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ABSTRACT

of the dissertation for the degree of Doctor of Science

MORPHOFUNCTIONAL CHARACTERISTICS OF SOME ENDOCRINE ORGANS AND PERIPHERAL BLOOD LYMPHOCYTES IN THE NORM, HYPOXIA AND INFECTION

Specialties: 3243.01 «Pathological physiology»
3242.01 «Pathological anatomy»

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GENERAL CHARACTERISTICS OF THE WORK

Relevance of the topic and degree of development. Since the endocrine and immune systems are at the center of pathological processes occurring in the body, great attention has been paid to studying the state of these systems in recent years. The endocrine system, along with the nervous and immune systems, is one of the most important regulatory systems that provide the body's response to various exogenous and endogenous factors, as well as adaptation processes to various environmental conditions[1,2].

There are many reports in the literature that exogenous and endogenous factors of various origins change cell morphology, expression of markers on the cell surface, metabolic activity, viability, phagocytosis, and secretion of cytokines by macrophages, as well as pathogenicity of the bacterium. According to research, among such microenvironmental factors, such as hypoxia and infection, are considered the main etiological factors in the development of various pathological processes in the body[3,4].

Hypoxia is a typical pathological process caused by a lack of biological oxidation and accompanied by a violation of the energy supply of vital functions[5]. But hypoxia is considered not only a pathological phenomenon. From another point of view, hypoxia is a natural physiological process that the body can encounter every day as a result of vital activity, and it occurs due to a violation of the use of oxygen by tissues. Intense physical work and periodically being in

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[1] Rubingh, J. The Role of Thyroid Hormone in the Innate and Adaptive Immune Response during Infection / J.Rubingh, A.van der Spek, E.Fliers [et al.] // Compr Physiol. – 2020. 10(4), – p. 1277-1287.

[2] Yada, T., Tort, L. Stress and disease resistance: immune system and immunoendocrine interactions // Fish Physiology. – 2016. 35, – p. 365-403

[3] Iakushko, O.S. The modern concept of morphological and functional features of the endocrine glands // СМБ. – 2016. 58(4), – p.153-159

[4] Hsiu-Chi Lee, Shaw-Jenq Tsai, Endocrine targets of hypoxia-inducible factors // Journal of Endocrinology, – 2017. – 234(1), – p. R53–R65.

[5] Ханум Айдын г., Ахундов, Р.А. Гипоксия, его дефицит в организме // – Баку: Здоровье , – 2013. № 5, – с.194-197

high mountain areas also cause different levels of hypoxic conditions in the body[6,7].

In scientific literature, various localized nosocomial infections, including staphylococcal infections, in particular, Staphylococcus aureus, as a very common causative agent, do not lose their relevance as the main medical and social problem of modern medicine[8]. This is justified by the fact that staphylococci play an important role as the main opportunistic microbe during various pathologies and at the same time have a high pathogenic effect. On the other hand, the probability of infection as a result of the effect of a pathogenic microbe, the main features of its development and progress depend on the functional state of the body's endocrine and immune systems. Endocrine glands, which have a wide range of hormonal effects on various organs and systems, as well as organs of the immune system, respond to any infectious antigens in the body, including infections of staphylococcal origin[9,10].

In both acute and chronic pathologies, hypoxia and infection often develop together and, as a rule, lead to negative clinical results in the body. Scientific studies conducted in recent years show that hypoxia and infectious inflammation are closely related pathological processes in the body at the molecular, cellular, and clinical levels, that

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6 Грачёв, В.И., Севрюков, И.Т., Маринкин, И.О. Гипоксия животного организма, причины и следствия // – Москва: Экология промышленного производства, – 2018. № 2, – с. 42-57.

7 Shamenko, V.O., Kadzharian, Ye.V., Abramov, A.V. Intermittent hypobaric hypoxia and neuroendocrine reaction of the parvocellular neurons of the paraventricular hypothalamic nucleus // Патологія. – 2019. 3(47), – p. 334-338.

8 Косинец, В.А., Федотов, Д.Н. Морфологические перестройки в эндокринных железах при экспериментальном распространенном гнойном перитоните // – Витебск: Ученые записки учреждения образования витебская ордена знак почета государственная академия ветеринарной медицины, – 2015. № 1, – с.230.

9 Гараев, Г.Ш. Структурные изменения поджелудочной железы при перитоните и роль функционального состония брыжеечных лимфоузлов в его патогенезе / Г.Ш.Гараев, А.Б.Юсифова, Н.Р.Дадашова [и др.] // Хирургия. – Москва: – 2010. № 1, – с. 32-37.

10 Ahmetagic, A. Etiology of peritonitis / A.Ahmetagic, F.Numanovic, S.Ahmetagic [et al] // Med Arh. – 2013. 67(4), – p. 278-281.

is, just as hypoxia can cause inflammation in the body, inflammation also can cause hypoxia[11].

Hypoxia and infection have a damaging effect on organs and tissues, including the endocrine and immune systems, change the functional state and metabolism of the body, lead to disruption of mechanisms of interaction between the endocrine and immune organs, as well as homeostasis, neurohumoral causes the formation of original pathologies, as well as deepens existing diseases[12].

At a time when endocrine and immune pathologies are widespread in the world, various stress factors, including hypoxia and infection, mainly the morphological picture of the endocrine and immune system during the combined effect of these factors, the body's response to these factors, including the endocrine glands and the lymphatic system, has not been investigated in detail[13]. From another point of view, the diversity of the tissue structure and reactivity of endocrine organs, the sufficient complexity of the mechanisms that form the pathomorphological basis of the relationships between them, and the assessment of the role of the endocrine and immune systems during compensatory-adaptation processes occurring in the body is one of the urgent issues in medical and biological sciences.[13] In particular, it should be noted that the study of the interaction of endocrine glands under the influence of stress factors, including hypoxia and infection, cannot be limited only to the analysis of structural changes occurring in them. The phasic progress of the formation of adaptation mechanisms against hypoxia and infection in the body and the separate participation of each of the endocrine glands (adenohypophysis, adrenal gland, and thyroid gland) as well as the

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[11] Biddlestone, J., Bandarra, D., Rocha, S. The role of hypoxia in inflammatory disease (Review) // International Journal of Molecular Medicine, – 2015. 35(4), – p. 859-869.

[12] Chen, Y, Gaber, T. Hypoxia / HIF Modulates Immune Responses // Biomedicines. – 2021. 9(3), – p. 260.

[13] Calzia, E. Hypoxia determines survival outcomes of bacterial infection through HIF-1alpha dependent reprogramming of leukocyte metabolism / E.Calzia, P.Asfar, B.Hauser [et al] // Science Immunology. – 2017. 2(8), – p. 2861.

lymphatic system (maternal lymph nodes and lymphocytes of the peripheral blood) in this process should be taken into account[14].

From this point of view, the research work that we are planning is a comparative study of the stress factors – hypobaric hypoxia and staphylococcal infection, mainly the cells of the endocrine and immune system during the combined effect of these factors, the interaction of these cells with hypoxic and infectious processes, as well as their role in the adaptation processes occurring in the body, constitutes the main core.

The purpose of the dissertation work is to conduct a comprehensive study of the pathogenesis and morphogenesis of structural changes in the adenohypophysis, thyroid gland, and adrenal glands, as well as mesenteric lymph nodes and peripheral blood lymphocytes in normal conditions, under conditions of hypoxia and infection, as well as under the combined influence of hypoxia and infection.

Objectives of the study:

1. To study the changes occurring in the cellular and extracellular structure of the adenohypophysis, thyroid, and adrenal glands, as well as the mesenteric lymph nodes in acute hypobaric hypoxia using anatomical, histological, electron-microscopic, immunohistochemical, and morphometric examination methods.
2. To study the changes in the cellular and extracellular structure of the adenohypophysis, thyroid, and adrenal glands, as well as the mesenteric lymph nodes, under long-term (chronic) hypobaric hypoxia, using anatomical, histological, electron-microscopic, immunohistochemical, and morphometric examination methods.
3. To determine the characteristic features of structural changes of peripheral blood lymphocytes during acute hypobaric hypoxia using histological, immunohistochemical, and morphometric examination methods.

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[14] Newby, E.A. Fetal endocrine and metabolic adaptations to hypoxia: the role of the hypothalamic-pituitary-adrenal axis [et al.] // Am J Physiol Endocrinol Metab. – 2015. 309(5), – p. E429-439.

4. To determine the characteristic features of structural changes of peripheral blood lymphocytes during long-term (chronic) hypobaric hypoxia using histological, immunohistochemical, and morphometric examination methods.
5. To assess the cellular and extracellular structural changes of the adenohypophysis, thyroid, and adrenal glands, as well as the cervical lymph nodes, using anatomical, histological, electron-microscopic, immunohistochemical, and morphometric examination methods.
6. Using histological, immunohistochemical, and morphometric examination methods to determine the characteristic features of structural changes of peripheral blood lymphocytes during the influence of staphylococcal infection.
7. To determine the changes in cells and extracellular structures of the adenohypophysis, thyroid, and adrenal glands, as well as lymph nodes and peripheral blood lymphocytes during long-term hypoxia against the background of infection.
8. Determine the main characteristic features of compensatoryadaptive processes that occur in the pituitary, thyroid and adrenal glands, lymph nodes under the influence of hypoxia and infection, both individually and combined.

Research methods. Anatomical, histological, electron-microscopic, immunohistochemical, enzyme immunoassay and morphometric examination methods were used in the research. The quantitative indicators obtained as a result of the study were calculated using the statistical methods of variation, discriminant, and dispersion using the MS EXCEL-2019 and IBM Statistics SPSS-26 software package.

The main provisions of the dissertation submitted for defense:

− Hypobaric hypoxia and staphylococcal infection, as «stress» factors, both individually and combined affect the morphology of the endocrine glands as well as mesenteric lymph nodes and peripheral blood lymphocytes, causing significant morphological and functional changes in the cellular and extracellular structure of tissues.

- Morphofunctional changes occurring in the endocrine glands, as well as in the mesenteric lymph nodes and peripheral blood lymphocytes as a result of both separate and combined effects of hypobaric hypoxia and staphylococcal infection, are a complex of closely related reactions.
- Depending on the duration of the infection and hypoxia (acute or chronic), repetition (single or repeated), as well as the degree of pathogenicity of the infectious agent and the rate of development and spread of the infectious process, tissue structures of the adenohypophysis, adrenal gland and thyroid gland, mesenteric lymph nodes, and peripheral blood lymphocytes react accordingly to in different ways.
- The changes that occur in the cells of the endocrine glands, mesenteric lymph nodes, and lymphocytes of the peripheral blood due to hypobaric hypoxia and staphylococcal infection, either separately or combined, are manifested in different forms in each tissue, which depends on the type of cells and tissues, morphofunctional characteristics and hypoxia, and it varies depending on its resistance to infection and the degree of sensitivity.
- In the case of hypobaric hypoxia and staphylococcal infection, both individually and jointly, the changes occurring in the endocrine glands, as well as in the mesenteric lymph nodes and lymphocytes of peripheral blood, are of a phase nature, and as the duration of the experiment increases, reparative-regenerative processes in cells and tissues accelerate and cells adapt to the new environment.
- With a prolonged course of hypobaric hypoxia and staphylococcal infection in the body as a whole, including the endocrine glands, mesenteric lymph nodes, and peripheral blood lymphocytes, compensatory adaptation processes are provided against the background of hypoxia and infection, as a result of which the structure of the endocrine gland and the immune system is reconstructed.
- Hypobaric hypoxia and staphylococcal infection, both individually and together, lead to a violation of the mechanisms

of interaction between the endocrine glands, mesenteric lymph nodes and peripheral blood lymphocytes, as well as between the endocrine and immune organs.

- Hypoxia can significantly change the infectious process and the subsequent course of pathology by regulating important immune effector pathways in body tissues. This leads to the combined development of hypoxia and infection in various pathological processes.

Scientific novelty of the study Using complex histological, electron microscopic, immunohistochemical, and morphometric research methods, the nature of morphological changes occurring in the tissue structures of the endocrine glands and the immune status of the body, especially in mesenteric lymph nodes and lymphocytes of peripheral blood, due to the combined effect of prolonged hypobaric hypoxia and staphylococcal infection, were studied, the results were evaluated by quantitative and qualitative indicators. The basic principles of these mechanisms have also been studied under the separate effects of hypoxia and infection.

