Histol Histopath (1989) 4: 193-200

Histology and Histopathology

Down regulation of hypertrophied follicular cell volume in thyroid hyperplastic gland

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Summary. In the present study, changes in thyroid follicular cell volume and its regulation have been investigated during the early involution of a hyperplastic goitre. Male Wistar rats were administered an iodine deficient diet for 6 months with propylthiouracil (PTU, 0.15%) during the last two months. At the end of iodine deficiency (day 0), some rats were killed and the others received a normal iodine diet. These rats were killed after different periods of iodine refeeding. Thyroid follicular cell volume was very high in hyperplastic gland whereas thyroid protein concentration was low. Thyroid follicular cell volume quickly decreased when rats were normally iodine refed, whereas thyroid protein concentration increased.

Electron microscopal observations showed that thyroid follicular cells retained their endocrine aspect in hyperplastic state and throughout the iodine refeeding period. Using concomitant stereological and biochemical techniques, it is shown that the amount of cellular iodide and an unknown iodinated compound strongly increased during the early iodine refeeding. Plasma TSH was high on day 0 and remained at this level until day 8 whereas plasma T3 and T4 were low on day 0 and remained at this low level until day 4.

The present data show that the involution of thyroid follicular cell volume is induced by iodide and mediated by an iodinated compound at least in the initial phase, and is independent of plasma TSH, T3, T4, so indicating the involvement of a thyroid autoregulatory mechanism. These changes in cell volume may be of importance in ion transport, i.e. in the metabolism of thyroid follicular cell during the early involution of the hyperplastic goitre.

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Key words: Thyroid, TSH, T3, T4

Introduction

It is well known that thyroid enlargement , which occurs during low iodine diet (Astwood and Bissel, 1944; Studer and Greer, 1965; Todd, 1986), is linked to follicular cell hyperplasia, hypervascularization, and follicular cell hypertrophy. Whereas thyroid hyperplasia (Santler, 1957; Sheline, 1969; Christov, 1985; Rognoni et al., 1986) and hypervascularization (Gorbman, 1947; Wollman et al., 1978; Ericson and Wollman, 1980; Zeligs and Wollman, 1981) are now well documented, very few studies have contributed to the knowledge of the regulation of thyroid follicular cell volume (Philp et al., 1969; Chow and Woodbury, 1965; Many et al., 1985).

This phenomenon has been related to cell water imbibition under TSH stimulation in vitro (Bakke et al., 1957) and in vivo (Solomon, 1961).

In this work, we have investigated the effect of iodide on thyroid follicular cell volume during the early phase of iodine refeeding of severly iodine deficient rats; during this period plasma TSH and iodide concentrations are very high and plasma T3 and T4 are low (Rognoni et al., 1982a).

Materials and methods

72 male Wistar rats were fed with low iodine diet (Remington and distilled water) for 6 months. During the last 2 months, propylthiouracil (PTU, 0.15 %) was added to the diet. At the end of the period of iodine deficiency (day 0), the rats received iodide in distilled water (2.235 µg of ^{127}I/ml) whereas Remington diet continued and PTU was withdrawn. The rats were killed on day 0 (just before iodine refeeding) and 1, 2, 4, 8, and 16 days after iodine refeeding. A group of 8 rats killed after 6 months of normal iodine diet served as a control

group. The experimental and control groups were subjected to a long term ^{125}I labelling by iodinated drinking water at a specific radioactivity of 0.15 $\mu Ci/\mu g$ ^{127}I.

After neck dislocation rats were exsanguinated; plasma were stored at -20°C. Thyroid glands were quickly excised, weighed and homogenized at 4°C in Tris-HCl buffer (pH 7.0) containing Triton X-100,0.4% methymazol ($5x10^{-2}M$), and mononitrotyrosin ($10^{-3}M$). Thyroid iodide and iodine bound on protein were separated by paper electrophoresis in acetate pyridine buffer (pH, 3.55). To determine the cellular iodide concentration, we have hypothesized that the colloid iodide amount is very low taking into account that this morphometric compartment is practically inexistent in hyperplastic goitre until day 4 of iodine refeeding (Rognoni et al., 1982b). In order to investigate some early iodinated compounds, an aliquot of 100,000 x g supernatant originating from the homogenate was submitted to 3.5% polyacrylamide gel electrophoresis in 0.5 M Tris glycine pH 8.4 during a 30 minute run.

