INTRODUCTION

Hypoxia is a common pathological process caused by impairment of biological oxidation resulting in disruption of the energy supply which is important for functioning and survival of each living organism [1-3]. To provide normal metabolism, mitochondria need to receive constantly the required amount of substrate and oxygen to be able to continuously synthesize sufficient amount of adenosine triphosphate (ATP) [4-6].

If the demand for ATP is not met, metabolic, functional and morphological changes occur in the endocrine glands, along with the organs of the respiratory, nervous and cardiovascular system.
and at the same time, various compensatory processes develop [7, 8]. Therefore, hypoxia is considered as a pathogenetic basis and an important component of many diseases. On the other hand, recently it was shown that modeling of limited oxygen deficiency may result in development of long-term adaptation against hypoxia, which may help to develop certain schemes for the prevention and correction of various diseases with a hypoxic component in their pathogenesis [9, 10].

Hypoxia is a powerful stress activating secretion of glucocorticoids by the hypothalamic-pituitary-adrenal system. Glucocorticoids activate the respiratory enzymes and stabilize the cell membrane, as well as the membrane of lysosomes thus reducing the risk of penetration of their hydrolytic enzymes into the cytoplasm [11-14].

In spite of numerous investigations on adaptation of the body to hypoxia, many aspects of this problem remain unclear, such as the scope and the range of morphofunctional changes in the endocrine glands, particularly the adrenal and thyroid glands, which play an important role in the body adaptation to hypobaric hypoxia [15-17].

The objective of this research is to study the ultrastructural changes in the cellular and extracellular structures of the adrenal and thyroid glands during acute hypoxia.

**Material and methods**

Animal research was carried out in Pharmacology and Experimental Surgery Departments, and the Electron Microscopy Laboratory of the Scientific Research Center of Azerbaijan Medical University. The design of experiment was approved by the Ethical Committee (Protocol No. 31 of the Ethics Rules Commission and Bioethics Committee under the Ministry of Health of the Republic of Azerbaijan on 21.04.2008). Total of 40 normal male white outbred rats weighing 180-200 grams, were used in the study. Experimental animals were kept in standard vivarium conditions with food provided ad libitum. The animals were divided into 2 groups: control and experimental, with 20 animals in each group.

The experimental animals were subdivided into 2 equal subgroups (subgroup 1 and subgroup 2) with duration of experiment for 2 and 5 days accordingly. All experimental animals were kept in a special barochamber, which was ventilated 2 times a day for 2 hours with 1 hour break at 10:00-15:00 hours, which is considered the lightest time of day. Temperature was 19-20°C, pressure is equal to the pressure at an altitude of 2000-3000 meters above sea level, particles of natron lime (Ca(OH)₂ 81%+NaOH 3,4%+H₂O 15,6%) were applied to absorb CO₂.

Experiment and control animals were euthanized by decapitation under anesthesia by injection of 2-2,5% of thiopental-sodium. Thyroid and adrenal glands were sampled and analyzed using histological, electron microscopic and morphometric methods.

Tissue processing for electron microscopy was done as recommended. Semithin (1-2 μm) and ultrathin (70-100 nm) sections of the embedded tissue were obtained on the ultratome LGB-III, Leica EM OC7. Semithin sections were stained 0,5% methylene blue, counterstained with 1% Azur II, mounted and viewed under light microscope «Olympus BX-41». Ultrathin sections 70-100 nm thick were stained with 2% uranium-acetate solution and 0,6% pure lead-citrate and studied under JEM-1400 transmission electron microscope (JEOL, Japan) with 80-120kV voltage.

Morphometric parameters were analyzed statistically using Statistica 10 (StatSoft Inc., USA) software and the Mann-Whitney U-test was performed.

**Results and discussion**

During the electron microscopic examination of the adrenal gland of the control animals, the cell membrane of the adrenocytes is clearly monitored, but in some parts, the microplacae of plasmalemma are somewhat thickened. The cell has a light-colored cytoplasm and a round nucleus located in the center of the cell, the nucleolus of which is located in the periphery.

