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ARCTIC MEDICINE

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STUDY OF DOPAMINE LEVELS IN PERIPHERAL VENOUS BLOOD AND IMMUNE PROTECTION STATUS IN RESIDENTS OF NORTHERN TERRITORIES OF THE RUSSIAN FEDERATION ACCORDING TO HEALTH STATUS

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The correlation between the dopamine concentration in the peripheralblood and the level of immune protection in Northerners was studied. 70 practically healthy people and 172 patients (including 67 people with cancer of the large intestine) were examined to study the level of dopamine in peripheral venous blood and the state of immune protection in residents of the northern territories of the Russian Federation, depending on their state of health. Thus, for the first time, it was established that the level of registration of the frequency of elevated dopamine concentrations in peripheral venous blood in practically healthy residents of the northern territories of the Russian Federation is high and amounts to 7.14±0.38%, the level of registration of the frequency of elevated dopamine concentrations in peripheral venous blood in sick people was recorded much more often (59.21±1.7%). A high level of registration of elevated concentrations of IL-10 and TNF-α was also established, both in practically healthy people and in people with oncologicaldiseases. There was an increase in the frequency of registration of phagocytic activity deficiency, circulating mature, activated lymphocytes, natural killers, and lymphocyte phenotypeswithцепторами к transferrin and IL-2 receptors. In cancer pathology, there was a high frequency of neutrophil deficiency, phagocytic activity, NK, mature, activated T cells, and lymphocyte phenotypes with transferrin and IL-2 receptors.

Keywords: dopamine, cortisol, thyroxine, T-lymphocytes, natural killers, T-helpers, cytokines, IL-10, TNF-α, phagocytes.

The correlation of dopamine concentration in peripheral blood with the level of immune protection in Northerners was studied. 70 practically healthy people and 172 patients (including 67 people with oncological pathology of the large intestine) were examined to study the level of dopamine in peripheral venous blood and the state of immune protection in residents of the northern territories of the Russian Federation, depending on the state of health. Thus, it was established for the first time that the level of registration of the frequency of elevated concentrations of dopamine in peripheral venous blood in practically healthy residents of the northern territories of the Russian Federation is high and amounts to 7.14±0.38%, the level of registration of the frequency of elevated concentrations of dopamine in peripheral venous blood in sick people was recorded much more often (59.21±1.7%). A high level of registration of elevated concentrations of IL-10 and TNF-α was also established, both in practically healthy people and in people with oncological diseases. There was an increase in the frequency of registration of deficiency of phagocytic activity, circulating mature, activated lymphocytes, natural killers and phenotypes of lymphocytes with transferrin and IL-2 receptors. In oncological pathology, there was a high incidence of deficiency of neutrophils, phagocytic activity, NK, mature, activated T cells, lymphocyte phenotypes with transferrin and IL-2 receptors.

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Introduction. The mechanisms of the effects of norepinephrine and epinephrine are well known, but the available data on the effects of dopamine are contradictory [5]. Dopamine, an intermediate precursor of norepinephrine and epinephrine, is secreted by the chromaffin cells of the adrenal medulla. Regulation of the activity of the adrenal medulla is carried out by sympathetic impulses. Each chromaffin cell at one end is in contact with the arterial capillary, and the other is turned to the venous sinusoid, where synthesized catecholamines are released. Sinusoids form the central vein of the adrenal gland, which flows into the inferior vena cava. This ensures simultaneous entry of both glucocorticoids and catecholamines into the circulation, which makes it possible for them to act together on effector organs.

It is known that dopamine can inhibit the secretion of thyroid-stimulating hormone and prolactin in hyperthyroidism. There is evidence that dopamine is involved in the regulation of arousal and inhibition in the central nervous system. The effect of dopamine on the state of the immune system can vary, from stimulation to a sharp suppression of activity. In

oncological diseases, there is a violation of the immune defense [2]. It was interesting to compare the results of studying elevated dopamine concentrations and associated changes in immune status in practically healthy people in comparison with sick people with malignant neoplasms of the intestinal tract in residents of the northern territories of the Russian Federation [1, 9].Current data on dopamine levels indicate that a lack of dopamine plays an important role in stress, aging of the body, and also restricts the growth and development of tumors [4]. From the literature sources of foreign authors, it is knownthat studies of the level of dopamine in various diseases пwere conducted in Scandinavian residents and the level of its content changed, relative to one or another pathology, but not in-all cases. At what level and whatcauses changes in dopamine levels, is of some interest [11].

