



Effects of Low Temperatures on the Formation of Adaptive Reactions: A Review

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Abstract

The review presents the results of studies on the effect of low temperatures of different durations on the formation of adaptive reactions in humans. The mechanisms of changes in the metabolic and hormonal processes and cellular and humoral immune response are discussed. (**International Journal of Biomedicine**. 2018;8(2):95-101.)

Key Words: cold • adaptation • variability • stability • hypothermia • immunity • metabolism

Basic Part

The cold factor has a strong stress effect on the body. In natural conditions, the effect of low temperatures can be multiplied in combination with the wind regime, high humidity and vibration. The peculiarities of the reaction of the adaptive systems of the body to low temperatures are determined by the duration of the action (short-term or long-term) and individual sensitivity. Many works have been devoted to studying the health of the indigenous and non-indigenous residents of the North. The results of the studies by V. Kaznachejev and colleagues testify to a change in all types of metabolism (proteins, fats, carbohydrates, vitamins, macro- and microelements) in native inhabitants of high latitudes. There is a switch from a carbohydrate to a lipid type of metabolism, enhancing lipid peroxidation (LPO) with the formation of the polar metabolic type.^(1,2) The effect of cold as a stress factor on the human body of newcomers is accompanied by a typical picture of the stress response with an increase in the neurotransmitters of the hypothalamus, pituitary hormones, and the adrenal cortex.^(3,4) At the same time, the concentration of these hormones in indigenous people is slightly higher than in people who live in milder climatic regions of Russia. This is due to the development of the so-called stress diabetes (i.e. a decrease in the blood insulin level, which plays the role of a

counter-hormone in relation to glucocorticoids).⁽⁵⁾ In addition, physical activity at low temperatures also contributes to an increase in the level of catecholamines and glucocorticoids, which must be taken into account since work in the open air is often shift work. L.Kapilevich and S.Krivoshchekov have shown that individuals differ in the direction of the shifts in systemic physiological responses to the cold, depending on the functional reserves and the level of energy expenditure of the body.⁽⁶⁾ At the same time, in newcomers, especially those working on a shift method, it is possible to attribute the state of “unfinished adaptation” to disturbances in the intersystem coordination of functions. These disturbances result in a depletion of existing reserves in the form of reduced ventilation function of the lungs, reduced adaptive reserve of the circulatory system, the predominance of sympathetic tone of the autonomic nervous system, and an imbalance in thyroid hormones.⁽⁶⁻⁹⁾ In cold-adapted people, as a mechanism for reducing heat loss, the core temperature of the body decreases by reducing the average skin temperature and changing the temperature sensitivity of the central hypothalamic thermoreceptors (set point). The functioning of any body system requires a large expenditure of energy (ATP), so energy homeostasis is crucial in the process of successful adaptation to any changes in the environment. The transition to lipid metabolism in cold conditions contributes to the formation of a large amount of energy consumed both for heating the body and for performing the functions that provide the body’s homeostasis.⁽¹⁰⁾ However, the intensification of lipid metabolism is one of the factors in the development of hypoxia, since in this type of metabolism the need for

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oxygen in tissues significantly increases. A decrease in the content of tocopherol and an increase in the content of LPO products (diene conjugates) and lyso-form phospholipids promote the formation of protein-lipid crosslinks in the erythrocyte membrane, which leads to an increase in the viscosity of membranes. In addition, cortisol, interacting with erythrocytes, also increases their microviscosity.⁽¹¹⁾ Accumulation in the blood of products of peroxidation creates oxidative stress and can cause destruction of cell membranes of erythrocytes (hypochromia, anisocytosis), as well as the relative neutropenia and reduction in the level of segmented neutrophils, etc.⁽¹²⁾ Another factor determining the development of tissue hypoxia is bronchospasm in breathing cold air, which also contributes to the formation of polar dyspnea, or circumpolar hypoxic syndrome.⁽¹³⁾ As a result of long-term immunological monitoring of the inhabitants of the northern territories, researchers have found that the character of the reactive shifts in the inhabitants of the north to various adverse factors is one type at the beginning and includes the activation of the immune system. Next, another type of shift occurs in which the prolonged activation reduces reserve capacity, which is manifested by a decrease in the content of functionally active mature T lymphocytes. Further, a persistent decrease in the blood levels of functionally active phenotypes of T-lymphocytes is formed, which is compensated by an increase in the number of the total pool of circulating lymphocytes, lymphoproliferative reactions, proliferative monocyte reactions, and activation of phagocytosis intensity.⁽¹⁴⁻¹⁸⁾

