Lack of effect of somatostatin on iodothyronine release from the perfused canine thyroid

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Summary

1. This study has evaluated the effect of somatostatin (0·1 or 3 μg/ml) on the release of thyroxine, 3,5,3'-tri-iodothyronine and 3,3',5'-tri-iodothyronine from perfused thyroid lobes.

2. Somatostatin did not affect either the total release of iodothyronines or the ratio between various iodothyronines in thyroid effluent from unstimulated and thyrotrophic hormone stimulated thyroid lobes.

3. The results lend no support to the idea that somatostatin present in the parafollicular cells of the thyroid should have regulatory function on thyroidal secretion of iodothyronines.

Key words: iodothyronine, somatostatin, somatotropin, thyroid gland.

Abbreviations: \(T_3\), 3,5,3'-tri-iodothyronine; \(T_4\), thyroxine; TSH, thyrotrophic hormone; \(rT_3\), 3,3',5'-tri-iodothyronine.

Introduction

Somatostatin was initially discovered in the hypothalamus and characterized as an inhibitor of growth hormone secretion. However, it has subsequently been found to have an inhibitory effect on the secretion of several other peptide hormones, both pituitary and non-pituitary. Further, immuno-reactive somatostatin has been demonstrated in several non-pituitary tissues including the thyroid (Hökfelt, Efendić, Hellerström, Johansson, Luft & Arimura, 1975; Parsons, Erlandsen, Hegre, McEvoy & Elde, 1976; Van Noorden, Polak & Pearse, 1977; Yamada, Ito, Matsubara & Kobayashi, 1977; Kronheim, Berelowitz & Pimstone, 1976).

Controversy exists on whether somatostatin also has a direct effect on thyroid hormone secretion (Ahrén, Hedner, Melander & Westgren, 1977; Loos, Raptis, Birk Escobar-Jimenez, Meyer, Rothenbuchner & Pfeiffer, 1978; Ahrén, Ericsson, Hedner, Ingemansson & Westgren, 1978; Faber, Gormsen, Friis, Kirkegaard, Birk, Lauridsen, Nerup, Rogowski & Siersbæk-Nielsen, 1977). The aim of the present study was to elucidate this problem by using a sensitive and precise thyroid-perfusion model.

Material and methods

Thyroid perfusions were performed in six mongrel dogs weighing 22–30 kg. Since the two thyroid lobes are totally separate in dogs, both lobes could be perfused independently, one acting as a control of the other. The technique has been described in detail (Laurberg, 1976, 1977). Once-through perfusions were performed in situ with a synthetic medium. The flow rate for each thyroid lobe was kept at 0·63 ml/min. The duration of the perfusions was 200 min. Cyclic somatostatin [0·1 μg/ml (61 nmol/l) or 3 μg/ml (1·83 μmol/l)] was infused in one of the thyroid lobes during the interval 60–200 min. Both thyroid lobes received 10
mu\text{units of thyroid-stimulating hormone (TSH)/ml (bovine TSH, the international standard preparation, a gift from the Medical Research Council, London) during the interval 90–200 min. In different experiments somatostatin was administered alternately to the left and right thyroid lobe. TSH was added to the perfusion medium in the final concentration. Somatostatin was diluted in NaCl solution (150 mmol/l) to a concentration of 10 or 300 \mu\text{g/ml. This stock solution of somatostatin was pumped into the medium through a cannula penetrating a rubber membrane on the afferent catheter, at a rate of 6·3 \mu\text{l/min. Mixing was obtained in a small volume drop-chamber introduced after the addition of somatostatin. It was ascertained by dye-dilution studies that somatostatin was evenly distributed in the perfused thyroid lobe. Somatostatin was almost quantitatively recovered in the effluent when measured by radioimmunoassay (measurements of somatostatin were performed by Dr Hans Orskov).

T_4, T_3 and rT_3 in thyroid effluent and pronase hydrolysate of thyroid tissue were measured by radioimmunoassays (Weeke & Orskov, 1975, 1978; Laurberg, 1978a). All samples from one experiment were measured in triplicate in one assay.

Student's t-test for paired comparisons was applied for statistical analyses, a 5% limit of significance being used.

Results

The influence of 0·1 \mu\text{g of somatostatin/ml on thyroid iodothyronine secretion was investigated in two experiments. Somatostatin infusion did not influence the TSH-induced release of T_4. In the first experiment the basal T_4 release before somatostatin was: from the control lobe, 25 nmol/l; from the somatostatin lobe, 23 nmol/l; after 140 min of somatostatin infusion and 100 min of TSH at 10 \mu\text{units/ml, T_4 in effluent from the control lobe was 129 nmol/l and from the somatostatin lobe 108 nmol/l. In experiment 2 the basal T_4 release from the control lobe was 26 nmol/l and from the somatostatin lobe 28 nmol/l; after somatostatin and TSH, T_4 release from the control lobe was 150 nmol/l and from the somatostatin lobe 176 nmol/l. The release of T_3 and rT_3 was also nearly identical from the two lobes.