The results obtained in the study of the endocrine glands are compared with the changes occurring in the lymphoid organs, and the coordinated mechanisms of interaction of gland cells with each other, and mesenteric lymph nodes with lymphocytes, are characterized.

The basic principles of complex, multicomponent reactions aimed at the isolation and elimination of the pathogenic factor in the body, as well as the restoration of homeostasis and the activation of regenerative processes, have been studied.

The main features of the adaptation of the endocrine glands, lymphocytes, and mesenteric lymph nodes to hypoxia – lack of oxygen and infection – by injection of a pathogenic microbe into the abdominal cavity – by gaining resistance, the course of reparative regeneration processes occurring in tissues, and the main ones, a comparative analysis of the mechanisms of adaptive processes that are formed in glands and lymph nodes.

Theoretical and practical significance of the study.

The obtained results can be used as the main criterion in the assessment of many diseases formed as a result of hormonal imbalance in the body, including pathologies occurring in the endocrine and immune systems, as well as adaptation mechanisms for the implementation of preventive measures during treatment with hypobaric hypoxia. At this time, by increasing the specific and nonspecific resistance of the body, it is possible to activate the internal mechanisms (mechanisms of sanogenesis) aimed at restoring impaired functions. Due to the internal sanogenic mechanisms, it is possible to increase the resistance of the body to any environment, thereby improving the lives of people, and reducing the number of diseases, mainly chronic nosological diseases, as well as their exacerbation. The application of hypoxia can be used in the prevention, treatment, and rehabilitation of various stress conditions and nosological diseases by activating genetically programmed mechanisms aimed at increasing the non-specific resistance of the body.

At the same time, the intensity of the regenerative reactions of the endocrine and immune systems in the body as well as the reserve capabilities of the endocrine glands should be taken into account in the development (formation) of compensatory-adaptative processes. From the results of the research, in order to increase the stress resistance of dangerous professions (pilots, sailors, emergency personnel, etc.) against extreme effects, special training for professional activity conditions, aviation and space flights, high-altitude and mining operations, aerospace medicine, in the practice of sports medicine and physical education, can be used by doctors for strengthening the effectiveness of the training process, the changes caused by irritating factors in their bodies, as well as the adaptation and recovery processes. Intermittent barochamber exercises of athletes, flight crews, and other hazardous professions can be used for the purpose of testing to evaluate the tolerance to various degrees of hypoxia and to detect hidden diseases that cause a decrease in individual resistance to hypoxia.

Approbation of dissertation materials. The main results of the dissertation work were presented at the «Internationaler Medızınıscher Kongress» (Hannover, 2015), at the International Scientific

Conference dedicated to the 110th anniversary of the honored scientist, professor K.A.Balakishiyev (Baku, 2016), at the Scientific Conference dedicated to the 70th anniversary of honored scientist, professor G.S. Garayev's (Baku, 2017), at the Scientific Conference dedicated to the 75th anniversary of A.T.Agayev's (Baku, 2019), at the International Scientific and Practical Conference dedicated to the 100th anniversary of the establishment of the Department of Human Anatomy and Medical Terminology of the Azerbaijan Medical University (Baku, 2019), «VIII International Eurasian congresses of surgery and hepatogastroenterology» (Baku, 2019), at the «XI International Congress of Forensic Medicine» (Tekirdag, 2019), held jointly with Tekirdag Namig Kemal University and TURAZ Academy, «2nd International Congress on Sports, Anthropology, Nutrition, Anatomy and Radiology» (Cappadocia, 2020), at the International Scientific Conferencethe dedicated to the 85th anniversary of the honored scientist, professor M.M.Davatdarova (Baku, 2020), at the XV Congress of the International Association of Morphologists (Khanty-Mansiysk, 2020), at the International Scientific and Practical Congress dedicated to the 90th anniversary of the establishment of Azerbaijan Medical University (Baku, 2020), at the II International Scientific Conference on Humanities and Social Sciences (Baku, 2020), at the International Scientific and Practical Congress dedicated to the 90th anniversary of the establishment of the Azerbaijan Medical University (Baku, 2020), the II International Scientific Conference on Humanities and Social Sciences (Baku, 2020), the conference dedicated to the 90th anniversary of the establishment of the Azerbaijan Medical University, at the 5th International Scientific Congress dedicated to the 80th anniversary of Higher Pharmaceutical Education in Azerbaijan on «Modern Problems of Pharmacy» (Baku, 2021), at the Scientific-Practical Conference on «Healthy Labor and Life Safety – 2021» dedicated to the 90th anniversary of the establishment of the Azerbaijan Medical University (Baku, 2021), XXVII International Symposium on Morphological Sciences «Cell, tissue, organs – experience, innovation and progress» (Almaty, 2021), «The role of innovative technologies in the medical educational process of fundamental disciplines and clinical medicine» – (Samarkand, 2021), at the International Congress dedicated to the 100th anniversary of professor T.A.Aliyev «Current issues of medicine» (Baku, 2021), at current issues «Biomedical Sciences of Scientific and practical conference» (Kharkov, 2021), at the «XIX International conference of the European Academy of Sciences & Research» (Hamburg, 2021), at the International Scientific and Practical Conference «Modern Medicine: New Approach and Relevant Research» among the medical organizations of Kazakhstan, near and far abroad, dedicated to the day of the world struggle with with osteoporosis (Aktobe, 2021), III International TURAZ Academy of Forensic Sciences, Forensic Medicine and Pathology Congress on «Violence and Media» (Baku, 2021), as well as at the Scientific Research Center of Azerbaijan Medical University (Baku, 2022, protocol No.1), at the interdepartmental meeting of pathological anatomy, pathological physiology, human anatomy and medical terminology, cytology, embryology and histology (Baku, 2022, protocol No. 1), was discussed at the scientific seminar of the BED 4.13 One-time Dissertation Council under the Azerbaijan Medical University of the Higher Attestation Commission under the President of the Republic of Azerbaijan (Baku, 2022, protocol No. 1).

Application of results. The results of the study are used in the teaching process of the Departments of Human Anatomy and Medical Terminology, Cytology, Embryology and Histology, Normal Physiology, Pathological Physiology, and Pathological Anatomy of the Azerbaijan Medical University, in the practice of sports medicine and physical education – during training with athletes, as well as during the treatment of patients with endocrinological pathology, as well as with hypobaric hypoxia during treatment, it can be used to implement preventive measures aimed at strengthening adaptation mechanisms. Evaluating tolerance to various degrees of hypoxia can be used for testing purposes to detect hidden diseases that lead to a decrease in individual resistance to hypoxia.

Published materials. 50 scientific works have been published on the topic of the dissertation. 32 of them are scientific articles, and 18 are theses. 9 of the journal articles were published in foreign press («World Science» – Warsaw, Poland; «Bulletin of Surgery

Kazakhstan» – Almaty, Kazakhstan; «Avicenna Bulletin» – Dushanbe, Tajikistan; «Medicine Science» – Turkey; «Clinical pathophysiology» – Russia, St. Petersburg, «Archiv Euro Medica» – Hannover, Germany; «Medical Biology Suite» («World of Medicine and Biology») – Poltava, Ukraine and 7 are included in the international summarizing and indexing system (Web of Science, SCOPUS) published in the periodical scientific publications.

Volume and structure of the dissertation. The dissertation consists of 394 computer pages (403785 characters) and contains «Introduction» (volume: 19032 characters), «The main content of the dissertation» (volume: 377815 characters), «Conclusion» (volume: 33116 characters), «Results» (volume: 4752 characters), «Practical recommendations» (volume: 2186 characters) and «List of used literature».

«The main content of the dissertation» section is divided into 7 chapters: Chapter I. «Summary of literature» (volume: 142144 characters), Chapter II. «Materials and methods» (volume: 16319 characters), Chapter III. «Experimental study of the morpho-functional properties of the adenohypophysis during normal, hypobaric hypoxia and staphylococcal infection (peritonitis)» (volume: 44527 characters), Chapter IV. «Experimental study of the morpho-functional characteristics of the thyroid gland during normal, hypobaric hypoxia and staphylococcal infection (peritonitis)» (volume: 58048 characters), Chapter V. «Experimental study of the morpho-functional characteristics of adrenal glands during normal, hypobaric hypoxia and staphylococcal infection (peritonitis)» (volume: 74491 characters), Chapter VI. «Experimental study of the morpho-functional characteristics of lymph nodes in normal, hypobaric hypoxia and during staphylococcal infection (peritonitis)» (volume: 31377 characters), Chapter VII. «Experimental study of morphofunctional properties of peripheral blood lymphocytes during normal, hypobaric hypoxia and staphylococcal infection (peritonitis)» (volume: 10909 characters).

The bibliography includes 268 sources, 4 of which are in Azerbaijani, 75 in Russian, and 189 in other foreign languages. The text of the dissertation contains 52 tables, 19 diagrams, and 119 photographs.

MATERIALS AND METHODS OF STUDY

The study was carried out on 140 adult white male rats weighing 180-200 g, bred under special conditions. In accordance with the goals and objectives of the study, the experimental animals selected as objects were divided into 4 groups: control, hypoxia, infection, and the main group (table). The first control group included 20 rats, and the experimental animals were intact. The model of hypoxia was created on 40 rats included in the II group of hypoxia. Experimental animals were placed in a special pressure chamber with ventilation, in which an environment was created corresponding to atmospheric pressure at an altitude of 2000-3000 meters above sea level.

The experimental animals included in the hypoxia group were divided into 4 subgroups, with 10 rats in each one. Subgroup I and II animals were kept in a barochamber for 2 and 5 days, 2 times a day for 2 hours (with a break of 1 hour), respectively, and animals of subgroup III and IV were subjected to acute hypoxia, and animals of subgroup III and IV were subjected to the same procedure 5 times a week and 2 hours each time (1 hour apart) were exposed to chronic hypoxia for 15 and 30 days.

In order to infect 40 rats included in the III infection group, a suspension of Staphylococcus aureus culture dissolved in a concentration of $1x10^9$ microbial cells/kg (per kg) was injected into their peritoneal cavity in a volume of 1 ml prepared by a standard method in a physiological solution.

40 rats of the IV main group were placed in a specially ventilated barochamber after being infected with an intraperitoneal S.aureus culture. Experimental animals were tied to the operating table on their backs, macromicroscopic studies were performed under surface ether anesthesia.

Table.

Distribution of experimental animals by groups.

№	Groups	Subgroups		Number of animals	Model of Experiment	Duration of experiment
1.	I Control Group	I		5	–	2nd day
		II		5		5th day
		III		5		15th day
		IV		5		30th day
2.	II Hypoxia group	I A	I	10	Acute hypoxia	2nd day
			II	10		5th day
		I B	I	10	Chronic hypoxia	15th day
			II	10		30th day
3.	III İnfection Group	I		10	İnfection	2nd day
		II		10		5th day
		III		20		15th day
4.	IV Main group	I		20	Hypoxia + infection	15th day
		II		20		30th day

In animals divided into groups, blood was taken from the tail vein and smears of peripheral blood were prepared on glass slides. Euthanasia of animals was carried out by introducing into the abdominal cavity a 2-2.5% solution of sodium thiopental (an anesthetic) at a dose of 100 mg/kg. After euthanasia of the experimental animals, the cranial cavity was opened, an incision was made along the midline, and the cervical and abdominal cavities were opened.

After opening the cranial cavity, the pituitary gland, located on the Turkish saddle at the base of the skull, was removed from the bed along with the dura mater. By cutting with scissors the muscles located below the hyoid bone in the neck area, the thyroid gland was removed from its bed. After opening the abdominal cavity, one of every 3 lymph nodes, starting from the arc of the colon clockwise, was cut with scissors with thin tips and removed from between the sheets of the mesentery. The posterior surface of the peritoneum was dissected, and the adrenal glands located on the upper pole of the kidneys in the peritoneal region were cut and removed.

The mass of the removed endocrine glands was measured. Mesenteric lymph nodes and glands were examined macroscopically

– after determining the color, shape, consistency, and condition of the capsule, they were placed in Petri dishes.