Total thyroid protein was determined by the technique of Lowry (1951) and expressed in µg of protein per milligram of gland. Plasma iodide was separated from PBI on Sephadex G25 in ammonium acetate buffer (0.2 M, pH 5.8). Iodine was determined by chemical procedure (Daugeras et al., 1976; Bastiani and Simon, 1977). Plasma TSH, T3 and T4 were determined by RIA as previously described (Berthier and Lemarchand-Béraud, 1978). In order to determine the thyroid follicular cell volume, thyroid glands were fixed for 24 hours in glutaraldehyde 2.5%, 0.177 M phosphate buffer. 5 µm slices were stained by hematoxyline-eosine colouration.

Fifty micrographs were obtained from six systematic sections per lobe by a regular, periodic system of quadrants superimposed at random on each section (Cruz-Orive and Weibel, 1980). A simple square lattice system (test area: 150 cm^2; number of test points: 150; distance between test points: 1 cm) was used to estimate stereological parameters at a magnification of 944. Volume density V_V was calculated for epithelium (V_{VE}) using the formula

$$V_{VE} = \frac{P_A}{P_T}$$

where P_A is the number of points found on morphological compartment (epithelium) and P_T the total number of points found on the analyzed part of the photography. The density of thyroid follicular cells was estimated from the density of the follicular cell nuclei N_V calculated by the Floderus (1944) relationship

$$N_V = \frac{N_A}{(D + t)}$$

where N_A is the numerical profile density of nuclei obtained by counting in a section plane; t, the section thickness and D the mean nucleus diameter. The section diameter of nuclei was measured with a Hewlett-Packard digitizer (9874 A). D was obtained from the size distribution of the nuclei sections considered as spherical (Penel et al., 1982), by a modified Wicksell method (Penel et al., 1981). The thyroid follicular cell volume was equal to V_{VE}/N_V. Stereological parameters were obtained by computing the original values on a Hewlett-Packard calculator (9825 A). For electron microscopical observations, small blocks of glands were fixed in glutaraldehyde (2.5%, phosphate buffer, pH 7.3) and postfixed in osmium (2%). The tissue was thereafter dehydrated in acetone and embedded in Epon. Thin sections were stained in uranyl acetate and lead citrate, and viewed by a Jeol 100 C (Department of Electron Microscopy of University of Aix-Marseille I). Statistical analyses were performed using Student's t test.

Results

Histological observations and stereological data

At the end of iodine deficiency a hyperplastic goitre was obtained. The weight of the gland was strongly increased (115 ± 5 versus 17 ± 2 mg in control gland). Thyroid gland was hypervascularized and appeared to be chiefly constituted by hypertrophied follicular cells whereas colloid had almost disappeared. Lysosomes, mitochondria and golgi apparatus (Fig. 1) were normally present. However, endoplasmic reticulum was hypertrophied with very dilated cisternae. Microvilli were no more developed than in follicular cells of normally iodine fed rats (control rats, Fig. 3). The mean cell height (measured with a magnification of 6,000) was very high as compared to the control value (20 ± 3 µm versus 9.5 ±1.5 µm). Their volume was increased two fold (Fig. 4) whereas the volume of the nucleus was 40% higher as compared to the control value (97.4 ± 1.14 μm^3 versus 59.6 ± 0.92 μm^3).

At the onset of iodine refeeding, the goitre started to involute early, since after 8 days of iodine refeeding the weight of the gland was no more than 70 ± 3 mg. After this delay, (Fig. 2), the general aspect of the follicular cell was similar to that observed in control rats (Fig. 3). Whereas endoplasmic reticulum was still developed, cisternae were much less dilated than before the iodine refeeding (Fig. 1). Lysosomes, mitochondria and microvilli were normally present. The height of the cell had strikingly decreased since it had reached the control value (10.5 ± 2 µm, see also Figs. 1, 2, 3). Similar observations could be described for the case of 16 days of iodine refeeding (not shown). The volume of follicular cell (Fig. 4) markedly decreased soon after the iodine refeeding (on day 1) and then progressively until day 16 at which time it reached the control value, whereas the volume of the nucleus decreased progressively reaching a similar value (64.8 ± 0.96 μm^3) to the control value (59.6 ± 0.92 μm^3).