To exclude that a lack of effect could be due to the use of insufficiently high concentrations of somatostatin in this system in vitro and to exceed any possible concentration of somatostatin involved in a possible paracrine regulation of thyroid hormone secretion, subsequent experiments were performed with the higher concentration of 3 \mu\text{g of cyclic somatostatin/ml (—)}. The mean T_4 concentrations in effluent from four thyroid lobes receiving 3 \mu\text{g of somatostatin/ml and four control lobes appear in Fig. 1. Infusion of somatostatin in unstimulated thyroid lobes did not induce any alteration in secretion rate. Bovine TSH (10 \mu\text{units/ml) stimulated the release of T_4. There was no difference in latency period before response or in shape of the curves in lobes receiving somatostatin and control lobes. Neither total nor fractional increase in T_4 release was significantly altered by somatostatin infusion.

Ratios of T_4/T_3 and T_4/rT_3 in thyroid effluent and in pronase hydrolysates of the thyroid lobes in the four experiments where 3 \mu\text{g of somatostatin/ml was employed are given in Table 1. Both T_4/T_3 and T_4/rT_3 were higher in thyroid hydrolysate than in thyroid effluent. Infusion of somatostatin did not alter the T_4/T_3 or T_4/rT_3 ratios in effluent from unstimulated or TSH-stimulated thyroid lobes.

Discussion

Previous studies employing this preparation have revealed that a considerable part of the T_3 and rT_3 secreted originates from T_4 monodeiodinated during the secretion (Laurberg, 1978b). However, the fraction of T_4 disappearing during secretion is
Somatostatin and thyroid secretion

TABLE 1. Ratio between iodothyronines in thyroid hydrolysate and effluent from various periods of perfusion

In each experiment one thyroid lobe received somatostatin (3 μg/ml) for the period 60–200 min. Both thyroid lobes received TSH (10 μunits/ml) for the period 90–200 min. Ratios are mol/mol. There was no statistically significant difference between data from thyroid lobes receiving somatostatin and control lobes (paired t-test).

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<th>175–200 min</th>
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small since inhibition of intrathyroidal iodothyronine deiodination does not induce major alterations in T₄ secretion (Laurberg, 1978b). Thus T₄ in thyroid effluent can be considered as a measure of overall thyroid secretory activity, and the difference between the T₄/T₃ and T₄/rT₃ ratios in thyroid effluent and in the iodothyronine stores in thyroglobulin is a measure of intrathyroidal iodothyronine deiodination. In the present study neither overall thyroid secretory activity nor intrathyroidal iodothyronine deiodinating processes were affected by somatostatin.

It is well established that somatostatin affects the pituitary–thyroid system in intact man and animals by suppressing TSH secretion (Snow, Scanlon, Mora, Heath, Hall & Comez-Pan, 1978). On the other hand, there is some controversy on a possible direct effect of somatostatin on thyroid secretion. Ahrén et al. (1977) studied the effect of somatostatin on thyroid ¹²⁵I release from mouse thyroids in a modified McKenzie bioassay for thyroid stimulators. It was found that somatostatin reduced the blood ¹²⁵I increase in response to TSH, isoprenaline or dibutyryl-cyclic AMP slightly, but statistically significantly.

Loos et al. (1978) reported that somatostatin enhanced thyroid radiiodine uptake after injection of TSH into human subjects, and the appearance of labelled protein bound iodine in serum was inhibited. Further the increase in T₄ and T₃ in serum was inhibited slightly.

Ahrén et al. (1978) reported that somatostatin infusion inhibited the TSH-induced increase in thyroid hormones in human thyroid veins. Blood samples were obtained during operation for hyperparathyroidism or atoxic thyroid adenomas in patients pretreated with T₃.

On the contrary Faber et al. (1977) found no effect of somatostatin infusion on the TSH-induced increase in serum T₃ in man.

The reasons for the discrepancy in reported results are not obvious. Naturally, some could be due to species differences. However, somatostatin has been demonstrated in parafollicular cells of normal dog thyroids (Yamada et al., 1977) and it can be measured in effluent from the perfused canine thyroid (P. Laurberg & H. Ørskov, unpublished work). Various preparations of somatostatin have been used in the different studies. However, the preparation employed by Ahrén et al. (1977) and Faber et al. (1977) was obtained from the same source. The preparation of somatostatin used in the present study has proved effective in a number of studies in vivo and in vitro in our laboratory (Hansen & Lundbaek, 1976). The relatively short duration of the somatostatin infusion in the present study seems not to be the cause for the difference in results, since all the above-mentioned studies showing an effect of somatostatin on thyroid secretion have been short-term studies. Our use of bovine TSH for stimulation of thyroid secretion cannot be the cause either, since bovine TSH has been used for stimulation in all studies, and the concentration of TSH used in the present study does not exceed that employed in earlier studies.
The interpretation of experiments in vivo are difficult, owing to the possibility of alterations in the distribution and deiodination of peripheral iodothyronines. Studies employing measurements of the distribution and deiodination of peripheral iodothyronines in blood. Further, alterations in blood flow are difficult to check, especially when vasoactive agents like somatostatin are used. The blood flow are difficult to check, especially when vasoactive agents like somatostatin are used. The blood flow are difficult to check, especially when vasoactive agents like somatostatin are used. The blood flow are difficult to check, especially when vasoactive agents like somatostatin are used.

The results of the present study obtained under well-defined and controlled conditions lend no support to the idea that intrathyroidal somatostatin modifies thyroidal secretion of iodothyronines. However, since treatment with somatostatin has been shown by some investigators to have an effect on thyroid secretion, it is possible that infusion of somatostatin can have some indirect effect on thyroid secretion.

Acknowledgments

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