POINT OF VIEW

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TYPE 2 THYROID ALLOSTASIS IN THE RESIDENTS OF YAKUTIA

Type 2 thyroid allostasis is a dynamic stress response to changes in thyroid homeostasis that may occur in response to chronic exposure to cold. It is believed that, under these conditions, type 2 allostatic reactions can increase the basal metabolic rate to maintain priority thermogenic mechanisms in the body. For the first time, this work assesses the allostatic response of the thyroid gland among residents of the central region Yakutia with the most extreme climate (from -47°C to -11°C) using a mathematical model called SPINA. The SPINA model reflects the total activity of peripheral deiodinase enzymes (SPINA-GD), as well as the secretory capacity of the thyroid (SPINA-GT). The results showed that the SPINA-GT parameter was within normal limits for all individuals in the study. However, the SPINA-GD parameter was also within normal limits in 30% of those examined, with an increased SPINA-GD value found in 70% of the individuals examined. It was revealed that individuals with elevated SPINA-GD had higher free triiodothyronine (fT3) levels (6.79±0.62 pmol/L) and lower free thyroxine (fT4) levels (13.82±1.51 pmol/L) than those with normal SPINA-GD (fT3=5.96±0.48 pmol/L; fT4=15.37±0.98 pmol/L; p<0.001). This indicates an increased rate of T4 deiodination to T3 in 70% of the most individuals, and the reason for this is likely due to type 2 thyroid allostasis in response to cold stress. Using the SPINA parameters for the first time allows us to identify changes in hypothalamus-pituitary-thyroid axis homeostasis during the winter-spring season among 70% of surveyed residents of Eastern Siberia.

Keywords: type 2 thyroid allostasis, SPINA-GT, SPINA-GD, free triiodothyronine (fT3), free thyroxine (fT4), Yakutia.

Introduction. Allostasis, or the allostatic response, is a dynamic stress response that helps maintain stability by adjusting the functioning of homeostatic systems [14]. This response can occur in stressful and life-threatening situations [24; 30], where changes in hormone, neurotransmitter, and biochemical signaling levels, as well as organ and tissue regulation, may be observed [25]. In 2012, researchers proposed the concept of allostasis to explain the adaptive response of the thyroid in certain stressful situations [6]. Two types of allostatic responses have since been identified [30]. Type 1 thyroid allostasis occurs when the body detects a change in environmental or physiological conditions (diet, hunger, strenuous exercise, life-threatening illness, and depression) and predicts that energy intake will be insufficient to meet energy needs, and, active thyroid hormones are selectively suppressed, resulting in suppression of whole body metabolism [12; 30]. Type 2 thyroid allostasis occurs when the body detects a change in environmental or physiological conditions (pregnancy, obesity, endurance training, and adaptation to cold climates) and predicts that the change in energy needs can be met by increasing caloric intake and from existing energy stores in white adipose tissue, and then circulating free triiodothyronine (fT3) levels will increase, increasing whole body energy expenditure [12; 30].

In humans, changes in thyroid hormone homeostasis were first described in starving obese patients in the 1970s, where a decrease in blood concentrations of triiodothyronine (T3) was found after several days of fasting, which gave rise to the concept of "low T3 syndrome" [28]. Later, a decrease in T3 concentrations has been described in various calorie-restricted diets [15; 28; 29], and in eating disorders, such as anorexia nervosa [9; 16]. Through a compilation, a large number of other studies have also discovered factors where thyroid allostasis could occur. These include physical exertion, serious illnesses, depression, pregnancy, obesity, and adaptation to cold climates [14; 30].

It is believed that people who live in cold climates have certain adaptation mechanisms. In particular, thyroid hormones have been noted as important components of adaptation to cold stress [3; 19], as they play a significant role in regulating the main metabolic processes and generating heat (nonshivering and shivering thermogenesis) [20; 22; 23]. Previously, higher basal metabolic rates were documented among the indigenous peoples of Siberia, the Yakuts, Evenks and Buryats, compared to predicted values obtained from European populations [4; 5; 8; 27; 32]. Among the Yakuts, seasonal variations in the basal metabolic rate have been observed. Young men and women under 50 years of age showed an increase in their metabolism in winter, whereas older people showed a moderate decline [19]. At the same time, young men showed a positive correlation between their basal metabolic rate and fT3 levels [19]. Signs of "polar T3 syndrome", characterized by a decrease in fT3 and free thyroxine (fT4) levels, were found in children and adolescents from the Arctic regions [18] and in adults from central regions of Yakutia in the winter season [1; 19; 21]. This suggests that changes in thyroid hormone homeostasis during winter in Yakut residents are a result of allostatic response to cold stress.

