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PAPER

GOITRE INVOLUTION : IODIDE AS AN HYPERVASCULARITY ANTAGONIST

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ABSTRACT

Goitre involution was studied in rats during an iodide refeeding period. A first phase (day 0-8) was characterised by a dramatical regression of the hypervascularity, which was induced by plasma iodide, but was thyrotropin independent. During a second phase (day 8-90), follicle formation occured, associated with the increase of the interstitial tissue in the gland and controlled by the plasma thyrotropin concentration.

INTRODUCTION

In the human, thyroid hyperplasia, hypertrophy, hypervascularity and lack of thyroglobulin (Ramalin-Gaswami, 1964) can be induced by chronic high plasma thyrotropin concentration caused by low dietary iodide. This physiopathological state (hyperplastic goitre) can also occur in mice (Denef et al.,1981) or rats (Wollman et al.,1978).We studied goitre involution in rats by biochemical and stereological methods during a period of 3 months.

MATERIALS AND METHODS

Male Wistar rats were given a low iodide diet (LID:Remington)during 6 months. During the last 2 months,propylthiouracil (PTU:0.15 %w/w) was added to the LID. At the end of this treatment, the LID was continued whereas PTU was removed and iodide given again in the drinking water (2.24 µg of 127 I/ml). The rats were sacrified on day 0 (the last day of LID) and during the iodide refeeding period on days

1,2,4,8,16,30, and 90. The control group received LID and iodide containing water during 6 months and were sacrified at the end of this period.

Biochemical techniques :the thyroids were homogenized in Tris buffer 0.1M,pH 7.0. Thyroglobulin (TG) was determined by the Lowry technique(Lowry et al.,1951).Deoxyribose (DNA) was dosed according to Burton (1955).Plasma thyrotropin(TSH) concentration was evaluated by radioimmunoassay(Berthier and Lemarchand-Beraud, 1978). Plasma iodide was determined by a colorimetric method.

Stereological techniques : the thyroid glands were fixed in phosphate-buffered (0.177M,pH 7.3) glutaraldehyde (2%) and embedded in paraplast. 40 micrographs were obtained by systematic subsampling of 4 sections per lobe with a random point lattice. A simple square lattice test system was used to estimate volume- and surface density (V_V and S_V) at a magnification of 600.

RESULTS

Biochemical results (table) : thyroid TG concentration did not vary significantly during the first 8 days, but thereafter increased to reach control values (C.V.) on day 90. Total thyroid DNA content was high and stationary during the first 8 days,thereafter it decreased to reach on day 30, a level 2 times higher than the control value. Plasma TSH concentration was very high (10 x C.V.) during the first 8 days and then strikingly decreased. It reached control values on day 90. Plasma iodide concentration was undetectable on day 0. It increased dramatically on day one

Iodide refeeding (days)	Thyroglobulin µg/ml	Deoxyribose µg/gland	Plasma TSH concentration µg/ml	Plasma iodide ng ^{127}I/ml
0	15.0 ± 2.5	43.0 ± 1.2	2.33 ± 0.09	< 2.5
1	18.0 ± 2.2	42.5 ± 2.0	2.46 ± 0.23	224.0 ± 22
2	14.0 ± 2.1	39.0 ± 5.6	2.30 ± 0.40	240.0 ± 32
4	12.1 ± 2.0	40.8 ± 3.6	2.68 ± 0.15	240.0 ± 34
8	19.5 ± 2.1	43.6 ± 2.6	2.20 ± 0.95	230.0 ± 18
16	24.0 ± 3.3	31.2 ± 2.5	0.50 ± 0.02	220.0 ± 30
30	33.5 ± 3.1	19.0 ± 3.2	0.20 ± 0.04	165.0 ± 20
90	57.5 ± 6.2	19.2 ± 2.0	0.15 ± 0.05	80.0 ± 20
Control	66.1 ± 4.3	8.0 ± 1.8	0.15 ± 0.06	110.0 ± 23

Table - Concentration of thyroglobulin (Tg), deoxyribose (DNA), plasma TSH, and plasma iodide (mean ± s.e. from 4 rats) during an iodide refeeding period

