METABOLIC ACTIVITY OF IMMUNOCOMPETENT CELLS IN ASSESSMENT OF INDIVIDUAL COLD SENSITIVITY

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The rapid switch on of the transient short-term responses involved in adjustment of homeostasis plays a key role in human adaptation to low temperatures that is essential for adjustment to low-temperature environment. The network of signaling pathways together with metabolic regulators provide sufficient plasticity of the cells of immune system, the normal function of which is extremely important for successful human adaptation. Sufficient energy supply to immunocompetent cells makes it possible to form an adequate immune response to any negative factor and to ensure adaptive functional rearrangements. The study was aimed to assess the variants of the immunocompetent cell metabolic pathways involved in acquiring individual cold sensitivity. A total of 180 people aged 25–55 (130 females, 50 males) were assessed before and after the short-term whole body cooling. Enzyme immunoassay was used to define the levels of IL10, IL6, TNFα, irisin, transferrin, sTfR, HIF-1α, Sirt3 in peripheral blood and cell lysate. The levels of glycogen (cytochemical methods) and ATP (luciferin-luciferase assay) in lymphocytes were defined. The decrease in peripheral blood lymphocyte levels after cooling was indicative of the formation of immediate adaptive response and activation of glycolysis amid less intense inflammatory response. The increase in the levels of circulating lymphocytes after the cold esposure was associated with activation of inflammatory responses. The lower ratio of HIF-1α/SIRT3 metabolic regulators was found in the surveyed volunteers who showed no changes in the levels of lymphocytes. This indicated predominance of mitochondrial activity in adaptation to low temperatures.

Keywords: cold, metabolic activity, glycogen, irisin, ATP, oxygen saturation

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МЕТАБОЛИЧЕСКАЯ АКТИВНОСТЬ ИММУНОКОМПЕТЕНТНЫХ КЛЕТОК В ОЦЕНКЕ ИНДИВИДУАЛЬНОЙ ХОЛОДОВОЙ ЧУВСТВИТЕЛЬНОСТИ

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Центральную роль в адаптации организма человека к холоду играет быстрое включение переходных краткосрочных реакций, которые участвуют в корректировке гомеостаза, необходимой для приспособления к низкотемпературной среде. Сеть сигнальных путей и регуляторы метаболизма обеспечивают достаточную пластичность работы клеток иммунной системы, нормальное функционирование которой крайне важно для успешной адаптации организма человека. Энергообеспеченность иммунокомпетентных клеток дает возможность формирования адекватного иммунного ответа на воздействие любого негативного фактора, обеспечения адаптационных функциональных перестроек. Целью работы было изучить варианты путей метаболической активности иммунокомпетентных клеток в формировании индивидуальной холодовой чувствительности. Проведено обследование 180 человек в возрасте 25–55 лет (130 женщин, 50 мужчин) до и после кратковременного общего охлаждения. В периферической крови и лизате клеток иммуноферментным анализом определяли уровни IL10, IL6, TNFα, иризина, трансферрина, sTfR, HIF-1α, Sirt3. В лимфоцитах определяли содержание гликогена (цитохимически) и АТФ (люциферин-люциферазный метод). Снижение уровня лимфоцитов в периферической крови после охлаждения свидетельствует о формировании срочной адаптивной реакции и активации гликолитических процессов в клетке на фоне более низкого уровня воспалительной реакции. Повышение уровня лимфоцитов в циркуляции после воздействия холода происходит на фоне активации воспалительных реакций. Для обследованных волонтеров, у которых не было зарегистрировано изменений в уровне лимфоцитов, выявлено более низкое соотношение регуляторов метаболизма HIF-1α/SIRT3, что свидетельствует о преобладании митохондриальной активности при адаптации к холоду.