Objective: to identify the level of dopamine in peripheral venous blood and the state of immune defense in residents of the northern territories of the Russian Federation, depending on their health status.

Materials and methods. The article analyzes the material carried out over the past ten years by employees of the laboratories of the Institute of Physiology of Natural Adaptations of the Russian Academy of Sciences named after Academician N. P. Laverov, including the examination of 70 practically healthy people who did not have a history of acute and chronic pathology at the time of examination for dopamine, cortisol, thyroxine, neutrophil granulocytes, % of active phagocytes, natural killer cells, T-lymphocytes, cytokines in peripheral venous blood. As a comparison group, 172 people with malignant neoplasms of the intestinal tract were taken. The examination was conducted in the medical company "Biokor", Arkhangelsk. The age of the subjects ranged from 21 to 75 years. The survey was conducted with the written consent of respondents in compliance with the basic norms of biomedical ethics in accordance with the document "Ethical principles for conducting medical research involving people as research subjects" (World Medical Association Declaration of Helsinki 1964 (as amended in 2008)). Blood sampling for the study was performed from the ulnar vein at 8-10 o'clock in the morning, on an empty stomach. The serum was separated from the formed blood elements (erythrocytes) by the method of centrifugation-separation of the liquid part of the blood from the cells in order to prepare the biomaterial for subsequent analysis. The complex of immunological research included the study of hemograms in blood smears stained according to the Romanovsky-Giemse method, the preparation of lymph suspension, and the phagocytic activity of neutrophil granulocytes. To detect the phagocytic activity of neutrophils, the following method was used: a mixture of 100 μl of latex was taken (the latex suspension was prepared by injecting 2 ml of buffer solution into a Latex bottle, shaking intensively for 2 minutes) and 100 μl of blood with heparin, mixed and put in a thermostat for 30 minutes, the temperature of the device was set to 37°C. Then the supernatant was sucked out of the test tube, mixed and a blood smear was made from it. Slides with smears were dried at room temperature. Then it was fixed in the Nikiforov mixture for 20 minut, stained according to Romanovsky-Giemsa for 40 minutes. Washed and dried slides were examined under a microscope at magnification of the x90 lens and the x7 eyepiece. The results obtained were evaluated using the phagocytic index, i.e., the percentage of phagocytic cells from the number of counted neutrophils, and the phagocytic number, i.e., the number of particles absorbed by one active neutrophil.

The level of T-cells (CD3+), T-helper cells (CD3+ CD4+), natural killer cells (CD3-CD16+CD56+), activated lymphocytes with transferrinreceptors трансферрину(CD71+) and IL-2 (CD25+) was evaluated using the indirect immunoperoxidase reaction method using monoclonal cells. antibodies (Sorbent, Moscow) and flow cytometry on цитометре «an Epics XL flow cytometer (Beckman Coulter, USA). HamburgThe content of dopamine (IBL Hamburg, Germany)пг, cortisol (DBC, Canada), thyroxine (Human GmbH, Germany), интерлейкинovand interleukins (IL) 1b, 4, and 6 was studied by enzyme - linked immunosorbent assay in peripheral venous blood serum., 10, 13 ("BIOSOURSE", USA). Statistical analysis of the research results was carried out using the application software package "Microsoft Excel 2010" and "Statistica 7.0" (StatSoft, USA). The boundaries of the normal distribution of indicators were determined. Сравнение расThe data distribution was compared with the normaldistribution and выполняwas performed using the Shapiro–Wilk criterionУилка. The distributions of the results turned out to be similar to the normal one, sothe arithmetic mean (M) and standard error of the mean (m) were calculated to describe the data.

Table 1

Frequency of registration of elevated concentrations of dopamine, cortisol, thyroxine and cytokines in peripheral venous blood in normal and oncological pathology of the large intestine in residents of the northern territories of the Russian Federation, depending on the state of health, %

Parameters studied	Frequency of registration of elevated concentrations in practically healthy people, n=70, %	Frequency of registration of elevated concentrations in patients with colon cancer, n=172, %	Physiological limits
Dopamine	7.14±0.38	59.21±1.7 ***	>30 pg/ ml
Cortisol	7.82±0.41	17.65±0.55 ***	>600 nmol/ L
Thyroxine (T4)	7.36±2.11	9.2±0.35*	10-25 pmol/ l
IL-1β	22.92±0.99	24.56±0.87*	>5 pg/ ml
IL-4	7.55±0.52	9.38±0.48*	>5 pg/ ml
IL-6	1.92±0.27	3.33±0.38*	>20 pg/ ml
of IL-10	8.93±0.53	17.86±0.75***	>10 pg/ ml
of IL-13	2.44±0.38	4.08±0.41*	>20 pg/ ml
TNF-α	1.89±0.08	42.11±0.38 ***	>20 pg/ml

Note: n is the number of people surveyed, ***p<0.001, **p<0.01, *p<0.05.