After macroscopic evaluation, the organs were prepared in 10% neutral formalin, Buen and Carnois solutions (36-72 hours) for histological examination, and for electron-microscopic examination in 2% phosphate buffer (pH=7.4). It was fixed in glutaraldehyde and 2% paraformaldehyde solutions and 0.1% picric acid solution and sent for microscopic examination.

Using immunohistochemical studies, CD4+ and CD8+ antigens were examined in the adenohypophysis, thyroid and adrenal glands, as well as in the mesenteric lymph nodes. TSH and cortisol hormones were determined by enzyme immunoassasy in blood plasm. In the course of microscopic studies, in addition to the qualitative characteristics of the morphological and functional characteristics of the objects of study, a number of quantitative indicators were also studied.

The quantitative and qualitative indicators obtained during the study were subjected to statistical processing, taking into account modern recommendations. Statistical analysis was performed using variational, discriminant, and dispersion methods; for longitudinal comparison, nonparametric U-Mann-Whitney (2 groups) and W-Wilcoxon (W-Wilcoxon) tests were used.

THE RESULTS OF THE STUDY AND THEIR DISCUSSION

Experimental study of endocrine glands, mesenteric lymph nodes, and peripheral blood lymphocytes in hypoxia

Hypoxia, which is one of the urgent problems of modern medicine, underlies various pathological processes that occur as a result of impaired oxygen supply to tissues as well as blood transport function. The dynamics of hypoxia-induced changes in the endocrine glands, mesenteric lymph nodes and peripheral blood lymphocytes was monitored, the results were compared with the control and other groups. During the analysis of the results, it turned out that under the influence of hypoxia in the glandular tissue, lymph nodes, and peripheral blood lymphocytes, structural changes occur. The degree of these changes is not the same in each organ, depending on the duration of hypoxia and the morphofunctional characteristics of the organs.

The morphological study of the endocrine glands of experimental animals under conditions of lack of oxygen at an early stage of the study is characterized by clearly pronounced dystrophic and disorganizational changes in gland tissue. From the first days of the experiment, dystrophy, accompanied by a change in the number of endocrinocytes, develops intensively and is replaced by sharp pathomorphological changes on the 5th day of the experiment. Under the influence of hypoxia, edema in the interstitial region increases; as a result of diffuse edema, reticulin fibers swell, cells separate from each other (separate), and the size and interaction of cells change dramatically. Violation of oxygen supply to organs is accompanied by maximum expansion and fullness of sinusoidal capillaries, signs of plethora, and increased density of blood vessels against the background of focal diapedesis hemorrhages.

Acute hypoxia creates a complex of deep structural changes, mainly in the adenohypophysis and adrenal cortex, adenocytes and adrenocorticocytes undergo acute dystrophic changes, gland tissues lose their morphological features, and organs are unevenly filled with blood. On the 2nd day of the study, hyperemia was observed in adenohypophysis adenocytes, accompanied by diffuse edema, and small inflammatory foci consisting of neutrophil-leukocyte elements were clearly detected in the interstitial space. As the duration of the experiment increased (5th day), a large number of vesicles, lysosomes, and microdroplets of fat in the cytoplasm of the cells reflected fatty (vacuolar) degeneration of the gland cells.

The lobular structure of the thyroid gland is not changed, only on some preparations the lobules are poorly distinguishable. However, in histological preparations, individual thyrocytes desquamated and absorbed by the colloid are visible, colloid thickening is observed inside of some follicles, and edema of the interstitial space causes compression of the follicles.

Tissue hypoxia, which occurs at the cellular level, affects the structure of organelles, causing their vacuolization and destruction.

Destructive changes are manifested by hypertrophy of organelles, especially mitochondria, expansion of the cisterns of the endoplasmic reticulum, and degranulation of the Golgi complex and lysosomes. Mitochondria, to a greater extent than organelles, undergo dystrophic changes, basically, the vast majority of mitochondria in the adenohypophysis and adrenal glands are edematous, and their outer shell has a wavy structure, they change their elongated shape and acquire a relatively rounded shape. Curved mitochondria can be found in the cytoplasm of adrenocorticocytes; the cristae of such mitochondria are smooth and indistinguishable. Microgrooves on the apical surface of thyrocytes are poorly visible, and on some preparations, they are not visible at all. The layers that make up the capillary walls, in turn, undergo ultrastructural changes.

Structural changes occurring in the cells of the gland during the acute period of the study are of a double nature, and the morphological picture observed in each of the glands is also confirmed by morphometric studies. Under the influence of acute hypoxia, the size of the endocrine glands increases significantly.

On the 5th day of the study, the diameters and areas of acidophilic and basophilic adenocytes were 8.1% and 17% in acidophiles (10.38 μm and 84.6 μm^2, intact – 9.6 μm and 72.3 μm^2), in basophils, respectively, compared to intact parameters. It increases by 18.5% and 40.3% (12.8 μm and 129.5 μm^2, intact – 10.8 μm and 92.3 μm^2) ($p<0.001$). The same parameters of chromophobes, which make up the main part of the gland, are reduced to 8.0 μm and 50.2 μm^2 (intact – 7.93 μm and 49.4 μm^2) ($p=0,079$).

Despite the fact that on the 2nd day of the experiment, the thickness of the adrenal cortex decreased by 20.2% (746.1 μm, intact – 896.9 μm, $p<0,001$), on the 5th day, the thickness of both the adrenal cortex and the adrenal medulla increased significantly. The decrease in the thickness of the adrenal cortex is mainly explained by the decrease in the thickness of the zona fasciculata to 418.1 μm (intact – 536.7 μm, $p<0,001$). On the contrary, the thickness of the glomerular zone increases, while the thickness of the fascicular and reticular zones decreases. The obtained results lead to a sharp changes of the mutual ratio of the adrenal cortex and the zones forming it (diagram 1.).

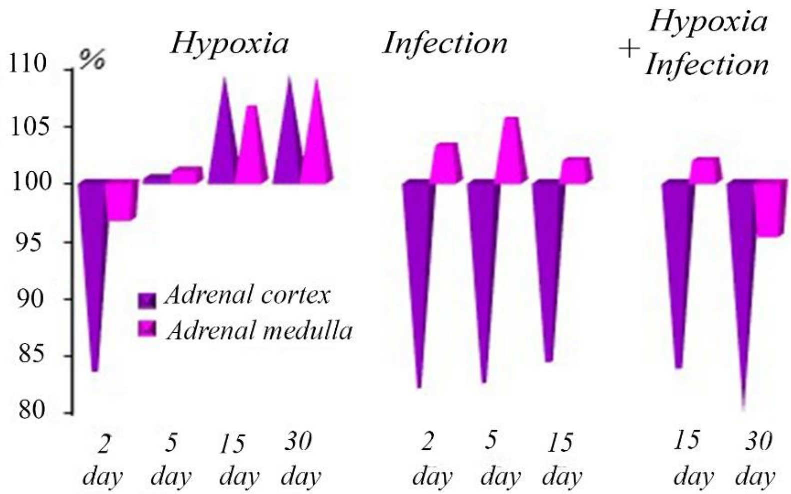

Diagram 1. Adrenal cortex/adrenal medulla ratio in hypoxia, infection, and in the main group.

At the same time as the diameter and area of follicles and thyrocytes decrease in the thyroid tissue, the height of the follicular epithelium increases. Thus, the diameter and area of follicles were 34 μm and 909.2 μm^2 in the center, 37.8 μm and 1119.5 μm^2 in the periphery ($p<0.001$), and the diameter and area of thyrocytes in the center were 6.94 μm and 37.8 mkm^2 ($p<0.001$), and in the periphery it decreases to 11.05 and 95.8 mkm^2 ($p=0.130$). It is noted that the height of the thyroid epithelium is 7.94 μm in the center ($p<0.001$) and 6.36 μm in the periphery, which is 14.6% and 10.8% higher, respectively, compared to intact parameters ($p=0.034$) (diagram 2.).

Cellular elements are unevenly distributed in all 3 glands. In the adenohypophysis, the ratio of cells changes as a result of an increase in the number of basophilic and chromophobic adenocytes simultaneously with a decrease in the number of acidophilic adenocytes per unit area (a decrease of 22.8% compared with the control group) (12:22:66, intact – 9:29:62) (diagram 3.).

The number of cells in the adrenal glands increases, starting from the early stage of hypoxia, on the 2nd day of the study, the number of cells significantly increases – 19.4% (35.6, intact – 32.5, p=0,049) in the medulla and 14.5% (35.6, intact – 32.5, p<0,001), 24.8% (36.4, intact – 30.6, p<0,001) and 19.4% (38.0, intact – 37.1, p=0,049) in the glomerular, fascicular, and reticular zones, respectively (p<0.05).

The number of thyroid cells, on the contrary, decreases – on the 5th day of the experiment, it decreases by 13.4% (25.3, intact – 29.2, p<0,001) in the central zone and by 14.7% (14.5, intact – 17.0, p=0,003) in the peripheral zone (diagram 5.).

By the end of the study, dystrophic changes in the endocrine glands under the influence of acute hypoxia are replaced by the restoration of the cellular structure and reparative-regenerative processes. Despite the positive dynamics observed in the histological examination of the endocrine glands in experimental animals included in the III and IV subgroups of the hypoxia group, different changes are noted between the glands.

Although the general structural plan of endocrinocytes is restored under the influence of prolonged repeated hypoxia, dystrophic changes and even disintegrated cellular complexes are visible in the adenohypophysis. Histological preparations also show apoptotic adenocytes. At the same time, fat drops are observed in the cytoplasm of some adrenocorticocytes, but this is local in nature and is explained by the fact that fat drops are not completely absorbed in the adrenal cortex. The blood supply and the location of the glands are close to normal, but the central part of the adenohypophysis, consisting of chromophobic adenocytes, is enlarged.

In the chronic period of studies (15th day) in the thyroid gland, significant recovery processes are registered. In the parenchyma of the gland, especially in the peripheral zone, the process of folliculogenesis proceeds with an increase in the number of small follicles with proliferative potential, thickening of the interfollicular septum in the stroma, as well as a focal or diffuse increase (growth) of the connective tissue.

On the last day of the study (30th), the structure of the adenohypophysis and adrenal glands is close to normal. With the proliferation, differentiation, and hypertrophy of endocrinocytes, the period of recovery of the glands after hypoxia ends. Electrograms clearly show repair and regeneration of parenchyma cells (increase in the area and diameter of the cytoplasm and nuclei), compensatory hyperplasia and differentiation of organelles at the ultrastructural level, and ultrastructural restoration of the cellular structure.

Morphometric study in the tissues of the gland also shows an increase in the total number of endocrinocytes with cell differentiation. On the 15th day of the study, on the background of a compensatory increase in the size of most adenocytes in the adenohypophysis, the number of basophilic adenocytes per unit area remains high (13.95%, intact – 9.3%, p<0,001), the number of acidophilic adenocytes is close to the control group (28,4%, intact – 28,9%, p=0,398), and the number of chromophores (58.4%, intact – 62.1%, p=0,002) is 1.1 times lower than in the control group. Compared with the 5th day, the ratio of the number of basophils and acidophils increases (14:28:58, the proportion of chromophobes decreases).

At the end of the study, the number of basophils and chromophobes did not reach the norm, despite the fact that the mutual ratio of the cell population was 13:29:58 against the background of a compensatory increase in the size of most adenocytes in the morphometry of cellular elements (diagram 3.).

A similar picture is recorded in the adrenal glands. The number of cells increases by 34% (30.6% intact – 41.0%, p=0.001) in the fascicular zone compared to the intact values and by 33.2% (37.1%, intact – 49.4%, p=0.001) in the reticular zone.

Positive dynamics are observed in the thyroid gland. On the 15th day of the experiment, the number of thyrocytes both in the central and peripheral zones of the gland increased and approached the parameters of the control group – 26.4 (intact – 29.2, p=0.001) in the center and 16.3 (intact – 17, p=0,328) in the periphery, which is similar to the control group and 9.6% and 4.1% less compared to the group, respectively. On the 30th day, the number of thyrocytes in the central and peripheral zones significantly increased by 6.8% (28.2) and 5.5%

(17.2) (p=0,009) respectively, compared with the previous period of the experiment (day 15) (diagram 5.).

