Diabetologia 19, 492–504 (1980)

Diabetologia

Review Articles

Secretion of Somatostatin from the Normal and Diabetic Pancreas

Studies In Vitro

K. Hermansen

Second University Clinic of Internal Medicine, Kommunehospitalet, Aarhus, Denmark

Key words: Pancreas, dog pancreas, diabetes, somatostatin, isolated perfused pancreas.

Rapid progress in the study of pancreatic somatostatin secretion has taken place, since its discovery in 1976 [65, 66, 79]. It has been shown that pancreatic D cell function is subject to a multitude of control mechanisms. This review, which deals mostly with in vitro results from mammals, will concentrate on three aspects: a) the mechanism and dynamics of pancreatic somatostatin secretion; b) the factors that influence its release; and c) secretory abnormalities of the D cell in experimental diabetes. The perfused dog pancreas preparation of Iversen and Miles [45] has turned out to be a useful and valid preparation for this purpose.

Methods for Studying Pancreatic Somatostatin Secretion

In Vitro Methods

The application of in vitro techniques provides a controlled environment free of the hepatic, humoral and nervous regulatory mechanisms present in vivo and makes it possible to dissect out individual factors which influence pancreatic somatostatin secretion. The isolated perfused pancreas preparation offers several advantages over the other in vitro techniques employed: a) it allows assessment of moment-to-moment changes in secretion; b) it makes possible the collection of control and experimental data from the same pancreas; c) it has considerable functional integrity with intact circulation to the islets; d) it is exposed to minimal enzymatic leakage from acinar tissue which could result in impaired islet cell responses. Methods using isolated islets and monolayer cultures are deficient in these respects. A further problem arises in incubation studies where islet hormones accumulating in the medium may interfere with the normal hormone secretion.

In many perfusion methods currently used a portion of duodenum remains attached [17, 19, 20, 30, 36, 38, 64, 95]. The question has often been raised whether the endocrine cells of the duodenum may contribute to or modify the secretion of pancreatic somatostatin measured in the pancreatico-duodenal efflux thereby making interpretation of results more difficult [40, 72, 76, 77]. It has, however, been found that in the dog identical release patterns of somatostatin as well as of insulin and glucagon were obtained whether or not the duodenum was excluded during either basal or stimulated conditions [25] (Fig. 1).

For the evaluation of somatostatin secretion perfused pancreas preparations from dog [30, 38, 76], pig [73], rat [17, 19, 20, 36, 46], and chicken [36] have been used. The perfused chicken pancreas is perhaps inappropriate if ones interest is primarily in mammalian systems since islet morphology and pancreatic hormone responses of the avian class differ distinctly from those of the mammalian e. g. insulin stimulates the pancreatic somatostatin secretion in the chicken [37] while leaving it unaffected in mammals [34, 46, 63, 67, 106]. Comparison of the secretory pattern of somatostatin from perfused dog and pig pancreas with that from perfused rat pancreas indicates that the latter is a relatively insensitive model with rather indistinct somatostatin responses to the various challenges and with basal somatostatin levels often at or below the detection limits of the assay [19, 36, 46].

0012-186X/80/0019/0492/$02.60

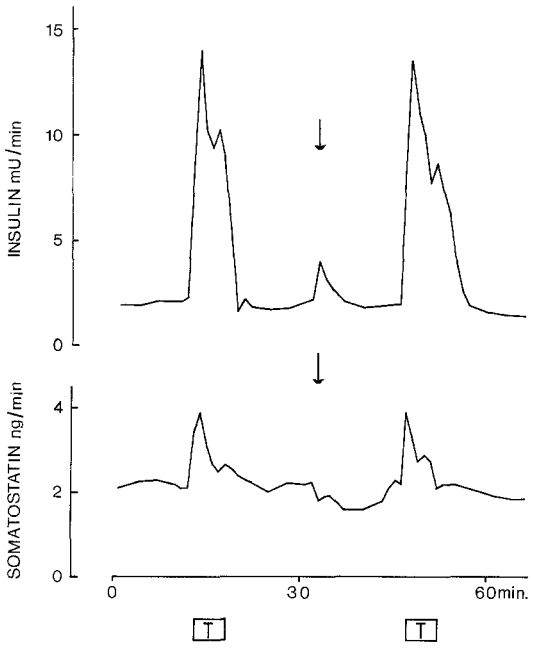

Fig. 1. Lack of effect of duodenal exclusion on tolbutamide (T) (50 μg/ml) – stimulated somatostatin and insulin release from the isolated, perfused dog pancreas. The clamping off of the duodenum is indicated by arrows

It is obviously necessary to be sure that the somatostatin immunoreactivity released from the pancreas is "true" somatostatin. Validation has come from the following findings: the somatostatin like immunoreactivity in pancreatic effluent samples shows parallelism in binding percentage with the synthetic standard on serial dilutions [8, 19, 26], and chromatographs in a single peak corresponding to that of synthetic cyclic somatostatin [8, 19, 26]. Further support has been obtained by purification and chemical structural analysis of the extracted immunoreactive material [57, 98].

In Vivo Methods

It is obvious that there must be reservations when trying to extrapolate in vitro findings to the in vivo state. Unfortunately the interpretation of the results of peripheral plasma somatostatin determinations in physiological and pathophysiological situations is hampered by various disadvantages. The widespread location of somatostatin secreting cells [53] implies that changes in the levels of somatostatin in the peripheral circulation may derive from variations in the release from almost anywhere. Moreover, in view of the portal-peripheral gradient [5, 86] and of the short half-life of somatostatin [71, 87, 97] it is apparent that changes in circulating somatostatin levels may bear only a slender relation to changes taking place in the pancreas. These problems can in part be circumvented by catherisation of the pancreaticoduodenal vein in large animals [84, 86, 88, 91]. Even such results cannot, however, be regarded as wholly quantitative since blood flow measurements were not performed simultaneously with blood sampling. Furthermore, the difficulty in obtaining reliable and sensitive somatostatin assays for measurements in plasma has slowed the progress of studies in intact man and animal.

Mechanism of Somatostatin Secretion

The term 'stimulus-secretion coupling' [13] has been used to cover the events occurring in a secretory cell exposed to its immediate stimulus. According to this concept calcium is regarded as a substance which couples the secretory signal to the discharge of the secretory product from endocrine cells [13]. Another potential messenger is cyclic AMP (cAMP). The question arises as to whether the effects of different modulators of pancreatic somatostatin secretion are also mediated via one or both of these second messengers. In this context the effects of cations and cyclic AMP upon somatostatin secretion are relevant to our understanding of the mechanisms of D cell secretion.