Biochemical data

The total thyroid protein concentration (Fig. 4) was low before iodine refeeding (day 0): 88.8 ± 4.8 versus 164 ± 5.3 µg/mg. It increased quickly to reach on day 8, 150% of the day 0 value and more slowly later on. The plasma iodide (Fig. 4) was undetectable on day 0 (< 2.5 ng ^{127}I/ml), its concentration strongly rose on day 1 (215 ± 30 versus 110 ± 17 ng ^{127}I/ml in control rats) and remained at this concentration until day 16. The iodide cell content and the iodide cell concentration (Table 1) were very low on day 0 as compared to the control value. On day 1 and 2, these parameters markedly increased (respectively, 28 and 37 times), and later on decreased, remaining however, above the control value on day 4. When an aliquot of a thyroid 100,000 × g supernatant was analyzed by polyacrylamide gel electrophoresis either on day 0 or during the first days of iodine refeeding, iodide migrated quickly and was no longer in the gel.

However, a peak of radioactivity was detected ahead the bromophenol blue whereas ^{125}I T3, MIT, T4 and DIT migrated behind. After elution of the compound «X» and iodine chemical determination its amount and its SRA were determined. Compound «X» was already

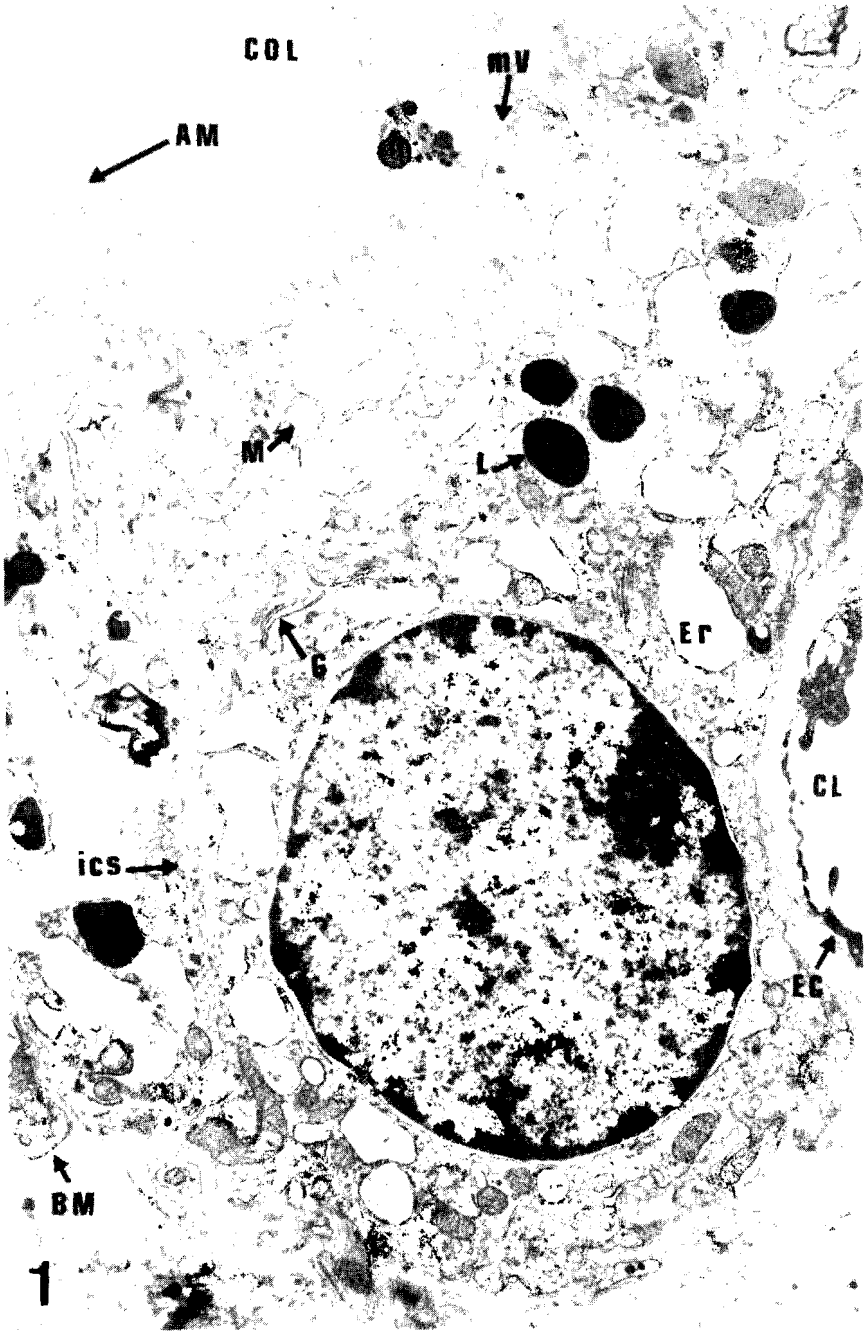

Fig. 1. Typical thyroid follicular cell of rats which have been previously iodine deficient (day 0). Rats were iodine deficient during 6 months. During the last two months propylthiouracil (PTU) was added to the diet. At the end of iodine deficiency (day 0), rats received iodine in drinking water (2.235 µg/ml) whereas PTU was withdrawn. COL: colloid; MV: microvilli; AM: apical membrane; Er: endoplasmic reticulum; L: lysosomes; G: golgi apparatus; M: mitochondria. BM: basal membrane; ICS: intercellular space; CL: capillary lumen; EC: endothelial cell; note the very dilated cisternae, and the large size of cell. × 15,000

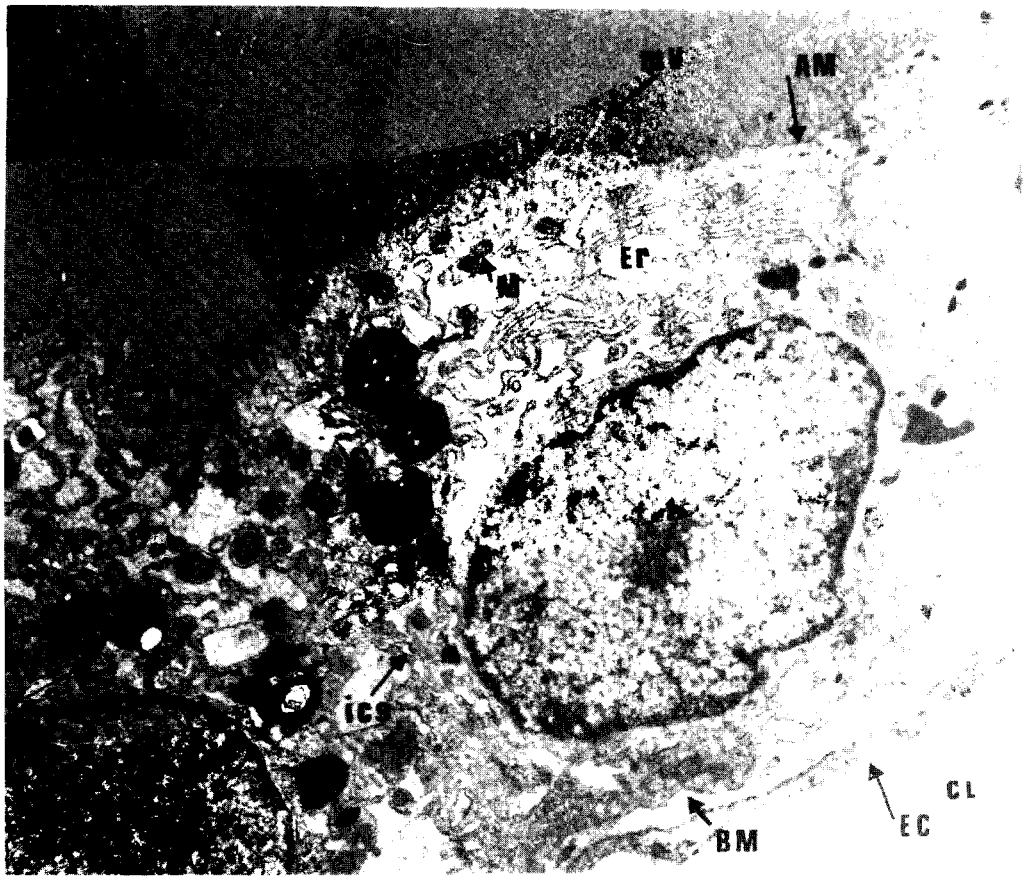

Fig. 2. Typical thyroid follicular cell of rats which have been iodine deficient and normally iodine refed for 8 days. For more details see legend of figure 1. × 15,000

