

The annual cycle of the pituitary-thyroid axis activity in healthy men under prolonged cold air exposure

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ABSTRACT

The monthly investigations of military guards ((19.1 ± 0.9) years, n = 20) in northern European region (62°N lat.) that daily spent outdoors from 6 to 10 h were carried out during the year (from November to October). In examined subjects, the serum FT₄ levels were high enough during all period of research especially from April till October when the hormone levels exceeded norm. The concentration of serum FT₃ was rather stable during the year and corresponded to the normal level. At the same time, the levels of total form of thyroid hormones (TT₄ and TT₃) displaced to lower limit of norm. Thus, staying outdoors of military guards in the North for all the year round is accompanied by activation of thyroid hormones use.

Keywords: Thyroid Hormones; Human; Adaptation; North; Cold

1. INTRODUCTION

The role of hormones regulating human energy metabolism in cold condition has not been finally clarified. The study of seasonally-related changes of the pituitary-thyroid system status in human is interesting so far a long time it was established that hormones of the thyroid gland (TG) play main role in resistance of animal organism to cold [1-3]. It has been shown that single cold-air or crushed ice exposure did not change the levels of serum thyroxin (T₄) and thyroid-stimulating hormone (TSH) in adult men [4,5]. It has been revealed that the pituitary- thyroid axis in adult human subjects is insensitive to short-time cold exposure that decreased the body core temperature by 0.4°C - 0.9°C [6]. At the same time, immersion of adult subjects into cold water that decreased tympanic membrane temperature by 1°C resulted in twofold increase in the plasma TSH level for 90 min [7]. Repeated 30-min cold-air exposures for 2 months did not lead to changes in the T₄ and TSH con-

centrations but decreased the level of serum total triiodothyronine (TT₃) [8]. In another report, the decrease of the serum total T₄ (TT₄) level at repeated cold-water immersion was revealed [9].

The problem of prolonged and seasonal effects of cold is especially important in relation to humans permanently living in the North. The concept proposed in previous studies suggested that the pituitary-TG axis (Pit-TG) is activated during the cold season, which is accompanied by an increase in the levels of serum TT₃ and TT₄ [10]. Later the increased T₃ production has been shown in Antarctic winterers [11,12]. At the same time, it was noted in a number of reports that the level of T₄ remained unchanged during the year, whereas TSH concentration increased in winter [13]. In northern Finland, the T₃ concentration in urine was increased in the residents working outdoors from 6 to 10 h daily but there were no significant changes in the levels of serum TT₃, TT₄, free T₄ (FT₄) and the T₄ concentration in urine [14]. In winter, the free T₃ (FT₃) level decreased in these subjects, whereas TSH level increased (December), which in authors' opinion might be related to changes in illumination. The authors agree that the thyroid hormones (TH) utilization was increased in cold seasons but recognize that the temperature effect was insignificant (the levels of TT₃ and TT₄ were unchanged) and the opposite changes of TSH and FT₃ were not simultaneous [6]. The decrease of FT₃ level during wintering in Antarctica was shown [9]. At the same time, the decrease of TT₃ production and the increase of tissue availability of T₃ during long-term cold exposures were noted [8,9,12,15].

Our research of subjects that worked on Svalbard (78° N) has shown that the levels of TT₃ and TT₄ increased twice in the year during sharp change of intensity of the light factor and depended on effect of day duration change rather than on the duration of stay in the North or air temperature [16,17]. Testing with a thyrotropin-releasing hormone (TRH) load in winter showed that rep-

representatives of aboriginal Northern populations were characterized by a more pronounced activity of the central part of Pit-TG system as compared to poorly adapted subjects that were also born in the North [18].

Thus, there are still divergences in opinions of the long-term cold-induced changes in the state of the Pit-TG system. Some discrepancies result from different methodical approaches as the time and the strength of exposure of the external factor in different studies varied wide enough, and the groups were hardly comparable by real conditions of living. It is also mentioned that several studies were conducted in the geographical areas in which seasonal temperature decrease below zero was rare, so that the examined subjects were insufficiently exposed to cold.

The aim of this research was to study the state of the human Pit-TG system in homogeneous group under the conditions of chronic cold exposures during the year.

2. MATERIALS AND METHODS

2.1. Subjects

Nineteen healthy male Caucasian volunteers (18 - 21 years) were recruited for the present annual study. The subjects were the soldiers (military guards) in Northern European regions of Russia (Syktyvkar, Russia, 62°N) that daily spent outdoors from 6 to 10 h. All the subjects were screened by military physical and physiological manners. The daily routine of the examined subjects was stable throughout the observation period. The subjects passed medical examination and were free of any diseases and disorders possibly affecting their ability to participate in study. The subjects were similar in age and body mass index (BMI). All the recruited persons were not obese (BMI < 30) and have been in the military unit from 4 to 6 months—the time need for acclimations to the North [16]. The study was approved by Institutional Review Boards and each subject signed a written consent prior to participation.

