CELL DIVISION IN THE ADENOHYPOPHYSIS AND THE THYROID AND PARATHYROID GLANDS DURING CHANGES IN THYROID FUNCTION

Yu. A. Romanov, B. S. Kasavina, A. N. Blokhina, and S. M. Kremli

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It has previously been shown [5-8] that an increase or decrease in the function of the thyroid is accompanied by regular changes in the activity of cell proliferation in various organs and tissues, including the thyroid gland and other organs of internal secretion. It has been concluded that cell division in the adenohypophysis and thyroid obeys the general principles regulating cell proliferation in the organism and, in particular, the stimulating effect of the thyroid hormones. However, the view is widely held that the thyroid hormones have an inhibitory action on cell division in the anterior lobe of the pituitary and the thyroid gland. Clearly this problem requires further study.

The object of the present investigation was to study cell proliferation in the thyroid and parathyroid glands and also in the adenohypophysis during changes in the thyroid caused by administration of methylthiouracil, potassium perchlorate, and potassium iodide.

Despite differences in the mechanisms of their blocking of hormone formation, the first two preparations are known to have a marked antithyroid action and to cause hyperplasia of the gland [1-4]. Potassium iodide also stimulates proliferative processes in the thyroid [10, 11]. These preparations are often used for the treatment of thyroid diseases. The analysis of the changes they produce in the cell proliferation of the endocrine glands is of definite practical interest.

EXPERIMENTAL METHOD

Experiments were conducted on 100 male albino rats weighing 90-160 g. In the experiments of series I the animals received a 0.1% solution of methylthiouracil (MTU) with the milk (10 mg per diem), in those of series II – a 0.1% solution of potassium perchlorate ($KClO_4$) with the milk (10 mg per diem), and in those of series III – potassium iodide (KI) intraperitoneally (0.5 mg per diem); the animals in series IV acted as controls. The organs were investigated on the 2nd, 4th, 8th, 12th, and 20th days of the experiment. The thyroid function was studied by determining the level of the protein-bound iodine (PBI) in the blood serum by a modified Barker's method [9]. The proliferative processes in the thyroid and parathyroid glands and in the adenohypophysis were assessed by the changes in the relative weight of the thyroid (in mg/100 g body weight), the mitotic index of the parenchyma and stroma, and the mitotic index of the epithelium of the parathyroid gland and the anterior lobe of the pituitary.

EXPERIMENTAL RESULTS

The results of the investigation of the PBI in the blood serum showed that the administration of MTU, of $KClO_4$, and of KI is accompanied by phasic changes in the concentration of thyroid hormone in the blood stream.

On the 4th day of the experiment the PBI level in the serum rose by 80% ($P = 0.008$) during administration of MTU, by 56% during administration of $KClO_4$ ($P = 0.049$), and by 100% during administration of KI ($P = 0.001$) compared with the control value. Later the PBI level fell, and on the 20th day of the action of MTU its value was 37% of the control level ($P = 0.005$), while in animals receiving $KClO_4$ and KI it was 80% ($P = 0.049$).

Hence, whereas at the beginning of administration of the preparations the animals showed an excess of thyroid hormones in the blood compared with the controls (the phase of hyperthyroidism), after 12-20 days (when MTU was administered from the 8th day) hypothyroidism began to develop.

Department of General Biology, N. I. Pirogov Second Moscow Medical Institute and Deaprtment of Laboratory Diagnosis, Institute of Experimental Endocrinology, Academy of Medical Sciences of the USSR (Presented by Active Member of the Academy of Medical Sciences of the USSR N. A. Kraevskii). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 62, No. 10, pp. 95-98, October, 1966. Original article submitted March 11, 1965.

In all three series of the experiment the mitotic index of the thyroid epithelium reached its maximum on the first days of the experiment. In the animals of series I it increased by 35 times by the 4th day ($P = 0.010$), in the animals of series II by 4 times on the 8th day ($P = 0.049$), and in the animals of series III by approximately twice by the 4th day ($P = 0.469$). By the end of the experiment in the animals of series I the number of cell divisions in the thyroid epithelium remained comparatively high (22 times higher than normal, $P = 0.003$). Meanwhile, in the animals of series II and III the mitotic index of the thyroid gland was significantly lower than normal – by 62% ($P = 0.049$) and 87% ($P = 0.040$) respectively.

Hence two phases were observed in the changes in the mitotic index of the thyroid epithelium during the action of MTU, $KClO_4$, and KI, and also in the changes in the PBI, the direction of the changes coinciding with the direction of the changes in the PBI of the experimental animals. This was particularly clear in the animals of series II and III.