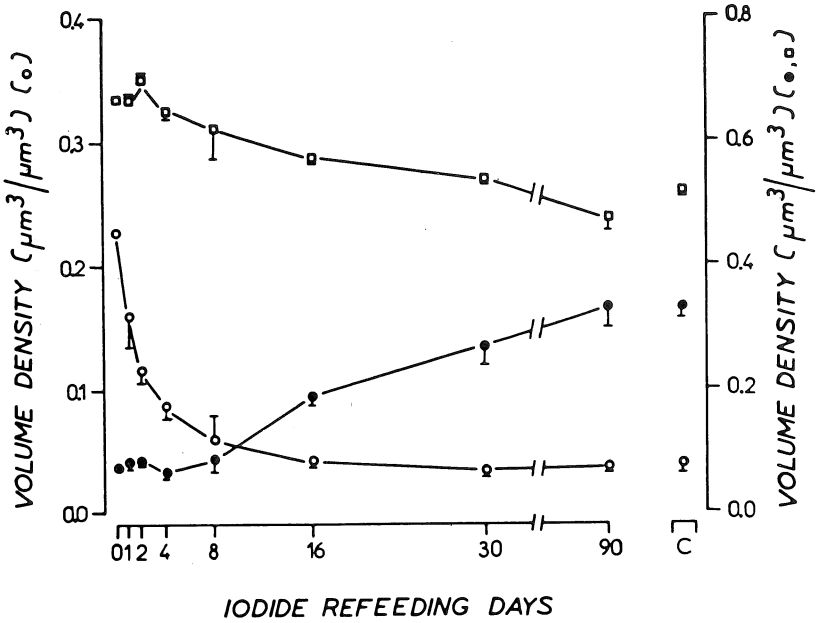

Fig. 1 -Evolution of volume density of colloid lumina (●), follicular cells (□) and vessels (o) (mean ± s.e. from 4 rats) during an iodide refeeding period

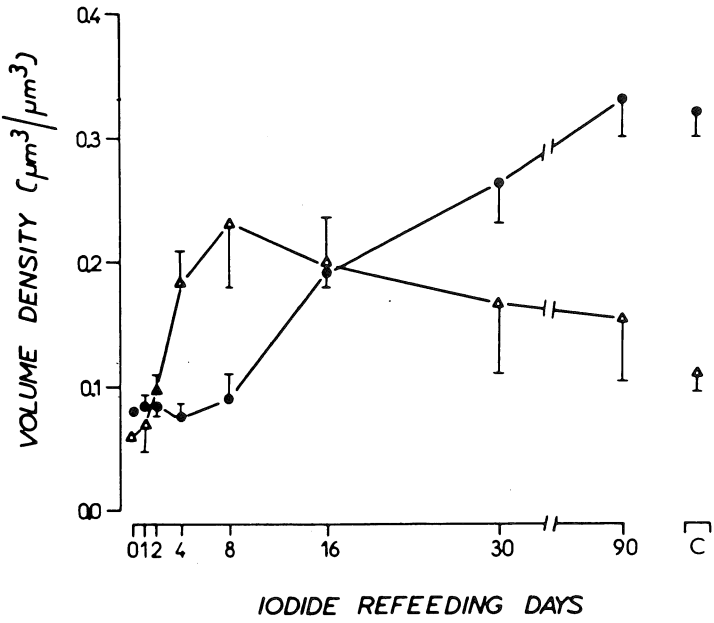

Fig. 2 -Evolution of volume density of interstitium (△) and colloid lumina (●) (mean ± s.e. from 4 rats) during an iodide refeeding period

(2 x C.V.) and then remained stationary until day 16. Thereafter it decreased and, on day 90 was slightly lower than in the controls.