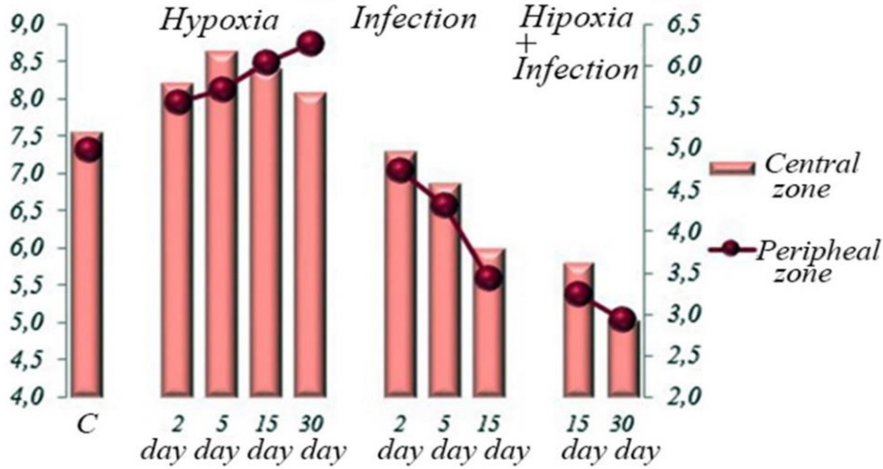

Diagram 2. Height parameters of thyroid epithelium in hypoxia, infection, and in the main group.

At the same time, under the influence of chronic hypoxia, the cell area in all zones of the adrenal cortex, mainly in fascicular and reticular zones, increases by 17.9% and 10.5%, respectively, compared to the indicators of the control group on the 30th day, these are 141.7 μm^2 (intact – 120.2 µm m^2) and 73.7 μm^2 (intact – 66.7 μm^2) ($p<0.001$). An increase in the area and number of cells leads to hypertrophy, a thickening of the adrenal cortex. On the 15th day of the study, the thickness of the adrenal cortex increases by 8.4% compared to the control group and is 972.3 µm (intact – 896.9 µm, p=0.001) (diagram 1.). This is explained by the thickening of the reticular zone. Thus, in the reticular zone, this parameter increases to 247.1 µm and is 19.8% (intact – 206.2 µm, p=0.001) higher than intact parameters (diagram 4.). Similarly, the thickness of the adrenal medulla changes and the growth dynamics are maintained (479.9 µm, intact – 458.2 µm, p=0.214).

On the last day of the experiment, the area of the central follicles of the thyroid gland increased by 11.7% (1100.5 μm^2, day 15– 985.3 μm^2, $p<0.001$) compared to the 15th day of the study, and the area of the peripheral follicles increases by 7.5% (1126.0 μm^2, day 15 – 1217.7 μm^2, p=0.093 μm^2) decreases, little different from intact parameters.

At the end of the study, the characteristics of gland cells, strengthening of reparative and regenerative processes, morphological changes, and restoration of the structure of microcirculatory capillaries in the vascular bed indicate that the glands are adapted to chronic hypoxia and are reconstructed from a structural and functional point of view. Thanks to the recovery processes occurring in the gland under the influence of hypoxia, the cells of the gland and interstitial tissue partially restore their normal structure.

In the formation of integral reactions and adaptive processes against the effects of hypoxia, an important role is played by the immune system, especially the lymph nodes, which have high potential and plastic properties. In preparations prepared from modern lymph nodes of experimental animals created on a model of hypoxia, morphological and functional changes of a systemic nature of different levels are noticeable both with short-term acute exposure and with repeated chronic exposure to hypoxia.

At an early stage of the experiment (2nd day), swelling of fibrous structures in the stroma of the lymph nodes leads to the separation of the follicles of the cortical substance from each other, but he parenchymal-stromal ratio remains unchanged. In histological preparations, attention is drawn to a decrease in the relative volume of the cortical substance under the capsule and an increase in the relative volume of the medullary substance in the center and also the paracortical zone due to the accumulation of edema. As a result of the growth of the medulla, the ratio between the cortex and medulla changes and is 1.02% (intact – 1.02%, p=0.001) and the ratio of the cortex, medulla, and paracortical zone is 48:48:4 (diagram 6.).

Acute pathomorphological changes in the mesenteric lymph nodes are noted on the 5th day of the experiment; under the influence of hypoxia, the cellular composition of the lymph nodes and the structure of the parenchyma is disturbed, edema develops in the parenchyma, and follicles noticeably swell. Diffuse edema of the parenchyma of the lymph nodes causes compression of the intraorganic pathways of lymphatic circulation, which is manifested by the expansion of the openings of the lymphatic sinuses. In particular, it should be noted that medulla edema is characterized by compression of the portal sinus. The lack of tissue oxygen causes changes in the blood and lymph circulation of the lymph nodes – an increase in the symptoms of stagnation, a sharp expansion of the capillary lumen, and an increase in the recirculation of lymphocytes into the lymphatic capillaries.

Under the influence of acute hypoxia, the lymphatic sinuses are covered with a network of reticular fibers and macrophages. This leads to an increase in the volume of the medulla, as well as the paracortical zone, and on the 5th day, these figures are 51.2% (intact – 38.3%) and 5.4% (intact – 3.3%), respectively ($p<0.001$). In the cortex, the size and volume of lymphoid follicles were sharply reduced to 43.4% (intact – 58.3%), which is 25.6% less than in the control group ($p<0.001$). At the same time, the cellular composition of the lymph nodes and the ratio of the cortex and medulla to each other change dramatically and amount to 0.85% (5:44:51, $p<0,001$), and the volume ratio increases in favor of the medulla (diagram 6.). This is due to the fact that the cortical substance undergoes more pronounced degenerative changes than the medullary substance.

The electronograms clearly show a changes of the cellular structure, hypertrophy of organelles, predominantly swollen mitochondria, their cristae are smoothed, and cisterns of the endoplasmic reticulum are expanded in the cavity form.

At later stages of the study (days 15 and 30), a morphological analysis of the mesenteric lymph nodes of animals adapted to prolonged hypoxia shows that pathomorphological changes are manifested by the development of proliferative processes. The parallelism of proliferative processes both in the parenchyma and in the stroma is considered as the main mechanism of compensatory-adaptative processes. The cortical substance expands due to the number of well-defined, but unevenly located follicles, and the volume on the 15th day is 7.5% compared to the 2nd day of the experiment (51.9%, 2nd day – 48.3 %, $p=0.023$), compared with by the 5th day significantly increased by 19.6% (5th day – 43.4%, $p=0.005$) (diagram 6.).

Ultimately, the restructuring of the parenchyma and stroma of lymphoid tissues occurs – the cells adapt to the new environment, and completely restore their normal structure and size. In particular, the cortical substance and its follicles, which have undergone pronounced dystrophic changes, attract attention with their normal structure. It was noted that the morphometric parameters obtained on the last day of the experiment (30th) were close to normal. The change in the ratio of the zones that make up the lymph nodes to each other occurs with a decrease in the volume of the medulla and an increase in the volume of the medulla (3:42:55; the volume of the paracortical zone is normal) (diagram 6.).

Degranulation of the endoplasmic reticulum and a pronounced increase in the number of lysosomes on electronograms due to acute hypoxia are replaced by compensatory hyperplasia of parenchymal cells and organelles due to chronic hypoxia at the end of the study.

In the first days of the study, the structure of lymphocytes in the peripheral blood of experimental animals included in the hypoxia group did not change morphologically, weak dystrophic changes were observed in the cells. On the 5th day, the cytoplasm of the cells becomes vacuolated, the size of the nuclei increases, and they are relatively swollen. Under the influence of hypobaric hypoxia on the 5th day of the experiment, a slight lymphopenia, a change in the number of small, medium, and large lymphocytes in cytological samples, a decrease in the number of lymphocytes in general, but an increase in the number of large-sized lymphocytes are noteworthy. In the early stage of acute hypoxia, the number of lymphocytes per unit volume of blood is reduced by 8.8% (67.3%, intact – 73.8%, $p<0.001$) compared with the control group. The number of neutrophils increases by 35.3% (25.3%, intact – 18.7%, $p<0.001$) compared with the control group and by 31.1% compared with 2nd day of the experiment. This is due to a significant increase in the number of stab and segmented neutrophils – 29.7% (2.4%, intact – 1.85%, $p=0.055$) və 33.9% (22.5%, intakt – 16.8%, $p<0.001$ respectively.

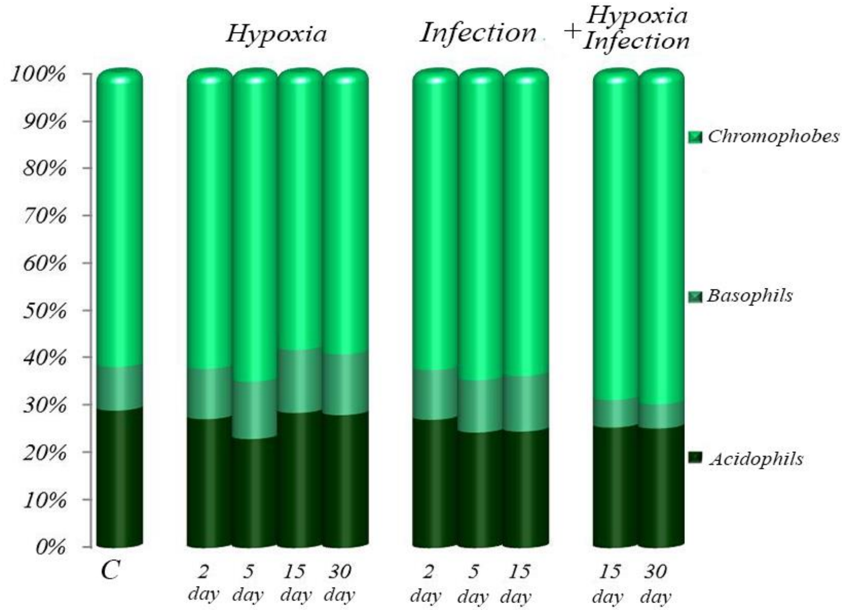

Diagram 3. The ratio of the number of adenohypophyseal adenocytes under conditions of hypoxia, infection and the main group.

In the 2nd and 5th days of the study, the quantitative parameters of peripheral blood lymphocytes were the lowest compared to the control group, and at the end of the study, they increased to the generally accepted norm. In particular, against the background of a decrease in the number of neutrophils, a significant increase in the number of lymphocytes is clearly visible. So, on the 15th day of the study, the number of neutrophils decreased to 20.7% (stab neutrophils – 2.14% and segmented neutrophils – 18.3%). The number of lymphocytes at this stage increases to 72.3%, on the 30th day to 73.8%, which significantly differs from the figures on the 5th day (7.3% and 9.7%, respectively) (p=0,001). A similar pattern is recorded in neutrophils; on the 30th day of the study, the number of neutrophils decreases and reaches the norm. At the end of the study, the ratio of lymphocytes to neutrophils was 3.52 (intact – 3.98, p=0,155) (Diagram 7).

According to the results of our studies, significant morphological and functional changes occur in the endocrine glands and mesenteric lymph nodes under the influence of acute hypoxia, and as hypoxia continues, these changes change the morphological state (structure) of the endocrine and lymphoid tissue. At the end of the study, the morphological and functional characteristics of the organs, the strengthening of reparative and regenerative processes, morphological changes, and the restoration of the structure of microcirculatory capillaries in the vascular bed indicate their adaptation to chronic hypoxia and restructuring from a structural and functional point of view. As a result, compensatory-adaptive processes develop in the glands and mesenteric lymph nodes.

The mechanisms of adaptation of the studied organs – adenohypophysis, adrenal glands, and thyroid gland, as well as mesenteric lymph nodes and peripheral blood lymphocytes to hypoxia, mainly to chronic hypoxia, are characterized by unique features in each tissue. This is explained by the fact that the changes that occur in organs under the influence of hypoxia and reflect their morphological state are different in individual organs.