2.2. Study Protocol

The study was conducted over a 12 monthly period. The examinations were carried out from Monday to Friday in 3-th decade of each month. The first examination was conducted in November 2004 and the last in October 2005. The subjects woke up at 06:00 a.m. and visited a nurse's office at 06:30 - 07:30 a.m. Fasting blood samples were obtained from the antecubital vein into vacutainer (Becton Dickinson BP) and physiological measurements were performed. Blood samples were centrifuged and serum was placed into eppendorf microcentrifuge tubes and was stored at -20°C until analyses. Daily mean temperature was obtained from the Province Meteorological Office.

2.3. Anthropometric Measurements

Body weight and height were measured using standard medical scale and anthropometer. BMI was determined as the ratio of body weight to height in meters squared ($\text{kg} \cdot \text{m}^{-2}$). Waist Circumference was measured to the nearest 0.1 cm at the umbilicus level and Hip Circumference was measured to the nearest 0.1 cm at the mid-point between the greater trochanter and the top of the patella.

The percentage of body fat mass was assessed according to the equations of Durnin and Wommersley [19]. For that purpose the skinfold thickness at four sites—biceps, triceps, subscapular and suprailiac—was determined using a Scinfold caliper. The skinfold thickness was measured three times to the nearest 0.2 mm. If result deviated more than 1.0 mm, the three measurements were repeated. Absolute and percent lean body mass (LBN) were calculated from body fat mass (%) and body weight (kg):

$$\text{LBM (\%)} = [100 - \text{body fat mass (\%)}],$$

$$\text{LBM (kg)} = [\text{weight} * \text{LBM (\%)} / 100]$$

2.4. Biochemical Measurement

Serum hormones concentration was determined by enzyme-linked assay with a “Power Wave 200” spectrophotometer (Bio-Tek Instruments, USA) using commercial kits according to the manufactures instructions. The reference ranges of normal values and conversion to SI units used for these assays are: TT₄ 64.4 - 148.0 nmol/l ($\text{nmol/l} \times 0.078 = \mu\text{g/dl}$), FT₄ 10.3 - 25.7 pmol/l ($\text{pmol/l} \times 0.078 = \text{ng/dl}$), TT₃ 1.2 - 3.0 nmol/l ($\text{nmol/l} \times 0.651 = \text{ng/ml}$), FT₃ 2.1 - 6.5 pmol/l ($\text{pmol/l} \times 0.651 = \text{pg/ml}$), TSH 0.23 - 3.4 $\mu\text{IU/ml}$ respectively.

The concentration of serum TT₄ was measured by commercial kits Randox Laboratories United Kingdom Cat. No TX 2112 with an intraassay coefficient of variance (CV) of 8%.

The concentration of serum TT₃ was measured by commercial kits T₃-total-IFA-BEST, Vector-Best, Russia, Cat. No X-3954 with an intraassay CV of 8% and assay detection limit of 0.2 nmol/l.

The concentration of serum FT₃ was measured by commercial kits Diagnostic Automation, Inc., Calabasas, CA, USA, Product Code 3148 with an intraassay CV of 5.2% and assay detection limit of 0.05 pg/ml.

The concentration of serum FT₄ was measured by commercial kits Randox Laboratories United Kingdom Cat. No FT 2137 with an intraassay CV of 8%.

The concentration of serum TSH was measured by commercial kits Tiroid-IFA-TSH-1, Alcor Bio, Russia with an intraassay CV 8% and assay detection limit of 0.05 $\mu\text{IU/ml}$.

2.5. Statistical Analysis

Data were analyzed with Statistica 6.0 (Statsoft, Tulsa, USA). Descriptive statistics was used to calculate mean and standard deviation (SD). Differences in annual dynamics of each parameter were tested by Friedman ANOVA. Where Friedman ANOVA revealed significant effect, a Wilcoxon test with Bonferroni correction for multiple comparisons was used to discern differences between months. Data in the figures and tables are present as mean and SD.

The accepted level of significance was $P < 0.05$.

3. RESULTS

The outdoor air temperature at 6 a.m. characterizing the weather during the study is presented in **Figure 1**.