Sometimes, lipid vesicles are not detected in the cells of the reticular zone. The cristae of the elongated mitochondria, are clearly visible. The edges of the crystal are smooth, sometimes dentate. The endoplasmic reticulum is composed of oval, small-sized vesicles, some of them are stretched. The existing tight contacts between mitochondria and lipid vesicles and the endoplasmic reticulum are well noticeable.

The Golgi complex consists of cisterns, vacuoles, and vesicles, located near the nucleus. A small number of lysosomes and ribosomes appear mainly around the Golgi complex (Fig. 1).

There are numerous microvilli on the surface of the thyrocytes facing to the follicle cavity, and finger-shaped protrusions on the lateral surfaces, are clearly distinguished. The penetration of these protrusions into the corresponding impressions of the lateral surface of the neighboring cells reflects a close relationship between the thyrocytes. Transparent cytoplasm of thyrocytes and intracellular organelles, unevenly distributed in the cytoplasm, the contacts between them are well noticeable (Fig. 2).

**Fig. 1** Electron micrograph of the reticular zone of the adrenal gland of the control animal. TEM. Stain: uranium acetate and pure lead citrate. Scale: 500 nm. 1 – Golgi complex; 2 – lysosome; 3 – mitochondria

**Fig. 2** Electron micrograph of the thyroid gland of the control animal. TEM. Stain: uranium acetate and pure lead citrate. Scale: 5 μm. 1 – thyrocytes; 2 – basal membrane of thyrocyte; 3 – capillary endothelium; 4 – Golgi complex; 5 – lysosomes; 6 – mitochondria
Table 1  Morphometric parameters of the nuclei of the adrenocytes (M±m), (min-max) in norm and acute hypoxia

|                         | Glomerular zone (Max±min) | Fascicular zone (Max±min) | Reticular zone (Max±min) | Adrenal medulla (Max±min) |
|-------------------------|----------------------------|---------------------------|---------------------------|---------------------------|
|                         | N                          | 2nd day                   | 5th day                   | N                          | 2nd day                   | 5th day                   | N                          | 2nd day                   | 5th day                   | N                          | 2nd day                   | 5th day                   |
| Diameter M±m            |                            |                           |                           |                            |                           |                           |                            |                           |                           |                            |                           |                           |
| 2nd day                 | 4.44±0.27                  | 4.63±0.26                 | 4.87±0.26                 | 5.55±0.20                  | 5.74±0.19                 | 6.03±0.21                 | 4.45±0.17                  | 4.63±0.17                  | 4.87±0.16                  | 5.47±0.19                  | 5.66±0.19**                | 5.94±0.22** |
| 5th day                 |                            |                           |                           |                            |                           |                           |                            |                           |                           |                            |                           |                           |
| Min-max                 | 2.66-5.82                  | 2.87-5.97                 | 3.01-6.14                 | 4.62-6.35                  | 4.88-6.57                 | 5.15-7.01                 | 3.77-5.26                  | 3.97-5.47                  | 4.19-5.75                  | 4.66-6.35                  | 4.87-6.57                 | 5.01-7.01 |
| Area M±m                | 46.0±3.83                  | 47.9±3.87**               | 50.1±3.92**               | 34.2±1.87                  | 36.1±1.84**               | 38.3±1.80**               | 23.9±2.16                  | 25.6±2.18**               | 27.6±2.28**               | 30.9±1.47                  | 32.8±1.38**               | 35.0±1.32** |
| 2nd day                 | 33.53-68.45                | 34.67-70.54               | 36.95-73.45               | 23.47-41.64                | 26.58-43.78               | 28.76-45.69               | 15.47-36.43                | 17.64-38.52                | 18.76-40.13                | 23.47-37.63                | 26.58-39.17                | 28.76-41.46 |
| 5th day                 |                            |                           |                           |                            |                           |                           |                            |                           |                           |                            |                           |                           |
| Min-max                 | 3.95-7.67                  | 4.11-7.82                 | 4.34-8.03                 | 38.63-86.61                | 38.74-86.78               | 38.97-86.91               | 3.59-7.92                  | 3.82-8.12                  | 4.01-8.35                  | 3.91-20.01                 | 4.09-20.16                 | 4.21-20.32 |

N – control group; M±m: M – average parameter of variation, m – standard error, ** – p<0.01

