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INFLUENCE OF LOW TEMPERATURES ON LIPID PEROXIDATION IN TISSUE OF EXPERIMENTAL ANIMALS DEPENDING ON EXPOSURE TIME

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ABSTRACT

The article reports the study on the influence of low temperatures on the intensity of free radical lipid oxidation and antioxidant protection in the tissues of internal organs (liver, kidneys, lungs, heart) in experimental animals, depending on the exposure time.

The few data available in the literature indicate that the effect of low temperatures on the organism of experimental animals is accompanied by the activation of free radical processes. We noted an increase in the concentration of low-molecular antioxidants in the organs of animals, whose exposure time in the cold lasted 1 hour. An increase in exposure time of rats in the cold to 3 hours is associated with an increase in catalase activity.

The purpose of this study was to study the effect of experimental animals on the processes of lipid peroxidation in tissues of internal organs (liver, kidneys, lungs, heart) during one-hour and three-hour exposure to low temperatures for 14 days.

The effect of cold on the processes of lipid peroxidation in the tissues of rats was investigated at a temperature (10 ± 20C below zero). The processes of lipid peroxidation and antioxidant protection parameters were quantitatively studied by spectrophotometric method, using SPECORD 40 spectrophotometer, determining the content of dienic conjugates and malonic dialdehyde in the tissues of the internal organs (liver, kidneys, lungs and heart), the total content of low molecular weight antioxidants and catalase activity.

Conclusion. The ecological and biochemical reaction of the rat organism to the effect of cold is the activation of antioxidant protection, due to the increase in the rate of lipid peroxidation. In the first group of animals, whose exposure time in the cold lasted one hour, biochemical mechanisms of antioxidant protection are realized by increasing the concentration of low-molecular antioxidants in organs. An increase in the exposure time to three hours of rats in the cold is associated with an increase in the activity of the antioxidant enzyme catalase.

Keywords: low-temperature effect, lipid peroxidation, free radical lipid oxidation, lipoperoxidation, active oxygen species, malonic dialdehyde, diene conjugates, experimental animals, spectrophotometric methods, electrothermometer with needle sensor, adaptation.

Introduction

One of the fundamental problems of biology at the present time is the study of the state of the organism under the influence of various negative factors of the external environment, as well as ways and means of increasing the resistance of the living organism to them. Such a factor in the extreme climatic and natural

conditions of the North is the effect of cold on tissues and the whole body.

Under the influence of low ambient temperatures there the biochemical, physiological shift of many functional systems of the organism occurs, which leads to the development of a new state, borderline between norm and pathology, called «adaptation».

At adaptation to the cold in the body of animals and humans, many metabolic processes are changing. At this time it is difficult to understand when the state of adaptation comes, accompanied by an increase in resistance of the organism. One of these indicators can be a state of biological membranes, which has an important role in the processes of cell life [1].

There is evidence in the literature testifying that the effect of low temperatures on the organism of experimental animals is accompanied by activation of peroxide processes [2, 9, 11, 12]. It is also known from literature data that a moderate intensification of peroxide processes in the body of animals and humans can contribute to an increase in the permeability of the cell membrane and facilitating the work of membrane proteins. However, excessive intensification of lipid peroxidation can lead to disruption of adaptation, which is manifested by denaturation and inactivation of proteins, delipidation of membranes, violation of cell division and growth, violation of the integrity of cell membranes [14, 17, 20]. Consequently, the functional state of cells, tissues, organs depends on the intensification of peroxide processes induced by exposure to low temperatures i.e. the ability of the body to adapt to the cold effects.

The purpose of our research was to study the effect of one- and three-hour exposure to low temperatures for 14 days on the processes of lipid peroxidation in the tissues of internal organs (liver, kidneys, lungs, heart) of experimental animals.

Material and methods of research

This study was approved by the local committee on biomedical ethics at the Yakut Scientific Center of Complex Medical Problems.