Ключевые слова: холод, метаболическая активность, гликоген, иризин, АТФ, сатурация кислорода

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Adaptation to the Northern environment is associatied with the body's ability to adapt to low temperatures, which results in the need for metabolic rearrangements. Glycolysis, that is used by cells during proliferation or when exposed to extreme loads, is the quickest way to acquire energy [1]. Mitochondria slower but more effectively facilitate ATP production, however, mitochondrial oxidative metabolism sensitizes cells to apoptosis [2]. Sirt3 is one of the key mitochondrial metabolic regulators [3–6]. The Sirt3 downregulation can be observed in individuals with cardiovascular disorders, diabetes mellitus, cancer and metabolic disorders, it is also involved in regulation of oxidative stress via the Sirt3-AMPK-α-PGC-1α pathway [7–11]. Hypoxia-inducible factor HIF-1α that increases glycolysis and suppresses mitochondrial activity is the other factor involved in regulation of cellular metabolism [12]. Evaluation of the relationship between these two regulators would make it possible to assess the direction of cellular metabolic activity. Our previous studies showed that people living in the North respond differently to the short-term whole body cooling, which was evident in altered peripheral blood lymphocyte levels (decreased levels, increased levels or no response) [13, 14]. Thus, it would be interesting to assess the role of the immunocompetent cell metabolic activity pathways in acquiring individual cold sensitivity. This consideration has become the aim of the study.

METHODS

Examination of 180 people (among them 130 females and 50 males) aged 25–55 before and after the short-term whole body cooling in the cooling chamber at –25 °C for 5 min was performed. Blood was collected from the cubital vein before and immediately after cooling. Inclusion criteria: healthy working-age people with no chronic and/or recurrent diseases at the time of examination. The leukogram patterns were defined with the XS-1000i haematology analyser (Sysmex; Japan). Concentrations of cytokines IL10, IL6, TNFα, irisin, transferrin, sTfR, HIF-1α, Sirt3 were measured by enzyme immunoassay using the Evolis (Bio-Rad; France) and Multiscan MS (Finland) enzyme immunoassay analyzers. Glycogen levels were assessed by cytochemical method (Abris+; Russia). Adenosine triphosphate (ATP) was quantified by luciferin-luciferase assay. The results of chemical reaction were assessed in the LUM-1 luminometer (Lumtek; Russia) using the Lumtek standard reagent kits. Oxygen saturation levels were defined with the pulse oximeter (Armed YX300; China). Body weight (kg), body length (cm) were measured and body mass index (kg/m^2) was calculated in all the surveyed individuals. Subcutaneous and visceral fat assessment was performed with the portable device by Omron (Japan). In accordance with the manufacturer's guidelines, visceral fat percentage of 1–9% was considered normal, the percentage of 10–14% was considered high, and the percentage of 15–30% was considered very high. The study results obtained were assessed in three groups based on alterations in peripheral blood lymphocyte counts after the short-term whole body cooling. In group 1, lymphocyte counts decreased by 1.5–2 times from 2.1 (1.77–2.44) to 1.69 (0.95–2.16) × 10^9 cells/L ($p < 0.001$); in group 2, lymphocyte counts increased from 1.49 (1.26–1.74) to 2.22 (1.48–2.61) × × 10^9 cells/L ($p < 0,01$); no significant changes were observed in group 3 (1.88 (1.46–2.17) and 1.82 (1.46–2.56) × 10^9 cells/L). There were no differences in age between groups; the average age was 33 years in group 1, 2–31 years in group 2, 32 years in group 3. Statistical processing of the results was performed using the Statistica 10 software package (USA). Trait distribution was non-normal (Shapiro–Wilk test), that is why the data were expressed as median and 25th-75th percentile (Me (25–75)). Multiple data samples (of three groups) were compared using the Kruscal–Wallis test ($p < 0.05$). Mann–Whitney U-test was used for pairwise comparison ($p < 0.017$).

RESULTS

There were no significant differences in body mass index between groups: it was 23.50 kg/m^2 in group 1, 24.16 kg/m^2 in group 2, and 24.78 kg/m^2 in group 3. Comparison of bio-impedancemetry data showed that higher visceral fat percentage of 12.1% (group 1 — 7.2%, group 2 — 5.3%; $p^{1–2}$, 1–3 < 0.01) was typical for people whose peripheral blood lymphocyte counts decreased in response to the short-term whole body cooling. However, there were no significant differences in the percentage of subcutaneous adipose tissue between the surveyed people: it was 31.8% in group 1, 30% in group 2, and 30.1% in group 3. High visceral fat percentage increases the risk of cardiovascular and metabolic disorders, and positively correlates with elevated fasting levels of triglycerides and glucose, as well as with the decreased levels of high density lipoproteins (HDL) [15–17]. It is known that dysfunctional visceral fat contributes to hypoxia [18]. This was reflected in lower oxygen saturation that made up 97% (min — 94%, max — 99%) in group 1, 98% (min — 97%, max — 99%) in group 2, and 99% (min — 98%, max — 99%) in group 3. After the short-term whole body cooling, oxygen saturation in group 1 actually equaled the values obtained on other two groups and rose to 98% (min — 97%, max — 99%). The combined effects of hypoxia and low temperatures resulted in activation of gene that encoded transferrin and transferrin accumulation in plasma (Table 1). The relatively high levels of soluble sTfR transferrin receptor and transferrin were detected in all groups: the concentrations exceeded 340 mg/dL in 75% of surveyed people in group 1, 77.8% in group 2, and 90.9% in group 3.

