ACTION OF THYROXINE ON CELL DIVISION IN VIVO

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A study of the effect of thyroxine on cell division in the small intestine, bone marrow, cornea, and liver of rats showed that it acts on cells in the G_2 and G_0 phases. It is concluded that a reserve pool of cells in the G_2 phase exists.

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The mechanism of the stimulant action of thyroid hormones on cell division in the living organism has not yet been explained. Since cells remain in the various phases of the mitotic cycle for several hours, there is good reason to investigate the action of thyroid hormones on cell division at time intervals of several hours.

The object of the present investigation was to study the effect of thyroxine on mitotic activity in the epithelium of the small intestine, the cornea, bone marrow cells, and glandular cells of the liver.

EXPERIMENTAL METHOD

Experiments were carried out on 48 male albino rats weighing 125-170 g. The animals received a single intraperitoneal injection of L-thyroxine in a dose of 10 μg/100 g body weight. Investigations were carried out 1, 3, 8, 12, 24, and 48 h after injection of the hormone. The level of thyroid hormones in the body was established by determining the concentration of protein-bound iodine in the blood serum of the rats (in mg%) by a modification of Barker's method [2]. Mitotic activity in the organs was judged by estimating the mitotic index (MI) in promille. MI of the small intestine epithelium was calculated for 4500-5000 cells in 50 longitudinally divided crypts, MI of the bone marrow cells for 5000-7000 cells in impression films stained with aceto-orcein, MI of the corneal epithelium was calculated for 20,000-30,000 cells in two-dimensional preparations, and MI for the glandular cells of the liver was calculated after examination of 35,000-45,000 cells in a section of the organ.

EXPERIMENTAL RESULTS

As Fig. 1 shows, after administration of thyroxine to the animals the concentration of protein-bound iodine in the serum rose sharply (by 414% after 1 h and 510% after 3 h compared with the control). The normal level of protein-bound iodine was not restored until after 48 h.

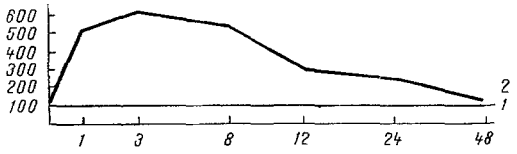

Fig. 1. Changes in serum protein-bound iodine concentration after injection of thyroxine. 1) control; 2) thyroxine. Abscissa, hours of experiment; ordinate, changes in concentration of protein-bound iodine in percent of control.

Counting the mitoses gave the following results. After 1 h of the experiment an increase in MI was observed in all organs studied (Fig. 2), although it varied from tissue to tissue. The increase in MI in the small intestine was 142% relative to the control (18.2 and 25.9‰; $P = 0.006$), in the bone marrow 176% (16.5 and 29‰; $P \to \infty$), in the cornea 242% (6.49 and 15.73‰), and in the liver cells 460% (0.26 and 1.20‰; $P = 0.008$). The normal value of MI in the tissues was restored 3 and 8 h after injection of thyroxine. After 12 h and at later stages of the experiment, a second increase in MI was observed in the bone marrow and cornea (rising to 130% relative to the control after 48 h in the

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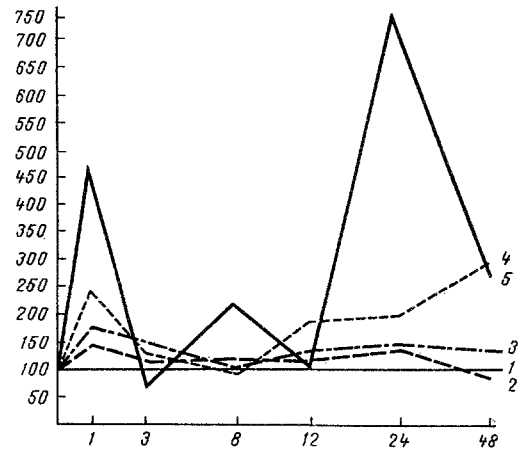

Fig. 2. Changes in mitotic index in organs after injection of thyroxine. 1) control; 2) small intestine; 3) bone marrow; 4) cornea; 5) liver. Abscissa, hours of experiment; ordinate, changes in MI in percent of control.

bone marrow—24.9 and 32.1‰; P = 0.001, and in the cornea 297%—4.72 and 14.03‰; P = 0.011). A second increase in the number of mitoses after 24 h of the experiment was observed in the small intestine (by 24% compared with the control MI; 19.2 and 23.7‰; P = 0.004) and in the liver (by 667%: 0.15 and 1.16‰; P = 0.05). By the end of the experiment the mitotic activity in these organs was reduced.

In the modern view the cell remains in the G_2 phase of the mitotic cycle on the average for 1-2 h. Consequently, if an agent stimulating the progression of cells from phase G_2 into mitosis is administered to a living organism, an increase in the number of mitoses would be expected 1-2 h or sooner after its administration. The results of this investigation show that 1 h after injection of thyroxine into animals an increase in the tissue MI takes place. This indicates that thyroid hormones influence phase G_2 of the mitotic cycle, an effect which can be described conventionally as the G_2-effect of thyroid hormones. Next the normal mitotic division is restored for a short time, although the blood level of thyroid hormones remains high. It can thus be postulated that thyroxine does not act on all cells in the G_2 phase but only on part of the G_2-cell population, which is heterogeneous from this point of view. Some cells thus pass through the G_2 phase of the cycle "in transit" for a few hours only and then start to undergo mitosis, while other cells can remain indefinitely in the G_2 phase. On the basis of these arguments, it can be postulated that the G_2 phase of the cycle includes a "reserve pool" of cells, which is small in organs with relatively high MI (small intestine, bone marrow) but fairly considerable in tissues with low mitotic activity (liver).

The second increase in the number of mitoses in the tissues, observed 12-24 h after injection of thyroxine, is evidence that thyroid hormones act on the reserve pool of cells in phase G_0 of the cell cycle, and this effect can be described conventionally as the G_0-effect of thyroid hormones.

The fact that the second increase in MI takes place in the liver cells more or less simultaneously with the increase in the number of mitoses in the epithelium of the small intestine and cornea and in the bone marrow cells suggests that the duration of the G_1 phase of the mitotic cycle in different tissues is not so variable as has been claimed [1]. One of the significant differences between the kinetics of cell populations with a high and low level of renewal is evidently the presence of quantitative differences between the "reserve pools" of cells rather than variation in the duration of the G_1 phase.

LITERATURE CITED

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