An experiment on the influence of low temperatures on lipid peroxidation in the tissues of the internal organs of rats was carried out on the Wistar line rats weighing 170-260 g. The effect of cold on the body of rats was investigated at a temperature of (10 ± 20C below zero) for 14 days. Animals were divided into two groups: the first group animals were exhibited in the cold for 1 hour, of the second - for 3 hours. The temperature of the legs and tail in rats was determined using an electrothermometer with a needle sensor. The control group consisted of intact animals.

The processes of lipid peroxidation and antioxidant protection parameters were quantitatively studied by spectrophotometric method, using SPECORD 40 spectrophotometer, determining the content of dienic conjugates and malonic dialdehyde in the tissues of the internal organs (liver, kidneys, lungs and heart), the total content of low molecular weight antioxidants and catalase activity.

At the end of the experiment removal of animals from the experience was carried out by decapitation in accordance with the requirements of humanity in accordance with Appendix No.4 to the Rules for carrying out work using experimental animals (The order of the USSR Ministry of Health No.755 dated 12.08.1977 «On the procedure for euthanasia (killing an animal)»).

100 mg of internal tissue (liver, kidney, heart and lung) were obtained from experimental animals that were washed with phosphate buffered saline (PBS) and homogenized in 1 ml of 1×PBS.

Diene conjugates, formed in a result of double bond migration in polyunsaturated fatty acids, were determined by Danilova method [3]. After extraction in a mixture of heptane-isopropanol (2:1) and subsequent addition of a solution of HCl (pH 2.0) the diene conjugates were detected in the heptane phase at λ = 233 nm, using a molar extinction coefficient of diene conjugates 2.2×105 M-1×cm-1. The amount of diene conjugates was expressed in μmol/ g tissue.

The principle of the method for determining malonic dialdehyde is based on the formation at a high temperature of a colored trimethine complex with thiobarbituric acid [10]. The optical density of the colored complex at λ=532 nm was determined in comparison with the control sample. The molar extinction of malonic dialdehyde is 1.56×105 M-1×cm-1. The concentration of malonic dialdehyde was expressed in nmol/g tissue.

The method for determining the total content of low-molecular antioxidants is based on the ability to reduce Fe (III) to Fe (II) in the presence of antioxidants in an alcoholic solution of the sample [5]. The amount of formed Fe (II) was determined by the addition of orthophenanthroline, resulting in the formation of a colored complex, which was determined at a wave length λ=510 nm. Using a series of standard solutions of dihydrotraquetin in the concentration range 0.10-0.025 mg/ml, the value of the molar extinction coefficient of the o-phenanthroline-Fe (II) complex was obtained which was equal to 5.28×104 M-1× cm-1. The level of the total content of low-molecular antioxidants was expressed in mg-eqQuercetin/g of tissue.

The catalase activity was determined at a wave length λ = 410 nm using a method based on the ability of hydrogen peroxide to form a stable colored complex with ammonium molybdate [6]. The millimolar extinction coefficient of hydrogen peroxide was 22.2×103 mM-1×cm-1. For the unit of catalase activity the amount of enzyme, involved in converting 1 mkat hydrogen peroxide in 1 sec. is taken under the given conditions.

Statistical processing of the data was carried out using the IBM SPSS Statistics 19 application statistical software package. The reliability of the differences between the averages was estimated using the Mann-Whitney U test. The data in the tables are presented in the form M±m, where M is the mean, m is the mean error. Probability of the validity of the null hypothesis was assumed for $p < 0.05$.

Results and discussion

The repeated, short-term effect of cold on the organism of experimental animals was chosen by us not accidentally, since it occurs quite often, both in everyday and in experimental situations.