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Fig. 3. Typical thyroid follicular cell in normally iodine fed rats. For more details see legend of figure 1. × 15,000

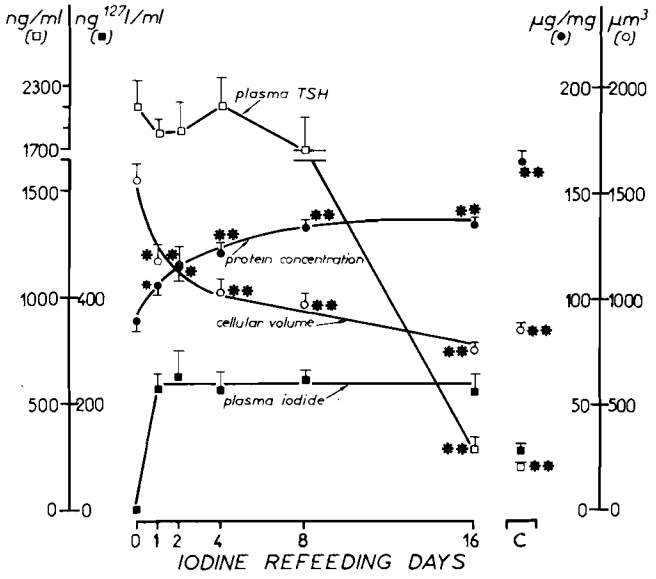

Fig. 4. Follicular cell volume, total thyroid protein, plasma TSH, and plasma iodide concentrations during the iodine refeeding of rats previously iodine deficient. The volume of thyroid follicular cell was expressed in μm^3 (○), the total protein concentration in μg/mg (●), plasma TSH concentration in ng/ml (□), and plasma iodide in ng of ^{127}I/ml (■). The value represents the mean ± SE. Statistical analyses were performed by Student's t test. Different from day 0 value: ⁎ $p < 0.05$; ⁎ $p < 0.01$; ⁎⁎ $p < 0.001$. For the number of determinations see Table 1.

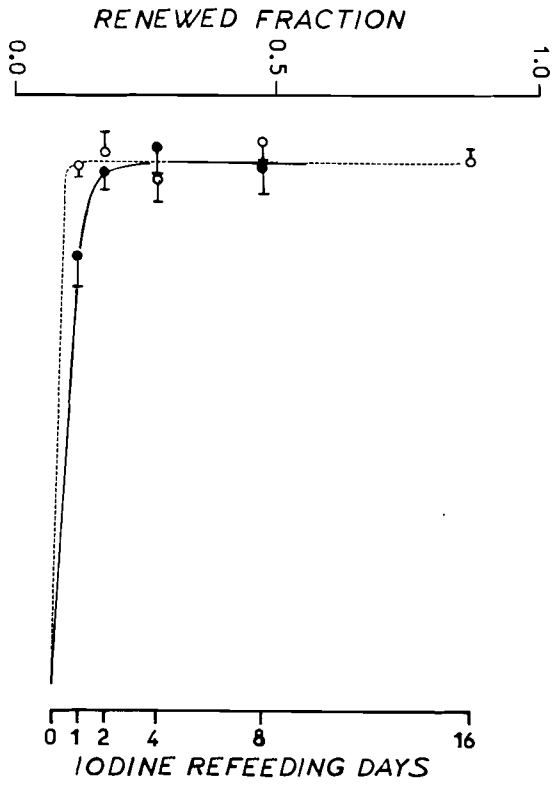

Fig. 5. Evolution of the renewed fraction of the thyroid iodide and iodinated compound «X». The rats were fed with 50 μg ^{127}I during 16 days after an iodine deficient (6 months, last day : 0). The specific radioactivity was calculated in each assay as the ratio of ^{125}I amount measured on a two channel Packard Autogamma spectrometer, and the ^{127}I chemically determined. The value for thyroid iodide (o) and for compound «X» (●) represent the mean ± SE. For the number of determinations see table 1. For more details see legend of figure 1.

Table 1. Cellular iodide and compound «X» amount during the iodine refeeding of rats which have been previously iodine deficient. The cellular iodide and compound «X» were expressed in fg of ^{127}I/cell and in fg of $^{127}I/\mu m^3$. Statistical analysis: different from day 0 value, ⁎ $p < 0.01$; ⁎⁎ $p < 0.001$. For more details, see legend on figure 1 and figure 5.