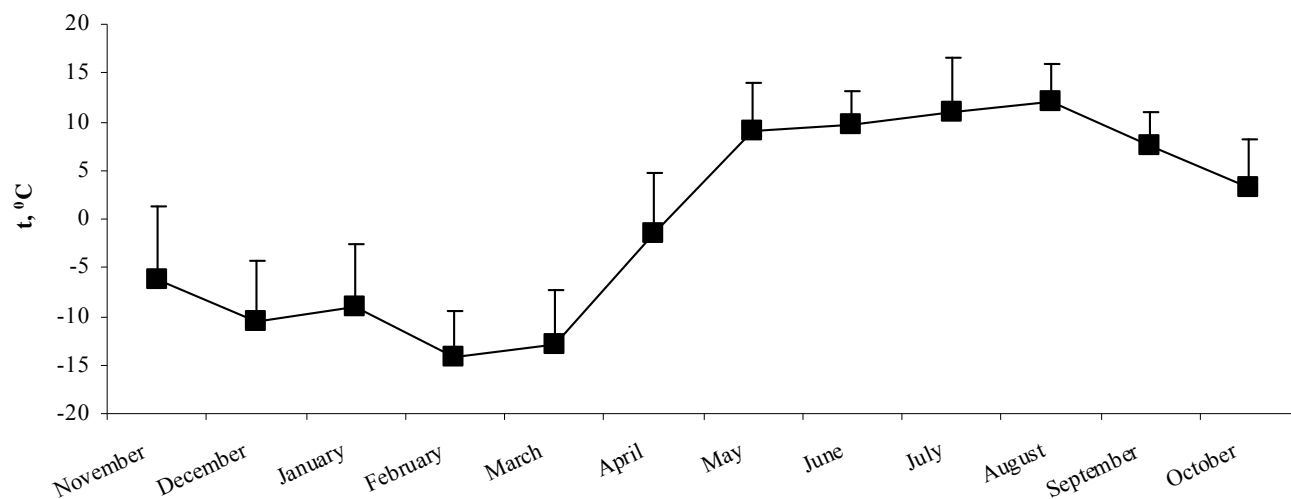


Figure 1. The outdoor air temperature at 6 a.m. during the study.

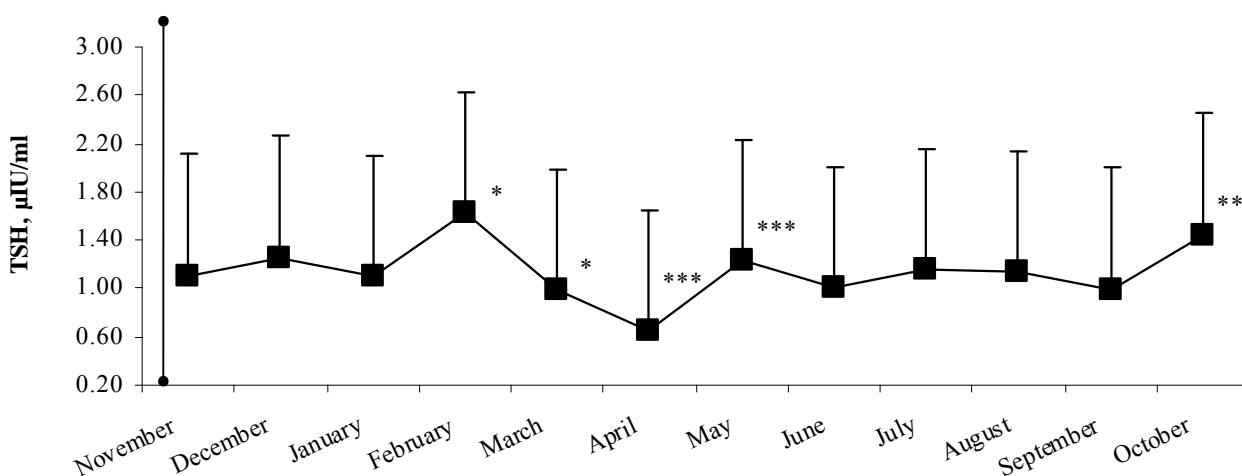


Figure 2. The concentration of TSH in blood serum of northern European male residents during year. The vertical arrow indicates the normative values of TSH (0.23 - 3.4 µIU/ml). Data are presented as mean ± SD. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared to previous month.

3.1. Anthropometric Characteristics

The anthropometric characteristics of the examined subjects are shown in **Table 1**. No significant changes in subjects' height and body weight were occurred over the observation period.

3.2. Thyroid Hormones Measurements

The serum TSH level at the first examination in November was (1.11 ± 0.42) µIU/ml and was invariable in December-January (**Figure 2**). The TSH concentration in the examined group at the first observation varied within normal range from 0.47 µIU/m to 2.09 µIU/m. The TSH level was the highest in February when the concentration of this hormone elevated significantly ($P < 0.05$) and

Table 1. Anthropometric characteristics of subjects.