Table 2

Frequency of registration of low concentrations of neutrophilic granulocytes, % of active phagocytes, natural killers and T-lymphocytes in peripheral venous blood with normal and elevated dopamine levels in residents of the northern territories of the Russian Federation, depending on the state of health, %

Studied parameters and physiological limits	Frequency of registration of low concentrations in practically healthy people, n=70		Frequency of registration of low concentrations in patients with small bowel cancer, n=172	
	With normal dopamine content, n=70	With increased dopamine content, n=70	With normal dopamine content, n=172	With increased dopamine content, n=172
Neutrophil granulocytes,<2×10^9 cells/l	2.86±0.24	5.71±0.34**	6.9±0.32	8.2±0.47*
% active phagocytes, <50	20.86±0.65	24.29±0.7*	72.41±0.97	84.62±1.66**
Natural killers CD3-CD16+CD56+,<0.4×10^9 cells/l	1.43±0.17	2.86±0.24***	63.95±1.45	76.92±1.34**
T-helper cells, CD3+ CD4+, <0.4×10^9 cells/l	4.29±0.29	5.71±0.34**	13.79±0.42	17.44±1.39**
CD3+, <1×10^9 cells/l	13.19±1.97	14.29±0.54*	40.23±0.73	45.92±0.95*
CD25+, <0.5×10^9 cells/l	15.27±2.83	17.14±0.59*	50.02±17.59	55.56±1.65*
CD71+, <0.4×10^9 cells/l	11.97±2.32	12.99±0.51*	42.86±3.13	54.88±0.90**

Note: n is the number of people surveyed, ***p<0.001, **p<0.01, *p<0.05.

Quantitativevalues between groups were comparedusing *t*the Student's t-test. The differences were considered statistically significant at the significance level of the t-test p< 0.05-0.001.

Results and discussion. A high level of registration of elevated concentrations of dopamine, IL-10, and TNF-α in peripheral venous blood has been established both in practically healthy people and in individuals with colon cancer (Table 1). High levels of cortisol can negatively affect the stateof the human immune system. Cortisol controls cell proliferation and antiproliferative activity against cancer cells, which is of interest. Thyroxine is the most influential thyroid hormone of the thyroid gland, regulating metabolism and energy. Increasing its concentration in the blood affects many functions in the body. Elevated levels of IL-1b may reflect the activity of the tumor microenvironment and the development of immunosuppression. IL-4 affects the growth and development of the tumor, and an increase in its production accelerates the development of pathological processes. High levels of IL-6 are associated with many diseases, including cancer, which are associated with disorders of the immune system. IL-6 can be produced by malignant cells of tumor formations, and when the production of this cytokine is activated, transcriptional mechanisms are triggered and active division of cancer cells occurs. IL-10 is a natural immunosuppressant, the main anti-inflammatory cytokine. Its special function is to prevent an excessive inflammatory reaction, because even with this reaction, not a physiological, but a pathological effect is observed. And, as a result, excessive inflammation damages healthy cells and tissues of the body. IL-13 plays an important role in cancer pathology, because its receptors are overexpressed and affect cell proliferation. It is also an autocrine cytokine growth factor of malignant cells. The tumor necrosis factor activates the receptors that recognize the malignant cell and prevents its further development. TNF-α, along with cytokines, enhances the inflammatory process in order to protect against foreign antigens [8]. Dysregulation of TNF-α is associated with many diseases, including ccancer.

As can be seen from the data in Table 1, patients with malignant neoplasms of the large intestine, compared with practically healthy individuals, as well as with physiological limits, are significantly more likely to detect elevated levels of dopamine, cortisol and cytokines (IL-10 and TNF-α). It is known that 75-90% of blood dopamine is mainlysecreted in the intestine [10, 12]. The development of a malignant neoplasm in the gastrointestinal tract is accompanied by an increase in the blood concentration of TNF-α with a parallel decrease in the migration of immunocompetent cells to the affected area [3]. In the gastrointestinal tract, dopamine provides vasodilation, increased blood flow in the mesenteric vessels against the background of reduced peristalsis [6].