Early damage to the adenohypophysis by adenocytes of adrenocytes of the adrenal glands and adrenocytes of the adrenal glands by thyrocytes of the thyroid gland can be regarded as a higher degree of sensitivity of the adenohypophysis and adrenal glands to hypoxia. The comparative analysis of preparations obtained from these glands shows that cellular and extracellular dystrophic and destructive changes due to acute hypoxia are observed in the cells of the adenohypophysis and adrenal glands at the early stage of the experiment (2nd day), while on the 5th day of the experiment, changes in the thyroid and cytoplasmic organelles are noted. Also, the structure of the thyroid gland adapts more and earlier to long-term hypoxia, and on the 15th day, the thyroid cells respond to this factor by remodeling. Morphological partial reconstruction of adenohypophysis and adrenal gland is recorded on the 30th day of the study. Under the influence of chronic hypoxia, lymphoid cells partially restore their normal structure.

Acute – short-term hypoxia causes a proportional decrease in the number of circulating lymphocytes and changes in their morphological structure, while chronic – long-term hypoxia causes a normalization of the number and structure of cells.

This morphological picture, noted in the histoarchitectonics of the endocrine glands and the immune system during hypoxia, can be considered as a nonspecific reaction of the body.

Experimental study of endocrine glands, mesenteric lymph nodes and peripheral blood lymphocytes in infection

The morphological picture of cells in preparations prepared from the endocrine glands and mesenteric lymph nodes of experimental animals infected with staphylococcal infection is characterized by pronounced parenchymal, stromal, and vascular changes. During experimental peritonitis, an increase in the thickness of the stroma and the volume fraction of the connective tissue exacerbates the destructive changes in parenchymal cells. This is due to damage and a decrease in cell volume due to exposure to staphylococcal infection, as well as focal infiltration of mononuclear cells. The infection also causes changes in the structure and number of lymphocytes in the peripheral blood.

The early stage of infection, on the 2nd-5th day of the study, is characterized by pathomorphological changes – the destruction of endocrinocytes and alteration of organelles in cells of the endocrine glands. On the 2nd day of the experiment, the histological structure of the glands reflects clearly visible progressive vascular changes on the background of intracellular vacuolization and intercellular edema: dilatation of capillaries, plethore, increasing vascular wall permeability, and small diapedesis hemorrhages, as well as edema of endotheliocytes. As a result of the development of peritonitis, accompanied by the syndrome of acute intoxication, at the next stage of the study (5th day), the interstitial zone expands sharply due to increased plasmorrhagia, reticulin fibers are dispersed, signs of mucoid swelling on the vessel walls are observed, and intercellular inflammation intensifies. Diffuse edema and disorganizational changes in the stroma lead to the formation of foci of focal necrosis in specialized cells of the gland parenchyma. Starting from the first stage of the study, the infiltration of mononuclear cells (lymphocytes and macrophages) in the stroma and at the end of the intraorgan capillaries increases intensively, reaches a maximum on the 5th day, and at the end of the experiment, the infiltrate weakens and is replaced by connective tissue.

During peritonitis of staphylococcal origin, acute destruction of organelles is observed at the ultrastructural level in gland cells. Ultrastructural changes in endocrinocytes include the annular transformation of nuclei, degranulation of mitochondria, Holci complex, and endoplasmic reticulum, and reduction of the number of lysosomes and ribosomes. In electrograms, the main part of the thyroid gland consists of small follicles formed by flattened thyrocytes.

In particular, it should be noted that as a result of an infection in the adenohypophysis and adrenal glands of experimental animals, a complex of deep structural damages is formed. Basically, adenocytes that have undergone necrotic changes predominate in the adenohypophysis. Against the background of necrosis of the glandular epithelium, mucoid degeneration is clearly visible in the interstitial region of the glands, as well as vascular changes, which are manifested by signs of endovasculitis, erythrostasis, and leukostasis.

On the 5th day of the experiment, in the acute stage of staphylococcal infection, the structure of the organ was disturbed simultaneously with compensatory hypertrophy of stromal cells in the adrenal glands, acute dystrophy and destruction of the interstitial space, localization of focal necrotic tissues consisting of neutrophilic leukocytes around adrenocytes – inflammatory infiltration reflects the general trend of damage.

In preparations made from the thyroid gland of experimental animals included in the infectious group, although the gland tissue retains its structural properties in the early stages, it is relatively edematous and changes its staining properties. However, during the experiment, swelling of the connective tissue elements between the follicles due to infection causes compression of the follicles, in particular, the follicles of the central zone decrease in size.

The parameters obtained as a result of morphometric analysis also indicate necrobiosis and necrosis of most cells. On the 5th day of the experiment in the adenohypophysis, according to the cellular composition, a decrease in the number of acidophilic and basophilic adenocytes and an increase in the number of chromophobic adenocytes leads to a change in the cell ratio (5:44:51, intact – 9:29:62) (diagram 3.). At the same time, at this stage of the study, the area of chromophils decreased (acidophils – 68.0 μm^2, intact – 72.3 μm^2, p<0,001), basophiles – 88.8 μm^2, intact – 92.3 μm^2, p<0,001), while the area of chromophobic cells, on the contrary, increased (50.6 μm^2, intact – 49.9 μm^2, p=0,013).

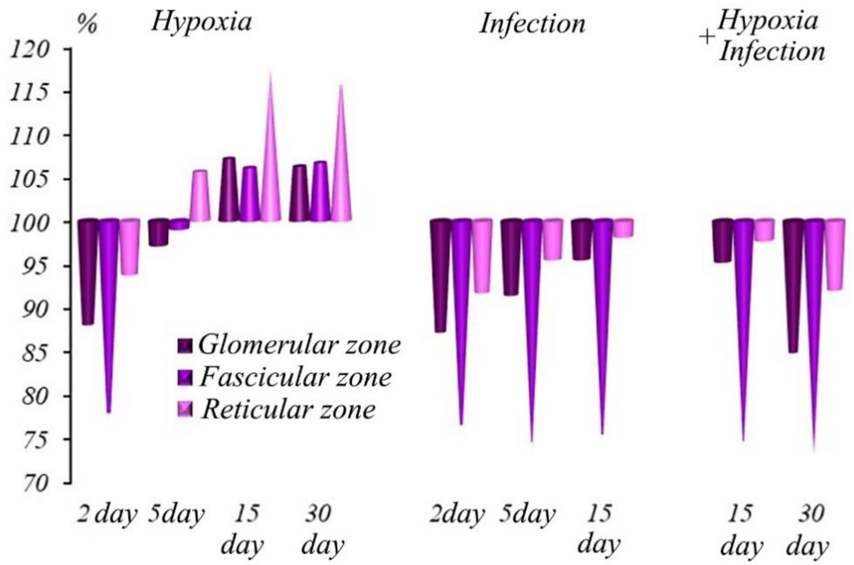

Diagram 4. The mutual ratio of zones of the adrenal cortex in hypoxia, infection, and in the main group.

In the early stages, the thickness of the medulla increases significantly, while the thickness of the cortex sharply decreases. Thus, the thickness of the cortex is 729.5 μm (intact – 896.9 μm) and the thickness of the medulla is 376.5 μm (intact – 458.2 μm), which is 18.7% (p<0,001) and 17.8% (p<0,001) less, respectively, compared to the intact ones (diagram 1). Morphometrical changes are more noticeable in the glomerular and fascicular zones of the adrenal cortex. The thickness of the glomerular zone is 133.5 µm (intact – 148.7 µm, p=0.051), and the thickness of the fascicular zone is 391.2 µm (intact – 536.7 µm, p<0.001). (diagram 4.). The obtained results reflect the change in the mutual ratio of both cortex and adrenal medulla and zones of adrenal cortex under the influence of infection.

On the 2nd day, the area and diameter of follicles in the thyroid gland decreases, respectively, in the center by 12.3% (1052.99 µm^2, intact – 1199.9 µm^2) and 6.4% (39.1 µm, intact – 36.6 µm) (p=0.007) and in the periphery by 8.7% (1375.1 µm^2, intact – 1505.8 µm^2) and 4.3% (41.9 µm, intact – 43.8 µm) (p=0.016). Along with the follicles, the area and diameter of thyrocytes sharply decreased, respectively, in the center 36.3 µm^2 (intact – 40.2 µm^2) and 6.8 µm (intact – 7.16 µm), on the periphery 94.9 µm^2 (intact – 98.1 µm^2) and 11.0 µm (intact – 11.8 µm) (p<0.001). Desquamation of thyrocytes absorbed by the colloid into the follicle leads to a significant decrease in their number (29.0 in the central zone, intact – 29.2, p=0.7624 and 16.4, intact – 17.0, p=0.597 in the periphery) (diagram 5.). On the 5th day of the study, due to infection, the height of the thyroid epithelium decreased sharply, in the center it was 6.13 µm (intact – 6.93 µm, p=0.013), on the periphery – 4.92 µm (intact – 5.74 µm, p=0.026) (diagram 2.).

During the experiment, structural changes that develop in the gland tissue against the background of endogenous intoxication deepen, the structure of the glands is partially destroyed, and a focal increase in connective tissue fibers between endocrinocytes attracts attention. The development of connective tissue leads to a sharp change in the parenchymal and stromal ratio of the glands. At the end of the experiment (15th day), endocrinocytes are located in separate groups and distributed unevenly, edema spreads to the parenchyma of the gland, the size of epithelial cells decreases and deforms, and the number of vacuolated cells increases.

In all three glands, necrobiotic and necrotic cells predominate. Necrotic parenchymal cells are replaced by connective tissue elements of the overgrown stroma. Individually, apoptotic cells are also found in histological preparations. At the ultrastructural level, clearly visible dystrophic changes are noted in the gland cells – vacuolization of the cytoplasm, expansion of the cisterns of the endoplasmic reticulum in the form of vacuoles, a sharp decrease in the number and size of mitochondria and a decrease in the number of vesicles and secretory granules.

Under the influence of staphylococcal infection, irreversible necrotic processes occur in the adenohypophysis, intraorganic hemodynamics are disturbed, and the glandular tissue loses its trabecular type structure. In the adrenal glands, the expansion of the interstitial space leads to a sharp decrease in the size of the gland parenchyma cells, their atrophy, and a change in their mutual relationship. Necrobiotic and necrotic changes occurring in the parenchyma of all three zones of the adrenal cortex and the medulla, on the background of an increase in the volume of the connective tissue as well as a decrease in the thickness of the gland, cause a partial replacement of the epithelial tissue with mesenchymal tissue. Necrobiosis of some follicles and thyrocytes in the thyroid gland leads to a relative change in the structure of the gland. These observed changes reflect the effect of infection on glandular tissues.

This stage of the study is also characterized by a decrease in the number of cells. The relative number of chromophobic cells, which are considered reserve cells in the adenohypophysis, decreases by about 9.9% (62.9%, 5th day – 69.8%, p=0.001) compared with the 5th day of the experiment, and the mutual ratio of adenohypophysis cell populations changes dramatically (diagram 3.).

As a result of the desquamation of thyrocytes toward the lumen of follicle, their number sharply decreases both in the central and peripheral zones of the gland, amounting to 26.7 (5th day – 27.3, p=0.037) and 15.8 (5th day – 15.9, p=0.728), respectively (diagram 5.).

As the duration of the experiment increases, a decrease in other studied sizes of endocrinocytes is recorded. Compared to the 5th day, changes in the area and diameter of adenocyites are also noted, the area of acidophils decreases by 3.7% (65.5 μm^2, 5th day – 68.0 μm^2, p=0.001), and diameter decrease by the diameter was 1.8% (9.14 μm, 5th day – 9.31 μm, p=0.001), the area of chromophobes decreases by 2.4% (49.4 μm^2, 5th day – 50.6%, p=0.015) and the diameter decreases by 1.2% (7, 93 μm, 5th day – 8.03 μm, p=0.015), while the area and diameter of basophils (88.8 μm2 and 10.6 μm) do not change.

The height of the thyroid epithelium is also sharply reduced compared to the 5th day, respectively – 4.57 μm (7.1%, 5th day – 4.93 μm, p=0.001) in the periphery and 5.83 μm (4.9%, 5th day – 6.13 μm, p=0.001) in the center (diagram 2.).

