MORPHOLOGY AND PATHOMORPHOLOGY

Effect of Methimazole on Thyroid Follicular Structure in Rats

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Methimazole enhances blood circulation in the thyroid gland, thus stimulating folliculogenesis. Spasm of blood capillaries contacting with follicles non-adjacent to proliferating follicles leads to blood redistribution, apoptosis of the thyroid epithelium, destruction of the follicular wall, and elimination of the follicle.

Key Words: *folliculogenesis; follicle elimination; apoptosis*

An upsurge of thyroid gland (TG) pathologies determines considerable interest to its structure and function in health and disease [1-5]. The dynamics of morphological changes in TG under the effect of long-term exogenous factors helps us to understand the role of parenchymal and stromal elements in the regulation of structural homeostasis.

Our aim was to study the structure of TG follicles during methimazole (Mercazolyl) treatment and after its cessation.

MATERIALS AND METHODS

Wistar rats (n=250) weighing 130-160 g were divided into 5 groups (50 rats per group). Intact animals served as the control (group 1). Groups 2 and 3 rats daily received methimazole in a dose of 10 mg for 7 and 14 days, respectively, and groups 4 and 5 rats received methimazole for 14 days and were sacrificed 7 and 14 days after cessation, respectively. The left lobe of TG was fixed in Bouin fluid for light microscopy and the right lobe was fixed in 2.5% glutaraldehyde and post-fixed with 1% OsO_4 for electron microscopy. Quantitative measurements of TG structures in histological preparations were performed with a standard ocular micrometer and an ocular grid. The each section, the minimum and maximum sizes of 10 randomly selected follicle cross-sections were determined. The total number of thyrocyte nuclei and the number of pyknotic nuclei in 1 mm^2 were determined.

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RESULTS

Methimazole treatment considerably increased weight of TG, the height of individual thyrocytes also significantly increased and varied in a wider range than in the control. Thyrocyte cytoplasm became heterogeneous and underwent vacuolization and destruction (Fig. 1). Dead cells typically had intensively stained cytoplasm and pyknotic nucleus. C cells were enlarged and had very light cytoplasm. Despite the increase in the thyrocyte height, spatial relationship in the cell remained unchanged. Methimazole stimulated intense proliferation of epithelial cells, especially after 14 days of methimazole treatment. The intensity of proliferation was different even in the same follicle: hyperplasia usually occurred in one pole of the follicle and determined different thyrocyte structure in active and inactive follicles. Accumulation and degranulation of mast cells were also observed.

Electron microscopy after 7-day methimazole treatment revealed increased number of mitochondria, en-

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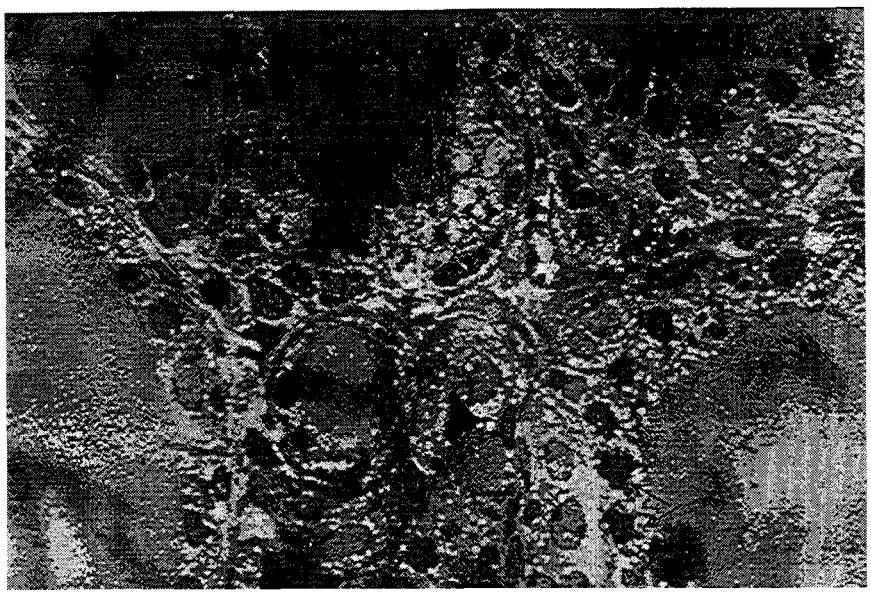