Such an increase in the levels of transferrin and sTfR is indicative of iron deficiency affecting tissues and hypoxia. Furthermore, high transferrin levels are a risk factor of cardiovascular disorders, since these facilitate activation of blood clotting factors and hypercoagulation [19, 20].

Table 1. Concentrations of transferrin and sTfR in peripheral blood, Me (25–75)

		Transferrin, mg/dL	sTfR, μg/mL
Group 1	Before cooling	455.9 (306.5–846.7)	27.1 (1.5–53.4)
	After cooling	430.3 (333.1–480.0)	35.9 (17.4–344.6)*
Group 2	Before cooling	371.4 (341.4–543.4)	20.0 (18.46–22.60)
	After cooling	573.8 (434.20–640.2)**	22.6 (21.54–46.2)
Group 3	Before cooling	434.2 (363.8–517.0)	22.3 (20.0–126.2)
	After cooling	434.2 (324.2–663.2)	25.6 (18.72–130.8)

Note: * — $p_{gr.\,1} < 0,01$; ** — $p_{gr.\,2} < 0,01$.

Таблица 2. Concentrations of HIF-1α of SIRT-3 in peripheral blood lymphocytes, Me (25–75)

Indicator	Group 1	Group 2	Group 3
HIF-1α, 10^6 cells/mL	1.3 (0.9–1.8)	1.8 (1.48–2.1)	1.3 (1.13–2.0)
SIRT-3, 10^6 cells/mL	0.2 (0.1–0.2)	0.3 (0.12–0.5)	0.3 (0.19–0.5)

Alterations in cellular metabolic activity determine the capability of adaptation to changing environment. For cells, glycolysis is the fastest way to acquire energy, and ATP synthesis takes an average of 2–4 min. The decrease in peripheral blood lymphocyte levels after the short-term cooling was associated with the decrease in lymphocyte glycogen levels from 4 to 2.83% (p = 0.0056); in other two groups, glycogen levels in lymphocytes did not change, these were 5.8 and 6.2% in group 2, and 3.6 and 4.8% in group 3, respectively. The decrease in glycogen levels results in the increased ATP production by lymphocytes (from 0.98 (0.42–2.87) to 3.16 (0.55–4.19) μmol/bn cells); cells are unable to deposit ATP for prolonged use due to the lack of specific mechanism, that is why such an increase in ATP levels is indicative of cell activation. The increase in the HIF-1α/SIRT3 ratio observed in the cells during the increased ATP production testifies in favor of the increased glycolytic activity, since HIF-1α has a predominantly inhibiting effect on the oxidative phosphorylation pathways and stimulates glycolysis, thus inducing both glucose uptake and expression of glycolytic enzymes (Table 2) [21–23].

Irisin, the member of myokine family, the receptors to which are found in all cells of the body, is involved in regulation of adaptation to low temperatures [24, 25]. Irisin enables thermoregulation processes due to activation of thermogenin (UCP1) and increases energy expenditure. Moreover, irisin exerts anti-inflammatory effects and protects cell junctions against damage due to interaction with Src tyrosine kinase and AMPK phosphorylation [26–28]. The highest levels of this myokine, 6.29 (3.04–7.98) μg/mL, were observed in group 1. The levels observed in other two groups were lower: 3.06 (1.59–6.70) μg/mL in group 2, and 4.32 (3.11–8.08) μg/mL in group 3 (p^{1-2} = 0,005). After exposure to low temperatures, irisin levels in group 1 significantly decreased to 3.17 (1.349–6.64) μg/mL (p < 0.01). Such a decrease in irisin levels after cooling could enhance endothelial permeability and increase cellular adhesion and migration. This was associated with the decrease in the levels of circulating lymphocytes in this group of surveyed people. Higher background levels of irisin increase the concentration of anti-inflammatory cytokine IL10 in peripheral blood amid lower concentrations of pro-inflammatory cytokines L6 and TNFα (see Fig.).