The lower activity of cell division in the epithelium of the glands in the conditions of action of $KClO_4$ and KI by comparison with this index during the action of MTU was reflected in the smaller increase in the relative weight of the glands in the animals receiving $KClO_4$ and in the absence of increase in weight of the gland in the rats receiving injections of KI. Both in the animals receiving MTU and in those receiving $KClO_4$ the largest daily increase in weight of the thyroid glands took place in the first days of the experiment (15-20 and 3-5% respectively), and 12-20 days after the beginning of the experiment the gain in weight did not exceed 2%.

Similar biphasic changes were found in the mitotic indices of the connective-tissue cells of the thyroid stroma and the epithelium of the parathyroid gland. The number of mitoses in the stroma of the gland in the animals of series I had increased 13 times ($P = 0.009$) by the 4th day of the experiment, after which it decreased, although on the 20th day of the experiment it was still higher (4 times) than normal ($P = 0.049$). In the gland of the animals of series II the number of mitoses in the connective-tissue cells of the stroma was significantly increased on the 8th day of the experiment (by about 5 times, $P = 0.035$), but by the 20th day of the experiment it showed a decrease to about half the normal value ($P = 0.083$). During the action of potassium iodide (series II) the number of mitoses in the stroma of the gland was practically unchanged in the first 4 days of the experiment, but by the 20th day it had fallen to one-quarter the normal value ($P = 0.049$). The number of mitotic divisions in the parathyroid gland during the action of MTU had risen by the 4th day of the experiment to more than 6 times the normal value ($P = 0.001$), while after administration of the preparation for 20 days it had fallen considerably and no longer differed significantly from the control level ($P = 0.104$). During administration of $KClO_4$ to the animals the mitotic index of the cells of the parathyroid gland on the 8th day of the experiment was about 50% higher than the analogous index in normal conditions ($P = 0.049$). After 20 days of administration of the preparation the index had fallen to half of the normal value ($P = 0.083$). Injections of KI into the animals led to an increase in the number of mitoses in the parathyroid gland on the 4th day of the experiment by 4 times ($P = 0.049$), but on the 20th day of the experiment the number of mitoses in this gland was only one twenty-seventh of the control value ($P = 0.025$). A positive correlation was observed between the changes in the mitotic indices of the epithelium and stroma of the thyroid gland and of the epithelium of the parathyroid gland throughout the experiment.

The mitotic index of the epithelium of the anterior lobe of the pituitary was higher than normal during the first days of the experiment in the animals of all three experimental series. This was especially marked in the animals receiving KI. Later the mitotic index fell, but whereas in the series in which the rats received $KClO_4$ and KI it was indistinguishable from the control value 12-20 days after the beginning of the experiment, during the action of MTU it was higher than normal by 720% on the 20th day of the experiment ($P = 0.016$). Until the 8th day of the experiment inclusive, the changes in the mitotic index of the epithelium of the adenohypophysis showed a positive correlation with the changes in the mitotic indices in the stroma of the thyroid and the epithelium of the parathyroid gland. On the subsequent days of the experiment no correlation was found between the changes in these indices.

It may be concluded from the results obtained that an excess of thyroid hormones in the body has a stimulant action on cell division in the epithelium and stroma of the thyroid and in the epithelium of the adenohypophysis and the parathyroid gland. At the same time, the effect of their action on proliferation in the endocrine glands is largely dependent on the functional state of the two glands and on interhormonal relationships.

The action of potassium perchlorate, when administered to animals, is accompanied by weaker proliferation of the parenchyma and stroma of the thyroid and of the epithelium of the parathyroid gland than in the case of MTU. Even weaker activity of cell division in the thyroid is observed in rats receiving potassium iodide. The well marked stimulation of proliferation observed after administration of methylthiouracil to the animals evidently can-

not be attributed entirely to the action of the thyroid hormones. It may perhaps be connected with the chemical structure and the corresponding pharmacological action of methylthiouracil on cell division.

SUMMARY

The object of study was the function of the thyroid gland and the cell division in the parenchyma and stroma of the thyroid gland, in the epithelium of the anterior lobe of the hypophysis and parathyroid gland upon injection to animals of methylthiouracil, potassium perchlorate and potassium iodide. The function of the thyroid gland according to the indices of protein-bound iodine under these conditions changed by two phases. In the beginning of the experiment, there was the phase of hyperthyrosis which was followed by the development of hypothyrosis. Changes in cell-division in the organs under study corresponded in time and direction to changes in the thyroid status of the body. The greatest stimulation of cell division was noted under the action of methylthiouracil. A conclusion has been drawn on the stimulating influence of thyroid hormones on mitotic division in the endocrine glands, under investigation. The peculiarities of the action of methylthiouracil on cell division are possibly due to the chemical structure and corresponding pharmacologic dynamics of a given preparation.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of the first issue of this year.