Cyclic AMP and Somatostatin Secretion

There is persuasive evidence that the release of somatostatin by the pancreatic D cell may be influenced by cyclic AMP dependent mechanisms. Barden et al. [3] first reported that high concentrations of 8-Br-cAMP stimulated somatostatin secretion from isolated islets in the presence of a normal glucose level. Agents that are supposed to increase the cellular level of the nucleotide, such as glucagon [11, 46, 63, 65, 67, 78, 79, 105, 106], β-adrenergic effectors [30, 33, 76, 77] and phosphodiesterase inhibitors (theophylline) [3, 20, 63, 78] increase the somatostatin secretion. Moreover dibutyryl cyclic AMP enhances somatostatin release [63]. Some evidence suggests, however, that elevated D cell cyclic AMP concentration alone is not a sufficient stimulus to somatostatin release. Thus the very high concentration of glucagon at 5 μg/ml [63, 78] and 1 mmol/l theophylline [20] were unable to cause a sustained stimulation of somatostatin release at a non-stimulatory glucose level. These findings conflict with other studies where glucagon at a low glucose [106] and theophylline in the absence of glucose [78] both elicited a modest somatostatin secretion.

Cations and Somatostatin Release

The Role of Calcium. The key role of calcium for somatostatin secretion has been established in studies with the perfused dog pancreas preparation [24, 26, 30–33]. Extracellular calcium is an absolute requirement for the stimulation of somatostatin release induced by glucose [33], arginine [33], isoproterenol [33], ouabain [24, 32], potassium [24, 31], and veratridine [24, 26]. The somatostatin responses increase progressively when perfusate calcium is increased from 0 through 1.25 and 2.5 to 5 mmol/l [24, 30]. It is suggested that the increase in extracellular calcium leads to an increase in intracellular calcium mainly via an increased calcium influx. The idea of a direct regulatory role of calcium is supported by the fact that a rise of the extracellular concentration of calcium augments somatostatin release in the absence of the glucose [30].

When evaluating the role of calcium in somatostatin secretion its relation to other cations especially the monovalent Na^+ and K^+ must be considered.

The Role of Na^+. Partial replacement of extracellular Na^+ by choline (100 mmol/l choline, 40 mmol/l Na^+) provokes enhanced somatostatin secretion in the presence of extracellular calcium [24, 26]. It is possible that this somatostatin secretion is due to a cholinergic effect of the high concentration of choline, since acetylcholine has been shown to stimulate D cell secretion [30]. The fact that the increase in somatostatin secretion which results from a decrease in extracellular Na^+ concentration is unaffected by the presence of 1 mmol/l atropine seems to rule out this possibility. When extracellular calcium is omitted from the medium, the somatostatin response to a drop in extracellular Na^+ concentration, however, disappears [24, 26]. This points to the existence in the D cell membrane of a Na^+–Ca^{++} counter transport mechanism analogous to that described for other excitable tissues [6]. The somatostatin responses induced by Na^+ deprivation may thus be caused by an increased influx of calcium into the D cell coupled to an increased egress of Na^+.

These findings emphasize the importance of extracellular Na^+ in somatostatin secretion. The role of intracellular sodium has been investigated by blockade of the Na^+/K^+ pump. This process, which increases intracellular Na^+ content in a wide variety of cells including pancreatic islet cells [93, 94], stimulates somatostatin secretion [24, 32]. Thus both the addition of ouabain and the omission of extracellular K^+ from the medium elicit an immediate somatostatin response [24, 32].

In addition, the alkaloid, veratridine, which increases Na^+ and calcium uptake through Na^+-channels in excitable tissue induces a biphasic somatostatin response [24, 26]. The response to veratridine is counteracted by tetrodotoxin (TTX) [24, 26], which selectively blocks Na^+-channels and thereby the inward Na^+ current in excitable membranes.

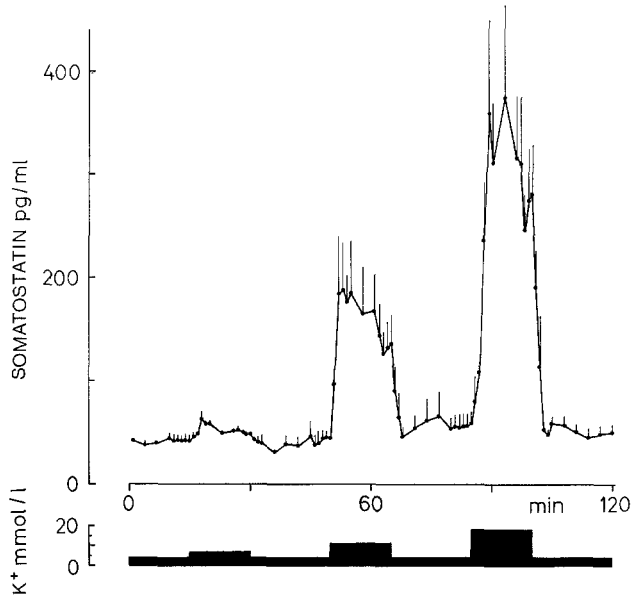

Fig. 2. Effect of 10 min increases of perfusate potassium from 4.4 to 6.9, 11.3 and to 18.2 mmol/l on pancreatic somatostatin release from the isolated dog pancreas. Perfusate calcium and glucose concentrations were 1.3 mmol/l and 5.5 mmol/l, respectively. Mean ± SEM (n = 3)

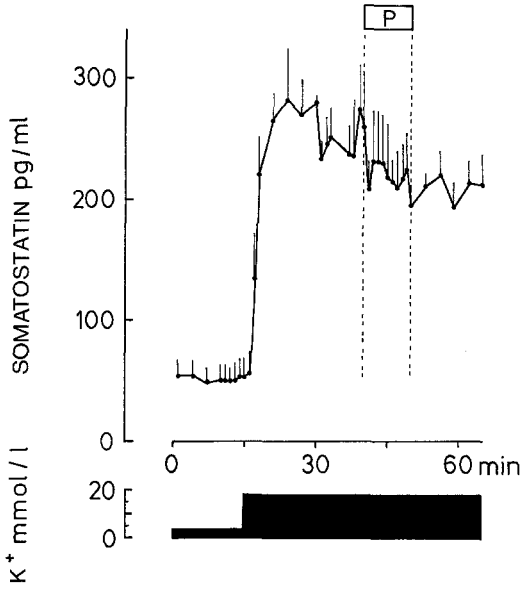

Fig. 3. Lack of effect of 1 μmol/l phentolamine (P) on potassium (18.2 mmol/l)-induced somatostatin release from the isolated dog pancreas. Glucose concentration was 5.5 mmol/l and calcium concentration was 1.3 mmol/l. Mean ± SEM (n = 3)

A clearcut distinction exists between effects obtained in the presence and in the absence of extracellular calcium. Thus no increase in somatostatin secretion occurs in the absence of calcium when veratridine [24, 26] or ouabain [24, 32] are added to the perfusate or K^+ is omitted [24, 32]. An increase in intracellular Na^+ is supposed to lead to somatostatin secretion mainly by causing a depolarization and an opening of voltage sensitive calcium channels and an increased calcium uptake into the D cell. Our findings make it unlikely, however, that an increase in intracellular Na^+ evokes somatostatin secretion per se or via mobilization of intracellularly bound calcium.