Variable	November (n = 17)	December (n = 19)	January (n = 18)	February (n = 16)	March (n = 17)	April (n = 16)	May (n = 17)	June (n = 15)	July (n = 16)	August (n = 18)	September (n = 19)	October (n = 17)
Age (years) range	18.4 ± 0.6 18 - 20	18.6 ± 0.9 18 - 21	18.7 ± 1.0 18 - 21	18.9 ± 1.1 18 - 21	19.0 ± 1.1 18 - 21	18.9 ± 0.9 18 - 21	19.1 ± 0.9 18 - 21	19.2 ± 0.6 19 - 21	19.3 ± 0.7 19 - 21	19.5 ± 0.7 19 - 21	19.6 ± 0.8 19 - 21	19.5 ± 0.7 19 - 21
Height (cm) range	173.9 ± 5.6 161.5 - 182.5	174.1 ± 5.4 162.0 - 182.0	174.9 ± 5.1 162.0 - 182.0	174.9 ± 6.0 161.5 - 183.5	174.1 ± 5.5 162.0 - 183.5	174.8 ± 6.0 162.5 - 183.5	174.6 ± 5.9 162.5 - 183.0	173.3 ± 5.6 162.5 - 181.0	175.1 ± 4.7 164.0 - 181.0	175.0 ± 5.5 163.0 - 183.0	175.0 ± 5.9 163.0 - 184.0	174.5 ± 5.9 162.5 - 184.0
Weight (kg) range	67.8 ± 5.7 56.5 - 73.0	68.8 ± 5.8 56.5 - 76.5	69.2 ± 5.4 58.0 - 76.5	68.4 ± 5.8 58.0 - 75.5	68.2 ± 5.6 57.5 - 73.6	68.1 ± 5.8 57.0 - 74.5	67.6 ± 5.8 56.3 - 74.0	67.4 ± 5.8 55.5 - 76.7	68.6 ± 4.6 60.0 - 74.8	68.8 ± 5.3 55.0 - 75.9	68.7 ± 6.3 54.8 - 76.6	70.0 ± 5.8 55.0 - 77.0
Body mass index (kg/m ²) range	22.4 ± 1.2 20.2 - 24.2	22.7 ± 1.2 20.3 - 24.6	22.6 ± 1.3 19.9 - 24.2	22.3 ± 1.1 20.4 - 24.0	22.5 ± 1.4 20.0 - 25.0	22.3 ± 1.4 19.9 - 24.7	22.2 ± 1.4 19.3 - 24.1	22.4 ± 1.5 19.4 - 24.5	22.4 ± 1.4 19.5 - 24.2	22.5 ± 1.3 20.2 - 24.3	22.4 ± 1.4 20.0 - 24.6	23.0 ± 1.2 20.4 - 25.1
Waist-hip ratio range	0.86 ± 0.03 0.80 - 0.90	0.86 ± 0.02 0.82 - 0.90	0.86 ± 0.03 0.81 - 0.90	0.86 ± 0.03 0.80 - 0.93	0.86 ± 0.03 0.80 - 0.90	0.86 ± 0.03 0.79 - 0.89	0.85 ± 0.02 0.81 - 0.89	0.84 ± 0.03 0.77 - 0.89	0.85 ± 0.02 0.80 - 0.90	0.84 ± 0.03 0.78 - 0.91	0.85 ± 0.03 0.80 - 0.92	0.86 ± 0.02 0.81 - 0.90
Fat (%) range	25.7 ± 2.4 20.3-29.8	25.9 ± 2.6 20.3 - 30.2	26.6 ± 2.9 19.5 - 30.9	25.3 ± 3.0 19.5 - 28.9	23.7 ± 2.1 20.9 - 26.1	25.8 ± 2.9 21.2 - 29.9	25.1 ± 2.5 21.1 - 29.1	25.6 ± 3.6 18.4 - 31.3	25.6 ± 2.7 21.3 - 30.2	26.2 ± 2.1 22.8 - 30.3	25.4 ± 2.1 22.1 - 29.8	26.3 ± 2.3 21.6 - 29.5
Lean body mass (kg) range	50.5 ± 4.0 41.6 - 55.7	50.9 ± 3.9 42.2 - 57.1	50.0 ± 4.0 41.2 - 55.6	50.6 ± 4.1 43.2 - 56.1	53.4 ± 3.2 48.5 - 57.3	50.4 ± 4.0 41.9 - 56.1	50.7 ± 3.3 46.2 - 56.2	50.1 ± 4.2 41.1 - 57.7	51.0 ± 3.0 45.4 - 55.5	50.7 ± 3.9 40.5 - 55.7	51.5 ± 4.1 40.9 - 55.7	51.6 ± 3.8 40.9 - 56.6

Values are means ± SD and range. Note: No differences were found in any variable over a year.

reached (1.54 ± 0.85) $\mu\text{IU/ml}$. Next two months the TSH level decreased consecutively and was the lowest in April at (0.64 ± 0.18) $\mu\text{IU/m}$ that was significantly lower than during the other months. The next examination performed in May demonstrated an increase in the TSH level to (1.24 ± 0.32) $\mu\text{IU/ml}$ ($P < 0.001$). In period of May-September, the TSH concentrations were accorded to levels observed in the subjects in November-January. In October, the TSH level elevated to (1.45 ± 0.53) $\mu\text{IU/ml}$ ($P < 0.01$). The range of TSH concentrations in March-October was 0.39 - 2.61 $\mu\text{IU/m}$.

The TT_3 concentration in the subjects at the first examination was (1.45 ± 0.69) nmol/l and ranged within limits of 0.71 - 2.93 nmol/l . In December, this parameters increased ($P < 0.01$, **Figure 3**) and was the highest for all observations. In February, the TT_3 level decreased slightly while that reduced extremely in March and approached the lowest level of (1.11 ± 0.49) nmol/l in April. In May, the TT_3 level was returned back to initial values and was stable up to September. In October, the TT_3 concentration decreased to (1.17 ± 0.41) nmol/l ($P < 0.01$).

The FT_3 concentration was (4.46 ± 1.21) pmol/l at the first examination in November and (4.68 ± 1.07) pmol/l at the last that in October (**Figure 4**). The FT_3 level fluctuated insignificantly within limits from 4.15 pmol/l to 4.79 pmol/l over the year.

The TT_4 level in the subjects at the first examination was (68.2 ± 17.7) nmol/l with range of 41.9 - 89.4 nmol/l (**Figure 5**). During the next eleven examinations, the TT_4 concentration fluctuated in narrow range from (62.3 ± 16.5) nmol/l in March to (91.0 ± 27.64) nmol/l in Au-

gust. Seasonal dynamics of the TT_4 level are given in more detail in **Figure 5**.