Measurement of temperature using an electrothermometer with a needle sensor showed that the effect of cold primarily manifested itself in lowering the temperature of the paws and tail of experimental animals. At the exposure for 1 hour, the temperature of the paws decreased to 20.5 ± 0.50° C, the temperature of the tail decreased to 21.4 ± 0.70C, at the exposure for 3 hours, the temperature of the paws was 22.2 ± 0,60C, tail - 23,8±0,30C. In the intact group of rats, the temperature of the paws was 27.3 ± 0.80C, the temperature of the tail corresponded to 25.1 ± 0.60C. Lowering of the temperature indicates a violation of microcirculation in the limbs of experimental animals. Microcirculation disorder leads to the hypoxia, which potentiates the generation of active oxygen species (initiators of lipid peroxidation) in mitochondria [14, 20].

The results of the evaluation of lipid peroxidation indicators in the tissues (liver, kidney, lung, heart) of rats obtained in the course of the experiment are presented in Table 1.

According to the data of the experimental animals of the first group in comparison with intact animals in the liver tissues the concentration of malonic dialdehyde was 1.6 times lower, but the content of diene conjugates was 1.7 times higher. In the tissues of kidneys the

Table 1

The concentration of diene conjugates (μmol/g) and malonic dialdehyde (nmol/g) in the tissues of the internal organs of experimental animals

Organ	Diene conjugates			Malonic dialdehyde		
	Control	1st group	2nd group	Control	1st group	2nd group
Liver	3,79±0,18	6,52±0,39*	2,56±0,13*	10,73±0,52	6,64±0,33*	6,16±0,36*
Kidneys	1,00±0,01	5,55±0,27*	3,66±0,18*	16,30±0,81	9,74±0,47*	18,86±0,84
Lungs	5,13±0,20	7,10±0,35*	2,77±0,12*	15,25±0,76	5,02±0,25*	9,17±0,43*
Heart	2,66±0,13	4,51±0,21*	3,31±0,16*	6,34±0,31	5,83±0,24	9,26±0,34*

* $p<0.05$ in comparison with control group.

content of malonic dialdehyde was 1.7 times lower, and diene conjugates were higher by 5.5 times. In the lung tissues we observed a decrease in malonic dialdehyde by 3 times and an increase in diene conjugates by 1.4 times. In heart tissue, the level of malonic dialdehyde was 1.1 times lower, and the content of diene conjugates was 1.7 times higher.

In the liver tissue of rats of the second group, we observed a decrease in the level of diene conjugates by 1.5 times and malonic dialdehyde - 1.7. We found an increase in the concentration of diene conjugates and malonic dialdehyde in the kidney tissue by 3.6 and 1.2 times, respectively. In lung tissues, the content of diene conjugates was 1.8 times lower, and the level of malonic dialdehyde was 1.6 times less than the control value. In heart tissue, the concentration of dienic conjugates was 1.2 times higher than the control value, and malonic dialdehyde - 1.4 times.

The indicators of catalase activity and the concentration of the total content of low-molecular antioxidants in tissues (liver, kidney, lung, heart) of rats are presented in Table 2.

In the liver tissues of experimental animals of the first group, we observed an increase in the concentration of low-molecular antioxidants by 1.8 times. The activity of catalase was 1.4 times lower than in intact animals. In the kidneys, the content of low-molecular antioxidants was 2.0 times higher, and catalase activity was 1.7 times lower. In the tissue of the myocardium, we noted a tendency to increase the low-molecular antioxidants by 1.02 times and a significant decrease in catalase activity by 1.5. In lung tissues, the level of low-molecular antioxidants was 22.0 times higher, and catalase activity was 1.7 times lower.

With an increase in the exposure time of rats in the cold in the tissues of the liver, kidneys, lungs, the level of low-molecular antioxidants was higher in comparison with the control by 4.2 times; 1.3 and 48.3 times, respectively. In heart tissue, the concentration of low-molecular antioxidants was less than control by 2 times. The catalase activity in liver and kidney tissues was 1.4 times higher than control and 1.3 times, respectively, and no significant differences were found in lung and heart tissues.

