Abstract. Thyrotrophin-releasing hormone (TRH) is present in the pancreas, mainly in the islets of Langerhans. We studied the effect of iv infused TRH on the plasma levels of pancreatic islet hormones in man, under different experimental conditions: 1) Arginine infusion. 2) Insulin induced hypoglycaemia. 3) Glucose clamp technique (maintainance of normoglycaemia by glucose infusion during insulin infusion). 4) TRH injection. Except for a minor inhibition of glucagon and pancreatic polypeptide following hypoglycaemic stimulation in one study, TRH had no significant effect on basal, stimulated or inhibited plasma glucagon, on insulin, somatostatin, pancreatic polypeptide or blood glucose. It is concluded that iv administration of TRH does not produce significant changes in peripheral plasma levels of pancreatic hormones.

Application of techniques, which allow studies closer to the pancreatic islet, is probably necessary to assess the role of TRH in the regulation of endocrine pancreas.

There is now considerable evidence for the presence of thyrotrophin-releasing hormone (TRH) in the rat pancreas (Koivusalo & Leppäluoto 1979; Engler et al. 1981). Recently TRH has also been found in the human pancreas (Koivusalo 1981; Dolva et al., in press). In the rat, pancreatic TRH is mainly localized to the islets of Langerhans (Martino et al. 1978) and in long term culture studies, pancreatic islets have been shown to produce and release TRH (Nielsen et al. 1982).

TRH has been shown to potentiate the glucagon release in perfused rat pancreas under certain conditions (Morley et al. 1979). However, the function of TRH in the endocrine pancreas is unclear. In this report we have studied the effect of iv infused TRH on the levels of pancreatic endocrine hormones in healthy man.

Materials and Methods

Thirty-nine subjects, 15 females and 24 males between 19 and 35 years who gave written consent, participated in these studies. All studies were started between 7.30–8.30 a.m. after a fast from midnight. Indwelling catheters were located in both antecubital veins. Blood samples were collected in ice-cold tubes containing heparin and aprotinin (TrasyloL®, Bayer, Leverkusen, FRG). After centrifugation, plasma was stored at −20°C until analysed. The following studies were carried out on different days in random order:

Arginine stimulation

Eight subjects, 4 females and 4 males were studied. After 30 min in recumbent position, 30 g arginine hydrochloride was infused iv over a period of 20 min. TRH (Roche) 1800 nmol/h or 0.9% NaCl was infused for 60 min, starting simultaneously with the arginine hydrochloride infusion.

Blood samples were collected as indicated in Figs. 1 and 2. Blood glucose and plasma levels of insulin, glucagon and TSH were analysed.
Insulin induced hypoglycaemia
Sixteen male subjects participated. Insulin Leo Neutral® 0.15 IU/kg was injected iv.
Eight subjects received iv infusion of 110 nmol TRH for 120 min. In the 8 other subjects 1400 nmol TRH/h for 90 min. 0.9% NaCl was infused as control at another day. The infusion of TRH or NaCl was started when the insulin was injected. Blood samples were taken as shown in Figs. 3 and 4. Blood glucose and plasma levels of insulin, glucagon, pancreatic polypeptide (PP) and TSH were measured (glucagon was only measured when TRH 1400 nmol/l was infused).

Glucose clamp study
To study the effect of TRH on the influence of insulin itself on glucagon secretion without hypoglycaemia, we used a glucose clamp technique.
Nine subjects, 6 females and 3 males participated. Insulin Leo Neutral® 0.05 IU/kg was injected iv and followed by infusion of insulin 0.1 IU/kg⋅h. Normoglycaemia was maintained by concomitant iv infusion of 12.5% glucose. The rate of glucose infusion was estimated following blood glucose measurements every fourth min (Eyetone, Ames). TRH 2 nmol/kg⋅h or 0.9% NaCl was infused iv simultaneously with the insulin and glucose infusion from 0–80 min. Blood glucose (control) and plasma levels of insulin, glucagon, somatostatin and TSH were measured.

TRH stimulation
Six subjects participated (1 male and 5 females). After 30 min in recumbent position 1100 nmol TRH was injected iv. Blood samples were collected as indicated in Fig. 7. Glucagon and TSH were measured.

Analyses
Blood glucose was measured by a glucose dehydrogenase method. Plasma levels of insulin, TSH, PP (Flaten & Myren 1981), glucagon (Von Schenck & Nilsson 1981) and somatostatin (Skare et al., in press) were measured by radioimmunoassay. Detection limit for somatostatin was 1.5 pmol/l in plasma [125I]glucagon (NOVO, Copenhagen, Denmark) was used as tracer. Wilcoxon's test for paired observations was used for statistical observations. P < 0.05 was considered as significant. The values are given as mean ± SEM.

Results
The arginine hydrochloride stimulated increment in glucagon (Fig. 1), insulin and blood glucose (Fig. 2)
was not influenced by TRH infusion. TSH increased in all subjects following TRH (data not shown).

The fall in blood glucose during insulin hypoglycaemia was unaffected by TRH 110 nmol/h (Fig. 3) and TRH 1400 nmol/h. The integrated glucagon values from 15–120 min was significantly lower during TRH infusion compared to the control experiment ($P < 0.05$), but maximal increment was not different (Fig. 3). TRH 110 nmol/h had no significant effect on the hypoglycaemic stimulation of PP (Fig. 4). However, during TRH 1400 nmol/h the PP values at 60–75–90 and 100 min were all significantly reduced compared to the control study (Fig. 4). In all, TRH infusion was followed by increased TSH (data not shown).

