CLINICAL STUDY

Development of the parafollicular cells in recurrent goiter

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Abstract

Objective: To provide more data for the discussion on whether thyroid hormones, iodide and other factors controlling the thyroid also influence the parafollicular (PF) cells, as the answer is of great importance for optimization of the medical treatment of medullary thyroid carcinoma (MTC) after surgery.

Design: We compared the density of the PF cells in patients who underwent surgery for the second time due to recurrent goiter with that in normal-sized thyroid glands after the first operation.

Methods: In 20 patients with only one operation, all specimens were taken from morphologically and functionally normal lobular thyroid parenchyma. The second group consisted of 30 patients who had already undergone a nearly total resection of at least one thyroid lobe several years before. Then another surgery of the same side was performed due to recurrent goiter. Immunohistochemical staining of the PF cells was performed using primary antibodies to calcitonin and chromogranin.

Results: An average of 78 PF cells (median 12.5) was found in the sections with the highest density of the first group. The average number of PF cells in the second group was just 5 (median 0). The Wilcoxon test revealed a highly significant difference in the total PF cell content between the groups P, 0.001†.

Conclusions: Our study suggests that the stimulating factors that lead to growth of the thyroid parenchyma do not influence the PF cells. Hence a non-suppressive thyroid hormone replacement seems to be sufficient after resection of an MTC.

European Journal of Endocrinology 144 485–489

Introduction

The question whether thyroid hormones, iodide and other factors controlling the thyroid, such as thyrotropin (TSH) or TSH-releasing hormone (TRH), also influence the parafollicular (PF) cells, is still discussed controversially (1–6). The answer, however, is of great importance with regard to the medical treatment of medullary thyroid carcinoma (MTC) after surgery.

Several studies suggest that TSH and TRH also regulate the PF cells. Some authors found mRNA for TSH receptors as well as for TRH receptors, Tg and even thyroperoxidase in PF cells and MTC (2, 7–9). Accordingly, a low TSH receptor expression was also detected in this tissue (10, 11). Another group showed that increased levels of TRH release calcitonin in normal PF cells as well as in MTC, similar to the effect of pentagastrin (12). Further, TSH leads to a discharge of serotonin in PF cells and MTC (4, 6, 13, 14). On the other hand, serotonin receptors have been detected on the FRTL-5 follicular cell line. Hence there is evidence that it may act as a paracrine factor controlling thyroid hormone release (15). Somatostatin, which inhibits serotonin excretion, was found to ameliorate a TSH-induced hyperthyroidism in patients with TSH-secreting adenomas (16). After administration of somatostatin, an injection of TSH in a thyroid artery during surgery leads to a significantly reduced increase of iodothyronines in the corresponding vein (17). Similarly, follicular thyroid cells also seem to be regulated by the blood calcium level (18).

However, some authors could not detect any TSH receptors in PF and MTC cells (1, 5, 19, 20). Other studies suggest that a stimulating effect of TRH on the release of calcitonin could only be observed in half of the cases (21) and that there is no influence of somatostatin on the stimulating effect of TSH in follicular cells (22).

Nevertheless, we can still assume that there are several interactions between follicular thyroid and PF cells, referring to the thyroid hormone release as well as to the calcium metabolism, which need to be further investigated.

In addition to functional aspects, it has been reported that high levels of TSH cause a hyperplasia of the PF cells (23, 24). Similar to the treatment of differentiated...
thyroid carcinoma, a TSH-suppressive hormone therapy may thus lead to a better prognosis after surgery of an MTC. However, usually a non-suppressive hormone replacement is still considered to be sufficient (25).

With this study, we tried to evaluate whether the usual factors that lead to growth of the thyroid also stimulate the PF cells, but without focusing on a specific aspect. Rather we looked at all factors in general by comparing the density of PF cells in patients who underwent surgery for the second time due to recurrent goiter with that in normal-sized thyroid glands after the first operation.

**Patients and methods**

**Patients**

This retrospective study included 50 patients. Twenty of them (19 women, 1 man) belong to the group with only one operation. In these cases, all specimens were taken from morphologically and functionally normal lobular thyroid parenchyma to prevent the density of the PF cells being influenced by alterations of the tissue. The volume of the resected lobes was either in the normal range or only slightly enlarged. Their average weight, which was measured after resection, was 8.8 g. Before surgery, six patients were treated with a thyroid hormone medication, five took a combination of thyroid hormones and low-dose iodide (50–150 µg/day) and one patient received a pure iodide medication at a dose of 200 µg/day. In the remaining eight cases, no thyroid medication was given. Surgery was performed due to circumscribed nodular changes suspicious of malignancy. In eight of these patients, a thyroid carcinoma was found intraoperatively.