Table 2  Morphometric parameters of the nuclei of the thyrocytes (M±m), (min-max) in norm and acute hypoxia

|                         | Diameter of cells (μm) | Area of cells (μm²) | Diameter of nuclei (μm) | Area of nuclei (μm²) |
|-------------------------|------------------------|---------------------|-------------------------|---------------------|
|                         | N                      | 2nd day             | 5th day                 | N                      | 2nd day             | 5th day                 | N                      | 2nd day             | 5th day                 | N                      | 2nd day             | 5th day                 |
| Diameter M±m            |                        |                     |                         |                        |                     |                         |                        |                     |                         |                        |                     |                         |
| 2nd day                 | 5.94±0.38              | 6.07±0.37           | 6.24±0.37               | 62.55±5.25             | 62.68±5.25           | 62.87±5.25             | 6.04±0.49               | 6.27±0.49           | 6.50±0.48               | 12.08±1.43             | 12.26±1.43           | 12.44±1.43             |
| 5th day                 |                        |                     |                         |                        |                     |                         |                        |                     |                         |                        |                     |                         |
| Min-max                 | 3.95-7.67              | 4.11-7.82           | 4.34-8.03               | 38.63-86.61            | 38.74-86.78          | 38.97-86.91            | 3.59-7.92               | 3.82-8.12          | 4.01-8.35               | 3.91-20.01            | 4.09-20.16          | 4.21-20.32            |

N – control group; M±m: M – average parameter of variation, m – standard error
Thus, the nucleus in the center of the cell, the eccentric nucleolus, lipid vesicles dispersed around the nucleus, ribosomes, mitochondria, lysosomes, endoplasmic reticulum, and Golgi complex attract attention with clear contours. In experimental animals of the 1st subgroups (2 days of exposure) the growth of the volume of the adrenal and thyroid glands of animals loosening of the capsule, pale-yellowish color and partial fragility of the consistency are observed.

During the examination of histological preparations, slight dystrophic and destructive changes in the cells of the adrenal and thyroid glands are detected. The morphometric parameters also did not show any significant changes compared to the control group (Tables 1, 2).

On the second day of the experiment, electron micrographs show the loosening of the basal membrane layers in the adrenocytes of the adrenal gland, and in some cells, it is possible to see even a disruption of the integrity of the basal membrane. The cytoplasm of adrenocytes has edema, vesicles, nuclei have blurred and unclear contours, even they are deformed in some cells, a nucleus with two nucleoli is also found. The nucleus and the nucleolus are located mainly on the periphery of the cell – adjacent to the cytolemma. Nuclear chromatin is pale, unevenly distributed, in some cells, especially in the cells of the reticular zone, the destruction of nuclear chromat is clearly noticeable. Edema, swelling of adrenocytes also causes dystrophic and destructive changes in intracellular organelles (Fig. 3).

From the electron micrographs it appears that the number of lipid vesicles in the basal membrane has decreased, the contours are not clear. Mitochondria have undergone dystrophic changes, the majority of them are edematous, in particular, the outer membrane has thickened and the crystae have become smooth.

Mitochondria changed their elongated forms and become rounded. In some cells, mitochondria with a bright matrix and normal crystae are also found. Lysosomes and ribosomes are unevenly dispersed in the cytoplasm, the endoplasmic reticulum and the Golgi complex are poorly noticeable. The cisterns of the Golgi complex are lightly increased, the numbers are reduced, the endoplasmic reticulum is not well noticeable. The cisterns of the Golgi complex are lightly enlarged. Ultrastructural changes in connective tissue and walls of capillaries are not detected. Endothelial cells of capillaries are relatively pale, endothelial cells that have undergone apoptosis locally in some areas, especially in the central part of the gland. On the 2nd day of the experiment, due to a decrease in oxygen supply, an increase in the area and diameter of the thyrocytes is observed. This growth is also recorded in similar indicators.

Under the influence of hypoxia, intracellular organelles, mainly mitochondria, have weak edema, their crystae have relatively changed shape and are distributed unevenly in the cytoplasm (Fig. 4). The size of lysosomes, ribosomes, and liposomes is relatively increased, the numbers are reduced, the endoplasmic reticulum is not well noticeable. The cisterns of the Golgi complex are lightly enlarged. Ultrastructural changes in connective tissue and walls of capillaries are not detected. Endothelial cells of capillaries are relatively pale, endothelial cells that have undergone apoptosis locally in some areas, especially in the central part of the gland. On the 2nd day of the experiment, due to a decrease in oxygen supply, an increase in the area and diameter of the thyrocytes is observed. This growth is also recorded in similar indicators.