Fig. 1. Thyroid gland after 14-day methimazole treatment. Vacuolization and increase in thyrocyte height. Thyrocytes containing lipid droplets are shown by arrows. ×60.

larged profiles of the endoplasmic reticulum, and dense inclusions in the cytoplasm. At the later stages (14 days), the number of mitochondria markedly decreased, which was accompanied by fragmentation of mitochondrial cristae, rounded cisterns of the endoplasmic reticulum did not communicate with each other and their content was similar in structure and electron density to follicular colloid. In the apical cytoplasm, vacuoles decreased in size, membranes of the endoplasmic reticulum were lysed and the content of cisterns were released into the cytoplasm. Microvilli on the apical plasmalemma disappeared. Cytoplasmic vacuoles and granules entered follicular colloid via numerous defects in the plasmalemma and lost their membranes.

Thus, stimulation of TG with methimazole induced phasic changes typical of protein-synthesizing cells. The release of secrete into colloid is effected via the apocrine mechanism. These structural changes attest to thyrocyte exhaustion and death due to enhanced functional activity caused by secretory stimulation.

Intense proliferation of thyrocytes was effected through active mitosis. Follicle lumens were deformed by proliferation processes in the follicle walls. These processes then approached each other and after the formation of capillary loops daughter follicle containing colloid segregated from the parent one. Newly formed follicles retained round shape and lay nearby the parent follicles without deforming their shape.

At the same time, many follicles collapsed and took a folded shape as a result of colloid resorption most pronounced on day 14 of methimazole treatment. Under these conditions C cells were still arranged peripherally and were not found in the folds. Morphometrical analysis revealed no significant differences in the structure of C cells between the control and experimental groups. In deformed follicles with folded epithelial layer the diameter of blood capillaries so increased that they come in contact and sometimes fused with each other. Some thyrocytes lost contact with the basement membrane, while other cells still bound to the basement membrane were markedly deformed and their spatial relationships with other epithelial cells changed. Apart from dilated capillaries, we observed an increase in the number of narrowed or even collapsed capillaries. Capillary spasm was noted both in the area of interfollicular contacts and in other areas of the follicle (Fig. 2).

After termination of methimazole treatment, the morphometrical parameters of follicle differentiation in the central and peripheral zones returned to normal. On day 7 we observed accumulation of the colloid, while vascular reaction became less pronounced. On day 14, the cytoplasm structure and spatial relationships between thyrocytes, basement membrane, and blood capillaries returned to normal. However, solitary foci with pyknotic thyrocyte nuclei and signs of hemorrhage in the follicular lumen were noted. The intensity of mast cell degranulation decreased, but remained above the control level even on day 14 after treatment.

In animals sacrificed on day 14 after termination of methimazole treatment, solitary follicular invaginations were noted, which were absent in control animals. These invaginations consisted of destructively changed epitheliocytes and exhibited marked thyrocyte desquamation: cytoplasmic fragments and thyrocyte nuclei surrounded by perinuclear cytoplasm were seen in the follicular lumen (Fig. 3). It should be noted that the size of invaginations correlated with the degree of thyrocyte destruction.

These changes in follicular cells of TG in rats during and after methimazole treatment reflect diffe-