The Role of K^+. An elevation of the potassium concentration resulted in a dose-dependent increase in the secretion of somatostatin [24, 31]. Even a small increase in K^+ from 4.4 to 6.9 mmol/l results in increased somatostatin secretion (Fig. 2). It has previously been demonstrated that a high external K^+ concentration induces depolarization [10] and raised calcium uptake in pancreatic islets [56]. The immediate somatostatin response to the sudden rise of external K^+ may therefore be the consequence of an increased calcium influx in the D cell. This is further supported by the finding that the absence of extracellular calcium abolishes somatostatin secretion in response to high K^+ [24, 31].

High potassium concentrations may also cause the release of neurotransmitters from nerve terminals. The question arises therefore whether the somatostatin response to high extracellular K^+ is also due to neurotransmitter liberation from nerve endings in the islets. It is unlikely that acetylcholine release or catecholamine release from the parasympathetic and sympathetic nerve terminals is responsible since high concentrations of atropine [24, 31], propranolol [24, 31], and phentolamine (Fig. 3) leave the potassium-induced somatostatin secretion unaffected. There is also no immunohistochemical evidence for the presence of somatostatin containing nerves in the pancreas [14]. The islets are, however, richly innervated with other peptidergic nerve fibres which contain somatostatin stimulating peptides such as CCK, VIP, and substance P [50, 52]. It cannot therefore be ruled out that such peptidergic nerves may to some degree be involved in the observed K^+ evoked somatostatin release.

Conclusions

The role of cyclic AMP in the control of somatostatin release may be primarily that of a modulator without being an essential factor for initiation of somatostatin release. Much work is, however, still required to elucidate the exact nature of the role of cyclic AMP in the secretory mechanism of the D cell. All of the present evidence, however, points to a key regulatory role for calcium in the cascade of events that proceeds to the somatostatin secretion [24, 26, 30–33]. The data indicate that the changes in somatostatin secretion provoked by alterations in the extra- and intracellular levels of Na^+ and K^+ are secondary to changes in the intracellular level of calcium in the D cell. Caution should, however, be exercised in deducing from the results from cation fluxes in whole islets because of the mixed cell population studied. They cannot be assumed to represent the responses of the D cell alone because these cells make up only 5–15% of the total cell mass in the islet.

Dynamics of Somatostatin Secretion

The secretory characteristics of somatostatin release have much in common with those of insulin release. Thus in the isolated perfused dog pancreas a square wave pulse of high glucose induces a biphasic increase in the secretion of somatostatin [27, 29, 36, 105]. It consists of a peak release starting 1–2 min after the glucose challenge (First phase); after about 5 min this is followed by a lesser more prolonged secretion (Second phase). Although one group has reported to the contrary [81, 82], the omission of glucose results in an immediate decline in somatostatin release [17, 29, 36, 38, 105].

The dynamics of the somatostatin release are concentration-dependent. Low concentrations of glucose thus merely elicit a transient burst of secretory activity, and the biphasic nature of the secretory response manifests itself only as the glucose level is increased [29]. Biphasic profiles of somatostatin secretion are also obtained with high concentrations of agents such as arginine [19, 20, 30, 106], leucine [38], glucagon [105], CCK-8-S [27, 40], substance P [27], isoproterenol [30], and tolbutamide [38]. Using the dog pancreas preparation it has been found that not all responses are typically biphasic. Thus the responses to potassium [31], dihydroxyacetone [29], and D-glyceraldehyde [29] differ from the usual response pattern. A monophasic response is prompted by potassium ([31] Figs. 2 and 3), while a gradually increasing release is seen in response to dihydroxyacetone [29].

The underlying mechanism responsible for the biphasic somatostatin response is obviously of interest. It may be due to the existence of two pools of somatostatin analogous to the proposals for the pancreatic B cell [9, 69]. Another suggestion is that

somatostatin released during the first phase inhibits subsequent secretion. Thus Ipp et al. [43] have demonstrated an inhibitory effect of somatostatin on somatostatin secretion by the dog pancreas.

Recently, Stagner et al. [99] made the interesting observation in the perfused dog pancreas of regular, sustained oscillations of somatostatin with a 10 minute period. The monophasic cycle curves in vitro were not produced by adrenergic or cholinergic mechanisms and were not a result of glucose changes [99]. The drive may come from spontaneous firing of peptidergic nerves in pancreas [50, 52]. By considering the pancreatic D cell as a neuroendocrine cell [68] spontaneous activity in the D cell itself becomes another possibility. The nature of the pacemaker that serves to drive islet cycles is, however, not known.

Factors Modifying Normal Pancreatic Somatostatin Secretion

Carbohydrates

Glucose stimulates somatostatin secretion in vitro [17, 19, 27, 29, 33, 38, 63, 79, 105] although one group of investigators were not able to demonstrate any increase in somatostatin release from incubated rat islets [3]. Increased perfusate glucose also markedly enhances the somatostatin response to agents such as calcium [24, 30], and substance P [27]. A sigmoidal curve characterizes the relationship between the glucose concentration of the extracellular medium and the rate at which somatostatin is released [29]. The D cell threshold for glucose is close to 5 mmol/l in the isolated dog pancreas [28, 29, 38] and to 10 mmol/l in incubated rat pancreatic islets [19, 78]. In the dog half maximal release occurs between 5 and 10 mmol/l and maximal release is reached at about 20 mmol/l [28, 29]. The steep portion of the dose-response curve for somatostatin release from the dog pancreas [29] corresponds to the range of glucose found in the blood postprandially, which suggests a possible physiological role for the glucose-induced somatostatin release.

How the pancreatic D cell recognizes and responds to glucose is unknown. In analogy with the suggested models for the B cell glucoreceptor [10, 49, 70] at least three explanations can be offered. Somatostatin release may be triggered by the intact glucose molecule itself or it may be that the metabolism of glucose within the D cell provides intracellular signals which initiate somatostatin secretion; finally the two models may function simultaneously. Several lines of evidence seem to indicate that the somatostatin stimulatory action of glucose is dependent on its metabolism.

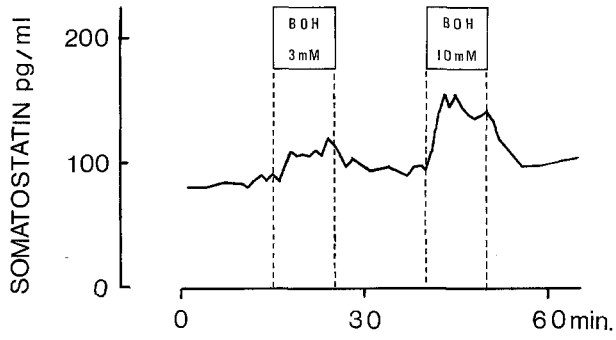

Fig. 4. Effect of 10 min infusion of 3 and 10 mmol/l DL-3-hydroxybutyric acid (BOH) on the somatostatin secretion from the isolated perfused dog pancreas. Perfusate glucose was 5.5 mmol/l

First, the trioses, dihydroxyacetone and D-glyceraldehyde, which enter the glyocolytic pathway at the triose phosphate level, both stimulate somatostatin secretion in the absence of glucose [28, 29]. D-Glyceraldehyde seems, however, to exert a dual action on pancreatic somatostatin secretion since high concentrations suppress D cell secretion [28, 29, 54, 78]. The inhibitory effect of large concentrations of D-glyceraldehyde could be explained by a decrease in islet cell levels of ATP [2].