Light microscopy and morphometry : on day 0, the thyroid was very enlarged and composed of epithelial cells and a small amount of colloid. Moreover it was hypervascularized. Thus a typical thyroid hyperplasia was observed. Subsequently changes occured, and on day 90, the glands' morphology had almost returned to normal. The V_V of colloid was practically constant until day 8, then it increased to reach control values on day 90 (Fig. 1). The V_V of the blood vessels (veins and capillaries) decreased between day 0 and 8 and reached control values on day 16 (Fig. 1). The V_V of the epithelium was high and practically constant during the first 8 days and then decreased slowly (Fig. 2). The V_V of the interstitial tissue increased between day 0 and 8 and thereafter decreased slowly (Fig. 2). The S_V of colloid lumina was low on day 0 (0.5 x C.V.) and remained stationary until day 8; thereafter it increased and reached control values on day 30 (Fig. 3). The S_V of the vessels was high on day 0. It remained at this level on day 1, and then decreased rapidly. On day 4, control values were reached (Fig. 3).

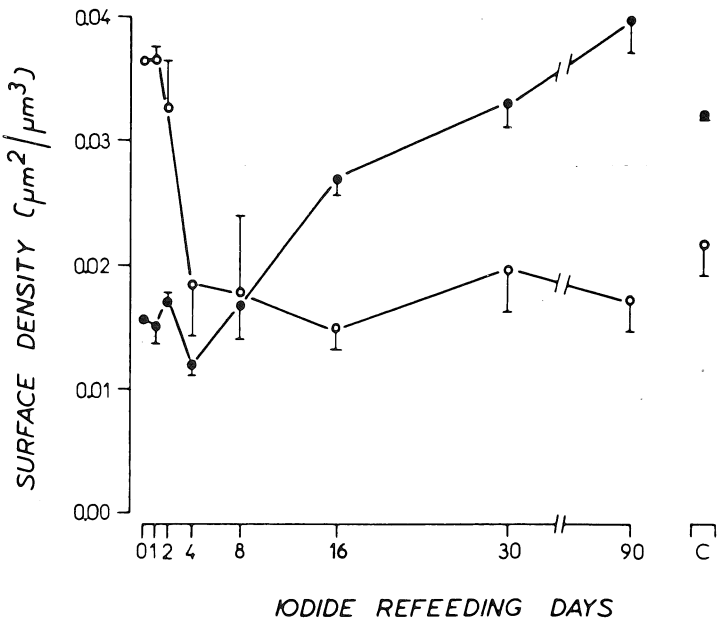

Fig. 3- Evolution of surface density of colloid lumina (●) and vessels (o) (mean ± s.e. from 4 rats) during an iodide refeeding period

DISCUSSION

Goitre hypervascularity results from the enlargment of capillaries, mainly induced by mitosis of endothelial cells and by fusion of adjoining wall of capillaries, (Wollman et al., 1978). Since hypervascularity gives to the gland a sponge like structure, no attempt was made to estimate the number of capillaries. Follicles are also very irregular in shape and the sphere model (Penel et al., 1981) cannot be applied to determine their size distribution. Nevertheless in our study, the most important of the different morphological parameters were the volume and surface area since they can be correlated to physiological parameters like fluxes of metabolites per unit surface area (Penel et al., 1981).

Denef et al. (1981) have shown a parallel evolution in the V_V of the thyroid vessels and the epithelium during two months of iodide deprivation. For the goitre involution, such a correlation was not observed since during the first 8 days of iodide refeeding, V_V of the vessels rapidly decreased whilst V_V of the epithelium did not change. Since during this period, the plasma TSH concentration was high and constant, it can be concluded that the thyroid vascular change was TSH independent but closely related to the plasma iodide concentration. The mechanism of iodide action could be the inhibition of secretion by the epithelial cells of substances like angiogenesis factor (Folkman, 1974). It must be emphasized that the parathyroid vascularity was not been modified despite its close proximity to the thyroid (unpublished observations). The decreased thyroid vascularity, by lowering the metabolite fluxes through the epithelial cells, could induce the death of some thyroid cells (Folkman, 1974), and thus could initiate an early goitre involution.

After 8 days, thyroid reorganization (neofolliculogenesis and filling with colloid of hyperplastic follicles) occured. It was linked to the TG pool accumulation and controlled by the decrease of the plasma TSH concentration. It must be emphasized that the V_V of the interstitial tissue reached a maximum value before the follicle formation began. This result suggests that the connective tissue could induce the organization of the thyroid (during the goitre involution) as recently shown by Alquier (1982) in the foetal rats.

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