Currently, there are no esTableished methods for assessing and differentiating the allostatic reactions of the thyroid gland. However, Dietrich and colleagues [2] have proposed using mathematical calculations based on the structural parameters of thyroid homeostasis (SPINA) to differentiate between these reactions. The parameter SPINA-GD measures the total activity of peripheral deiodinases, which catalyzes the conversion of thyroxine (T4) into T3 [31]. The parameter SPINA-GT represents the theoretical secretory capacity of the thyroid gland, or the maximum amount of T4 it can produce under stimulated conditions [31].

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Therefore, the aim of the present study is to evaluate the homeostasis thyroid hormone using SPINA parameters in the context of allostatic response to chronic exposure to cold.

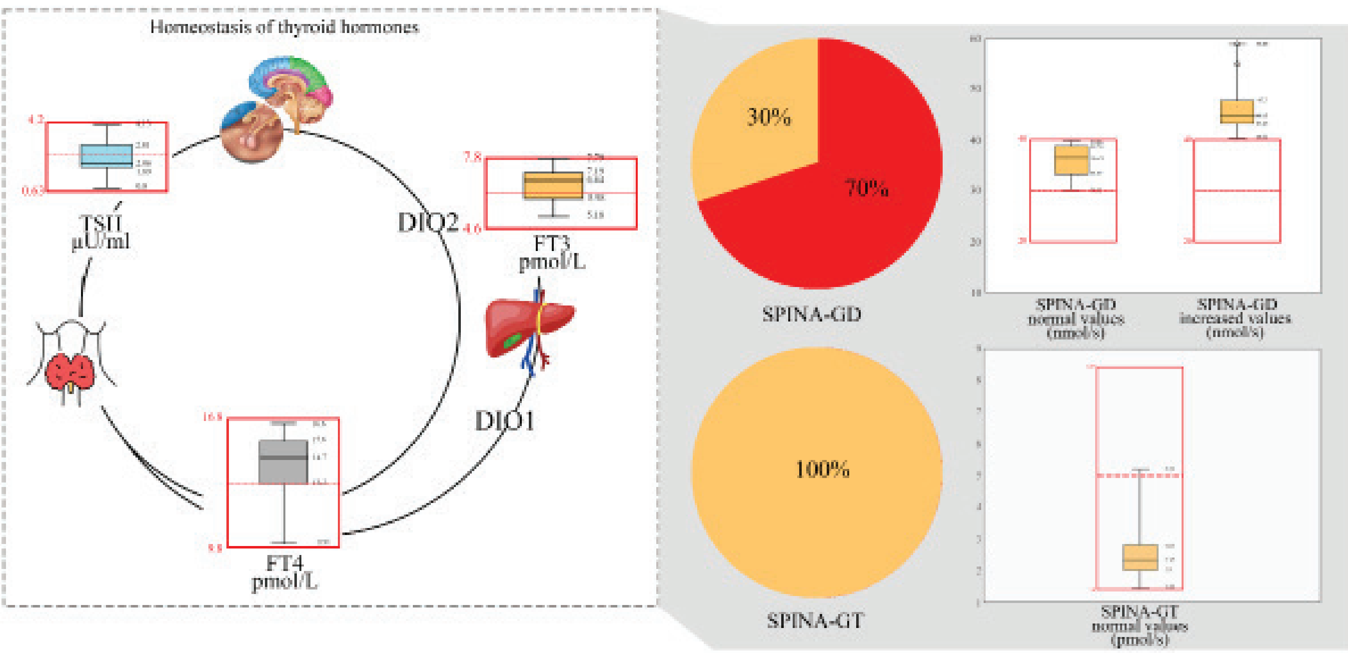
Materials and methods. *Subjects.* The research sample comprised of 92 individuals (with an average age of 19.91±1.88 years) who presented no health concerns at the time of the study. They independently completed a questionnaire which asked about their gender, ethnic background, age, the presence of chronic diseases and experience of taking antidepressants. All participants gave written informed consent for participation in the study. Study was approved by the local Biomedical Ethics Committee at the Yakut Scientific Center of Complex Medical Problems, Siberian Branch of the Russian Academy Scientific of Medical Sciences, Yakutsk, Russia (Yakutsk, Protocol No. 16, and 13 December 2014).