Despite the fact that the impact of cold determines a variety of adaptive shifts in the neuroendocrine system, with an increase in the concentration of catecholamines, corticosteroids, histamine and β -endorphin,⁽¹⁹⁻²³⁾ many researchers agree that cold is primarily a catecholamine stress associated with an increase in the level of norepinephrine and adrenaline in blood, and is initiated along the axis hypothalamus—pituitary gland—adrenal glands.⁽²⁴⁻³²⁾ Catecholamines exert their regulatory influence through adrenoceptors located on virtually all cells of the body. It is known that the thermogenic effect of norepinephrine is realized through the activation of β -adrenergic receptors due to the enhancement of noncontractile thermogenesis and heat production.^(33,34) Ionophoretic introduction of norepinephrine into the skin, where the thermoreceptors are concentrated, leads to a decrease in the temperature thresholds of the cold-protective reactions. On the 30th day of cold adaptation, under the influence of adrenaline, the pressor action on arteries increases and the systemic pressure decreases, which contributes to the preservation of heat and the redistribution of blood flow from the surface vessels into core of the body.⁽³⁵⁾ After 10 days of cold adaptation, the reactivity of the systemic pressure decreases equally for norepinephrine and epinephrine by more than 2 times.⁽³⁶⁾ Depending on the duration of exposure to cold, the number of the active α 1-ARs (α 1-adrenergic receptors) is changed in the musculoskeletal area. So, after a single cooling, the number of these receptors increases almost twofold, and on the 30th day of cold adaptation the sensitivity of α 1-ARs is normalized and the number of active α 1-APs is about 10% lower than those in the control group.⁽³⁷⁾

Activation of catecholamines occurs with the participation of Ca^{2+} , which enters the cell or in the endings of the sympathetic nervous system. In addition, calcium ions participate in the mechanisms that activate processes aimed at maintaining the body's temperature homeostasis and that accelerate the development of the vascular response to heating through the heat-sensitive ion channel TRPV1, which determines the modality of the temperature signal and the direction of the effector reactions.⁽³⁸⁾ The effect of low temperatures is mediated through cold-sensitive TRP-ion channels.^(39,40) They are sufficiently well studied and are represented by two channels, TRPA1 and TRPM8.⁽⁴¹⁻⁴³⁾ T.Kozyreva and colleagues⁽⁴⁴⁾ showed that TRPM8 takes part in the modulation of the immune response. Thus, the pharmacological activation of the TRPM8 ion channel with menthol, without changing the temperature, leads to an increase in the content of IL-6 and IL-1 β , a significant increase in the antigen-binding properties of spleen cells, and a decrease in the blood level of IgG.⁽⁴⁴⁾ It has been found that the preliminary activation of the TRPM8 ion channel with menthol weakens the depressing effect of subsequent deep cooling on the immune response.⁽⁴⁵⁾

It is also assumed that there is a genetic predisposition to cold adaptation. Scientists of the University of Cambridge (2013) discovered genes responsible for survival in cold conditions: the UCP1 gene encodes a dissociating protein, which is responsible for adaptation to cold and for heat generation; the ENPP7 gene encodes an enzyme involved in intestinal digestion, which allows one to consume fatty foods without significantly increasing the level of the atherogenic lipid fraction; the PRKG1 gene encodes an enzyme that activates the contraction of the smooth muscle of blood vessels.

According to a study by G.Beloborodov,⁽⁴⁶⁾ under the influence of a strong cold stimulus eosinocytosis develops. This condition is associated with the increased formation of histamine in the skin in the first minutes of irritation. An increased amount of eosinophils absorbs and cleaves histamine. In the following minutes, the amount of eosinophils decreases and the vasodilator effect of histamine is manifested—severe skin hyperemia. Temperature conditions also change the response of the body to agonists and antagonists of serotonin.^(47,48) A number of authors suggest as the temperature changes, the state of serotonin receptors changes, or, conversely, under the influence of serotonin receptors, changes occur in the sensitivity and/(or) the functions of temperature-controlling neurons.⁽⁴⁹⁾

The acute cold effect, in contrast to the chronic one, leads to depletion of the body's adaptive reserves, primarily energy reserves, to a decrease in tissue metabolism, and to the formation of proliferative-dystrophic and trophic disorders in all organs.⁽⁵⁰⁻⁵²⁾ The main sources of energy in the cell are mitochondria; under the influence of low temperatures, in mitochondria the intensity of oxidation of succinic acid is inhibited,⁽⁵³⁾ and consequently, the formation of ATP decreases, resulting in a drastic decrease in the contractile activity of all muscles.⁽⁵⁴⁾ The main bioenergetic mechanism for increasing the organism's resistance to cooling is the enhancement of free oxidation and a decrease in the proportion of phosphorylating

oxidation in mitochondria of thermogenic tissues.⁽⁵⁵⁾ In turn, the mechanisms of dissociation of oxidative phosphorylation and activation of free oxidation, providing thermogenesis, are controlled by a system of calcium homeostasis.^(56,57) The impact of a strong stress factor leads to a decrease in the calcium-transport function of mitochondria, as a result of which the energy deficit of cells and tissues increases.⁽⁵⁸⁾