Secondly, mannoheptulose, which markedly inhibits islet glucose metabolism but not that of D-glyceraldehyde, dramatically inhibits glucose stimulated somatostatin secretion [28, 29, 79, 83] while it has no effect on the D cell response to D-glyceraldehyde [28, 29].

Thirdly, the D cell secretion is unaffected by non- or poorly metabolized sugars such as ribose [29], fructose [29], and galactose [29, 63].

Non-carbohydrate Nutrients

Arginine [17, 19, 20, 30, 33, 63, 66], leucine [38, 78], a 10 amino acid mixture [38] and the amino-acid metabolite α-ketoisocaproic acid [78] are all powerful stimulators of somatostatin secretion. The implications of the finding that α-ketoisocaproic acid-stimulated D cell secretion is inhibited by epinephrine [83] but not by mannoheptulose [83] is uncertain.

The ketone body 3-hydroxybutyrate also augments somatostatin secretion by the isolated dog pancreas (Fig. 4). In this context it is interesting to note that heparin and intralipid in vivo cause a clear-cut increase in circulating somatostatin levels [104]. The increase may be attributed to either free fatty acids or to ketone bodies.

Effects of Pancreatic Islet and Gut Hormones

It is apparent from in vivo studies [86, 90] that the responses of pancreatic somatostatin to the administration of nutrients are mediated, by other factors as well. These additional mediators could be endocrine or nervous. Thus a somatostatin stimulating peptide present in nerves and/or endocrine cells of the islets may be an important component of a physiological somatostatin response without showing alterations in the peripheral plasma levels.

Islet Hormones. Insulin [34, 46, 63, 65, 67, 106] and PP [39] have no demonstrable effects on somatostatin secretion by mammalian pancreas. In contrast, glucagon has consistently been reported to stimulate pancreatic somatostatin secretion [11, 46, 63, 65, 67, 79, 105], the effect being dose dependent [46, 105].

The question whether somatostatin exerts a direct inhibitory action on its own secretion is of obvious importance since such a feed-back mechanism may contribute to the biphasic nature of the somatostatin response to various agents. Two somatostatin analogues ((D-Trp^8-D-Cys^{14})-somatostatin and Asn^5-(D-Tyr^8)-somatostatin) which are non-immunoreactive to certain somatostatin antibodies inhibit D as well as A and B cell secretion in response to glucose, arginine, and CCK-PZ [43]. According to the paracrine theory of Orci and Unger [61] such a decrease in somatostatin secretion could, however, theoretically be promoted indirectly via a suppression of endogenous glucagon secretion. The finding that a high analogue concentration is also capable of blocking D cell secretion despite the coperfusion of 10 ng/ml glucagon, however, points towards a self-inhibiting action on the native hormone [43]. The final proof must await the development of an analogue with a selective effect on the D cell.

Gastrointestinal Polypeptides. The somatostatin releasing potency of a large number of gastrointestinal polypeptides has been examined in vitro. Among these all of the established hormones, CCK-PZ [38], gastrin [40, 73], gastric inhibitory polypeptide (GIP) [40], and secretin [40] augment the secretion of somatostatin from the isolated perfused pancreas. In addition the synthetic octapeptide (CCK-8), exerts an enhancing effect on somatostatin release [27, 40]. Smaller molecular forms of CCK also stimulate D cell hormone secretion. Thus CCK-3, CCK-4, and CCK-5 at doses ranging between 10^{-7} to 10^{-3} mmol/l cause a dose-related somatostatin secretion from the isolated porcine pancreas [73]. CCK-4 is far the most potent of these peptides [73].

Somatostatin secretion is also stimulated by vasoactive intestinal polypeptide (VIP) [27, 41] and substance P [27], both of which are found in neurones in the pancreas [50, 52]. It is unknown whether the stimulant action on the D cell is aided by a vasodilator effect on islet capillaries. Our results are consistent with the view that substance P even at concentrations which can be delivered to the pancreatic islet cells by the circulation stimulates the secretion of somatostatin in a dose-related manner [27].

In contrast bombesin, a newly recognized tetradecapeptide contained in endocrine cells in duodenum, has no effect on somatostatin secretion [27]. The reported effects of neurotensin are, however, puzzling. Dolais-Kitabgi [11, 12] found that 100 nmol/l neurotensin stimulated somatostatin release at low glucose (3 mmol/l), that it did not alter somatostatin secretion in response to high glucose (12 mmol/l) and glucagon (2 μg/ml) and indeed inhibited D cell secretion during stimulation with very high glucose (23 mmol/l) or arginine (20 mmol/l) concentrations. Since the D cells of their preparation of isolated islets are unresponsive to variation in glucose from 3 to 23 mmol/l and to addition of 2 μg/ml glucagon [11, 12] the results must be viewed cautiously.

The demonstration of immunoreactive enkephalin in pancreas [50] points to a possible regulatory role of this opioid on islet cell function. Ipp et al. [42] have reported that another endogenous opioid, β-endorphin, and the exogenous opiate, morphine sulphate, exert inhibitory effects on somatostatin secretion, which could be abolished by the antagonist naloxone hydrochloride. Whether locally secreted enkephalin influences such hypothetically opiate receptors in the islets is, however, unknown.

The physiological meaning of the observations of peptide-induced alteration in D cell secretion is still obscure since no data are avaiable on the concentration of the peptides surrounding the islet cells in different physiological conditions.

Nervous Control of Pancreatic Somatostatin Secretion

In most mammals three main types of nerves have been demonstrated in the pancreas: adrenergic, cholinergic and peptidergic [50, 52].

Using the isolated dog pancreas, Samols et al. have shown that α-adrenergic stimulation inhibited somatostatin secretion [76, 77], a conclusion that is supported by the results of Ipp et al. [39]. Furthermore, Samols et al. [76, 77] showed that the β-adrenergic effects of epinephrine and isoproterenol were to enhance somatostatin secretion. Our studies confirm this latter finding [30, 33]. The administration of epinephrine alone, at doses of 2 μg/ml and

10 ng/ml, respectively, elicits an inhibition in somatostatin release from rat islets [79, 83] and dog pancreas [39]. Using the smaller epinephrine dose of 2 ng/ml Samols et al. [76, 77], however, could find no significant change in somatostatin secretion.

Dopamine, which is present in pancreatic islets in high concentrations [107] has also been shown to alter somatostatin secretion. Dopamine (10^{-4} mmol/l) inhibits somatostatin release, an action which can be prevented by the dopaminergic antagonist (+) butaclamol (5×10^{-5} mmol/l) [4]. It is not known if dopamine is a neurotransmitter in the pancreas, and the significance of these findings remain therefore to be elucidated, but a role for other adrenergic agents seems possible.