Anthropometric parameters, enzyme immunoassay and temperature parameters. Blood samples from the men we studied were carried out from December to May in 2014-2015. Venous blood for the study was collected in the morning after 8 hours of fasting from all participants. For each day of blood collection, the average ambient temperature (°C) was determined using archived data on weather reports (https://www.timeanddate.com). Anthropometric parameters (body weight in kilograms, height in centimeters) were measured in all participants using standardized methods. Body mass index (BMI) was calculated by dividing body mass by the square of height. The sample was divided into three groups according to BMI categories [10]: underweight (≤18.49 kg/m^2), normal weight (18.5–24.99 kg/m^2), and overweight/obese (≥25 kg/m^2). The levels of thyroid-stimulating hormone (TSH, µU/ml), fT3 (pmol/L) and fT4 (pmol/L) in blood serum were determined by time-resolved immunofluorescence analysis using the "DELFIA hTSH Ultra", "DELFIA Free Thyroxine", "DELFIA Free Triiodothyronine" (Perkin-Elmer Inc., USA). The concentrations of the three hormones in the samples were measured at a wavelength of 450 nm using a VICTOR X5 Multilabel Plate Reader (Perkin Elmer Inc., USA). The References values according to the kit recommendations were TSH 0.63-4.2 µU/ml, fT3 4.6-7.8 pmol/L, fT4 9.8-16.8 pmol/L.

SPINA parameters. Parameters for assessing thyroid homeostasis were calculated using the program SPINA Thyr (SPINA Thyr, RRID:SCR_014352, doi 10.5281/zenodo.3596049) [2; 6]. This program calculates the structural parameters of thyroid homeostasis based on the equilibrium concentrations of hormones TSH, T3 (total or free) and T4 (total or free) [2; 6]. The results of the evaluation studies and the algorithms underlying the mathematical theory have been published in several papers [6; 7; 26; 30]. The References values according to the recommendations of the SPINA Thyr program were SPINA-GT - 1.4-8.7 pmol/s, SPINA-GD - 20-40 nmol/s. TSH levels were within normal ranges (2.20±0.83 µU/mL) in the entire group of individuals. However, in one individual, we found elevated levels of fT3 (7.96 pmol/L) and fT4 (17.2 pmol/L). Elevated fT4 levels were also found in five other individuals (17-18.8 pmol/L). Elevated levels of fT4 were also found in five other individuals (17-18.8 pmol/L). In order to calculate parameters for assessing thyroid homeostasis, we normalized the sample by BMI and levels of fT3 and fT4. We excluded individuals who were underweight or overweight, as well as those with elevated of fT3 and/or fT4 levels (n=27) and excluded those selected during the warmer season (>0°C) (n=4). As a result, we calculated SPINA parameters for 61 healthy male with normal BMIs and normal TSH and fT3/fT4 levels.

Statistical analysis. The results were analyzed using a computer program for statistical data processing Statistica 13.5 (TIBCO Software Inc., USA). Quantitative results are presented as mean ± standard deviation. To compare the two groups, the nonparametric Mann-Whitney U test for small samples was used, p values ≤0.05 were considered statistically significant.

Results. *Parameters of thyroid homeostasis - SPINA in residents of Yakutia.* The results of calculating the parameters of SPINA homeostasis showed that, in all examined individuals, the parameter SPINA-GT was within normal limits and averaged 2.61±0.76 pmol/s. Elevated levels of SPINA-GD were found in 43



Homeostasis of thyroid hormones and parameters SPINA-GD and SPINA-GT

Comparative analysis of hormone levels of the pituitary-thyroid axis between groups according to SPINA-GD values

Hormones	Normal SPINA-GD values	Increased SPINA-GD values	p
TSH, µU/ml	2.15±0.92	2.34±0.81	0.676
FT3, pmol/L	5.96±0.48	6.79±0.62	<0.001
FT4, pmol/L	15.37±0.98	13.82±1.51	<0.001

individuals (70%; 45.7±4.1 nmol/s), and in the remaining 18 individuals (30%), SPINA-GD was within the normal range (35.94±2.90 nmol/s). There was a statistically significant difference in SPINA-GD values between individuals with normal SPINA-GD and those with elevated SPINA-GD (p<0.001) (Figure).

To detect changes in thyroid hormone levels, we calculated median, percentile (Q25; Q75) values, minimum and maximum values for the hormones TSH, fT3, and fT4. We compared these values with the median and minimum/maximum values of the References intervals. As a result, we found that the median fT3 value (6.58 pmol/L) and the median fT4 value (14.6 pmol/L) were both increasing from the median References intervals (6.2 and 13.3, respectively). The median TSH value was decreasing from the median of the References interval (2.05 vs 2.42, respectively) (Figure).

Comparative analysis of pituitary-thyroid axis hormone levels between groups based on SPINA-GD values. A comparative analysis was performed on the pituitary-thyroid hormone levels in individuals with normal and elevated SPINA-GD scores (Table). The analysis showed that those with elevated scores SPINA-GD had higher fT3 levels and lower fT4 levels, indicating an increased rate of T4 deiodination into T3. In contrast, those with normal scores SPINA-GD had a slower rate. The results indicate a change in thyroid hormone homeostasis in 70% of individuals examined living in extreme cold conditions in central Yakutia.

