DIURNAL RHYTHMS OF FUNCTION AND MITOTIC ACTIVITY OF THE NORMAL AND REGENERATING THYROID GLAND

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Biological rhythms of the function of organs are an adaptive property of living systems, formed in the course of evolution and aimed at maintaining their homeostasis [1, 2, 10]. The endocrine glands, which influence many physiological processes, are characterized by an intrinsic circadian rhythm of hormone production and cell renewal [6, 10, 13, 14]. In the case of the thyroid, for instance, which is heterogeneous from both structural and functional respects, two peaks of mitotic activity are found in the course of the 24-h period [8, 9]. A variable level of mitosis in different populations of thyroid cells of certain mammals has been found during postnatal ontogeny [3, 9] and also under the influence of experimental procedures [4, 5, 7, 11, 12].

The object of this investigation was to study and compare circadian rhythms of function and mitotic activity of the thyroid gland of albino rats under normal conditions and after resection of the gland giving rise to changes in the metabolism of its cells.

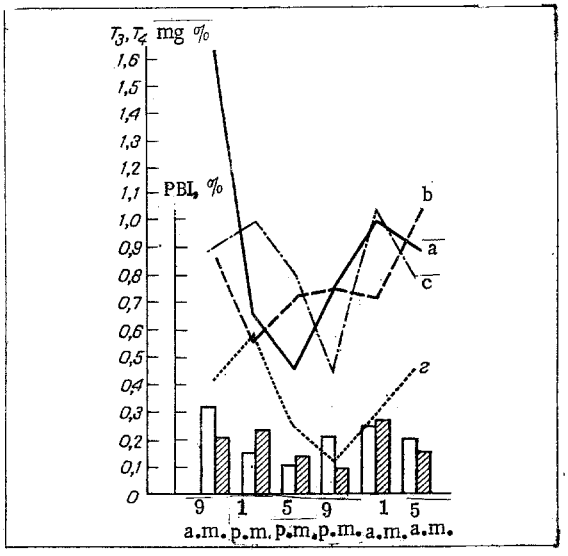

Fig. 1. Circadian rhythms of thyroid function in albino rats: a) Thyroxine (T_4); b) tri-iodothyronine (T_3) in blood plasms of intact animals; c and d) the same hormone on the 5th day after resection of the thyroid gland. Unshaded columns – PBI before resection, shaded columns – PBI after resection of the gland. Here and in Fig. 3: abscissa, time.

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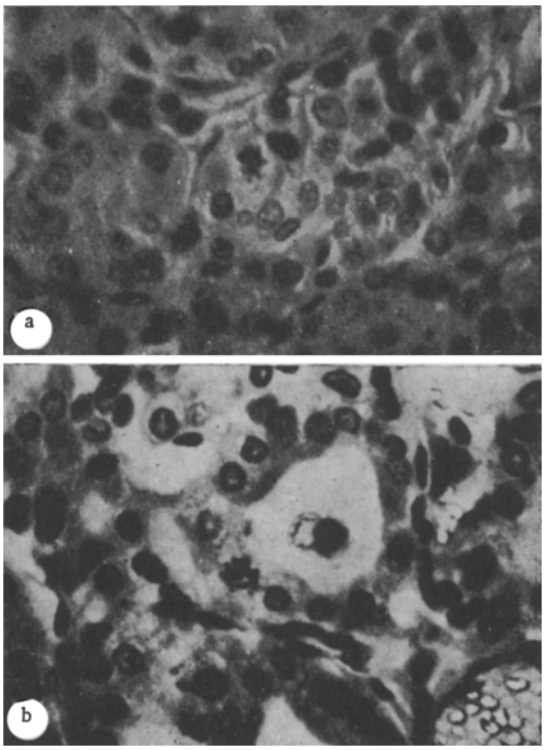

Fig. 2. Proliferation in the thyroid gland: a) Mitosis of epithelial cells in zone of resection; b) division of thyrocytes of small follicles in "uninjured" zone of thyroid gland (5 days after resection). Hematoxylin-eosin, 200×.

EXPERIMENTAL METHOD

The investigation was carried out in May and June on 80 sexually mature male rats with a mean weight of 245 ± 12.6 g, kept under identical conditions in the animal house. The animals of group 1 were intact, and those of group 2 underwent resection of two-thirds of the thyroid gland (5 days). The animals were killed at intervals of 4 h during the 24-h period: at 9 a.m., 1, 5, and 9 p.m., and 1 and 5 a.m. (from 5 to 7 animals at each time). To assess the state of thyroid function, blood levels of protein-bound ^{131}I (PBI), thyroxine (T_4) and tri-iodothyronine (T_3) were determined by means of Rez-o-Mat kits. The thyroid glands were fixed in Carnoy's fluid and embedded in paraffin wax. The number of mitotically dividing cells was counted in sections 5-7 μ thick, stained with hematoxylin-eosin (50,000-60,000 cells at each time). Considering the heterogeneity of differentiation and morphological properties of the thyroid epithelium of the different structural units, the mitotic index (MI) was calculated in promille for the whole gland, and also for cell populations of interfollicular islets, and small (under 25 μ in diameter), medium-sized (under 55 μ), and large (over 55 μ) follicles. MI in the resected gland was studied separately for the zone of resection and for the "uninjured" rest of the gland.