Acetylcholine, the transmitter of the parasympathetic nervous system, exerts only a minor and variable effect on hormone secretion from D cells as compared to the action on the A, B, and PP cell secretion [35]. Samols et al. [77] reported a mild suppressive effect of 10 μmol/l acetylcholine on somatostatin secretion. In contrast we found a modest stimulation of somatostatin release by 1 μmol/l acetylcholine [30, 33]. By using another source of acetylcholine [35], we, however, were unable to demonstrate any effect on the somatostatin release. A significant point in this context may be that there is large interindividual differences between pancreases in the sensitivity of the D cells to acetylcholine. Thus current experiments with the more stable carbamylcholine chloride demonstrate that while a definite dose-related stimulation of somatostatin release is obtained in some pancreata, others are refractory (K. Hermansen, unpublished observations). The reason for this puzzling phenomenon is unknown, but it seems that cholinergic mechanisms play no major regulatory role in pancreatic D cell secretion.

Peptidergic nerves are also found in the pancreas. They can release substance P, VIP, enkephalin, and gastrin/CCK [50, 52]. The effects of these peptides on the pancreatic somatostatin secretion have already been described. No somatostatin containing nerves are, however, present within the pancreas [14] i. e. the somatostatin measured in the efflux from islets or the entire pancreas derives exclusively from endocrine cells. The fact that certain of the effects on pancreatic hormone secretion induced by pancreatic nerve stimulation cannot be prevented by adrenergic or cholinergic blockade, strongly suggests an important regulatory role of the peptidergic nerves.

In conclusion, the rates at which somatostatin is released from the pancreas is now known to be modified by the autonomic innervation. However, the evidence is as yet fragmentary and the extent to which neural mechanisms may be integrated in the production of the somatostatin responses to physiological stimuli certainly needs further exploration.

Somatostatin Release in Response to Pharmacological Agents

Ipp et al. [38] have demonstrated that tolbutamide in the presence of 5.5 mmol/l glucose stimulates somatostatin secretion. Similarly Samols et al. [74] found a stimulatory effect of tolbutamide (130 μmol/l) on D cell secretion, greater, however, at low (0.8 mmol/l) than at normal glucose levels (4.9 mmol/l). The somatostatin response to the sulfonurea, glibenclamide, was also found to be lowest at high glucose concentrations [15]. Furthermore, glibenclamide (1 μg/ml) significantly enhanced the effect of arginine on somatostatin release [16]. In contrast, the hyperglycemic sulfonamide, diazoxide (130 μmol/l) inhibits somatostatin secretion [77]. With respect to the effects of sulphonylureas, there is thus again a striking similarity between D and B cell responses.

Functional Role of Pancreatic Somatostatin

Local Role?

The presence in pancreatic islets of D cells in juxtaposition to the B and in particular the A cells had led to the postulate of a local regulatory role for somatostatin on the pancreatic release of glucagon and insulin, that is a paracrine function of the D cell [61]. The facts that the pancreatic D cells secrete somatostatin and that islet cells can be influenced by the secretory products of other islet cells make this an attractive possibility. The assertion of Larsson et al. [51] that the pancreatic D cells have nonluminal cytoplasmic processes serving as pathways for paracrine secretion suggest that the D cells may regulate secretion of neighbouring islet cells through somatostatin release from both the cell body and cytoplasmic processes. The presence of tight junctions [60] and gap junctions [62] may also be of functional importance. The demonstration by Kohen et al. [48] of a glucose-enhanced transfer of fluorescein from an islet cell directly into neighbouring islet cells supports the view that cell-to-cell communication may be important for the secretory function of all islet cells. Whether somatostatin itself or ions or metabolites serve as signals between D cells is unknown.

One approach to answer the question about direct within-islet actions has been the attempt to

neutralize pancreatic hormones with antibodies. In vivo, administration of anti-somatostatin serum left both basal and stimulated glucagon and insulin levels unchanged, although plasma growth hormone levels rose [1, 89, 102]. Similarly, active immunization resulted in an increase of serum growth hormone levels, but did not affect basal and stimulated secretion of glucagon [100]. This has been interpreted as indicating that any influence of endogenous somatostatin on hormone secretion from the A and B cells takes place via a pathway inaccessible to the blood borne antisomatostatin serum [1, 89]. The dissociation of the effects of antisomatostatin serum on islet hormones and growth hormone levels may, however, reflect a differential sensitivity to somatostatin. Thus insufficient somatostatin antibody may have been administered to neutralize enough somatostatin to alter insulin and glucagon secretion. Higher concentrations of islet hormone antibodies can, however, be obtained in the vicinity of the islet cells when antibodies are applied to isolated islets. Using this technique Taniguchi et al. [101] found that insulin secretion was increased at low (3.3 mmol/l) and moderate (8.3 mmol/l) glucose levels, while it was unchanged at high glucose (16.7 mmol/l). In contrast, Barden et al. [4] found no elevation of insulin secretion at a normal glucose level (5.5 mmol/l) whereas a marked increase in glucagon release appeared following neutralization of endogenous somatostatin. Antiglucagon serum has also been shown to produce a small decrease in basal secretion of somatostatin from rat islets whereas attempts to neutralize insulin leave somatostatin release unaffected [63]. It has been suggested that if neutralisation of an islet hormone alters the release of one of the other islet hormones this favours the existence of a paracrine system of secretory control within the pancreatic islets [1, 63]. This is, however, not necessarily correct since it remains probable that the detected changes in release of islet hormones are due solely to neutralisation of the hormone stored between and not within islets.

Other anatomical features could also be relevant to a local role for somatostatin. The local portal vessel system in the islets [18] may allow secreted somatostatin to act on islet cells within the same islet. Although local such a mechanism should be considered as endocrine.

The qualitative heterogeneity of the responses of A, B, and D cells to different agents seems, however, difficult to interpret in terms of intra-islet feed-back mechanisms. The development of specific D cell agonists or antagonists may help to gain further insight to this problem.

Endocrine Role?

In addition to potential actions within the islets several lines of evidence point to an *extra-islet* endocrine role for pancreatic somatostatin. First of all, pancreatic somatostatin secretion is stimulated by nutrients and gastrointestinal hormones both in vivo [74, 86, 88] and in vitro [4, 17, 19, 27, 30, 33, 38, 40, 63, 65, 66, 79, 105, 106]. Also, in the peripheral circulation variations in the somatostatin level can be seen in response to physiological stimuli.

Secondly, biological actions can be produced by physiological increments in the somatostatin level. The intraportal infusion of synthetic somatostatin at a rate which induces a physiological rise in peripheral somatostatin is associated with a significant decrease in the rate of entry of nutrients from the gut into the circulation [85]. Moreover, inhibition of insulin and glucagon secretion from the isolated dog pancreas is elicited by somatostatin concentrations which can easily be achieved in the periphery in vivo in response to various physiological stimuli [35]. Although somatostatin has a short half-life [71, 87] and despite the difficulties in adressing the multiple actions of somatostatin on endocrine and exocrine functions (for reviews see [22, 53]) substantial evidence indicates that the action of this peptide extends beyond those of a potential paracrine nature.

