along with the suppression of reproductive function, short photoperiod is also reported to influence immune functions [35]. In wild animals, an increased level of melatonin in winter suppresses reproductive function, and stimulates immunity [15]. Apparently, elevated levels of melatonin in winter are associated with an increase in autoimmunity, which is demonstrated by significantly higher levels of ASAB in the studied men in winter compared to summer (p = 0.01).

Conclusion. Thus, while the effects of seasonal variations in length of daylight at high latitudes may be mitigated by the amount of artificial lighting in today's society, we were able to demonstrate significant seasonality in the levels of several hormones that affect human reproductive biology. Among the considered climatic factors, atmospheric pressure has the largest number of negative correlations with the levels of the studied hormones, which demonstrate a slight decrease in the autumn-winter period, characterized by increased atmospheric pressure and low air temperature. In general, the weather conditions in the winter months in Russia require much more effort from the human body to maintain normal life than in the summer months. Such climatic factors of the study area as the length of daylight and air temperature are statistically interrelated, they cannot be considered in isolation from each other, since an increase in daylight hours corresponds to an increase in air temperature. An increase in day length and air temperature is associated with an increase in estradiol and dopamine levels and a decrease in ASAB values. We believe that the seasonality of estradiol and ASAB is a daylight effect mediated by changes in melatonin levels, just as dopamine seasonality is mediated by changes in vitamin D levels.

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