Since dopamine is produced by cells of the diffuse endocrine system, it can be assumed that an increase in dopamine concentrations in the blood occurs by increasing its secretion by APUD cells, although no one excludes the possibility of dopamine secretion by endotheliocytes. The relationship between elevated levels of dopamine and TNF-α in the blood may be mediated by the effect of the source of distress on cortisol secretion.

An increase in the concentration of dopamine in peripheral venous blood occurs due to dopamine sulfate. Once in the peripheral blood, dopamine in high concentrations naturally affects hemodynamics. There is reason to believe that dopamine inhibits the development and activity of a wide variety of reactions through direct effects on the membrane and mainly through the regulation of the autonomous system. It was of interest to study the content of dopamine in the blood of patients with diseases of the intestinal tract, since it is known that blood dopamine is mainly represented by an amine synthesized in the intestinal tract. After a meal, the content of dopamine in the blood of mesenteric vessels increases by 50 times, and even prolonged fasting reduces its concentration very slightly. In addition, significant concentrations of dopamine secrete APUD cells of the kidneys and adrenal glands, reduce the resistance of renin and aldosterone.

Установлены Elevated dopamine concentrations were found, концентрации , and blood concentrations of cortisol and thyroxine в крови were also sig-

nificantly increased. Thus, the obtained data confirm the revealed regularity of dopamine involvement in interoceptive visceral signaling about the presence of elevated cortisol and thyroxine concentrations. Given that dopamine secreted in the central nervous system does not enter the blood, it can be assumed that an increase in dopamine content is one of the stages in the implementation of interoceptive signaling to the brain about these changes.

The frequency of registration of reduced concentrations of neutrophilic granulocytes, active phagocytes, natural killercells, T-lymphocytes, and lymphocyte phenotypes with transferrin and IL-2 receptors in the blood was determined depending on the level of dopamine in practically healthy people and cancer patients. The studied parameters were compared with physiological limits (Table 2). Отмечалось There was an increase in the frequency of registration of phagocytic activity deficiency, circulating matureых T-lymphocytes, T-helpers, natural killers, and lymphocyte phenotypes with transferrin and IL-2 receptors, and an increased level of dopamine in the blood in practically healthy people. Inacute pathology, there was a high frequency of neutrophil deficiency, phagocytic activity, NK, T helper cells, mature forms of T cells, lymphocyte phenotypes with transferrin and IL-2 receptors, as well as an increased level of dopamine.

The decrease in the concentration of circulating immunocompetent cells at elevated levels of dopamine in the blood can be explained by the peculiarities of the effect of dopamine on hemodynamics. The action of dopamine injected into the vein occurs quickly and ends in 5-10 minutes. Administration of dopamine by intravenous drip in low concentrations leads to an improvement in coronary blood supply by dilating the coronary vessels, increasing the volume of systolic blood output of the heart, reducing the resistance of peripheral vessels, and sharply dilating the vessels of the mesentery [7].

It is possible that the decrease in the concentration of immunocompetent cells in the venous blood from the ulnar vein is caused by the redistribution of cells in the vessels of the gastrointestinal tract from the circulating to the marginal pool.

Thus, an increase in the concentration of dopamine in peripheral venous blood in patientswith intestinal diseases was found. A very high level of deficiency in the activity of effector cells, namely phagocytes, natural killers, mature forms of T-lymphocytes and activated lymphocytes with transferrin and IL-2 receptors, was revealed. It is of interest for further scientific research to study changes in the level of dopamine depending on gender and age in residents of the northern territories of the Russian Federation, since the probability of its change from age and gender characteristics of blood parameters depending on the state of health is not excluded.

Conclusion. So, when examining practically healthy residents of the northern territories of the Russian Federation, the frequency of elevated dopamine concentrations is 7.14±0.38%, in patients with elevated dopamine concentrations in the blood are recorded 7 times more often (59.21±1.7%). Elevated concentrations of cortisol, thyroxine, IL-10, and TNF-α were found in healthy subjects. There was a slight increase in other pro-inflammatory and anti-inflammatory cytokines. This pattern is more pronounced when examining patients. Elevated dopamine concentrations inthe peripheral blood cause a decrease in the level of activated, differentiated T-lymphocytes and natural killers, which is most pronounced in cancer pathology. A decrease in the concentration of immunocompetent cells at elevated dopamine concentrations is possible as a result of their redistribution from the circulating to the marginal pool.

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