IODINE REFEEDING (DAYS)	n	CELLULAR IODIDE fg ^{127}I/cell	CELLULAR IODIDE 10^{-3}fg $^{127}I/\mu m^3$	COMPOUND «X» fg ^{127}I/cell	COMPOUND «X» 10^{-3}fg $^{127}I/0m^3$
0	6	3.6 ± 0.5	2.3 ± 0.4	6.82 ± 0.72	4.4 ± 0.4
1	6	99.8 ± 12.1**	85.1 ± 7.5**	10.86 ± 0.75*	9.3 ± 0.8**
2	6	103.7 ± 10.8**	89.6 ± 9.5**	14.43 ± 1.15**	12.5 ± 0.9**
4	6	53.6 ± 4.5**	52.3 ± 4.8**	10.76 ± 0.98*	10.5 ± 0.9**
8	6	29.2 ± 3.2**	30.0 ± 3.6**	1.24 ± 0.25**	1.3 ± 0.1*
16	6	9.9 ± 1.5*	13.0 ± 0.9*	undetectable	undetectable
CONTROL	6	17.4 ± 1.6**	20.5 ± 1.8**	undetectable	undetectable

Table 2. Plasma T3 and T4 concentrations during the iodine refeeding of rats which have been previously iodine deficient. Plasma T3 and T4 were expressed in ng/ml. Statistical analysis: different from day 0 value: ⁎ $p < 0.01$; ⁎⁎ $p < 0.001$. For more details see legend of figure 1 and figure 4.

IODINE REFEEDING (DAYS)	n	T3 (ng/m1)	T4 (ng/m1)
0	6	0.24 ± 0.01	11.00 ± 1.78
1	6	0.21 ± 0.02	10.08 ± 0.56
2	6	0.17 ± 0.04	11.45 ± 0.84
4	6	0.18 ± 0.03	11.40 ± 2.02
8	6	0.80 ± 0.14*	18.12 ± 1.30*
16	6	0.73 ± 0.05**	30.95 ± 2.84**
CONTROL	6	0.74 ± 0.12**	53.63 ± 3.00**

present in hyperplastic gland before the iodine refeeding (Table 1). It increased strongly on day 1 and 2 and then decreased to be undetectable on day 8. It was not detectable in control thyroid glands. Figure 5 shows that the curve relative to the renewed fraction of this compound is quite similar to that of thyroid iodide. It must be emphasized that on day 2 the pool of compound «X» is completely renewed. The plasma TSH concentration (Fig. 4) was very high on day 0, remained at this high level until day 8 and then had markedly decreased by day 16. The plasma T3 and T4 concentrations (Table 2) were low on day 0, remained so until day 4, and then had increased by day 8.

Discussion

Morphological observations and functional state of the hyperplastic thyroid gland

The changes of thyroid follicular cell volume have been studied in a biological model in which the hormone (TSH), well known to be responsible for the activation of this cell, was secreted at a high rate whereas plasma T3 and T4 were low and plasma iodide elevated (Rognoni et al., 1982a,b, 1986). The delay of 4 days observed for the secretion of T3 and T4 could be due to a pathological deficiency of follicular cells which have been chronically stimulated for a long time.

The ultrastructural observations showed that, in spite of its hypertrophy, the follicular cell retained almost all known characteristics of an endocrine cell. Moreover the large iodide trapping during the first 4 days, as is shown by the high iodide cell amount and iodide cell concentration, suggests that follicular cells, after a long iodine deficiency is in a good functional state at least for the iodide pump.

Iodide deficiency period

Two important processes probably linked to TSH stimulation seem to induce the hypertrophy of the thyroid follicular cell. One process depends on the increase of anabolism which is characterized by a larger membrane pool (present observations). The second process corresponds to cell water imbibition. Bakke et al. (1957) and Solomon (1961) have shown that TSH increases this phenomenon. More recently Chow et al. (1982) have pointed out that the percentage of thyroid follicular cell water strongly increased in methymazol treated rats. Moreover the total protein concentration was reduced in hyperplastic goitre (present data) as it was with acute TSH treatment (Chow et al., 1982). It must be also emphasized that in these pathological conditions an iodinated compound «X» was detected while it was not in the control glands. Moreover it is shown that its turnover is very high, so it is probably an early iodinated compound. It is also probably identical to the compound isolated by Spira et al. (1971) in vitro since both migrate very quickly in front of the bromophenol blue.