In addition to regulating nutrient influx from the gastrointestinal tract, somatostatin may have other actions which contribute to nutrient homeostasis. Thus it may affect glucose metabolism by directly or indirectly altering hepatic glucose output (for review see [55]), glucose disposal to tissues [44] or central nervous system actions on glucoregulation [7]. At present, a cybernetic system with pancreatic somatostatin acting as a regulatory messenger in the gastroenteroinsular axis seems possible. In response to ingestion of nutrients, the gastrointestinal hormones, the gastrointestinal nervous system and the absorbed substrates may determine the secretory rate of pancreatic somatostatin which in turn acts as modulator of the secretion of gastrointestinal hormones (for review see [22, 53]), of neuronal function (for review see [53]), and of substrate absorption [85, 92, 103].

Fasting and D Cell Function

Fasting results in a decrease in portal somatostatin level in rats [47, 96] indicating a decreased secretory activity of pancreatic D cells during fasting. These two studies are not consistent with the in vitro results of Schauder et al. [80] which showed that islets from fasted rats release significantly more somatostatin

than controls in the presence of 3.3 mmol/l glucose, whereas the release at 10 or 25 mmol/l glucose was in the normal range. However, basal somatostatin secretion from the perfused rat pancreas is attenuated [95]. Of interest is the finding that in the fasted state somatostatin release is apparently independent of the prevailing glucose concentration (3.3, 10 or 25 mmol/l) [80] suggesting that the fasted islet D cells have at least temporarily lost their ability to recognize glucose, whereas they still respond to arginine [95].

Diabetes and D Cell Function

The observations of both an increase in the islet and pancreatic contents of somatostatin [58, 64], of an augmentation of D cell number [59] and of increased plasma somatostatin levels in insulin-deficient diabetes [47, 84] has raised the possibility that abnormalities in pancreatic somatostatin secretion may be present in diabetes. This suggestion is supported in a recent report of Schusdziarra et al. [90] demonstrating that the variations in peripheral plasma somatostatin levels in alloxan diabetic dogs differed from those of normal dogs. In the experimental diabetic dogs the rise in plasma somatostatin levels to a protein rich meal is delayed, but surpasses that seen in normals [90]. The postprandial as well as the fasting plasma somatostatin levels were unchanged in normals [90] while they were diminished although not to normal, in the diabetic dogs during insulin administration [90]. In contrast to what is seen in normal dogs no significant change in plasma comatostatin level appeared in response to orally or parenterally administered glucose [90].

We have also found that neither somatostatin nor glucagon secretion from the isolated pancreas of streptozotocin diabetic dogs altered in response to variations in perfusate glucose, manoeuvres which in pancreata from normal animals are invariably accompanied by swift but opposite changes in hormone release from the D and A cells [34]. In contrast other substances such as arginine, the β-adrenergic agonist isoproterenol, calcium, and glucagon (Fig. 5), all stimulated the release of somatostatin from the diabetic pancreas [34] as in the normal pancreas. Hara et al. [22] found that both basal and arginine stimulated somatostatin release from perfused pancreas of alloxan diabetic rats were approximately twofold increased as compared to normals, whereas the glucagon levels were decreased.

It is not clear whether the D and A cell abnormalities described [34] are secondary to insulin deficiency. However, the finding that insulin treatment in

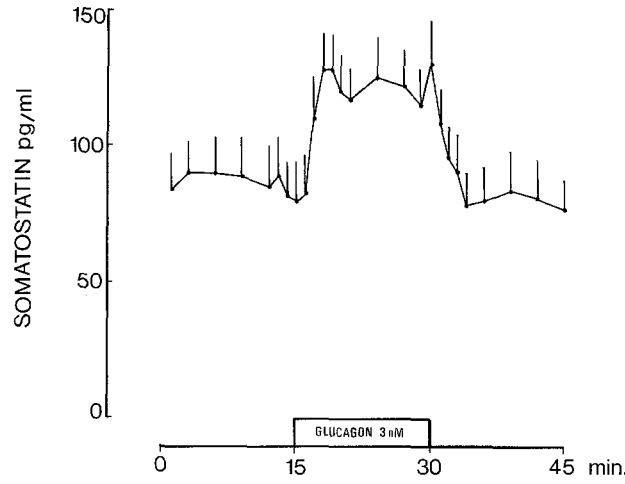

Fig. 5. Somatostatin secretion from the isolated pancreas of streptozotocin diabetic dogs (n = 5) during 10 min infusion of 3 nmol/l glucagon. The glucose concentration was 8.3 mmol/l. The dogs were operated on 3 to 5 days after the administration of streptozotocin (50 mg/kg)

vitro did not cause even a hint of normalization of D and A cell secretory responses to glucose favours the view that the D and A cell dysfunctions represent abnormalities independent of insulin secretion [34]. The diversity between in vivo [90] and in vitro results [34] concerning the effect of insulin on the somatostatin level in diabetes remains unexplained. However, similar secretory characteristics exist for glucagon.

It could be speculated that the increased somatostatin levels in acute experimental diabetes [47, 84, 90] were at least partly induced by either increased concentrations of ketone bodies or high glucagon levels, the latter being able to augment somatostatin secretion from the isolated pancreas of streptozocin diabetic dogs (Fig. 5).

A possible explanation is that experimental diabetes might be an overall islet cell disease due to a common, rather selective dysfunction of the glucoreceptor, which in this context includes both models: the regulator site and the substrate site models [70]. The metabolic abnormalities characterizing the diabetic state may be caused by a dysfunction of D as well as of A and B cells in the pancreas (or possibly of all cells?) [34].

To explore the molecular basis of the D cell impairement in experimental diabetes we have investigated the influence of various carbohydrates on somatostatin secretion in vitro and compared them with the normal responses [28]. The glucose metabolites D-glyceraldehyde (1.25 and 2.5 mmol/l) and dihydroxyacetone (11 mmol/l) which normally stimulate somatostatin secretion do not augment

somatostatin secretion from the perfused pancreas of streptozotocin diabetic dogs [28]. Although D-glyceraldehyde at high doses causes an inhibition of somatostatin secretion in normal [28, 29, 54, 78] as well as in diabetic pancreas [28] this may well be due to nonspecific effects through ATP depletion [2]. In addition mannoheptulose (5 mmol/l) has no effect on somatostatin secretion from the diabetic dog pancreas [28]. Thus the diabetic D cell has lost its ability to respond to glucose and its metabolites. Whether the D cell abnormalities are caused by a direct action of streptozotocin, by longstanding insulin deficiency in the vicinity of the D cell or are secondary to alterations in intermediary metabolism remains to be solved.

If one physiological function of pancreatic somatostatin is to restrain nutrient entry from gut as suggested by Unger et al. [92, 95, 103] it could be expected that abnormalities in pancreatic somatostatin secretion would also contribute to the metabolic derangement in experimental diabetes. If the normal increase in plasma somatostatin to glucose is extinct, one would predict, that the negative feed-back control over the rate of glucose entry should disappear. This would result in a more rapid entry of glucose and an augmentation of the arterial concentration of glucose. The absent increase in somatostatin secretion to glucose may further indirectly contribute to the metabolic abnormalities in diabetes due to the potential loss of glucagon suppression thereby allowing enhanced heptatic glucose production and ketogenesis. On the other hand the hypersomatostatinaemia in insulinopenic diabetes may reflect a futile compensatory effort to correct the hyperglycaemia.