The FT_4 level in the subject group in November was (23.2 ± 5.4) pmol/l and ranged from 13.3 pmol/l to 33.4 pmol/l (**Figure 6**). In November-March, the FT_4 level changed slowly. The FT_4 concentration in April increased significantly ($P < 0.001$) approaching (28.9 ± 4.0) pmol/l , and individual data ranged within limits of 18.6 - 32.0 pmol/l . This FT_4 level was higher than normal range proposed by manufacturer to this hormone. The following examinations showed that this elevated level of FT_4 remained unchanged in May-October.

4. DISCUSSION

The present study demonstrates that long-term influence of cold air results in formation of the adaptive response of the Pit-TG system. Our results indicate that the chronic effect of low temperatures on human organism (guard service) is accompanied by activation of the TH metabolism. It is necessary to noted that this activation caused by the cold influence during most part of the year results in accumulation of FT_3 and FT_4 .

Reed *et al.* have concluded [20] that in the euthyroid subjects (41 years and older) in condition of prolonged Antarctic residence, the increase in the serum TSH level (approximately 30%) was observed without change of the T_4 concentration during the winter months. While in the young euthyroid subjects (age 19 to 41), there was no circannual pattern in the TSH or T_4 levels but the increase in the plasma T_3 clearance rate and production rate (approximately 30%) was revealed during winter

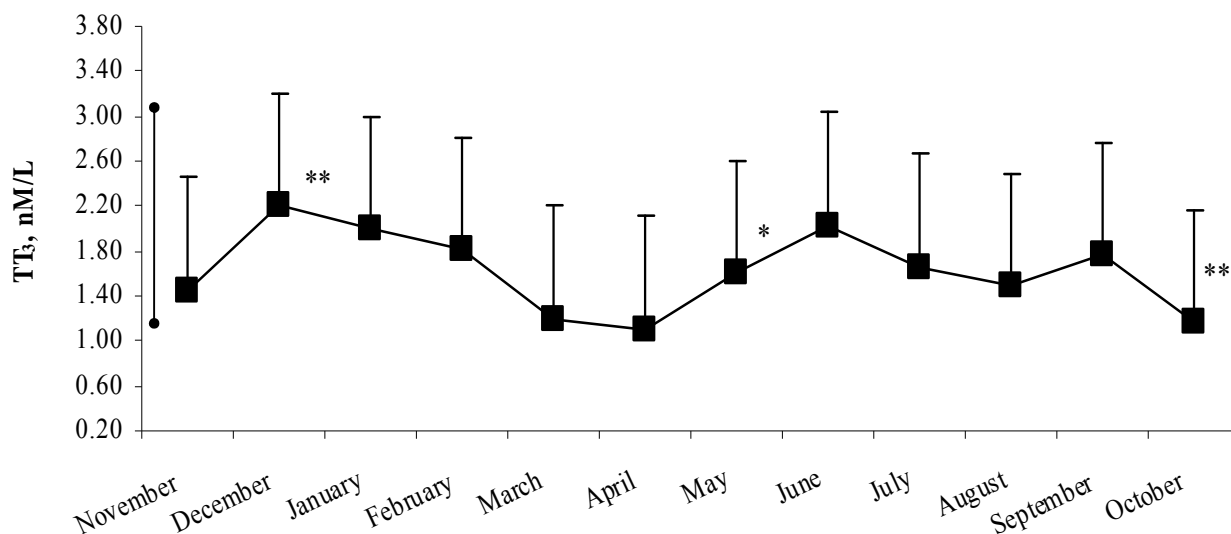


Figure 3. The concentration of TT_3 in blood serum of northern European male residents during year. The vertical arrow indicates the normative values of TT_3 (1.2 - 3.0 nM/l). Data are presented as mean \pm SD. * $P < 0.05$, ** $P < 0.01$ compared to previous month.