It has been shown recently that Na^+ K^+ ATPase acts as a driving force for transepithelial thyroid sodium transport (Penel et al., 1987a) which like in other systems, could be positively correlated to cell water volume (Macknight, 1985). Then thyroid Na^+ K^+ ATPase could be implicated in regulating the cell volume in these pathophysiological conditions since it has been shown that TSH stimulates this enzymatic system (Turkington, 1962; Chow et al., 1982).

Finally, in hyperplastic goitre, a larger cellular retention of thyroglobulin in dilated cisternae of endoplasmic reticulum could also induce an increase in cellular water amount, taking Gibbs-Donnan effect into account. This hypothesis is strengthened by the work of Baumont and Fragu (1985) who have shown that in similar iodine deficiency conditions, peroxydase positive exocytic vesicles, which are known to contain thyroglobulin molecules, accumulated at the apical pole of the cell.

Iodine refeeding period

When PTU was removed from the diet, it remained in the thyroid gland for four days (Cooper et al., 1983), allowing iodide to accumulate dramatically in the thyroid cell (37 and 40 times on day 1 and 2). A slightly amplified result was obtained when PTU was not withdrawn from the diet (data not shown here). This large amount of iodide entering the cell, which is transported iodide and not internal, was responsible for (i) the regulation of the iodide concentration as shown by Halmi (1964), (ii) the blocking of thyroperoxydase at the apical membrane (Wolff and Chaikoff, 1948, Wolff-Chaikoff effect); Pommier et al., (1973). This last process induced a latency in the T3, T4 neosynthesis and neosecretion and led to an unexpectedly extended period of TSH hypersecretion after the iodine refeeding had been started again.

During the iodine refeeding period the most striking result was the decrease of the follicular cell volume as early as the first day whereas plasma TSH and thyroid hormones were unchanged. The disappearance of a cell population, the volume of which would be larger, has been indirectly controlled since, with a ^{3}H-thymidine prelabelling experiment before iodine refeeding, only 0.64% of follicular cells were killed by iodide (Rognoni et al., 1986). Moreover the total population of follicular cells did not significantly change during the 16 days after the onset of iodine refeeding (Rognoni et al., 1986).

Using short iodine deficiency period Many et al. (1985) have also shown a decrease in follicular cell volume when animals are iodine refed. However in their work plasma iodide and TSH and thyroid iodide are not determined.

As early as the first day of iodine refeeding, the volume of the follicular cell decreased. Since the increase of protein concentration, which was not due to changes in thyroglobulin amount (15.3 ± 4.8 µg/mg on day 0 versus 16.8 ± 4.3 µg/mg on day 8) (Rognoni, 1980), closely matches the decrease of the cellular volume, a loss of water was likely, iodide or an iodinated compound

(Spira et al., 1971; Van Sande et al., 1975) being the first factor responsible for this phenomenon. From this point of view it has been shown that thyroid iodide acts in an opposite manner to TSH by decreasing the number of TSH receptors (Fayet and Hovsepian, 1977).

In this work, using concomitant stereological and biochemical techniques, it has been possible to evaluate the thyroid follicular cell iodide concentration in normal and physiopathologial conditions. Our data on cellular iodide agree with those of Penel et al., (1987a) determined by compartmental and stereological analyses.

The high level of plasma TSH observed during the iodine deficiency period implicates the role of this hormone in thyroid follicular cell hypertrophy. However the cell volume markedly decreased when the rats were iodine refed. It is remarkable that this process took place at a time of iodine refeeding when plasma TSH and thyroid hormones were unchanged relative to the goitrogenic period, whereas iodide level was markedly increased. This suggests an iodide dependant short loop regulation on the follicular cell volume. The fact that an iodinated compound «X», preexisting in hyperplastic gland, significantly increased in early iodine refeeding period allows us to hypothesize that the iodide effect is mediated by this compound.

Acknowledgements. The authors wish to thank Mrs Geneviève Rosselet for her valuable technical assistance. We are indebted to Mr Francis Beccherini and to Mr Jean-Jacques Roccabianca for their help in electron microscopy and in the realization of microphotographies. This work was supported by grants from the Association pour la Recherche sur le Cancer (ARC, contract n° 6534) and from Mr and Mrs Simonian (Marseille).

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Accepted November 11, 1988