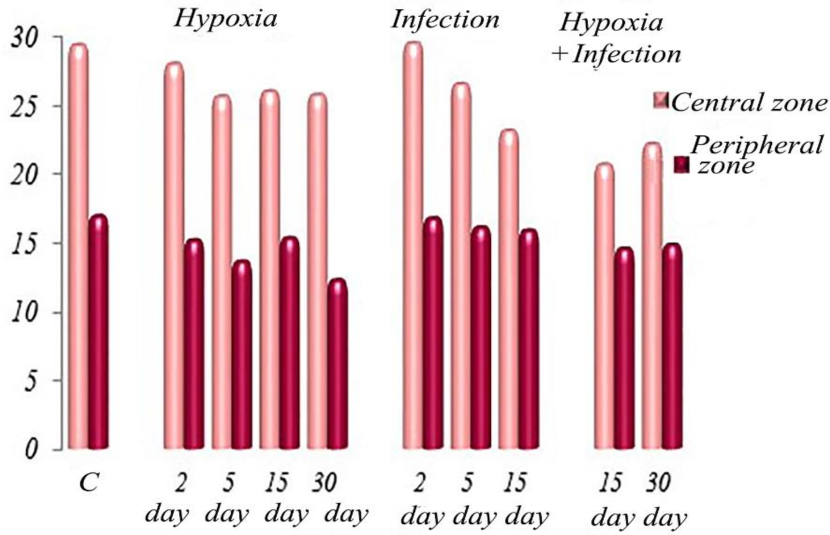

Diagram 5. Hypoxia, infection and the number of thyrocytes in the main group

While the thickness of the adrenal medulla decreased significantly compared with the parameters of the control group, by about 15.9% (385.4 μm, intact – 458.2 μm), the thickness of the adrenal cortex decreased by about 16.9% (745.0 μm, intact – 896.9 μm) (p=0.001), compared with the 5th day (diagram 1.). The obtained statistical indicators differ significantly from those of the hypoxia group (p<0.001).

As a result of staphylococcal infection, significant histological changes develop in the mesenteric lymph nodes and peripheral blood lymphocytes, which lead to a sharp decrease in the number of lymphocytes. Initial signs of structural changes are noted on the 2nd day of the experiment, and acute signs – on the 5th day.

In the early stages, dystrophic changes occurring in the epithelial component of the lymph nodes are mainly characterized by a decrease and deformation of the follicles, a change in the ratio between small and large follicles. On the 5th day of endogenous intoxication, the morphological structure of the cortex and medulla is disturbed. The stroma is dominated by widespread edema and lympho-monocytic infiltration, the lymphatic sinuses are dilated, and well-marked free macrophages and lymphocytes are accumulated. Some macrophages are in a state of destruction. An increase in lympho-monocytic infiltration in the interstitial region leads to depletion of the lymphatic tissue, and in some preparations even to its disintegration. Edema of medullary trabeculae is observed in histological preparations, and medullary trabeculae are strongly infiltrated by macrophages and eosinophils in some preparations. Violation of microcirculation in both the parenchyma and stroma of lymphatic nodes, the increase in vascular pathologies is manifested by the porosity of the vessel walls, stasis and slac phenomenon of erythrocytes.

At the end of the study, due to the influence of staphylococcal infection, necrobiotic and necrotic processes develop in the lymph nodes, it can be seen that most of the lymphoid follicles are in a necrobiotic state, the follicles are located in small tissue groups. As a result of endogenous intoxication, the number and volume of cells of the lymphoid series, as well as germinal centers, are significantly reduced. The dispersion of sinuous reticular fibers that make up the reticular basis of the follicles is clearly visible, as well as a large number of cellular elements scattered in the reactive center. In parallel, vascular pathologies in the lymphoid tissue are replaced by secondary changes, numerous small bleeding foci.

On the electronograms, there is an expansion of the cisterns of the endoplasmic reticulum, hypertrophy of some mitochondria, and the Golgi complex is poorly visible. Endogenous intoxication causes a decrease in the number of lysosomes and an increase in the number of vesicles. The surfaces of lymphocytes become smooth, dispersal of the majority of lymphocytes, and aggregation of some cells is noted.

Under the influence of infection, the interaction of the cortical and medullary substance, as well as the paracortical zone, is disturbed.

With a decrease in the volume of cortical substance, the volume of medullary substance and the paracortical zone increases. On the 2nd day of the experiment, the relative volume of medullary substance noticeably increases to 54.7% (intact – 38.3%), and the relative volume of the paracortical zone to 6.52% (intact – 3.3%) and differs from normal indicators by 42.8% and 97.6%, respectively. The relative volume of cortical subatance, on the contrary, sharply decreases to 38.8%, which is 33.4% (intact – 58.3%) lower than the results of the control group. At this stage, the ratio of cortical and medullary substance to each other is 0.71% (intact – 1.52%) ($p<0.001$).

On the last day of the experiment, the volume of the cortical substance in comparison with the indicators of the control group and the 5th day of the experiment decreased by 18.7% and 9.9% (on the 5th day – 52.6%), respectively, and amounted to 47.4% ($p=0.001$). The volume of the medullary substance compared with the control group and the 5th day of the experiment increased by 25.8% ($p=0.001$) and 10.3% ($p=0.002$), and the volume of the paracortical zone by 36.4% and 23.3%, respectively, 48.2% in the medullary substance and 4.5% in the paracortical zone ($p=0.001$). On the 15th day, it is noted that the ratio of cortical and medullary substance is 0.98% ($p=0,001$) (diagram 6.).

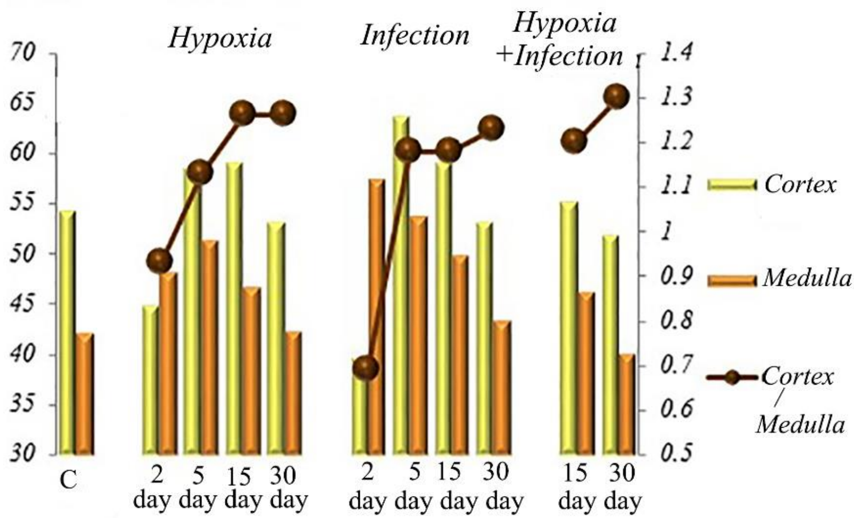

Diagram 6. Parameters of lymph nodes in hypoxia, infection and in the main group.

Endogenous intoxication in blood smears taken from experimental animals included in the infection group from the first days of the experiment leads to a microscopic change in the structure of lymphocytes, and at the end of the experiment, lymphocytes are dispersed and depleted. Microscopic changes are manifested by damage to the cell membrane, deformation, a decrease in the size of the cytoplasm and nuclei, and disintegration of nuclear chromatin. As a result of endogenous intoxication, the number of lymphocytes per unit volume of blood decreases sharply, small-sized lymphocytes are not noticeable, and medium- and large-sized lymphocytes are rare.

As a result of endogenous intoxication, the number of lymphocytes per unit volume of blood decreases sharply, small-sized lymphocytes are not noticeable, and medium- and large-sized lymphocytes are rare. The decrease in the number of lymphocytes to 63.1% (intact – 73.8%, $p<0.001$) on the 5th day of the experiment is explained by the process of lymphocytolysis occurring in the peripheral blood. Parallel to lymphocytes, the number of neutrophils increases by 52.8% to 28.6% (intact – 18.7%, $p<0.001$), with a change in their ratio to each other (2.23, intact – 3.98%, $p<0.001$).

On the last day of the study, dystrophic changes deepen in cytological preparations obtained from peripheral blood smears of animals of the infectious group, and a sharp change in morphometric parameters characterizing the leukocyte formula is also observed. Neutrophilic leukocytes differed by 24.8% (p=0.001) less than on day 5, despite an increase of 15.0% (p=0.003) compared to the control group. And lymphocytes are 3% lower than those of the control group, and 13.5% higher than those of the 5th day (p=0.001) (diagram 7.). The results obtained reflect the impact of infection.

According to our results, acute release of mediators from the early stage of infection, massive transfer of toxic substances and enzymes from the abdominal cavity into the blood leads to toxic damage to cells of the endocrine glands and lymph nodes, increased permeability of the vascular wall, the development of hemorrhage and edema, increased cell migration as a result of fibrosis.

Morphofunctional transformations in the form of dystrophic changes caused by infection, as well as changes in hemodynamics, are most often found in the adenohypophysis and adrenal glands.

Compared with the endocrine system in the mesenteric lymph nodes, the severity of inflammatory and destructive changes (cell degranulation, edema and destruction of the connective tissue components of the stroma, accumulation of infiltrate around damaged cells) is more pronounced. Diffuse edema causes necrosis of individual follicles, as well as the transition of antigenic determinants into the blood, which leads to the development of immunological changes in the immune system, the accumulation of antibodies and the formation of immune complexes.

In response to infection, the body develops complex, multicomponent reactions aimed at eliminating and destroying the pathogenic factor, as well as restoring homeostasis and activating regenerative processes. The ongoing changes lead to a pathological reorganization of the glandular structure and lymphoid tissue by the end of the experiment. This is due to the reaction of cells to hypersensitivity to infection.

Experimental study of endocrine glands, mesenteric lymph nodes and peripheral blood lymphocytes under the combined effect of hypoxia and infection

The authors argue that inflammation associated with infection as well as increased proliferation of intracellular pathogens, have the ability to deprive infected cells of oxygen. Hypoxia that occurs during infection directly affects tissues by regulating the expression of oxygen-dependent genes and causes morphofunctional changes in tissues at various levels[15].

On the background of the combined action of hypobaric hypoxia and staphylococcal infection in experimental animals included in the main group compared to the previous groups, the morphofunctional organization of the endocrine and immune systems, which complement each other and interact, significantly changes. The frequency of polymorphic changes occurring in endocrine and lymphoid tissues is higher, and these changes mainly attract attention by changing the ratio of epithelium to connective tissue.

On the 15th day of the experiment, under the influence of stressors, noticeable destructive changes in the epithelium, necrobiosis and necrosis of most endocrinocytes and lymphoid follicles, and atrophy and apoptosis of some became more intense compared to other groups and more noticeable. At the same time, interstitial spaces expand sharply, and focal or diffuse hypertrophy and proliferation of connective tissue occur. Stromal proliferation continues to increase throughout the experiment and is of a compensatory nature. This leads to a violation of intraorganic hemodynamics, and the formation of focal diapedesis. Disseminated vascular changes manifest mainly in the form of sludge, stagnation, and microthrombosis.

Morphological manifestations of destructive changes occurring in tissues and cells continue throughout the experiment and deepen by the end of the study. Alteration and necrosis of the epithelium in histological preparations are characterized by the arrangement of cells in the form of scattered bundles, the formation of slit-like spaces

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[15] Iakushko, O.S. The modern concept of morphological and functional features of the endocrine glands // СМБ. – 2016. 58(4), – p.153-159

between them, as well as the depletion – atrophy of parenchymal cells as a result of necrobiotic and necrotic processes.

Electron microscopic examination reveals focal or complete destruction of the plasmalemma and karyolemma, multiple invaginations, deformations of organelles, vacuolization of the cytoplasm, pyknotic nuclei, pronounced expansion of the endoplasmic network occupying almost the entire intracellular region, reduction of the Golgi complex, as well as lysosomes and a sharp decrease in the number of ribosomes and electron density indicates atrophy of most endocrine and lymphoid cells. At the end of the experiment, electron microscopic changes reach a maximum – this stage is characterized by depletion of parenchyma and violation of intercellular contacts. With a noticeable decrease in the number of mitochondria and secretory granules, there is a change in the structure of cells at the ultrastructural level, a large number of cells subjected to apoptosis are also detected on electrograms, and an apoptotic body is found in the cytoplasm.

Structural changes occurring in glandular tissues are of a mixed nature, and the heterogeneity of damage to each gland attracts attention.

