EFFECT OF FOLLICLE SIZE ON DIURNAL CHANGES IN MITOTIC ACTIVITY IN THYROID CELLS

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A study of mitotic activity in the epithelial cells of thyroid follicles of different sizes showed that the cells of large thyroid follicles in rats have lower mitotic activity than those of small or medium-sized follicles. The dynamics of the diurnal mitotic rhythm also differs in these types.

An important aspect of the study of cell division in organs is the relationship between mitotic activity and cell differentiation. The existence of a diurnal rhythm in the number of mitoses in rat thyroid epithelium was demonstrated previously [2].

The object of the present investigation was to study mitotic activity in the thyroid epithelium of follicles of different sizes in rats with allowance for the fact that the cells of large follicles have existed for a longer time than those of small follicles and, consequently, they are in later stages of differentiation.

EXPERIMENTAL METHOD

Experiments were conducted on 40 male albino rats (mean weight 107 g) kept on an ordinary diet and under natural conditions of illumination. The animals were sacrificed at 9 a.m., noon, 3, 6, and 9 p.m., midnight, and 3 and 6 a.m. The thyroid gland was fixed in Zenker-formol and acetic acid, and sections cut to a thickness of 6 μ were stained with hematoxylin and eosin. The total mitotic index (TMI) was calculated for 60,000-70,000 thyroid cells, and the mitotic indices of the follicular (MIFC) and interfollicular cells (MIIFC) were determined by the method described previously [1]. To calculate the mitotic indices in the epithelium of follicles of different sizes, the number of cells in the wall of each of 100 follicles, examined in mutually perpendicular directions, was determined. The follicles were grouped into classes depending on the number of cells forming their wall in the section: class 1—follicles with 2-5 cells (microfollicles), class 2—follicles with 6-15 cells, and class 3—follicles with 16-25 cells, and so on. The wall of the follicles of each successive class was larger by 1-10 cells than in the preceding class. The total obtained by adding the numbers of cells in the follicles of each class made up the total number of cells in 100 follicles. If the value of MIFC was known, the number of mitoses belonging to a cell population in 100 follicles could be calculated. When the mitoses were counted, their localization in the classes of follicles was noted. The number of mitoses in the follicles of each class was then determined and expressed as a percentage. The absolute number of mitoses occurring in the follicles of each class among 100 follicles examined was found, and the mitotic indices of the follicular epithelium in each class was then calculated (MI_1, MI_2, etc.). The number of mitoses found in the peripheral zone, equal in thickness to the diameter of the field of vision of the microscope (7 × 40) and in the central zone, occupying the rest of the section through the organ, was expressed as a percentage of the total number of mitoses.

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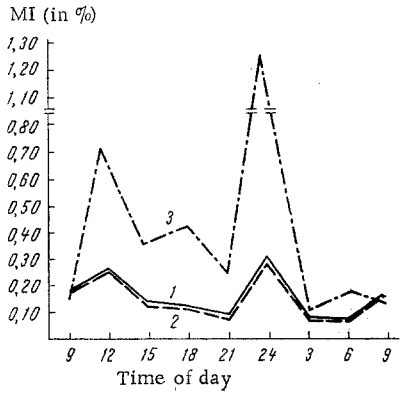

Fig. 1. Changes in number of mitoses in thyroid epithelium of adult rats during 24 h period: 1) TMI; 2) MIFC; 3) MIIFC.

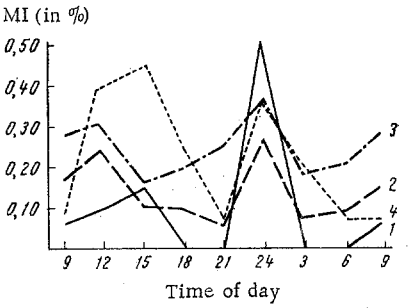

Fig. 2. Changes in number of mitoses in thyroid follicular epithelium of adult rats during 24 h period: 1) MI_1; 2) MI_2; 3) MI_3; 4) MI_4.

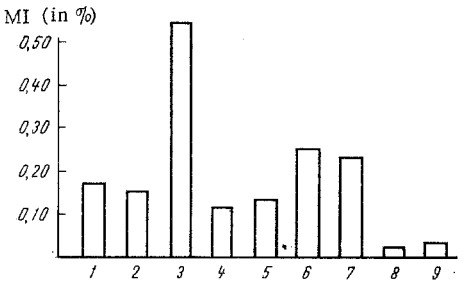

Fig. 3. Mean mitotic indices for the 24 h period in the thyroid epithelium of adult rats: 1) TMI; 2) MIFC; 3) MIIFC; 4) MI_1; 5) MI_2; 6) MI_3; 7) MI_4; 8) MI_5; 9) MI_6.