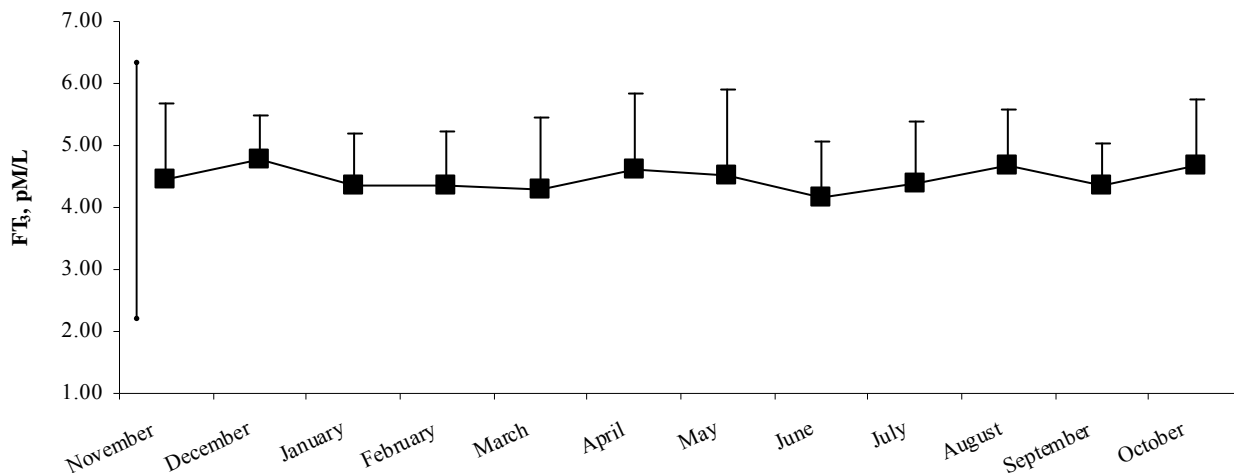


Figure 4. The concentration of FT₃ in blood serum of northern European male residents during year. The vertical arrow indicates the normative values of FT₃ (2.1 - 6.5 pM/l). Data are presented as mean ± SD.

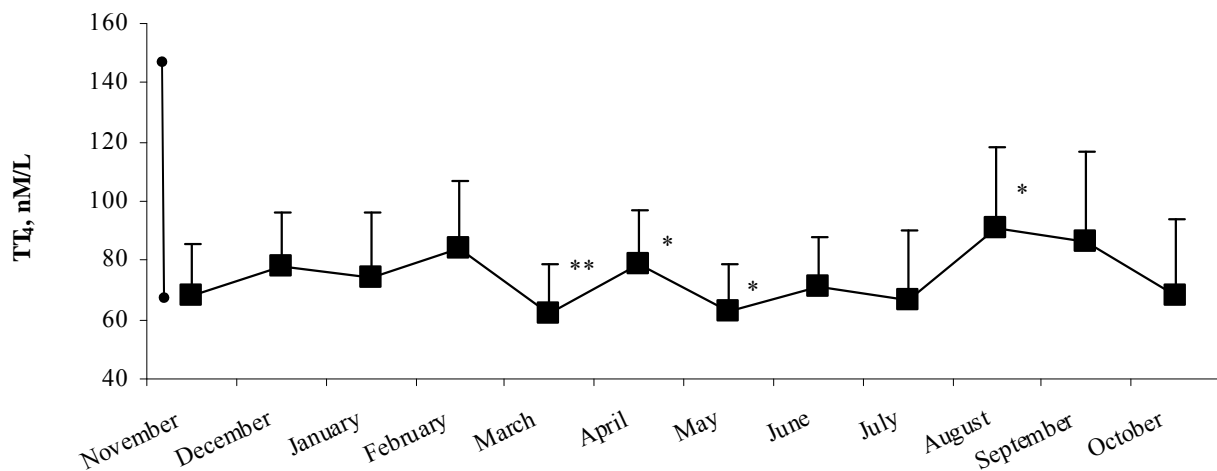


Figure 5. The concentration of TT₄ in blood serum of northern European male residents during year. The vertical arrow indicates the normative values of TT₄ (64.4 - 148 nM/l). Data are presented as mean ± SD. **P* < 0.05, ***P* < 0.01 compared to previous month.

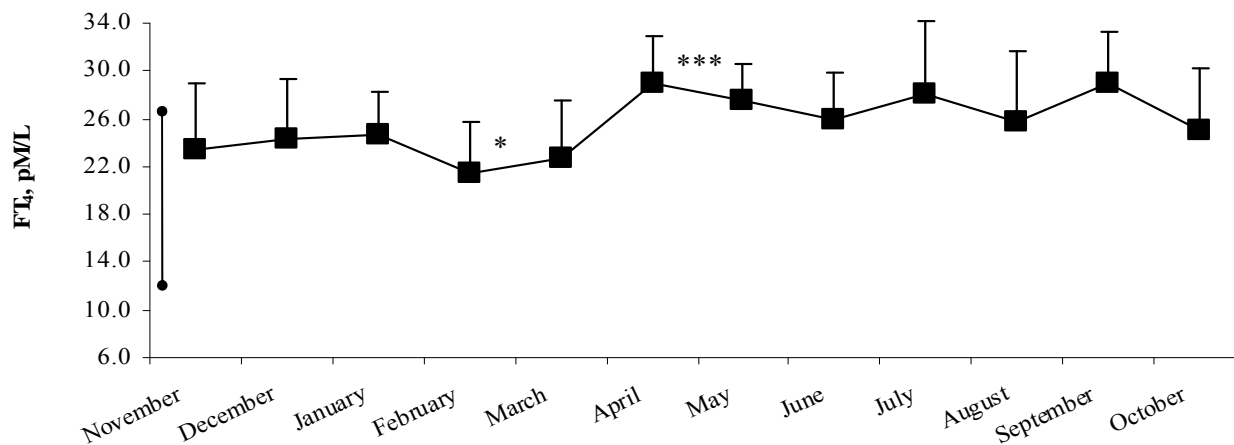


Figure 6. The concentration of FT₄ in blood serum of northern European male residents during year. The vertical arrow indicates the normative values of FT₄ (10.3 - 25.7 pM/l). Data are presented as mean ± SD. **P* < 0.05, ****P* < 0.001 compared to previous month.

seasons. Young subjects living in Antarctica more than 5 months had a decline in the serum T_3 and T_4 levels, and the increase in the T_3 clearance and production rate. Authors have supposed that the T_3 kinetic changes have seasonal dependence, and the cold exposure provides this mechanism.