The trabecular structure of the adenohypophysis is completely changed and is characterized by atrophic changes. Almost all adenocytes undergo deformation and degranulation, so the majority of cells are structurally similar to chromophobes. The development of connective tissue manifests itself in the form of the thickening of the septa.

In the adrenal tissue, the cells of the cortical substance that have undergone mainly acute dystrophic and necrotic changes are mosaically replaced by cells of the adrenal medulla that have undergone relatively small dystrophic changes. At the same time, decompensation of cells is observed in the reticular zone as a result of atrophy of the depleted glomerular and fascicular zones of the adrenal cortex.

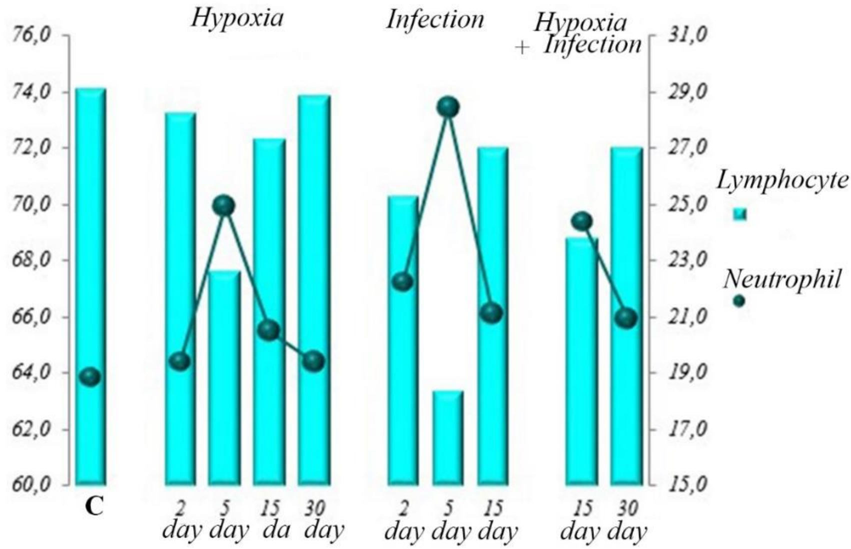

Diagram 7. The ratio of lymphocytes and neutrophils in hypoxia, infection and in the main group.

The thyroid gland tissue is dominated by small, narrow, slitshaped follicles of small size, devoid of colloids, with thickened follicular epithelium. In some areas, mainly in the peripheral zone of the gland, large follicles expand sharply and resemble follicular cysts. On the other hand, cystic-enlarged follicles are randomly replaced by smaller follicles. In the lumen of large follicles, a vacuolized eosinophilic colloid is noted, the colloid is firmly adherent to the walls of the follicles, and in small follicles, and the colloid is reduced and almost invisible. The desquamation of thyrocytes continues to increase, sometimes thyrocytes, which are desquamated in groups, are found in the lumen of large follicles. On the other hand, desquamation of follicular cells leads to colliquational necrosis of individual thyrocytes.

The early stage of endogenous intoxication, which develops against the background of hypoxia and peritonitis, is characterized by both damage and progressive death of lymphatic follicles, as well as the follicular epithelium. Hyperplasia of the connective tissue compresses the follicles, causes a sharp decrease in their size, causes the formation of local foci of necrosis, and leads to narrowing and reduction of the mouth of some follicles. The relative expansion of the lymphatic sinuses, and the accumulation, and aggregation of individual mononuclear (macrophages and lymphocytes) and polynuclear cells are observed in their walls, which open, especially into the lumen of the subcapsular sinus.

On the 30th day of the experiment, prolonged and progressive damage to endocrinocytes and lymphatic follicles is observed, as a result of which the histoarchitecture of the endocrine glands and mesenteric lymph nodes is disrupted. A sharp decrease in the number of cells, consisting of randomly located and atrophied individual cells of glands and lymph nodes, indicates the depletion of the epithelium. However, most of the depleted and lost parenchyma is replaced by a compensatory overgrowth of connective tissue, as a result of which glandular tissue and lymphoid follicles undergo microtransformation and remodeling in the form of small foci. On the other hand, the proliferation of connective tissue not only compensates for the loss of parenchyma but also creates locally determined stability for the remaining tissue, preventing complete atrophy of the epithelium.

The parameters obtained during morphometric studies in the main group also reflect morphofunctional changes occurring in cells under the combined influence of stressors. In this group, the critical limits of the studied parameters were determined, and it was found that their level is many times lower than normal.

On the 15th day of the study, the number and size of endocrinocytes are sharply reduced due to the combined action of stress factors. A decrease in the number of acidophils and basophils in the adenohypophysis leads to the fact that the cellular composition of the gland consists only of chromophores (5:22:73, intact – 9:29:62) (diagram 3.).

Adrenocorticocytes decrease to 26.1% in the zona glomeruli, to 24.3% in the zona fasciculata, and to 32.4% in the reticular zone. The obtained parameters are lower (p=0.001) compared to the control group by 19.7% (intact – 32.5%), 20.3% (intact – 30.6%), 12.7% (intact – 37.4%), respectively.

The number of thyrocytes is also 27.3% in the center and 15.8% on the periphery, which differs from the parameters of the control group by a lower value of 6.5% (intact – 29.2%, p=0.001) and by 7.1% (intact – 17.0%, p=0.065) (diagram 5.).

At the same time, at this stage of the study, a decrease in the area and diameter of cells in all 3 glands, as well as the volume of lymph nodes, is observed. The volume of the cortical substance of the mesenteric lymph nodes decreases by 9.8% (52.6, intact – 58.3), the volume of the medulla increases by 15.4% (44.2, intact – 38.3) (p=0.001) (diagram 6.).

On the last day of the study, most of the morphometric parameters were below normal, which indicates that the cells underwent necrotic and atrophic changes.

Hypoxia and infection as a single factor also strongly affect lymphocytes, which are characterized by dystrophic changes – damage to lymphocytes, changes in their structure, and a decrease in their size and quantity. On the 15th day of the study, in cytological preparations of smears taken from the blood of experimental animals included in the main group, it is generally clearly visible that most of the large lymphocytes undergo deformation and lysis. Deformation and invagination of the basement membrane of lymphocytes, and vacuolization of their cytoplasm and nuclei, are noted (diagram 7).

At the end of the experiment, the morphological changes occurring in the cells deepen with a change in the ratio of the small, medium, and large lymphocytes. The number of lymphocytes decreased by 6.8% (73.8% intact – 68.8%) on the 15th day of the experiment, while neutrophils increased by 34.6% (24.6% intact – 18.7%) (p=0.001). On the 30th day, the number of lymphocytes increases to 71.2% and the number of neutrophils decreases to 20.9% (diagram 7.).

The observed structural changes in the histoarchitectonics of the endocrine glands, both separately and against the background of hypoxia and infection, are accompanied by their hormonal hypo- or hyperfunction. When analyzing the results of examinations conducted by enzyme immunoassay in all 3 groups, it became clear that the level of TSH and cortisol circulating in the blood changes under the influence of stress factors.

Although the level of hormones is high in the early stages of hypoxia, it has been recorded as approaching the norm under the influence of chronic hypoxia. As a result, on the fifth day of hypoxia, TSH rises by 15.4 μU/ml (0.39 μU/ml, intact – 0.45 μU/ml), cortisol rises by 27.1 ng/ml (0.48 ng/ml, intact – 0.61 ng/ml) and on the 30th, these values fall to 0.42 μU/ml and 0.48 ng/ml, respectively.

As a result of endogenous intoxication in the infectious group, the level of TSH increases and is at its maximum on the 15th day of the experiment (0.44 μU/ml). The level of cortisol under the influence of infection is also recorded with upward dynamics on the 2nd and 5th days, 0.54 μU/ml and 0.64 μU/ml, respectively, and decreases on the 15th ng/ml day to 0.49 ng/ml.

In the main group, compared with the previous groups, the level of TSH (0.4 μU/ml) and cortisol (0.52 ng/ml) in the blood plasma, although it increased on the 15th day, but sharply decreased on the 30th day (TSH – 0.33 μU/ml, cortisol – 0.37 ng/ml).

The combined effect of hypoxia and infection, as well as the decrease in hormone levels, reflect the remarkable interaction between the endocrine glands. The results obtained are explained by a compensatory increase and decrease in the functional activity of the endocrine glands.

The histological results obtained are confirmed by immunohistochemical studies. During the analysis of the features of immunohistochemical staining of the CD4+ and CD8+ adenohypophysis, it was found that on the 2nd and 5th days of hypoxia and on the 5th day of infection, staining of the adenohypophysis and adrenal glands was not completely visualized, while intensive staining was noted on the 15th day of infection and in the combined model (diagram 8).

On the 2nd day of hypoxia and infection in the thyroid gland and on the 2nd and 5th days of hypoxia in the mesenteric lymph nodes, CD4+ and CD8+ lymphocytes are not stained.

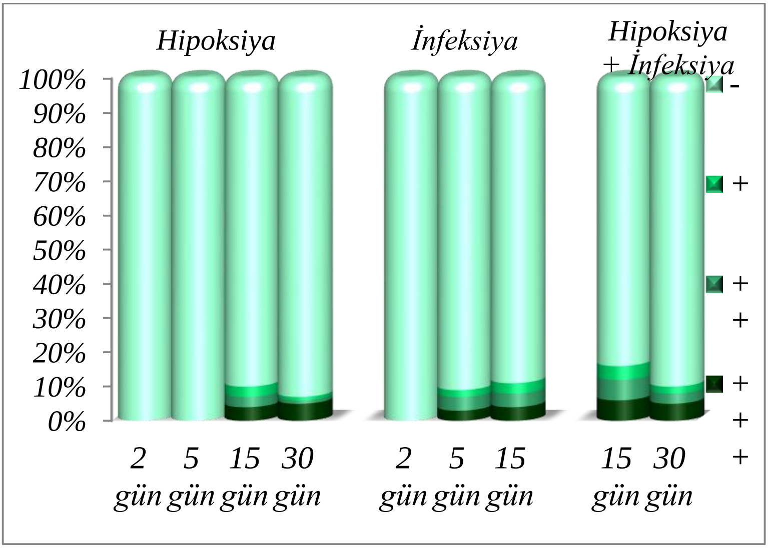

Diagram 8. Features of immunohistochemical staining of CD4+ of the adrenal gland in hypoxia, infection and in the main group.

On the 30th day of the combined model, CD4+ and CD8+ lymphocytes are intensively stained in the thyroid gland, and on the 15th day of the same model, in the mesenteric lymph nodes (diagram 9). The absence of staining is due to the lack of proliferation of lymphocytes, and intensive staining is due to an exacerbation of inflammatory processes.

Thus, in the early stages of the experiment (2nd and 5th days), under the influence of short-term (acute) stress factors, cellular and extracellular structural changes (dystrophy, edema, disorganization, necrosis, vascular pathologies (diapedesis hemorrhages, infiltration of plasma along the vessels, etc.) occur in organs and tissues, and there is a tendency to a decrease in cell size. Morphofunctional changes that develop sequentially in the organs of the endocrine and immune systems under both individual and combined exposure to stress factors manifest themselves differently and are characterized by unique features in each organ. This is explained by the fact that the tissue structure of the organs of the endocrine and immune systems, as well as the mechanisms that make up the pathomorphological basis of the relationship between them, are quite complex.

As the effect and duration of stress factors increase, reparative-regenerative and compensatory-adaptive processes in organs and tissues accelerate. According to the authors, the most important component of the specific changes that occur in the body during adaptation is the morphofunctional restructuring of tissues and cells in response to stress factors. They believe that the immediate adaptive reactions that occur during acute stress are primarily manifested in the form of morphofunctional changes. With prolonged exposure to stress factors and their repetition, a long-term or chronic adaptation is formed in the body, which is based on morphofunctional and metabolic adaptive reactions[16].