Our data have demonstrated that the state of lipid peroxidation in the body of experimental animals depends on the exposure time in the cold. In animals of the first group, peroxide processes in all organs proceeded more actively at the initial stages, as evidenced by the accumulation of primary products of peroxidation - diene conjugates. The level of malonic dialdehyde (the final product of lipid peroxidation) was below the control values in all organs.

With an increase in the exposure time of experimental animals in the cold, the intensity of free radical reactions in the tissues of internal organs changes, as evidenced by a change in the concentrations of diene conjugates and malonic dialdehyde. So, we noted a decrease in the concentration of diene conjugates and malonic dialdehyde in the tissues of the liver and lung and their increase in the tissues of the kidneys and heart.

In the first group of animals exposed to cold, an increase in the concentration of

Table 2

The total content of low-molecular antioxidants (mg-eqQuercetin/g) and catalase activity (μcat /g) in the tissues of internal organs of experimental animals

Organ	Total content of low-molecular antioxidants			Catalase		
	Control	1st group	2nd group	Control	1st group	2nd group
Liver	16,54±2,14	29,78±1,45*	69,57±2,54*	21,15±1,78	15,14±2,52*	29,38±1,74*
Kidneys	38,12±2,47	76,57±3,62*	49,45±2,87*	17,48±1,65	10,45±4,62*	22,45±1,51*
Lungs	2,14±0,18	44,18±2,35*	103,32±3,78*	17,12±0,12	9,89±4,45*	16,41±0,79
Heart	32,47±0,17	33,21±1,47	16,39±1,18*	13,24±1,35	8,56±1,21*	14,50±4,08

low-molecular antioxidants in all tissues of the organs (liver, kidney, lungs, heart) may be related to their mobilization in response to stressful exposure to low temperatures. The increase in the concentration of low-molecular antioxidants in the tissues of the kidneys is probably due to the fact that in response to the effects of cold, catecholamines and glucocorticoids are released which are necessary for thermoregulatory heat production [1, 4, 7].

In the second group of animals, with increasing of exposure time, a high content of low molecular weight antioxidants (LMWA) in the lung tissues is noted. Our results coincide with the literature data. There is information in the literature that the main component of mucus is mucin, secreted by epithelial cells and possessing antioxidant properties. It is shown that type 2 pneumocytes secrete α-tocopherol, in mucus we also reveal an increase in the concentration of reduced glutathione [15, 18], ascorbic acid [13]. Uric acid, flavonoids and bilirubin also enter the non-enzyme system of the lungs, as they have antioxidant functions [16, 19]. An increase in the concentration of low-molecular antioxidants in the liver tissues is due to the fact that most endogenous antioxidants are synthesized in it, both low-molecular and high-molecular. In addition, hepatocytes are able to accumulate fat-soluble antioxidants - α-tocopherol, retinol.

Reducing the concentration of low-molecular antioxidants in the tissues of the kidneys and heart is associated with the depletion of their reserve due to the acceleration of the processes of lipid peroxidation. Earlier we showed that an increase in the concentration of products of lipid peroxidation – malonic dialdehyde and diene conjugates is a consequence of increased generation of reactive oxygen species and, first of all, superoxidanion-radical, which turns into hydrogen peroxide under the action of superoxide dismutase [7]. Therefore the activity of catalase in the tissues of the organs of both groups is increased as a result of an increase in the concentration of its substrate-hydrogen peroxide.

The decrease in the activity of catalase in all tissues of the experimental animals of the first group confirms the fact that in the mechanism of adaptation of the organism of rats to a multiple, one-hour exposure to cold low-molecular antioxidants have a leading role. With an increase in the exposure time of experimental animals to 3 hours, the enzymatic activity of catalase in the tissues of the liver and kidneys increases by 1.4 and 1.3 times, respectively. It is

likely that in these tissues the content of low-molecular antioxidants is insufficient to inhibit free-radical reactions.