DISCUSSION

It is known that the early period of acclimatization to low temperatures (within 7 days) is associated with the increase in the levels of HIF-1α protein that facilitates activation of glycolysis and β-oxidation [29, 30]. Our study showed that even the short-term exposure to low temperatures for 5 min contributes to adaptive responses, as determined by the background immune defenses and regulatory mechanisms that underly cellular metabolic activity. The combined effects of hypoxia and low temperatures are associated with the elevated levels of transferrin and soluble transferrin receptor, that are the risk factors of cardiovascular disorders prevalent among residents of the Northern territories, in almost all the surveyed volunteers. Transferrin is a principal carrier of the iron ions involved in various metabolic pathways [31, 32], which have a direct impact on the response to cold exposure due to immediate or long-term adaptive responses. Thus, the determined decrease in peripheral blood lymphocyte levels in response to the short-term whole body cooling is indicative of the establishment of immediate adaptive response associated with activation of glycolysis in the cells that ensures rapid boosting of the energy reserve essential for lymphocyte activation. Higher background levels of irisin found in group 1 of the surveyed people ensure regulation of inflammatory response due to stimulation of the higher anti-inflammatory cytokine levels. The increased levels of circulating lymphocytes found in group 2 of the surveyed people are associated with the more intense inflammatory response reflected in the levels of pro-inflammatory cytokines. Furthermore, this group is characterized by the higher visceral fat percentage that is also capable of promoting more severe inflammation. No activation of immediate adaptive response has been found in the surveyed individuals who have shown no changes in lymphocyte levels (group 3). This group shows lower ratio of the HIF-1α/SIRT3 metabolic regulators, which indicates predominance of mitochondrial activity in adaptation to low temperatures.

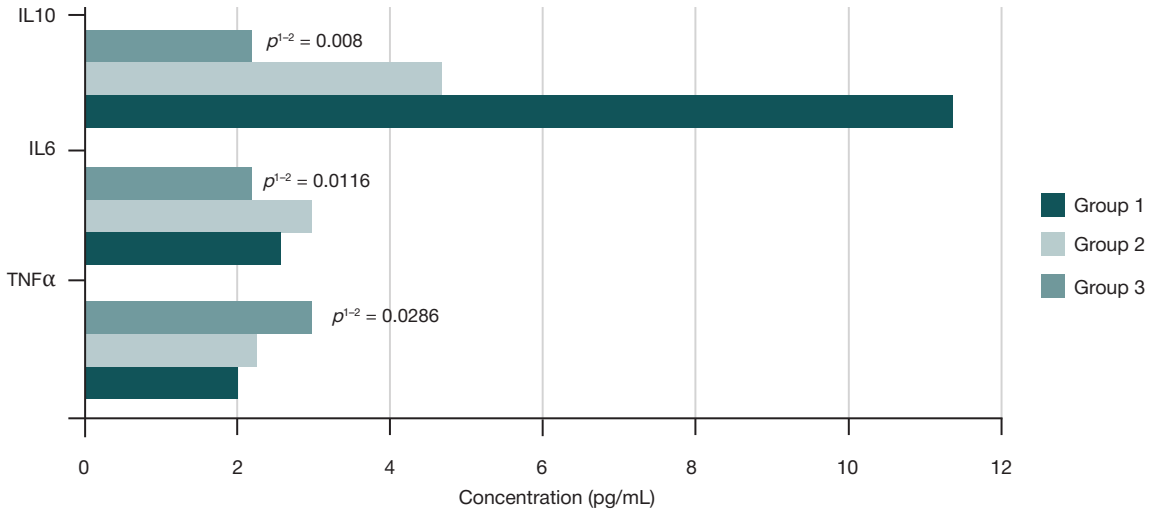

Fig. Cytokine levels in peripheral blood

CONCLUSIONS

Background immune defense and the concentrations of pro- and anti-inflammatory factors are associated with immediate and long-term adaptive responses to the cold exposure. Assessment of changes in the levels of circulating lymphocytes is a simple and affordable method for prediction of human adaptive capabilities ensured by regulation of the cellular metabolic pathway activation.

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