To comment these results, it is to be noted that the researches of inhabitants of the North have shown that the total tension of endocrine system and the impairment of metabolism were found during the first 6 months after arrival in circumpolar regions [16]. Therefore, the examined group in our research consisted of subjects living on the North no less than 6 months.

Data of Indian Antarctic expedition have shown that the levels of total and free fractions of TH varied during wintering. At the end of the Antarctic summer in March, the TT_3 concentrations were found to be significantly lower ($P < 0.01$) compared to values recorded before wintering and showed the significant increase ($P < 0.05$) during the Antarctic winter. The TT_3 levels from May to December were found to be significantly higher than the March or April values. The plasma TT_4 concentrations remained unaltered during wintering in Antarctica. The FT_4 , FT_3 levels did not show any appreciable change. Though, the $TT_3:TT_4$ ratio tended to decline in March and April suggesting decreased peripheral conversion of T_4 to T_3 as the possible mechanism for a decline of TT_3 level in March. While the monthly studies did not reveal changes in the FT_3 and FT_4 levels during wintering, the authors have suggested that the serum TH levels during Antarctic wintering were affected by various factors of which the physical activity and the sharp change of day duration were the most significant. The TSH concentrations in March, April, November and December were found to be significantly higher than before wintering [21]. These data testify on our opinion about an important role of ethnic origin of the examined groups.

Thus, our results indicating the increase of use and excretion of T_3 in condition of long-term cold exposure correspond to data of Reed *et al.* [12] and Hassi *et al.* [14]. At the same time, it is to be noted that our data show that the TT_3 and TT_4 levels varied insignificantly near lower limit of norm at different temperature regimes during the year. This confirms active conversion of the connected forms of hormones to the active forms at long stay outdoors in the North during the year. Moreover, our results indicate that the produced stimulus did not cause tension in the central component of the Pit-TG system despite of activation of conversion of TH in the free forms. This is shown by the steadily low level of TSH and testifies that the feedback mechanism is inactive.

In research conducted on the similar examined group

in Alaska, the essential seasonal variations of the TH concentration were described in the infantry soldiers during different seasons of the year [22]. The TT_3 and TT_4 levels were the highest in winter while the FT_3 and FT_4 levels were the highest in early spring. The correlation between melatonin and T_3 was revealed in spring (light period of year). The seasonal distinctions were also shown between indigenous and newly arrived people, which may be related not only to cold acclimation but also to day duration. At the same time, this examined group was more heterogeneous in ethnic structure, time spent in the North and professional work than our group, which in the certain degree explains the results received by authors. In another study, the decrease (on 20%) in the serum FT_3 level to the 76th day was shown in young military men in Alaska during three monthly field operations [23].

In our study, the temperature of air in February has gone down below -15°C , which was accompanied by slight increase of the TSH level that testified about involving of the central mechanisms of regulation. At the same time, the content of TG peripheral hormones both total and free form was almost unchanged. These two facts, slight increase of the TSH concentration and the stable level of TH in condition of accumulation of free forms of hormones, testify in our opinion that the formed adaptive hormonal profile was still sufficient for compensation of external influence due to accumulation of active forms of hormones.

At the same time, the increase of the TSH level in this period is an adaptive reaction on complex of external influences. In Leppaluoto's opinion [4], the decrease of the body core temperature more than on 1°C causes the TSH release. It is possible to suggest that the decrease of air temperature below -15°C and the long stay of our examined group in these conditions are a critical level followed by the reaction of the central component of the Pit-TG system. Thus, the central stimulus for activation of the TH production is formed. However, the activation of the TH formation in the examined subjects at this period was not observed. It is possible to suppose some reasons for explanation of observed phenomenon. Firstly, the decrease of air temperature occurred gradually and the gradient of this influence was possibly insufficient for realization of mechanisms of TH synthesis activation in the TG. Secondly, the cold effects may reduce efficiency of TH action forming relative resistance to TH effects in tissues. It is known that actions of TH are determined by intracellular concentration of free hormones. It was demonstrated that the cytosolic T_3 -binding proteins from human red blood cells rapidly lost activity at low temperature [24]. Moreover, it is necessary to consider that the role of cellular transport in modulating

intracellular concentration of TH has still been poorly understood but the TH extrusion which can modulate availability and action of TH in mammalian cells has been described [25]. It has been demonstrated that temperature-sensitive TH efflux mechanism that may control cellular TH-content and TH responsiveness presumably by modulating access of TH to its nuclear receptors is presented in mammalian cells. The altered hormone transport represents one potential explanation for hormone resistance syndromes. So the active hormone efflux constitutes a novel mechanism for physiologic regulation of TH action that act through the nuclear hormone receptor.