Conclusion

Thus, the ecologic-biochemical reaction of the rat organism to the effect of cold is the activation of antioxidant protection due to an increase in the rate of lipid peroxidation. In the first group of animals, whose exposure time in the cold lasted 1 hour, biochemical mechanisms of antioxidant protection are realized on account of increasing the concentration of low-molecular antioxidants in organs. An increase in the exposure time (to 3 hours) of rats in the cold is associated with an increase in the activity of the antioxidant enzyme - catalase.

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METHODS OF DIAGNOSIS AND TREATMENT

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ANALYSIS OF FREQUENCY OF OCCURRENCE OF BACKGROUND AND PRECANCEROUS DISEASES OF A CERVIX BY RESULTS OF A PREVENTIVE AND DIAGNOSTIC CYTOLOGICAL TESTING

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ABSTRACT

The analysis of results of a cytological research in women aged from 18 up to 88 years as a method of early diagnosis of background and precancerous diseases of a cervix is carried out. The received results confirm the high predictive value of this method. Early detection and treatment of background and precancerous diseases of a cervix will promote real decrease in incidence and cervical cancer mortality.

Keywords: screening, oncocytology, diagnostics, dysplasia, cervical cancer.

Relevance

The cervical cancer (CC) is one of the most widespread oncological diseases of reproductive system of women: its specific weight fluctuates from 12 to 20% of all malignant tumours of a female genital [5]. Remaining in top three in structure of incidence of female reproductive organs after a breast cancer and endometrium and without yielding the position in structure of mortality where it takes the second place among oncological diseases at women, cervical cancer continues to cause irreplaceable damage in the most active layers of female population [13].

Annually in the world 528 thousand new patients with cervical cancer and 266 thousand deaths from this disease (7.9% of the total number of the women malignant tumours) are registered. Wide circulation of cervical cancer is noted in developing countries of which 78% of cases are the share, and his share reaches 15% of number of all malignant tumours at women (in the developed countries of 4.4%) [2].

Many authors note a certain staging and staging of pathological processes of a cervix in the course of carcinogenesis. Development of cervical cancer isn't lightning process: according to WHO data, on average 3-8 years, 10-15 more years undergo transition of a dysplasia to in situ cancer before development of microinvasive cancer and as much – before transition to a spread form [9].

Cervical cancer arises against the background of the benign processes which have received the name of background diseases which in itself aren't precancerous states more often, but on their background focal proliferative changes of an epithelium can develop. These processes differ in a big variety of pathological changes, each of them has morphological criteria. They can have the dyshormonal, inflammatory and post-traumatic cause [3, 10]. Precancerous processes consist of a dysplasia of various degrees.

Most often cervical cancer is revealed in the senior age group (60–70 years and more), however recently appears many publications describing cases of developing of this disease at women of reproductive age [3]. So, growth of incidence of cervical cancer among young women is noted: at the age of 15–24 years — by 4 times; 25–34 years — by 2,5 times [11,12]. Unfortunately, it should be noted that find in a considerable part of patients of cervical cancer already at late stages of a disease (III-IV) when the efficiency of modern methods of treatment sharply decreases [13].

In this regard early diagnosis and treatment of background and precancer diseases and also initial forms of cervical cancer, certainly, can be the important actions directed to decrease in cancer cases and reduction of number of the started forms [8].

Research objective: to study occurrence of background and precancerous diseases of a cervix and also their combination by results of a cytological research.

Materials and methods of a research

The analysis of cytological material of a cervix of 7600 women aged from 18 up to 88 years with the preventive and diagnostic purpose, during 2017 is carried out to laboratory of a pathomorphology, histology and cytology of Clinic of Medical institute of NEFU.

Material of a cytological research were smear from a mucous layer of cervix and the cervical channel. Age classification of Y.Y. Eliseev (2006) according to which persons of 18-29 years treat young age, 30-44 years to mature, 45-59 years – an average, 60-74 – by advanced age