Although still at an early stage studies on D cell function in normal and diabetic animal models seem to be a fertile field. The results indicate that much can be learned from such studies and with respect to diabetes it may prove fruitful to use other experimental models.

References

1. Arimura A, Coy DH, Chihara M, Fernandez-Durango R, Samols E, Chihara K, Meyers CA, Schally AV (1978) Somatostatin. In: Bloom SR (ed) Gut hormones. Churchill Livingstone, Edinburgh London New York, p 437–445
2. Ashcroft SJA, Chatra L, Weerasinghe C, Randle PJ (1973) Interrelationship of islet metabolism, adenosine triphosphate content and insulin release. Biochem J 132: 223–231
3. Barden N, Alvarado-Urbina G, Cote J-P, Dupont A (1976) Cyclic AMP-dependent stimulation of somatostatin secretion by isolated rat islets of Langerhans. Biochem Biophys Res Commun 71: 840–844
4. Barden N, Cote J-P, Lavoie M, Dupont A (1978) Secretion of somatostatin by rat islets of Langerhans and gastric mucosa and a role for pancreatic somatostatin in the regulation of glucagon release. Metabolism 27 [Suppl 1]: 1215–1218
5. Berelowitz M, Kronheim S, Pimstone B, Shapiro B (1978) Somatostatin-like immunoreactivity in rat blood. Characterization, regional differences, and responses to oral and intravenous glucose. J Clin Invest 61: 1410–1414
6. Blaustein MP (1974) The interrelationship between sodium and calcium fluxes across cell membranes. Rev Physiol Biochem Pharmacol 70: 33–82
7. Brown M, Rivier J, Vale W (1979) Somatostatin: Central nervous system actions on glucoregulation. Endocrinology 104: 1709–1715
8. Conlon JM, Srikant CB, Ipp E, Schusdziarra V, Vale W, Unger RH (1978) Properties of endogenous somatostatin-like immunoreactivity and synthetic somatostatin in dog plasma. J Clin Invest 62: 1187–1193
9. Curry DL, Bennett LL, Grodsky GM (1968) Dynamics of insulin secretion by the perfused rat pancreas. Endocrinology 83: 572–584
10. Dean PM, Matthews EK (1970) Electrical activity in pancreatic islet cells. Effect of ions. J Physiol (Lond) 210: 265–275
11. Dolais-Kitabgi J, Freychet P (1979) Neurotensin inhibits glucose but not glucagon-induced insulin and somatostatin release in isolated islets. Diabete Metab 5: 275–277
12. Dolais-Kitabgi J, Kitabgi P, Brazeau P, Freychet P (1979) Effect of neurotensin on insulin, glucagon, and somatostatin release from isolated pancreatic islets. Endocrinology 105: 256–260
13. Douglas WW (1968) Stimulus-secretion coupling: the concept and clues from chromaffin and other cells. Br J Pharmacol 34: 451–474
14. Dubois MP (1975) Immunoreactive somatostatin is present in discrete cells of the endocrine pancreas. Proc Natl Acad Sci USA 72: 1340–1343
15. Efendić S, Enzmann F, Nylén A, Uvnäs-Wallensten K, Luft R (1979) Effect of glucose/sulfonylurea interaction on release of insulin, glucagon, and somatostatin from isolated perfused rat pancreas. Proc Natl Acad Sci USA 76: 5901–5904
16. Efendić S, Enzmann F, Nylén A, Uvnäs-Wallensten K, Luft R (1980) Sulphonylurea (glibenclamide) enhances somatostatin and inhibits glucagon release induced by arginine. Acta Physiol Scand 108: 231–233
17. Efendić S, Nylén A, Roovete A, Uvnäs-Wallensten K (1978) Effects of glucose and arginine on the release of immunoreactive somatostatin from the isolated perfused rat pancreas. FEBS Lett 92: 33–35
18. Fujita T, Yanatori Y, Murakami T (1976) Insulo-acinar axis, its vascular basis and its functional and morphological changes caused by CCK-PZ and caerulein. In: Fujita T (ed) Endocrine gut and pancreas. Elsevier, Amsterdam, p 347–357
19. Gerich J, Greene K, Hara M, Rizza R, Patton G (1979) Radioimmunoassay of somatostatin and its application in the study of pancreatic somatostatin secretion in vitro. J Lab Clin Med 93: 1009–1017
20. Goto Y, Seino Y, Taminato T, Kadowaki S, Chiba T, Note S, Imura H (1979) Theophylline: Potentiation of arginine-induced somatostatin release from the isolated rat pancreas. Diabetes 28: 457–459
21. Grodsky GM, Batts AA, Bennett LL, Vcella C, McWilliams NB, Smith DF (1963) Effects of carbohydrates on secretion of insulin from isolated rat pancreas. Am J Physiol 205: 638–644