On the 5th day of the experiment, noticeable acute dystrophic and disorganization changes, diffuse edema and damage of tissue characteristic for hypoxia effect on the tissues of the adrenal and thyroid glands are noted. Cells, intracellular organelles of both glands have lost their morphological features and are subject to acute destruction. Similar results were obtained in morphometric indicators of the study (Tables 1, 2).

During the study of ultrathin sections, acute ultrastructural changes in connective tissue and plasmalemma of capillaries are not visible. So, the fenestrae of the endothelial cells of the capillaries surrounding the adrenocytes are clearly visible. Capillaries were plethoric, the lumen was slightly enlarged, the walls were subjected to weak ultrastructural changes.

During the examination of the adrenal gland, the area and diameter of nuclei of adrenocytes in the glomerular, fascicular and reticular zones of the adrenal cortex, as well as in the adrenal medulla, are increased (Table 1).

On the 2nd day of the experiment electron microscopically are detected weak dystrophic changes in the thyroid follicles, as well as in the epithelial cells of thyrocytes on the ultrastructural level. These changes are manifested mainly by an increase in the volume of thyrocytes and hypertrophy of intracellular organelles, especially mitochondria. In electron micrographs, the basal membrane of the thyrocytes is loosened, although the cytoplasm and nuclei are slightly edematous, contours are clearly visible. The protrusions on the lateral surface of the thyrocytes are swollen, the shape of which is relatively changed. The nucleus is located outside the center adjacent to the plasmalemma, and contours are unclear.

**Fig. 3** Electron micrograph of the reticular zone of normal structure of cells of the suprarenal gland. TEM. Stain: uranium acetate and pure lead citrate. Scale: 500 nm. 1 – lysosome; 2 – ribosome; 3 – destroyed lysosome; 4 – destroyed mitochondria; 5 – plasmalemma

**Fig. 4** The 2nd day of hypoxia. Electron micrograph of mitochondria in the cell of the thyroid gland. TEM. Stain: uranium acetate and pure lead citrate. Scale: 5 μm. 1 – thyrocyte; 2 – basal membrane of the follicle-contact portion of the thyrocytes; 3 – complete crystae; 4 – looseened plasmalemma
Macroscopically, the adrenal and thyroid glands were grayish-yellow, sharply increased in volume, softened and became fragile. With the growth of its volume, the connective tissue fibers of capsule covering the glands were loosened, and in some parts, there was an interruption of its integrity, which resulted in the destruction of trabeculae going from the capsule into the gland. The grayish-pink color appearance in the transverse section shows the damage of tissues of the adrenal gland.

On the 5th day of acute hypoxia, most of the cells of the adrenal gland were subjected to degranulation and vacuolization, organelles were subjected to destructive changes, and cytoplasmic proteins were subjected to coagulation and colliquation. In the ultrathin preparations, the cytoplasm and nucleus of adrenocytes are edematous, dark and foamy, and hypertrophied (Fig. 5).

Some cells exhibit, nuclei that have been exposed to karyopiknosis, karyolysis, with nuclear chromatin dispersed and destructed in most cells, mainly in the glomerular zone. In the cytoplasm, a large number of fat droplets are found (Fig. 6). In the cytoplasm, a large number of fat droplets are found, they have arranged under the plasmolemma, almost adjacent to it.

Ultrastructurally, the loosening of mitochondria, the swelling and locally lysis of mitochondrial cristae, vacuolisation of the endoplasmic reticulum and lysosomes are clearly visible. The cisterns of the endoplasmic reticulum are expanded. The absence of lysosomes and ribosomes can be evaluated as a result of acute hypoxia. The intercellular space is expanded, the fibrous structures of the connective tissue are dispersed, the capillaries are plethoric. Ultrastructure of the walls of the capillaries and basal membrane were changed, the completeness integrity of most of them was disrupted. Around some adrenocytes, the local accumulation of cellular elements – neutrophil leukocytes, lymphocytes and histiocytes is clearly visible.