It is well known that low temperatures contribute to reduction of skin microcirculation, redistribution of blood flow, and reduction of systolic pressure.⁽⁵⁹⁻⁶¹⁾ The positive effect of cold on the functional state of the central nervous system is due to its ability to modulate the temperature homeostasis.^(62,63) van Marken Lichtenbelt and colleagues⁽⁶⁴⁾ revealed a negative correlation between the mean skin temperature and the level of cognitive activity. There are data on gender differences in response to cryogenic training conducted in a closed air sauna with preliminary adaptation of patients to cold air in the pre-chamber at $t=-30\pm 5^{\circ}\text{C}$ for 30 seconds followed by cooling in the main chamber at $t=-110\pm 5^{\circ}\text{C}$ for 2.5-3 minutes. It was found that such loads have a more positive effect of on the bodies of men than of women, which was manifested in a decrease in the overall level of psychoemotional stress.⁽⁶⁵⁾

Changes in metabolism directly affect the state of cell membranes/energy balance and this applies to all cells of the body, including immunocompetent ones. The results of investigations of the cold effect on immunological reactivity are very ambiguous. A great deal of research has been carried out on the therapeutic effects of cold, in particular, cryosauna. For example, good positive results are recorded in the treatment of such diseases as psoriasis, bronchial asthma, and rheumatoid arthritis.⁽⁶⁶⁻⁶⁹⁾ With the air cryotherapy technique, the blood levels of pro-inflammatory cytokines (IL-1, IL-6, TNF α) and circulating immune complexes decrease, the content of lysosomal proteins in neutrophils increases, and IgA concentration increases, as does the number of mature T-lymphocytes, the CD4/CD8 ratio, and the production of anti-inflammatory cytokines.⁽⁶⁹⁾ At the same time, lower temperatures significantly reduce the greater number of pro-inflammatory cytokines.⁽⁷⁰⁾ The positive effect is explained by the fact that cryotherapy promotes the outflow of lymph from the tissues, limiting vascular edema, improving the microcirculation of arterial and venous blood flow, reducing muscle tone, and stimulating regeneration.⁽⁷¹⁾

According to a study by V.Khasnulin, low temperatures reduce the quantitative and qualitative indices of cellular immunity with a 10%-15% reduction in the number of T-helpers and T-suppressors and a general decrease in the functional activity of T-lymphocytes.⁽⁷²⁾ V.Nikolaev and colleagues⁽⁷³⁾ found that adapting rats to cold is also accompanied by weakening of cellular immunity and nonspecific adaptive reactions, and the degree of expression of such changes depends on the length of stay in conditions of low temperatures. Depending on the adaptability of animals, the response rate to cold factor, estimated by the blood LPO level (intermediate products), changes (in adapted animals on the 30th minute of cold exposure, in unadapted animals on the 15th minute).⁽⁷⁴⁾ Similar results were obtained by cooling laboratory mice for 3 hours at a temperature of $+7/+8^{\circ}\text{C}$, and the reaction

of humoral and cellular immunity was suppressed.⁽⁷⁵⁾ In another experimental study, it was shown that hypothermal action (5 sec at $+7/+9^{\circ}\text{C}$ for 5 days) promotes an increase in the thymus index and the level of lymphocytes in the bone marrow, a decrease in the absorption activity of phagocytes, an activation of the phagocyte metabolic activity and cellular immunity, and a suppression of humoral immunity.⁽⁷⁶⁾ It was shown that the systemic effect of low temperatures inhibits synthetic nuclear processes in macrophages, reduces their absorbing activity, and reduces the number of leukocytes, erythrocytes and monocytes, with an increase in the activity of cellular immunity.^(69,77)