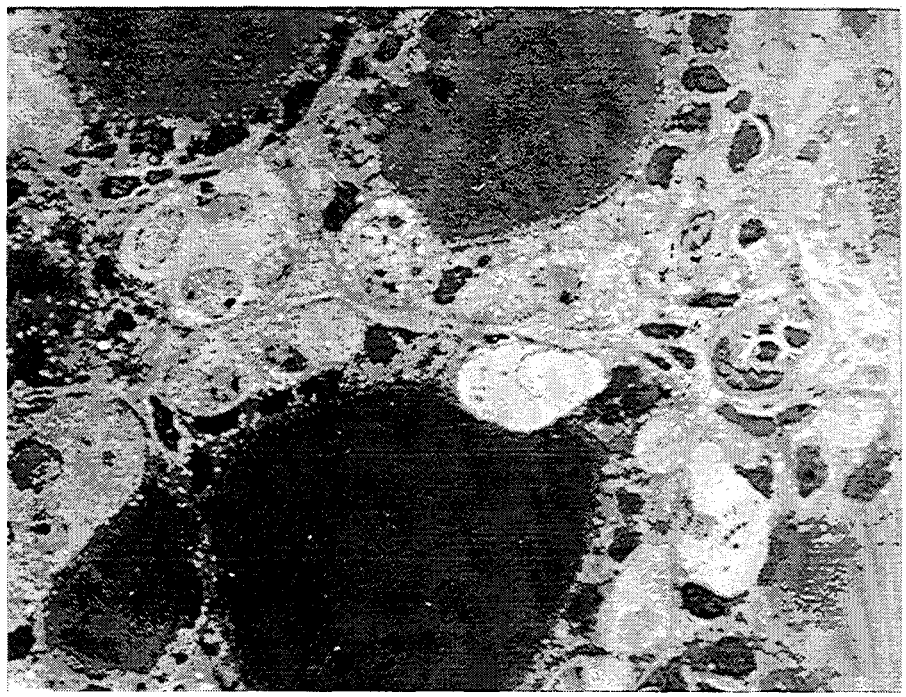

Fig. 2. Thyroid gland after 7-day methimazole treatment. Increase in height in some thyrocytes and flattening of others. C cells had very clear cytoplasm. ×100.

Fig. 3. Thyroid gland in rats treated with methimazole for 14 days and sacrificed 14 days after termination of treatment. Invagination of follicular wall. Destructively changed cells in the follicular lumen. Blood capillary in invagination. ×40.

rent levels of its functional activity. The maintenance of hormone production in the TG is determined by metabolic changes and structural homeostasis. The maintenance of structural homeostasis requires active function of all structures of TG and therefore long-term stimulation is accompanied by dystrophic changes: accumulation of thyrocytes with pyknotic nuclei, destruction of thyrocytes in follicles adjacent to collapsed capillaries and in the lumen of follicles with preserved blood supply. Rapid elimination of abnormal follicles is probably effected via invaginations in the follicular wall with altered thyrocytes followed by their fusion. The mechanism of follicle elimination can be considered as an analog of apoptosis. The observed thyrocyte destruction (pyknosis of thyrocyte nuclei, lysis of the cytoplasm, fragmentation and condensation of cytoplasmic structures) and their appearance in the follicular lumen correspond to morphological signs of apoptosis described for other cell structures [6,7]. This apoptosis is probably triggered by elevated concentration of thyroid hormones, which via the feed-back mechanism regulates blood supply in

different follicle regions thereby modulating the conditions of thyrocyte function.

Thus, long-term pathogenic influences stimulate proliferative activity of the TG. Under these conditions, blood supply is inadequate to increased metabolic requirements.

REFERENCES

1. B. V. Aleshin and V. I. Gubskii, *Hypothalamus and Thyroid Gland* [in Russian], Moscow (1983).
2. V. A. Mironov, A. A. Mironov, and Yu. V. Pogorelov, *Endocrine Glands. Scanning Electron Microscopy Atlas* [in Russian], Moscow (1987).
3. V. B. Shadlinskii, *Azerbaidzh. Med. Zh.*, No. 5, 94-97 (1997).
4. C. Als, M. Listewnik, and H. Rosler, *Nuklearmedizin*, Bd. 34, 92-99 (1995).
5. H. G. Bohnet, U. A. Knuth, and M. J. Seeler, *Gebirtshilfe Frauenheilkd*, Bd. 55, 134-136 (1995).
6. Th. L. Deckwerth and E. M. Johnson, *J. Cell. Biol.*, **123**, 1207-1222 (1993).
7. D. N. Woo, *N. Engl. J. Med.*, **333**, 18-25 (1995).