EXPERIMENTAL RESULTS

The results of determination of the mitotic indices in the thyroid epithelium are shown in Figs. 1 and 2.

These results show that the TMI and MIFC rose to a maximum twice in the 24 h period (at noon and midnight), when their values differed significantly from the minima at 9 p.m. and 3 and 6 a.m. ($P = 0.043$-0.050). Similar changes affected the MIIFC. In the microfollicles (follicles of class 1) mitoses were observed from 9 a.m. to 3 p.m. and at midnight, while at other times no mitoses were found in the microfollicles on analysis of 4000-5000 cells. The value of MI_2 (in class 2 follicles) was higher at noon and midnight than at 9 p.m. and 3 and 6 a.m. ($P = 0.048$-0.050). The value of MI_3 varied during the 24 h period, but the differences in its values were not significant. MI_4 was higher at 3 p.m. and midnight than at 9 p.m. and 6 and 9 a.m. ($P = 0.045$-0.050). A small number of mitoses was observed in the class 5 follicles at 3 and 9 p.m. Very few mitoses also were found in the cells of the class 6 follicles.

The curves reflecting the diurnal rhythm of TMI, MIFC, MIIFC, MI_1, MI_2, and MI_4 thus have two maxima, at noon and midnight. The MI_4 curve differs slightly from the rest: the increase in number of mitoses in the class four follicles in the afternoon occupied a longer time interval than in the follicles of other classes, and the maximum of mitotic activity was shifted to 3 p.m. In the class 3 follicles, the number of mitoses showed no significant change during the 24 h period. Consequently, depending on the degree of differentiation of the thyroid cells (i.e., on the size of the follicles), the periodic changes in the number of mitoses in the follicular epithelium of the thyroid gland varied.

Calculation of the mean values of the indices of cell division in the thyroid gland for the 24 h period showed (Fig. 3) that MIIFC was about 3.5 times greater than MIFC ($P = 0.001$), MI_1 was 4.7 times greater ($P = 0.003$), MI_2 4 times greater ($P = 0.002$) MI_3 2.2 times greater ($P = 0.021$), MI_4 2.4 × ($P = 0.016$), MI_5 26.7 × ($P < 0.0001$), and MI_6 18.4 times greater ($P < 0.0001$). The mean values of MI_3 and MI_4 for the 24 h period were 1.7-2.1 times greater than MI_1 and MI_2 ($P = 0.016$-0.050). The number of mitoses in the follicles of classes 5 and 6 was very small (8.4-11.3 times smaller than MI_3 and MI_4; $P = 0.001$-0.003). At the end of differentiation of the thyroid cells, the ability of the cells to divide was thus sharply reduced.

A decrease in the number of mitoses in differentiating cells is regarded as characteristic of tissues with a stratified squamous epithelial type of structure (the epidermis of the skin, the epithelium of the cornea, esophagus, etc.). However, the present investigation showed that a similar pattern is also characteristic of organs with epithelium of a different structural type. At the same time, whereas in stratified squamous epithelia migration of cells from one cell system to another (from the stratum basale into the

stratum spinosum, and beyond) is an essential factor determining the decrease in mitotic activity, and a decrease in mitotic activity is thus observed in the early stages of cell differentiation, in the thyroid follicles the factor responsible for the decrease in the number of mitoses in the cells (which do not leave the system) is evidently aging of the cells developing in the last stages of their differentiation.

Deviations in the values of TMI during the 24 h period from the mean values ranged from −48 to +86%, those of MIFC from −48 to +81%, of MIIFC from −77 to +132%, of MI_1 from −100 to +346%, of MI_2 from −65 to +100%, of MI_3 from −37 to +50%, and of MI_4 from −67 to +100%. Consequently, the greatest amplitude of fluctuations in the number of mitoses at the time of extreme values of mitotic activity was observed in the microfollicles.

On the average for the 24 h period 50% of all mitoses were located in the central zone of the gland and 50% in the peripheral zone. No regular changes were observed in the distribution of the mitoses by zones during the 24 h period. Allowing for the fact that the area of the peripheral zone as a whole is less than that of the central zone, it can be concluded that more intensive cell division takes place at the periphery of the gland over the whole 24 h period. This agrees, in particular, with morphological findings indicating that the largest follicles lie in the peripheral parts of the thyroid gland.

LITERATURE CITED

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