EXPERIMENTAL RESULTS

In intact animals a rhythm of thyroid function could be clearly discerned during the 24-h period. The highest concentrations of PBI, T_3 and T_4, for instance, were observed between 1 and 9 a.m., and at other times the hormone levels were relatively stable (Fig. 1).

Mitotic activity of the glandular cells reached its highest levels at 1 p.m., i.e., at a time of a fall in the blood hormone levels. Consequently, negative correlation exists between the proliferative and hormone-forming activity of the thyroid cells of adult animals. The results of calculation of the mitotic index for different cell populations are summarized in Table 1. Most mitoses in all cases occurred in thyrocytes of the interfollicular islets, which are regarded as the main source of formation of new functional units of the gland [2, 4]. The only exception was at 5 p.m., when proliferative processes were about equal in the interfollicular cells and in the small follicles. Mitotic activity of thyrocytes of medium-sized and, in particular, of large follicles was low throughout the 24-h period.

The level of thyroid function five days after resection was altered (Fig. 1c, d). The levels of endogenous T_4 and T_3 on the whole were lower and reached minimal values at 9 p.m.; the transport-organic phase of hormone production of the resected thyroid gland likewise was not compensated (as shown by the PBI level). Proliferative and morphogenetic processes were well defined in the gland, evidence of development of regenerative hypertrophy of the thyroid gland (Fig. 2). The follicular epithelium was hypertrophied, the height of the thyrocytes of the intact group was $4.5 \pm 0.12\ \mu$, and five days after resection it was $6.5 \pm 0.21\ \mu$ ($P < 0.005$). A significant increase in mitotic activity of the thyrocytes was found in the zone of resection and in the uninjured part of the gland, rising to peaks at 9 a.m. and 9 p.m., whereas the minima of cell division (as in the intact animals) occurred at 1 and 5 a.m. (Fig. 3). The main source of proliferation was cells of the interfollicular islets and small follicles. However, cell proliferation also was increased in medium-sized and even in large follicles (Table 1), as was most clearly seen during the period of maximal mitotic activity (9 a.m.). Multinuclear cells could be seen in the walls of individual follicles.

TABLE 1. Mitotic Activity (in promille) of Epithelial Cells of Normal and Regenerating Albino Rat Thyroid Gland

Group of animals	Time of day	MI	MI in cell populations			
			interfollicular epithelium	small follicles	medium-sized follicles	large follicles
1	9 a.m.	0,849	0,545	0,180	0,098	0,026
	1 p.m.	1,544	1,315	0,128	0,096	0,005
	5 p.m.	0,523	0,183	0,202	0,080	0,058
	9 p.m.	0,618	0,486	0,069	0,043	0,020
	1 a.m.	0,363	0,134	0,106	0,096	0,027
	5 a.m.	0,183	0,104	0,059	0,020	—
	$M \pm m$	0,680±0,19	0,461±0,17	0,124±0,02	0,072±0,01	0,02±0,005
2. In region of resection	9 a.m.	3,912	2,734	0,667	0,420	0,091
	1 p.m.	2,038	1,365	0,409	0,184	0,080
	5 p.m.	1,372	0,646	0,545	0,161	0,020
	9 p.m.	1,445	0,834	0,384	0,187	0,040
	1 a.m.	0,514	0,365	0,126	0,020	0,003
	5 a.m.	0,491	0,445	0,040	0,006	—
	$M \pm m$	1,628±0,5	1,064±0,36	0,362±0,10	0,163±0,05	0,04±0,01
In uninjured part	9 a.m.	2,915	1,705	0,659	0,441	0,110
	1 p.m.	1,135	0,547	0,264	0,276	0,048
	5 p.m.	1,722	0,522	0,940	0,196	0,064
	9 p.m.	2,046	0,626	1,126	0,190	0,104
	1 a.m.	0,291	0,230	0,056	0,05	—
	5 a.m.	0,461	0,300	0,146	0,10	0,005
	$M \pm m$	1,428±0,4	0,655±0,19	0,532±0,20	0,194±0,06	0,055±0,01

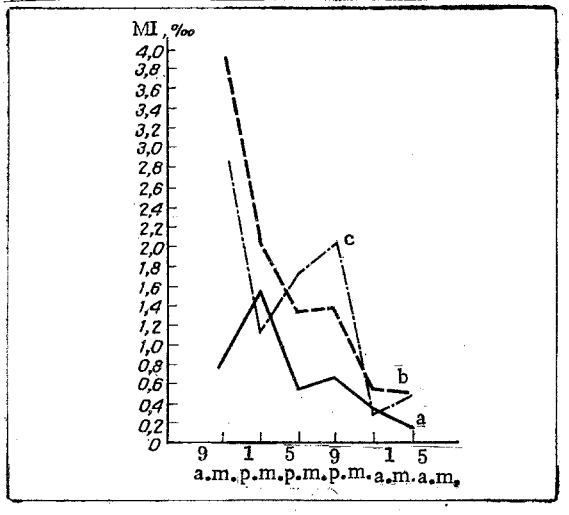

Fig. 3. Circadian rhythms of mitotic activity of thyroid gland of albino rats 5 days after resection: a) intact group; b) zone of resection; c) remainder of gland.

In the intact and resected albino rat thyroid gland a diurnal rhythm of functional and mitotic activity is thus observed. Differences in the proliferative properties of different cell populations of the thyroid parenchyma are observed in repair processes associated with physiological renewal and reparative regeneration.

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