During an experiment with laboratory mice with local cooling $+8^{\circ}\text{C}$ for 5 sec, the researchers also noted an increase in the thymus index, the number of leukocytes in the peripheral blood, the metabolic activity of macrophages, and a nearly twofold increase in the functional activity of cellular immunity (the level of delayed-type hypersensitivity reaction was $26.2\pm 1.3\%$ and $57.6\pm 4.3\%$ in the control and experiment, respectively).⁽⁷⁸⁾ Cooling causes degranulation of tissue basophils and edema of the dermis under the action of mediators, which leads to tissue infiltration by mononuclear cells, neutrophils, and eosinophils, and damage to the endothelium with the deposition of immune complexes and the development of necrotizing vasculitis.⁽⁷⁹⁾ The effect of cold factor for one day causes a decrease in the granularity of mast cells, expanding lymphatic vessels and capillaries and loosening the basal membrane, and an increase in the size of endothelial cells.^(80,81) Under the influence of a single 3-minute exposure at -20°C , the mice showed a decrease in the serum levels of IL-2, IL-3, IL-5, and IL-10.⁽⁸²⁾ In a study of the immune system in those affected by cold trauma, deficiency of T-lymphocytes was already determined in 4-8 days. In the first days after the cold stress, the number of B-lymphocytes was within the lower limit of the norm, with a subsequent slow decrease. The increase in the number of T and B lymphocytes begins from 18-21 days during frostbites of III-IV degree.⁽⁸³⁾ It was found that in the early period of frostbites, the reactions of cellular immunity, including macrophages and lymphocytes, prevail and the production of pro-inflammatory cytokines (IL-1 β , TNF α , IL-6, IL-8) increases.⁽⁸⁴⁾ The level of IL-18 in the blood increases slightly, but its concentration in the bubble fluid during frostbites exceeds the concentration in the total blood flow by more than 2 times.⁽⁸⁵⁾ Cases of cold trauma exhibit immunity disorders, which are expressed as a decrease in the absolute number of T-lymphocytes, T-helpers, T helper/T suppressor ratio, the concentration of C1q, and C3 components of the complement system; and as an increase in the level of IgA, IgM, C-reactive protein, $\alpha 1$ -antitrypsin, $\alpha 2$ -macroglobulin, orosomucoid, prealbumin, and transferrin.⁽⁸⁶⁾

During the development of inflammatory reaction in deep frostbite, thrombus formation is activated in the damage zone, the content of cytokines and leukocytes in the blood increases, and the processes of repair and neoangiogenesis are triggered.⁽⁸⁷⁾ During deep hypothermia, angiogenesis is restored slightly and the content of mast cells increases.⁽⁸⁸⁾ Persons undergoing fatal hypothermia display a high content of reticulocytes (by 9.5%) and plasmocytes (by 23.9%) in the lymphoid tissue of the upper respiratory tract, while the levels

of fibroblasts, lymphocytes, macrophages and cells in mitosis are reduced.⁽⁸⁹⁾ Patients with local cold trauma of the lower limbs exhibit a decrease in the intensity, speed, and potential of platelet aggregation.

It is known that lymphocytes do not contain an actomyosin complex and are unable to independently pass through a damaged vascular wall into tissues to participate in cellular and humoral immunity.^(90,91) Platelets provide contact of lymphocytes and collagen fibers, and as a result, facilitate the migration of lymphocytes through the damaged wall of blood vessels deep into the injured area.⁽⁹²⁾ In the early reactive period of local cold trauma, the leukocyte tissue factor (TF) expression increases, then decreases with recovery, but remains higher than that of healthy individuals.⁽⁹³⁾ Activation of TF is inevitably accompanied by an increase in the level of atrombogenic factors of the endothelium and other cells, including TFPI. K.Golokhvast⁽⁹⁴⁾ studied macrophages and lymphocytes of bronchoalveolar lavage in white mongrel rats after cooling in a climatic chamber at a temperature of -15°C for 15 minutes. After the experiment, the number of viable cells decreased from 88.2% to 61%, the ratio of macrophages/lymphocytes changed from 30% to 70%. Inverting the pool of macrophages and lymphocytes can be explained not by the death of macrophages, but by the increase in the pool of lymphocytes; accordingly, the inhibitory function of macrophages falls due to a decrease in their synthetic activity.

Moreover, low temperatures have a direct effect on the induction of lymphocyte apoptosis. When lymphocytic suspension is cooled (-18-21°C), the morphological signs of apoptosis are observed 2-3 hours after stimulation, which is manifested in a decrease in the size of the cell and the appearance of apoptotic bodies. In such a case, the frequency of recording lymphocyte apoptosis directly depends on the temperature and the duration of exposure.⁽⁹⁵⁾ However, in the presence of pathology, for example in patients with cold urticaria, a decrease was shown in the number of T-helpers and cytotoxic lymphocytes, expressing the marker of apoptosis, the absolute amount of CD3+T-lymphocytes, and regulatory CD4+CD25+high T-lymphocytes.^(96,97)

Thus, as can be seen from the presented data, studying the effect of low temperatures on the body does not lose its relevance and many questions of regulatory aspects are still unresolved. The reactivity of the regulatory systems providing homeostasis varies depending on the level of adaptation, genetic characteristics, and the strength and duration of influence of cold factor.

Competing interests

The authors declare that they have no competing interests.

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