Discussion. *The SPINA-GD parameter as a marker of type 2 thyroid allostasis.* The present study was the first to evaluate thyroid hormone homeostasis in the context of chronic cold exposure using SPINA parameters among residents of the coldest region of Siberia. A total of 61 individuals were included in the study. Our findings showed that the median values of fT3 and fT4 increased compared to the median levels within the References interval. However, the median TSH values decreased compared to the median levels within the References interval (Figure). All participants had normal SPINA-GT levels, while 43 individuals (70%) had elevated SPINA-GD, which is associated with an increased rate of T4 deiodination to T3 (p<0.01). Similar to the characteristic phenotypic changes described by Chatzitomaris et al., who described changes associated with type 2 thyroid allostasis [30]

Since the sample was collected during the winter-spring period (from December to April), at ambient temperatures ranging from -47°C to -11°C, normalized by weight (excluding underweight and overweight individuals), sex (all males), age (18-27 years old), ethnicity (only Yakuts), and level of health (no acute or chronic diseases), the main cause of type 2 thyroid allostasis in 70% of studied residents of Yakutia is likely due to a general stressor - cold. The pronounced allostatic reaction in response to cold in our sample is probably associated with young age (average age 19.91±1.88 years); we assume that in other age groups this reaction may not be as pronounced. Several authors have suggested a similar allo-thyroid response type 2 may occur in response to cold exposure [12; 30], but this has only been previously confirmed in animals [30]. In this study, for the first time, evidence of type 2 thyroid allostasis has been found in people living in the extremely cold climate of central Yakutia.

Negative and positive aspects of thyroid allostasis. Currently, it is difficult to determine the health effects of thyroid allostasis, as there are few studies available. However, based on the classical view of allostasis, it is believed that short-term allostatic responses have a protective effect, but longer-term allostatic responses ("allostatic overload") can lead to pathological conditions and be life-threatening [14; 30]. This is why maintaining a balance between homeostasis and allostasis is essential for good health.

Chatzitomaris et al. [30] suggest that the direct negative impact of allostasis can only occur with "allostatic overload" in the terminal stages of thyroid diseases, such as thyroid storm and myxedema coma. An indirect negative effect of the allostatic reaction may occur in the diagnosis of thyroid diseases, which may pose some difficulties in making an accurate diagnosis and may cause problems or complications during treatment. Since high basal levels of fT3 and fT4 can be supported by mechanisms of type 2 allostatic reaction, this can cause difficulties in identifying hypothyroidism conditions (not detected/detection at a late stage).

On the other hand, allostatic responses are, first and foremost, a protective mechanism of the body against changes in the external environment or physiological states, helping the body to adapt to these changes [11]. Type 2 thyroid allostasis has been previously observed in pregnant women and those with obesity, and it has been interpreted as an adaptation mechanism characterized by an increased secretion of T4 from the thyroid gland and an increased deiodination [30]. We suggest that, in current conditions of physical inactivity, increased consumption of fast carbohydrates, and high levels of energy intake and basal metabolism, type 2 thyroid allostasis under cold stress may help to reduce the risk of obesity-related complications (cardiovascular disease and type 2 diabetes).

Conclusions. For the first time in this work, using the SPINA parameters, it has been possible to identify changes in the homeostasis of the hypothalamic-pituitary-thyroid axis in response to chronic cold stress in more than 70% of the examined residents of Yakutia.

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RATIO OF NEUTROPHILS TO LYMPHOCYTES AND APOPTOSIS OF LYMPHOCYTES IN PATIENTS WITH HBV AND HCV DEPENDING ON THE STAGE OF LIVER FIBROSIS

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A common complication of HBV and HCV is liver cirrhosis, which is based on chronic systemic inflammation associated with immune dysfunction that affects the progression of the disease. **The purpose of the study.** Determination of NLR and lymphocyte apoptosis index as a marker of the degree of inflammation and systemic immuno-inflammatory response in various degrees of liver fibrosis in patients with viral hepatitis.

Materials and methods. 107 patients underwent the study, of which 53 patients were diagnosed with HBV and 54 with HCV. The blood levels of leukocytes, neutrophils, and lymphocytes were studied in the studied patients and the neutrophil/lymphocyte ratio (NEU/LYM) was determined. In order to verify structural changes in the liver, ultrasound elastometric examination was performed on a 2D – Supersonic Aixplorer SWE device (France) for all persons with esTableished viral hepatitis. The examination of patients was carried out according to the Cut–off scale, and liver fibrosis was determined by the METAVIR scale. A group of 10 practically healthy individuals was selected as a comparison group. The values of the indicators were expressed in kPa, the value of the indicator 7.1 kPa corresponded to F2, 9.2 kPa – F3, F4≥13.5 kPa. Verification of HBV and HCV was carried out by PCR on the device “Rotor Qene Q” (Germany).