Failure of exogenous secretin to induce secretion of calcitonin in man

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Abstract. The effect of secretin on calcitonin secretion from the human thyroid gland was studied in 15 patients undergoing thyroid and parathyroid surgery. Secretin was administered into the inferior thyroid artery at two different doses (0.75 and 7.5 CU) and into a peripheral vein at a dose of 75 CU. Blood samples for measurements of calcitonin and calcium were collected from thyroid or peripheral veins. However, neither intraarterially nor iv administered secretin was able to evoke any significant calcitonin response as measured in thyroid or peripheral venous blood. The calcium level was unaffected by secretin. The results demonstrate that secretin does not act as a calcitonin secretagogue in man.

The role of calcitonin in the regulation of calcium homeostasis is still a matter of controversy in spite of 20 years of active research (Austin & Heath 1981). An important physiological role for calcitonin has been proposed by Talmage et al. (1980). According to their hypothesis calcitonin is released post-prandially in order to direct calcium, obtained by intestinal absorption into bone fluid and thus opposing the action of parathyroid hormone. A functional axis between the thyroid and the gastrointestinal tract has been postulated, but the physiological messenger is still not clearly defined. Several gastrointestinal hormones have the ability to release calcitonin from the thyroid C-cells and have been proposed as physiological secretagogues (Care et al. 1971; Cooper et al. 1978; Heath & Sizemore 1977; Parthemore & Deftos 1978). However, it is doubtful if the physiological serum levels of these gut hormones are of such magnitude that they can elicit release of calcitonin as measured in peripheral blood. Following selective stimulation of the thyroid by injection of secretagogues in a thyroid artery and blood sampling from a thyroid vein quite remarkable increments of thyroid venous calcitonin are registered and these alterations pass undetected in peripheral venous blood (Ericsson et al. 1981a,b). Thus it can not be excluded that the physiological post-prandial levels of gut hormones can induce calcitonin secretion, not detectable in peripheral blood. Recently Sethi et al. (1981) have proposed secretin as a secretagogue to calcitonin and parathyroid hormone secretion in man.

The aim of present investigation was to establish the role of secretin as a secretagogue to calcitonin release in man by means of our peroperative method for thyroid stimulation (Ericsson et al. 1981a).

Patients and Methods

Patients
A total of 15 patients (12 women and 3 men) were included in the study. Their age ranged from 30 to 79 years (mean 49 and median 44 years). Three patients had mild hyperparathyroidism due to a single parathyroid adenoma and S-calcium was in no case exceeding 2.8 mmol/l. The remaining 12 patients had different surgical procedures due to follicular adenoma or small nodular goitres. The patients were divided into three groups, which did not differ from each other as to number, age, sex and diagnosis.

The study was approved by the Ethical Committee of
the University of Lund and all patients gave informed consent to participate in the study. No complications were noted.

Experimental performance and protocol
The investigations were performed during thyroid and parathyroid surgery. The experimental model has been described previously (Ericsson et al. 1981a). Briefly, after exposure of the thyroid gland the inferior thyroid artery was dissected free and used for intraarterial (ia) injection of porcine GH secretin (Secretin®, Kabi Diagnostica, Stockholm, Sweden). Thyroid venous blood samples were obtained from a thyroid vein draining that part of the thyroid lobe which was supplied by the artery utilized for ia injection. Peripheral venous blood samples were collected from a cubital vein. Secretin was administered in three different modes. The patients in groups I and II were studied after ia administration of 0.75 and 7.5 CU secretin, respectively. The subjects in group III were given 75 CU secretin as a bolus in a peripheral vein. Blood samples were collected from both thyroid and peripheral vein 10, 5 and 1 min before stimulation and 1, 2, 5, 10, 15, 30, 45 and 60 min after the secretin injection. In some cases a low blood flow made sampling impossible within 1 min. Hence, in the figures the S-calcitonin concentration at 2 min is the mean concentration between 0 and 2 min. All blood samples were centrifuged within 45 min after termination of the experiment and serum specimens were stored at −20°C until assayed.

Biochemical analysis
S-calcitonin was determined by a radioimmunoassay described by Thorell & Larson (1978). Antiserum against synthetic human calcitonin was prepared in rabbit. Synthetic human calcitonin was also used for tracer and reference standard. The reference interval for the assay for healthy subjects is < 50 pmol/l in peripheral serum and the lower limit of detection is 3 pmol/l. The coefficient of variation for the assay is 8%. S-calcium was determined by flame emission photometry and the reference interval is 2.2−2.6 mmol/l.

Calculations
All values are expressed as mean ± SEM. Data were subjected to statistical analysis using Student’s t-test for paired and unpaired observations or Man-Whitney rank sum test.