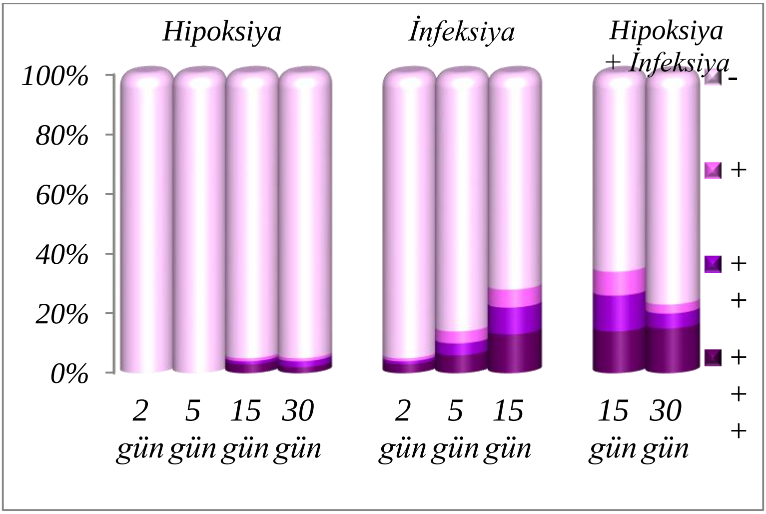

Diagram 9. Features of immunohistochemical staining of CD8+ of the mesenteric lymph nodes in hypoxia, infection and in the main group.

[16] Собуров, К.А., Темирова, С.А. Механизмы взаимоотношения гормональной и иммунной систем при адаптации к высокогорью // – Бишкек: Наука, новые технологии и инновации Кыргызстана, – 2019. № 3, – с.131-135

And the result of the adaptation process is changes aimed at maintaining the structure of the organ at the maximum level. First of all, this is achieved due to the processes of microscopic cell restructuring – hyperplasia and hypertrophy of organelles, an increase in the number of mitochondria and their crystae, many morphometric parameters, as well as cell proliferation and differentiation – tissue adaptation to new conditions. Mechanisms of emergency adaptation to stressful factors are formed gradually, while creating optimal conditions for the survival of the body in new, extreme situations.

The emergence of «long-term» adaptive processes as a result of repeated exposure to stress factors is due to «urgent» adaptive mechanisms that left deep «traces» in the body[17].

At the same time, there are numerous adaptation mechanisms in the body that facilitate the survival of cells and tissues in a hypoxic condition with an impaired oxygen supply. The authors claim that compensatory adaptation processes are a complex, evolutionarily formed reaction of the body in oxygen deficiency conditions, which ensures the maintenance of energy synthesis both at the systemic and cellular levels as well as increasing its resistance to hypoxia and developing gradually.

Adaptation is the ability of an organism to perform its activities even at low oxygen concentrations, which can be life-threatening, while maintaining an optimal level of biological oxidation in cells. Also, as a result of the «depletion» (disadaptation) of a prolonged adaptive reaction, even decompensation may occur, as well as a number of functional changes accompanied by the development of destructive changes in organs and tissues[18]. The results obtained by us once again confirm the opinion of the authors.

According to our findings, structural changes in the endocrine glands and mesenteric lymph nodes, as well as in lymphocyte B, are

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[17] Брилль, Г.Е. Механизмы компенсации и адаптации к гипоксии / Г.Е.Брилль, Н.П.Чеснокова, Е.В.Понукалина [и др.] // Научное обозрение. медицинские науки, – Москва: – 2017. № 2, – с. 55-57

[18] Horii, A. Hippocampal gene expression, serum cortisol level, and spatial memory in rats exposed to hypergravity / A.Horii, K.Mitani, C.Masumura [et al.] // J. Vestib Res. – 2017. 27(4), – p. 209-215

caused by both the individual and combined effects of hypoxia and infection as factor stressors, resulting in a significant restructuring of tissues and cells. Remodeling processes, on the other hand, improve the mechanisms of the stress response in the body, as well as their pathogenic effect by increasing the sensitivity of cellular receptors to hypoxia and infection. In this regard, the spread of infection in the body and a prolonged course of hypoxic stress (chronic hypoxia) complicate the situation even more. Experimental animals cannot adapt to the combined effects of severe chronic hypoxia and infection; irreversible destructive processes develop in the organs of the endocrine and immune systems, which can lead to physiological changes or even pathological consequences, the protective mechanisms of the body are significantly weakened.

However, morphofunctional changes in gland and lymphoid tissue cells cause a hypersensitivity reaction, accelerate the regeneration of the endocrine and immune systems, and increase the body's overall resistance to the combined effects of hypoxia and infection, and organs adapt to these conditions, which is regulated by organ structural restructuring processes.

The study's findings provide evidence for the conclusion that pathomorphological changes and organ responses in the endocrine glands and lymphoid tissues, both individually and in combination with hypoxia and infection, are compensatory and adaptive processes from a biomedical standpoint. With a gradual increase in the resistance of organs to stress factors, mechanisms of long-term adaptation are formed in the body, so long-term adaptation is considered a set of reactions involving structural, functional, and metabolic adaptation.

Given the diversity and complexity of endocrine regulation, the authors note that the variability of pathological processes and their complications directly depends on the state of the immune system. On the other hand, they argue that the various mechanisms of action of hormones secreted by the organs of the endocrine system, especially the pituitary gland, on different body systems, pathological processes and severe complications resulting from these effects lead to disruption of the immune system[19]. In this regard, the pathogenesis and progression of the morphofunctional features of the endocrine glands may be associated with a violation of local immunological homeostasis.

At the same time, morphological changes occurring in the endocrine glands cause hypo- and hyperfunction of the hormone-producing structures of the body. A decrease or increase in the number and size of active cells leads to a weakening or strengthening of the secretory activity of the glands. This mechanism is based on dysmetabolic, toxic, infectious, and hypoxic damage to endocrinocytes.

Violation of the processes of hormonal regulation of the body can lead to the development of many serious diseases, including diseases of the endocrine and immune systems, which in turn can lead to serious complications, organ failure, morphofunctional changes in the body, endocrine and immune pathologies, as well as deeper metabolic changes in target organs.

Summarizing the results of the study, we can conclude that hypoxia serves as an impetus for the complex activation of compensatory-adaptive reactions in the body aimed at restoring the normal oxygen supply to tissues. As a result of an adequate change in the morphofunctional characteristics of organs, processes of mutual integration between the endocrine and immune systems and compensatory-adaptive processes are formed.

Adaptive changes in organs based on their unique features and characteristics resulted in a quantitative and qualitative restructuring of cell structure, regulating the morphofunctional state of the endocrine and immune systems. Morphological changes found in the endocrine glands, mesenteric lymph nodes, and peripheral blood lymphocytes of experimental animals exposed to the combined effects of chronic hypoxia and infection can lead to the formation of a

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[19] Hueston, C.M., Deak, T. The inflamed axis: the interaction between stress, hormones and the expression of inflammatory-related genes within key structures comprising the hypothalamic-pituitary-adrenal axis // Physiology & behavior. – 2014. 124, – p.77-91

persistent hypofunctional state in the organ as well as a complex of immunological changes in glandular tissue.

RESULTS

1. The progressive damage and decrease in the number of endocrinocytes in the early period, the acceleration of regeneration processes as a result of cell proliferation and differentiation at the end of the study, and the effectiveness of these reactions determine the degree of tissue hypoxia are the structural basis of the morpho-functional changes in the endocrine glands during both individual and combined effects of hypoxia and infection [15, 25, 34, 40, 44, 45, 48].
2. With a prolonged course of hypoxia and infection, the endocrine glands' resistance to these factors increases, and the glands adapt to these conditions, which is regulated by organ structural restructuring processes. Changes in the number and size of endocrinocytes in groups are the result of compensatory-adaptive processes that have developed in the endocrine glands. [5, 12, 17, 29, 33, 35, 46, 47].
3. Despite detecting a similar complex of microscopic and ultrastructural changes in the cells of the endocrine organs, both with individual and combined exposure to hypoxia and infection, these pathomorphological changes manifest themselves differently in each gland. The resulting changes depend not only on the type, nature, duration, and intensity of the pathogenic factor but also on the morphofunctional features of the organs [12, 24, 33, 38, 41].
4. Since the adenohypophysis is exposed to hypoxia and infection earlier and to a greater extent than the adrenal gland, and the adrenal gland is more susceptible to hypoxia and infection than the adrenal gland, dystrophic and disorganizational changes in the adenohypophysis and adrenal gland are more pronounced. Early damage to the adenohypophysis and adrenal endocrinocytes compared to thyroid thyrocytes can be regarded

as a higher sensitivity of these glands to hypoxia and infection [25, 27, 39, 49, 50].

5. During hypoxia, an increase in the number of basophilic adenocytes by 43.5% in the adenohypophysis and by 33.2% in the number of adrenocorticocytes in the reticular zone indicates an increase in reparative-regenerative processes and restoration of the structure of organs, indicating a restructuring of the glands from a structural and functional point of view. Due to the influence of staphylococcal infection, a decrease in the number of acidophils by 16.6%, the number of adrenocorticocytes by 9.5%, and the number of thyrocytes by 8.6% leads to a change in the ratio of epithelium and connective tissue, accompanied by the predominance of stromal proliferation processes in the endocrine glands [9, 11,14, 34, 35, 41, 42].
6. With the combined effect of hypoxia and infection, the reserve capabilities of the body are depleted, the body loses energy resources, and the atrophied parenchyma of the endocrine glands is replaced by connective tissue as a result of a decrease in the number and area of endocrinocytes. Morphologically, the pathological compensatory reorganization of the glands can be considered pathological tissue regeneration [43, 44, 48].
7. Hypoxia and infection simultaneously lead to suppression of the immunological activity of lymph nodes and peripheral blood lymphocytes, an increase in the volume density of the lymphatic sinuses, and a decrease in the intensity of transendothelial transport in endothelial cells. Due to the combined action of hypoxia and infection, most of the cells of the immune system, especially peripheral blood lymphocytes, are destroyed, and the destruction of 14,5% of lymphocytes is considered an indicator of immunodeficiency that occurs in the body [6, 8, 24, 26, 32, 48, 49].
8. Hypoxia and infection, both individually and combined, have a dual effect on the organs of the endocrine and immune systems - both damaging and adaptive. Changes in the concentration of TSH, somatostatin, and cortisol in blood plasma form the morphofunctional basis of adaptation to new conditions. At the

beginning of the study, the concentration of cortisol was 0,6 ng/ml in the hypoxia group, 0,49 ng/ml in the infection group, and 0,37 ng/ml in the main group, which is explained by the different sensitivity of the endocrine glands to stress factors [34, 40, 44, 45, 48].

PRACTICAL RECOMMENDATIONS

1. The data obtained and the results obtained to supplement the existing data in the field of functional and clinical morphology of the endocrine and immune systems reflect the main features of the cellular and extracellular structural reorganization of the endocrine glands as well as the immune system under the influence of any acute and chronic stress factors.
2. During the development (formation) of compensatory-adaptive processes, one should take into account the intensity of recovery reactions that occur in the endocrine and immune systems under the influence of acute and chronic stress factors, as well as the reserve capabilities of tissues and cells in the body.
3. The results of the study can be used in assessing the complex of compensatory-adaptive reactions aimed at the combined action of irritating factors that cause any pathology on the body, as well as prevention or elimination, as well as the elimination of homeostasis protection, in the preparation of diagnostic and prognostic criteria for the state of the body in general from a morphofunctional point of view.
4. It can be used in the prevention, treatment, and rehabilitation of various stress conditions and nosological diseases, including endocrine and immune pathologies, by activating internal mechanisms (sanogenesis mechanisms) aimed at increasing the specific and nonspecific resistance of the body and restoring its impaired functions.
5. In order to increase the stress resistance of representatives of harmful professions to extreme influences, special training for the conditions of professional activity, aviation and space flights, high-altitude and mining work, sports medicine, and

physical education, changes caused by irritating factors in their bodies as well as adaptation and can be used by doctors as a criterion in enhancing recovery processes.

6. Intermittent hyperbaric gymnastics of athletes, flight crews, and other dangerous professions can be used to test tolerance to various degrees of hypoxia, to ensure the implementation of preventive measures in the treatment of hypobaric hypoxia, as well as to identify hidden diseases that lead to a decrease in individual resistance to hypoxia.
7. Information about the morphology of the endocrine and immune systems, plasticity, and correction of the endocrine glands and lymphoid tissue under the influence of stress factors can be used in the educational process when writing the relevant sections of textbooks and monographs.

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