EFFECT OF THYROTROPIC HORMONE ON CELL DIVISION IN VIVO

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Injection of pituitary thyrotropic hormone into rats increases the mitotic index 4, 24, and 72 h later in the small intestine, bone marrow, and liver, and 24-72 h later in the thyroid. Thyroid hormones increase mitotic activity by acting on cells in the G_0- and G_2-phase of the cycle. The existence of a reserve pool of cells in the G_2-phase is postulated.

Previous investigations [1] showed that activation of cell division in vivo by thyroid hormones is connected with the action of these hormones at certain periods of the mitotic cell cycle.

The present investigation is a continuation of the study of the action of thyroid hormones on cell division. Mitotic activity was studied in the epithelium of the small intestine, bone marrow cells, parenchymatous cells of the liver, and epithelium of the thyroid gland following administration of pituitary thyrotropic hormone (PTH), which stimulates thyroid function, to rats.

EXPERIMENTAL METHOD

Experiments were carried out on 55 male albino rats weighing 148 g. The animals received a single intraperitoneal injection of 20 mg PTH/100 g body weight (≈1.5 i. u.), once a day. Tests were carried out 2, 4, 8, 12, 24, 48, and 72 h after the first injection of PTH (at each time of the experiment 5-6 animals were studied). Thyroid function was estimated by determining the content of protein-bound iodine (PBI) in μg% in the blood serum by a modification of the method described in [2]. Mitotic activity in the organs was estimated by calculating the mitotic indices (MI) in promille. MI for epithelium of the small intestine was determined in 4500-5000 cells in 50 longitudinally divided crypts, MI for bone marrow cells was calculated for 5000-7000 cells in impression films stained with aceto-orcein, MI for the glandular cells of the liver was calculated after examination of 35,000-45,000 cells in a section through the organ, and MI for the thyroid epithelium was calculated for 50,000-60,000 cells examined in the section.

EXPERIMENTAL RESULTS

During the first few hours of the experiment, the PBI concentration in the blood serum increased (by 45% after 2 h and by more than 200% after 4 h compared with the control; $P = 0.044$ and 0.005, respectively). The normal PBI level was restored after 24 h of the experiment, and after 72 h the PBI concentration was lowered by 40% ($P = 0.007$).

After injection of PTH, a thyrotropic response developed in the thyroid gland (increased resorption of colloid, increase in height of the follicular cells), and this was most marked 12-24 h after injection of the hormone.

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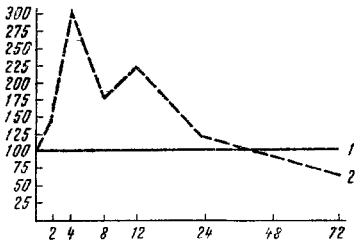

Fig. 1.

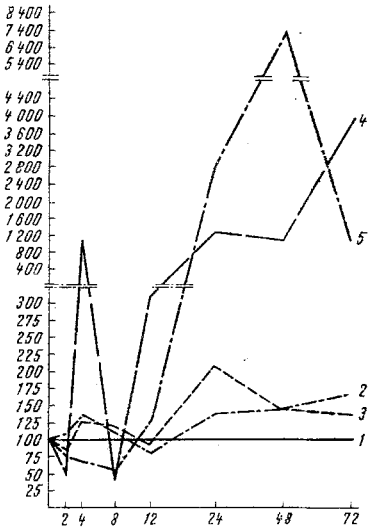

Fig. 2.

Fig. 1. Changes in PBI concentration in blood serum after injection of PTH: 1) control; 2) PTH. Abscissa, number of hours of experiment; ordinate, changes in concentration of protein-bound iodine (in % of control).

Fig. 2. Changes in MI in organs after injection of PTH: 1) control; 2) small intestine; 3) bone marrow; 4) liver; 5) thyroid gland. Abscissa, number of hours of experiment; ordinate, changes in MI (in % of control).

Four hours after injection of PTH into the animals, MI was increased in the intestine by 28% compared with the control ($P = 0.006$), in the bone marrow by 30% ($P = 0.047$), and in the liver by 761% ($P = 0.050$) (Fig. 2). In the thyroid epithelium, the number of mitoses at this time of the experiment showed a tendency to fall. By 8-12 h of the experiment, MI in the intestine, bone marrow, and liver had fallen to normal levels. After 24 h a second increase in MI took place in the intestine (by 32%, $P = 0.009$), in the bone marrow (by 34%, $P = 0.050$), and in the liver (by 11×, $P = 0.047$). The number of mitoses in the thyroid after 24 h of the experiment showed an increase of 28 × over the normal level ($P = 0.002$), and after 48 h an increase of 73× ($P < 0.0001$). A higher value of MI in the organs of the experimental animals compared with the controls was also observed after 72 h of the experiment.

It is clear from these results that the first increase in mitotic activity in the investigated organs (except the thyroid) started simultaneously with increased production of thyroid hormones through stimulation of the thyroid gland by PTH. The second increase in the number of mitoses in the organs, including the thyroid, developed approximately 20 h after an increase in the serum PBI level. The increase in mitotic activity was greater in organs with a small number of mitoses normally (liver, thyroid) than in organs with intensive cell division (intestine, bone marrow).

The results for cell division in vivo obtained in the present investigation agree with those of the investigation of cell division after administration of thyroxine to animals [1]. It must thus be assumed that the initial increase in mitotic activity during the action of PTH, just as during the action of thyroxine, is the result of stimulation by thyroid hormones of the transfer of cells from the "reserve pool" of G_2 phase into mitosis, whereas the later increase in MI reflects the G_0 effect of thyroid hormones, consisting of the departure of cells from the G_0 phase under their influence into the mitotic cycle. The hypothesis regarding the entry of cells into mitosis from the reserve pool of the G_2 phase under the influence of thyroid hormones 4 h after injection of PTH is supported by results showing that after 8 and 12 h of the experiment, no increase was observed in mitotic activity in the tissues, although the PBI concentration in the blood serum was raised. The fact that no increase in mitotic activity was observed in the thyroid gland at the beginning of the experiment may have been because stiumulation of thyroid function by PTH is an inhibitory factor so far as the entry of cells of the reserve pool of the G_2 phase into mitosis is concerned. However, functional excitation of the gland did not prevent division of cells which had already left the G_0 phase of the cycle and started mitosis.

LITERATURE CITED

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2. S. B. Barker, J. Biol. Chem., 173, 715 (1948).