Under the influence of hypoxia, along with karyopyknosis of the nuclei of adrenocytes and the disintegration of chromatin substance, noticeable changes in the number and size of cells, as well as the nuclei are manifested.

The area of cells in all areas of the adrenal cortex, including the adrenal medulla, has increased dramatically compared to the control group. The same dynamics are observed in the area and diameter of the nuclei (Table 1).

On the 5th day of the experiment, under the effect of hypoxia in the ultrathin sections of the thyroid gland, pathological changes in cells – the destruction of thyrocytes and alterations of cytoplasmic organelles attract attention. The layers of the basal membrane of the thyrocytes are swollen and smoothed, thickened and deformed in some parts of the basal membrane. The cytoplasm of cells is edematous, the nuclei are dark, the membrane is not visible, the chromatin is condensed. In some cells, the shrunken nucleus is split into separate particles. Changes in the ultrastructural level in cytoplasmic organelles – complete vacuolization of lysosomes and ribosomes, expansion of the endoplasmic reticulum vesicles, smoothing and swelling of mitochondrial cristae, destruction of the Golgi complex are clearly visible. In the cytoplasm of thyrocytes, especially in the cytoplasm of the peripheral part, it is possible to see the accumulation of numerous large-sized fat droplets, glycogen grains. The interfollicular area is enlarged, edematous, fibrous structures, mainly collagen fibers are dispersed, signs of fibrinoid swelling are noted. The layers of the capillary walls, also have undergone ultrastructural changes (Fig. 7).

Morphometric data obtained as a result of electron microscopic studies have increased compared to the control group. These changes are also clearly visible in the area and diameters of the nuclei (Table 2).
As a result of the study, it can be concluded that hypobaric hypoxia affects the structure of the adrenal and thyroid glands as the main «stress» factor, causes cellular and extracellular structural changes in the glands. Because the resistance of the adrenal and thyroid glands to hypoxia, especially short-term hypoxic effects, is different, the cells (adrenocytes and thyrocytes), vessels and connective tissue structures of the glands respond with varying degrees of damage and changes with different morphofunctional reactions. It depends on the type of gland tissues or cells, their morphofunctional properties, resistance to hypoxia, the speed of development and duration of oxygen starvation, as well as the intensity of metabolism. Dystrophic and destructive changes in the adrenal gland, compared to the thyroid gland, especially at the ultrastructural level, are more pronounced. These changes, which occur under the influence of hypoxia, are associated with the fatty degeneration of the glandular cells.

The thyroid and adrenal glands play an important role in the adaptation of the body to hypoxia. The morphological effect of experimental hypoxia on the endocrine glands depends on the duration (short-term – acute or long-term – chronic) and degree of hypoxia [18]. Despite the research work devoted to the study of morphofunctional, histological and histopathological changes occurring in the thyroid and adrenal glands during hypobaric hypoxia, the ultrastructural changes occurring in these glands during acute hypoxia have been less studied and the obtained literature data are fragmentary. Therefore, it is difficult to compare the results of our research with those of other researchers.

The adrenal cortex plays an important role in adaptation against the various stress factors, including hypoxia. During acute hypoxia, ultrastructural changes occur in all three zones of the adrenal cortex, and they are accompanied by an increase in the weight of the gland. However, Mohri et al. (1983) [19] and Gosney (1985) [20] show an increase in adrenal gland weight on the 14th weight of the gland. However, Mohri et al. (1983) [19] and Gosney adrenal cortex, and they are accompanied by an increase in the hypoxia, ultrastructural changes occur in all three zones of the research with those of other researchers.

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Thus, in the comparative analysis of electron micrographs taken from ultrathin sections of both glands, due to acute hypoxia cellular and extracellular acute dystrophic and destructive changes of adrenocyte of the adrenal gland – separation of basal membranes into layers, edema of cells, hypertrophy, and vacuolization of organelles as a compensatory reaction is observed at the early stage of the experiment (2nd day), the same changes are observed on the 5th day of the experiment in thyrocytes and cytoplasmic organelles of the thyroid gland. Early damage of the adrenocytes of the adrenal glands compared to the thyroid gland may be considered as a higher degree of sensitivity of the adrenal gland to hypoxia.

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