There are data about interrelation of the thyroid function level and the food status. It has been shown that there is significant correlation between the T_3 and T_4 levels and the actual food consumption in Evenki, aboriginals of Siberia [26]. The interrelation between the serum T_4 concentration and the daily consumption of protein and fat was especially strong. The T_3 level positively correlated with the fatless weight of body and negatively correlated with fatty weight of body in the examined subjects. It has also been noted that there was interrelation between the TH concentration, especially with T_4 , and body weight in the examined subjects. Authors consider that the received results testify about interrelation between the thyroid function parameters and the basal metabolism level in aboriginals of the North and also reflect importance of account of role of food factor in estimation of basal level of metabolism in northerners.

The study of inhabitants of northern Norway has shown that the TSH level positively correlated with BMI in non-smoking inhabitants whereas there was no this correlation in smokers [27]. In our research, the BMI parameters remained stable during most part of the year. It is possible to note that the significant increase of the air temperature in March-April was accompanied by the decrease in the TSH level to minimal values found for all time of observation. This can confirm supposition that the TSH increase has been caused by the temperature factor. At the same time, the TT_3 level decreased to minimal values in March-April, and the TT_4 concentration also reduced in March though the level of free forms of hormones was stably high. Thus, the reduction of external cold influences is accompanied by decrease of activity of the central component of the Pit-TG system, which affects in the certain degree secretion of the TG hormones. The mechanisms providing accumulation of free forms of hormones are maintained. Moreover in April, the FT_4 concentration exceeded the normal level. When the air temperature in May increased considerably (by 25°C concerning March), the TSH level came back

to January value (preceding significant increase of the TSH level). Simultaneously, the TT_3 concentration rose insufficiently from the minimal annual levels. At the same time, the increased FT_4 level (above the normal values) in the examined subjects was kept up to September. In October, the FT_4 parameters returned to norm. It is interesting to note that the hormone profile in October (the last month of the research) was similar to that in February. In this time, the air temperature approached 0°C that might be a critical value characterizing the termination of the warm period of year. This allows to propose that the mechanism described by us is typical enough for conditions of Arctic region where the environment conditions and the temperature factor alter critically twice during the year. The similar mechanism could be characterized as a certain "medium-term reaction" so far as the accumulation of external factor effect is required for change of functional state of separate components of the Pit-TG system in conditions of aspiration of this system to preservation of stability.

There is a supposition that the cold exposure may enhance the T_3 production by deiodisation of T_4 in skeletal muscle via change in muscle fiber type, which could explain the high level of T_4 in the examined subjects in summer [2]. Moreover, we should not exclude possibility that the increase of the FT_4 level was caused by the fact that the air temperature was low (from $+10^\circ\text{C}$ to $+15^\circ\text{C}$) even in summer. This conditioned the formation of TH active forms as FT_3 level was stably high.

The study has shown that the long-term cold exposures result in activation of use of TH active forms- FT_3 and FT_4 . The change of action intensity of temperature factor can cause acceleration of conversion of total forms of TH in free forms of that. This process is accompanied by the decrease of levels of connected forms of hormones to lower limit of norm and the accumulation of FT_3 and FT_4 in blood serum to higher limit of norm. Under these conditions, the central component of the Pit-TG system is not activated keeping constancy of functional state. The activation of the central component of the Pit-TG system is occurred when influence of cold stimulus exceeds a certain limit. This activation is shown by increase of the level of serum TSH. The decrease of cold factor influence intensity results in reduction of tension of the central component of the Pit-TG system and lowering of the serum TSH level.

It is necessary to note specially that mean parameters of the FT_3 in our examined group varied from (4.15 ± 0.91) pmol/L in June to (4.79 ± 0.69) pmol/L in December. These results completely correspond to data obtained Hassi *et al.* [14] in the annual research of young outdoor workers from northern Finland. While our data on the FT_4 level, which varied from (21.4 ± 4.3) pmol/L to

(28.9 ± 4.0) pmol/l, do not conform to data of Hassi *et al.* that FT₄ level averaged 15 pmol/L. This is probably caused by the fact that determination of both FT₃ and FT₄ in our and above-mentioned studies was performed by various methods and reagents of different producer therefore there could be diverse reference ranges. Despite in both studies, the levels of free forms of hormones were high and accorded height limit of norm.

In report of Hassi *et al.* [14], the important fact showing significant elevation of the TSH content during period of the minimal temperatures observed in northern Finland in December has been described. In our research, the TSH level also raised significantly at achievement of the minimally low temperatures that were in conditions of our region in February. Thus, these data also confirm the phenomenon described earlier and allow to explain its origin that was not possible to make in the above-mentioned report.

5. CONCLUSIONS

Thus, the central and peripheral components of the Pit-TG system can show certain plasticity in conditions of long-term exposure of cold air. The results of our research allowed to show that adequate selection of the examined groups is important for revealing effect of external long-term stimulus on human organism as it defines obtained results. Our materials allow differentiating the adaptive response of the Pit-TG system as a whole on chronic cold air exposure showing activation of T₃ and T₄ active forms use at the “moderate” intensity of the external factor action. The central component of the Pit-TG system is activated in conditions of excess of a certain limit-excess of exposure doze. In conditions of the North, this activation of the central mechanisms can not cause mediated reaction from peripheral target organs, and a certain resistance to TSH effect in the TG is observed.

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