Results
The concentrations of calcitonin in thyroid and peripheral venous serum are demonstrated in Figs. 1, 2 and 3. Thus neither ia (Figs. 1 and 2) nor iv (Fig. 3) administration of secretin was able to induce any significant increments in thyroid venous or peripheral venous concentration of calcitonin. In group III (given 75 CU secretin iv) the mean thyroid venous calcitonin concentration increased from 37.1 ± 10.7 to 52.3 ± 8.6 pmol/l during the first 2 min. The calcitonin level increased by 58 and 33 pmol/l in 2 subjects, whereas the level decreased by 19 pmol/l in 1 subject and was unchanged in 2 subjects. The values are not significantly (0.2 < P < 0.3) different from each other.
S-calcium in peripheral venous blood was unchanged throughout the period of observation in all subjects (data not shown).

**Discussion**

The results in the present paper show failure of secretin infused in a thyroid artery to induce calcitonin secretion in man. IV administration of secretin bolus was succeeded by as well increased as decreased calcitonin levels in thyroid venous blood. This problem will need further exploration, including different doses and modes of administration of secretin.

The peroperative method used in this study is a sensitive tool in the study of iodothyronine and calcitonin secretion from the human thyroid gland (Ahrén et al. 1978; Ericsson et al. 1981a,b). Thus following ia pentagastrin S-calcitonin in thyroid venous blood will increase 8- to 10-fold while the level in peripheral blood was unaffected (Ericsson et al. 1981a). Therefore it is reasonable to assume that not even small increments in calcitonin secretion have passed undetected.

Hypercalcaemia has previously been observed after iv infusion of secretin (Isenberg et al. 1973). This observation could not be reproduced in the present study and a similar observation has been made by Sethi et al. (1981). These divergent results can be explained by different doses and modes of administration of secretin. In the study of Isenberg et al. (1973) secretin was administered as a continuous infusion of 3 CU · kg⁻¹ · h⁻¹ during 90 min.

According to the hypothesis of Talmage et al. (1980) calcitonin is released post-prandially from the thyroid C-cells. The means by which this calcitonin secretion is induced is still obscure. Several factors have been proposed as humoral messengers between the gastrointestinal tract and the C-cells. Oral ingestion of calcium, which elevates S-calcium within the normal range, has been shown to raise the serum level of calcitonin. The increments of calcium and calcitonin were correlated temporally and peaking after 120–240 min (Austin et al. 1978). Several gastrointestinal peptide hormones are also secretagogues to calcitonin secretion. These hormones include gastrin (pentagastrin), cholecystokinin, glucagon and caerulein (Heath & Sizemore 1977; Parthemore & Deftos 1978; Care et al. 1971). The physiological significance of these secretagogues in man is disputed. In most studies supraphysiological serum levels of gut hormones have been utilized. Thus following iv administration of 0.0625 μg · kg⁻¹ body weight of pentagastrin, the gastrin level will increase 5- to 10-fold more than after a meal (Owyang et al. 1978). In experimental animals (pig) infusion of gastrin in a peripheral vein, barely doubling the gastrin level, which is within the physiological post-prandial range, is associated with a 3-fold increase of thyroid venous calcitonin concentration (Cooper et al. 1978). However, similar findings have not been reported in humans.

Secretin, which is released from the duodenal and upper jejunal S-cells in response to food and duodenal acidification (Häcki 1980; Chey et al. 1978), has recently been proposed as a secretagogue to calcitonin and parathyroid hormone release (Sethi et al. 1981). In previous studies in pig secretin has been shown to lack calcitonin liberating properties (Care et al. 1971). Similar results were obtained in neoplastic human C-cells in long-term maintenance monolayer cultures (Roos & Deftos 1976a). In vitro studies utilizing trout C-cells have demonstrated a dose-related stimulating effect of secretin on calcitonin secretion (Roos & Deftos 1976b). When tested in combination with maximally effective doses of pentagastrin a synergistic effect was noted with secretin (Roos & Deftos 1976a). Evidently secretin has lost its calcitonin-releasing property during the evolutionary process.
In the report by Sethi et al. (1981) the calcitonin response in peripheral venous samples was measured after iv infusion of secretin during 90 min. The results obtained in the present study are contrary to those of Sethi et al. (1981) and the reason for these divergent findings is not quite apparent. However, it cannot be excluded that secretin infused during 90 min will release some other substance in the human body, which in its turn can be a calcitonin secretagogue. The secretin preparation used in this study is highly purified and does not contain biologically demonstrable amounts of contaminating substances being calcitonin secretagogues. This is demonstrated by lack of calcitonin response in thyroid venous samples after ia administration.

During the last years several new gastrointestinal hormones have been discovered. It is reasonable to assume that the occurrence of still more gastrointestinal hormones will be disclosed. Following ingestion of a meal several hormones, known as well as unknown, are released. Therefore it is hard to conclude to what extent a separate hormone is responsible for a distinct biological effect. Selective methods which can verify or dismiss a biological effect are preferable. Regarding the thyroid the peroperative method is an appropriate tool to achieve this goal.

In summary, by means of the peroperative method we found failure of secretin to induce calcitonin secretion, both following selective ia and iv administration.

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