The second group consisted of 30 patients (24 women, 6 men) who had already undergone a nearly total resection of at least one thyroid lobe several years before. Accordingly, only a small part of residual thyroid tissue had postoperatively been detected on the respective side. Then a second surgery of the same side was performed due to recurrent goiter. The average time span between the first and the second operation in this group, according to the time in which the recurrence developed, was 27 years. In four patients, the last intervention had already been preceded by two operations. In these cases, the period between the second and the last surgery was taken, as it represents the time in which the recurrence developed. The average weight of the finally resected lobes was 61 g. The last medication of the 30 patients directly before the second surgery was a thyroid hormone substitution (n = 23), an iodide supplementation (n = 1) or no medication (n = 6). However, in most cases, no treatment was performed for a long period before that time, which led to the development of the recurrence.

**Methods**

If the total weight of the resected thyroid lobe was up to 50 g, three blocks with a size of about 5 × 15 × 15 mm were obtained and embedded in paraffin. In the case of
a total weight between 50 and 100 g, and between 100 and 150 g, five and seven of these blocks respectively were preserved.

Immunohistochemical staining was performed with the alkaline phosphatase–anti-alkaline phosphatase technique using primary antibodies to calcitonin (polyclonal, 1:300; DAKO Diagnostika GmbH, Hamburg, Germany) and chromogranin (DAK-A3, 1:100; DAKO). For technical reasons, chromogranin antibodies were preferred, but the results have been confirmed by calcitonin antibodies, since it is known that a depletion of chromogranin can be observed in marginal regions of adenomas and under stress.

For quantitative assessment of the PF cell content of the specimens, all sections of the preserved blocks were examined for visualized PF cells. In the section with the maximum PF cell content, the number of PF cells within 1 cm$^2$ of the region with the highest PF cell density was counted. For further evaluation, only this highest count rate of the specimen was used.

Figure 2 Groups of PF cells (red) in a thyroid specimen of a patient after the first surgery, stained with antibody to chromogranin (magnification 20×12).

Figure 3 Distribution of different numbers of PF cells in the groups with first surgery or recurrent goiter.
Results
As expected, PF cells were not homogeneously distributed in the group with the first surgery. Rather they were observed in localized areas, whereas the surrounding tissue contained virtually no PF cells (Figs 1 and 2). Altogether, more than 99% of the PF cells of all investigated sections were concentrated within 1 cm². An average of 78 PF cells (range 0 to approximately 500, median 12.5) was found in the sections with the highest density. It was further observed that PF cells were only found in regular thyroid parenchyma. Adenomatoid lesions or carcinomas never contained any PF cells. The tissue of the patients with recurrent goiter always presented with severe adenomatoid changes. Accordingly, most of the investigated specimens did not reveal any PF cells at all. Only in 4 out of the 30 cases could PF cells be detected, and these were all located in small parts of regular, lobular thyroid parenchyma. In two of these cases, this normal tissue containing the PF cells was found peripherally rather than in a central part of the resected lobe. The average number of PF cells in the entire group was just 5 (range 0–70, median 0). However, the density of PF cells in the exploited 1 cm² of the section with the highest count rate showed no difference compared with that of the first group. The non-parametric Wilcoxon rank-sum test revealed a highly significant difference in the total PF cell content between the groups (0.001 > P > 0.0001). The total results are shown in Fig. 3.

Discussion
Recurrent goiter does not develop due to homogeneous hyperplasia of regular, lobular parenchyma, but predominantly by asymmetrical proliferation of nodular tissue, which principally did not contain any PF cells in either group. This explains why hardly any PF cells were found in the tissue of recurrent goiter. We therefore assume that the foci in the four cases of recurrence with detectable PF cells remained at the first surgery. This idea is further supported by the atypical, peripheral localization of the respective tissue in two of these specimens. In addition, as the density of the PF cells in the foci of recurrent disease did not differ from that in primary operated patients, we have evidence neither for a further proliferation nor for a ‘diluting effect’, i.e. a spreading of the remaining PF cells in larger parts of the recurrent tissue due to proliferation of the surrounding normal thyroid parenchyma.

The results suggest that the stimulating factors that lead to a growth of the thyroid parenchyma do not influence the PF cells. Hence after resection of an MTC or in the case of multiple endocrine neoplasia type 2, a suppressive thyroid hormone replacement does not seem to be required.

The fact that the resected thyroid lobes could not be examined in total, but a selection of the specimens was used due to the retrospective evaluation of the preserved samples, may be considered as a limitation of our study. This also explains why in some cases from the first group no PF cells were found either. However, considering that the specimens in both groups were chosen according to the same criteria, a major influence on the results is not to be expected.

Acknowledgements
The authors thank Professor Dr K-W Schmid, Department of Pathology, University Medical Center, Essen, Germany for supportive discussion.

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Received 17 October 2000
Accepted 25 January 2001