Glucose clamp study. Normoglycaemia (with minor changes in blood glucose) was obtained in this study (Fig. 5). After cessation of the infusions at 80 min a decrease in blood glucose occurred (Fig. 5). The peripheral insulin concentration increased immediately after the insulin injection (Fig. 5). Thereafter serum insulin concentration was maintained at a somewhat lower level until the insulin infusion was stopped (Fig. 5). A decrease in glucagon from basal levels (44.5 ± 4.8 pmol/l) was observed 30 min after the start of insulin infusion (Fig. 6) ($P < 0.01$). Nadir glucagon (31.8 ± 3.4 pmol/l) occurred at 45 min and glucagon was maintained at this level during the insulin infusion (Fig. 6). When the insulin infusion was stopped, glucagon increased concomitantly with the fall in blood glucose (Figs. 5–6). Maximal increment occurred at the end of the study (Fig. 6). Basal somatostatin was 2.8 ± 0.5 pmol/l. Following insulin administration, no significant changes in somatostatin occurred (Fig. 6).

Concomitant TRH infusion 2 nmol/kg·h had no significant effect on the plasma levels of glucagon, insulin or somatostatin (Figs. 5–6), whereas TSH increased in all subjects (data not shown).

TRH injection. No significant changes from basal glucagon values (35.0 ± 2.5) pmol/l was observed after injection of TRH 1100 nmol iv (Fig. 7). TSH increased in all cases (data not shown).

Discussion

The results of this study do not clarify the role of TRH in the regulation of endocrine pancreas. TRH had no effect on basal, stimulated or inhibited glucagon levels in peripheral blood. Insulin and blood glucose were unaffected by TRH, which is in agreement with earlier studies (Dolva et al. 1978).

In perfused rat pancreas, potentiating effect of TRH on the arginine stimulated glucagon release

![Graph](image-url)
has been reported (Morley et al. 1979). In our study, where arginine was infused iv to healthy men, TRH had no effect on the glucagon release. Both experimental design and different species may explain this discrepancy.

The observed minor inhibition of glucagon release following hypoglycaemia during TRH infusion (Fig. 3) was scarcely significant. Since TRH was without effect on the arginine stimulated glucagon release, the observed inhibiting effect of TRH on the glucagon release is uncertain.

The inhibiting effect of TRH on the PP release may be of some importance. Both TRH (Gullo & Labo 1981) and PP (Adrian et al. 1979) have inhibiting effect on the exocrine pancreatic enzyme secretion. However, since this modest effect first occurred after 60 min of TRH infusion it is probably an indirect action of TRH.

The results from the glucose clamp study confirm the observation that insulin inhibits, whereas hypoglycaemia stimulates the glucagon release (Service et al. 1978). Stimulating effect of glucagon (Epstein et al. 1980) and hypoglycaemia (Wass et al. 1980) on the somatostatin release has been reported. The effect of insulin itself (without hypoglycaemia) has been conflicting.

Plasma PP following insulin induced hypoglycaemia (0.15 IU/kg iv). Broken line: effect of TRH 110 nmol/h (upper panel) and TRH 1400 nmol/h (lower panel). Solid line: increase during 0.9% NaCl infusion (∗ = P < 0.05, ∗∗ = P < 0.01).

Fig. 4.
Plasma insulin and blood glucose measured in peripheral blood in a 'glucose clamp study' (see text). Broken line: results during iv infusion of TRH 2 nmol/kg·h. Solid line: results during 0.9% NaCl infusion.

Plasma glucagon and plasma somatostatin response in a 'glucose clamp study' (see text). Broken line: results during iv infusion of TRH 2 nmol/kg·h. Solid line: during 0.9% NaCl infusion.
In the present study we did not observe significant change in the somatostatin levels neither during insulin, nor following modest hypoglycaemia in spite of the fluctuations in endogenous glucagon. Comcomitant TRH infusion had no effect on the hormone levels.

In these studies we have used various doses of TRH. The lack of effect in the initial studies with smaller doses of TRH (110 nmol/h) prompted us to increase the dose of TRH in the following experiments. All doses of TRH which were used stimulated the pituitary TSH release. In spite of this we were unable to demonstrate effect of TRH on the endocrine pancreas. However, it cannot be concluded that TRH has no effect on the pancreatic regulation. The sensitivity to TRH in the endocrine pancreas may be different from the pituitary, and the doses of TRH which were used may be too low. The localisation of TRH in the pancreatic islets (Martino et al. 1978) and the ability of these islets to produce and release TRH (Nielsen et al. 1982) indicate that the pancreatic TRH may be of physiological importance. It is possible that the islet TRH act on the exocrine pancreas. TRH has been shown to have a dose-dependent inhibiting effect on the pancreatic enzyme secretion in men (Gullo & Labo 1981). This concept is supported by the recent demonstration of a 'portal venous system' in the pancreatic circulation (Fraser & Henderson 1981). Approximately 25% of the venous blood from the endocrine islets arrives directly at the exocrine tissue (Lifson et al. 1980). TRH from the islet may in part reach the exocrine circulation. The endocrine pancreas may in part regulate exocrine pancreatic function.

References


Fig. 7.

Plasma glucagon and after iv injection of TRH 1100 nmol. No significant variation is seen.


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