22. Hansen AaP, Lundbæk K (1976) Somatostatin: A review of its effects especially in human beings. Diabete Metab 2: 203–218
23. Hara M, Patton G, Gerich J (1979) Increased somatostatin release from pancreases of alloxan diabetic rats perfused in vitro. Life Sci 24: 625–628
24. Hermansen K (1979) Characterization of somatostatin release from the isolated, perfused canine pancreas: The role of cations. Excerpta Medica 481: 90–91
25. Hermansen K (1980) Duodenal contribution to pancreaticoduodenal vein islet hormones during stimulation of the canine pancreas with calcium. Diabetes 29: 361–364
26. Hermansen K (1980) The role of sodium in somatostatin secretion: Evidence for the involvement of Na^+ channels in the release mechanisms. Endocrinology 106: 1843–1847
27. Hermansen K (1980) Effects of substance P and other peptides on the release of somatostatin, insulin and glucagon in vitro. Endocrinology 107: 256–261
28. Hermansen K (1980) Characterization of the abnormal D-cell function in streptozotocin diabetes (Abstr). Diabetologia 19: 283
29. Hermansen K (in press) Pancreatic D cell recognition of D-glucose. Studies with D-glucose, D-glyceraldehyde, dihydroxyacetone, D-mannoheptulose, D-fructose, D-galactose, and D-ribose. Diabetes
30. Hermansen K, Christensen SE, Ørskov H (1979) Characterisation of somatostatin release from the pancreas. The role of calcium and acetylcholine. Diabetologia 16: 261–266
31. Hermansen K, Christensen SE, Ørskov H (1979) Characterisation of somatostatin release from the pancreas: The role of potassium. Scand J Clin Lab Invest 39: 717–722
32. Hermansen K, Christensen SE, Ørskov H (1980) The significance of Na^+/K^+ pump for somatostatin release. Horm Metab Res 12: 23–25
33. Hermansen K, Christensen SE, Ørskov H, Lundbæk K (1978) Release of somatostatin in response to calcium, glucose, arginine, acetylcholine, and isoproterenol. Acta Endocrinol (Kbh) 88 [Suppl 219]: A 36
34. Hermansen K, Ørskov H, Christensen SE (1979) Streptozotocin diabetes: A glucoreceptor dysfunction affecting D cells as well as B and A cells. Diabetologia 17: 385–389
35. Hermansen K, Schwartz TW (1979) Differential sensitivity to somatostatin of pancreatic polypeptide, glucagon, and insulin secretion from the isolated perfused canine pancreas. Metabolism 28: 1229–1233
36. Honey RN, Schwart JA, Mathe CJ, Weir GC (1980) Insulin, glucagon, and somatostatin secretion from isolated perfused rat and chicken pancreas-duodenum. Am J Physiol 238: E150–E156
37. Honey RN, Weir GC (1979) Insulin stimulates somatostatin and inhibits glucagon secretion from the perfused chicken pancreas-duodenum. Life Sci 24: 1747–1750
38. Ipp E, Dobbs RE, Arimura A, Vale W, Harris V, Unger RH (1977) Release of immunoreactive somatostatin from the pancreas in response to glucose, amino acids, pancreozymin-cholecystokinin, and tolbutamide. J Clin Invest 60: 760–765
39. Ipp E, Dobbs RE, McCorkle K, Harris V, Unger RH (1978) Further evidence for similar secretory responses of pancreatic somatostatin and insulin. Clin Res 26: 33A
40. Ipp E, Dobbs RE, Harris V, Arimura A, Vale W, Unger RH (1977) The effects of gastrin, gastric inhibitory polypeptide, secretin and the octapeptide of cholecystokinin upon immunoreactive somatostatin release by the perfused canine pancreas. J Clin Invest 60: 1216–1219
41. Ipp E, Dobbs RE, Unger RH (1978) Vasoactive intestinal peptide stimulates pancreatic somatostatin release. FEBS Lett 90: 76–78
42. Ipp E, Dobbs R, Unger RH (1978) Morphine and beta-endorphin influence the secretion of the endocrine pancreas. Nature 276: 190–191
43. Ipp E, Rivier J, Dobbs RE, Brown M, Vale W, Unger RH (1979) Somatostatin analogs inhibit somatostatin release. Endocrinology 104: 1270–1273
44. Ishida T, Röjdmark S, Bloom G, Chou MCY, Field JB (1980) The effect of somatostatin on the hepatic extraction of insulin and glucagon in anesthetized dogs. Endocrinolgy 106: 220–230
45. Iversen J, Miles DW (1971) Evidence for a feed-back inhibition of insulin on insulin secretion in the isolated, perfused canine pancreas. Diabetes 20: 1–10
46. Kadowaki S, Taminato T, Chiba T, Mori K, Abe H, Goto Y, Seino Y, Matsukura S, Nozawa M, Fujita T (1979) Somatostatin release from isolated perfused rat pancreas. Possible role of endogenous somatostatin on insulin release. Diabetes 28: 600–603
47. Kazumi T, Utsumi M, Yoshino G, Ishihara K, Hirose Y, Makimura H, Baba S (1980) Somatostatin concentration responds to arginine in portal plasma. Effects of fasting, streptozotocin diabetes, and insulin administration in diabetic rats. Diabetes 29: 71–73
48. Kohen E, Kohen C, Thorell B, Mintz DH, Rabinovitch A (1979) Intercellular communication in pancreatic islet monolayer cultures: A microfluorometric study. Science 204: 862–865
49. Landgraf R, Kotler-Brajtburg J, Matschinsky FM (1971) Kinetics of insulin release from the perfused rat pancreas caused by glucose, glucosamine, and galactose. Proc Natl Acad Sci USA 68: 536–540
50. Larsson L-I (1979) Innervation of the pancreas by substance P, enkephalin, vasoactive intestinal polypeptide and gastrin/CCK immunoreactive nerves. J Histochem Cytochem 27: 1283–1284
51. Larsson L-I, Goltermann N, de Magistris L, Rehfeld JF, Schwartz TW (1979) Somatostatin cell processes as pathways for paracrine secretion. Science 205: 1393–1395
52. Larsson L-I, Rehfeld JF (1979) Peptidergic and adrenergic innervation of pancreatic ganglia. Scand J Gastroenterol 14: 433–437
53. Luft R, Efendić S, Hökfelt T (1978) Somatostatin – Both hormone and neurotransmitter? Diabetologia 14: 1–13
54. McIntosh C, Schauder P, Arnold R, Frerichs H, Creutzfeldt W (1978) Somatostatin release from isolated rat pancreatic islets: Reversal of D-glyceraldehyde induced inhibition and the dynamics of release in a perifusion system. In: Bloom SR (ed) Gut hormones. Churchill Livingstone, Edinburgh London New York, p 453–456
55. McQuillan MT (1977) Somatostatin, vol I: Annual research reviews. Churchill Livingstone, Edinburgh, p 87–88
56. Malaisse-Lagae F, Malaisse WJ (1971) Stimulus-secretion coupling of glucose-induced insulin release. III. Uptake of ^{45}calcium by isolated islets of Langerhans. Endocrinology 88: 72–80
57. Noe BD, Spiess J, Rivier JE, Vale W (1979) Isolation and characterization of somatostatin from Anglerfish pancreatic islet. Endocrinology 105: 1410–1415
58. Orci L, Baetens D, Dubois MP, Rufener C (1975) Evidence for the D-cell of the pancreas secreting somatostatin. Horm Metab Res 7: 400–402
59. Orci L, Baetens D, Rufener C, Amherdt M, Ravazzola M, Studer P, Malaisse-Lagae F, Unger RH (1976) Hypertrophy and hyperplasia of somatostatin-containing D-cells in diabetes. Proc Natl Acad Sci USA 73: 1338–1342
60. Orci L, Malaisse-Lagae F, Ravazzola M, Rouiller D, Renold AE, Perrelet A, Unger RH (1975) A morphological basis for

the intercellular communication between α- and β-cells in the endocrine pancreas. J Clin Invest 56: 1066–1070
61. Orci L, Unger RH (1975) Functional subdivision of islets of Langerhans and possible role of D-cells. Lancet II: 1243–1244
62. Orci L, Unger RH, Renold AE (1973) Structural coupling between pancreatic islet cells. Experientia 29: 1015–1018
63. Patel YC, Amherdt M, Orci L (1979) Somatostatin secretion from monolayer cultures of neonatal rat pancreas. Endocrinology 104: 676–679
64. Patel YC, Weir GC (1976) Increased somatostatin content of islets from streptozotocin-diabetic rats. Clin Endocrinol (Oxf) 5: 191–194
65. Patton GS, Dobbs RE, Orci L, Vale W, Unger RH (1976) Stimulation of pancreatic immunoreactive somatostatin (IRS) release by glucagon. Metabolism 25 [Suppl 1]: 1499
66. Patton GS, Ipp E, Dobbs RE, Orci L, Vale W, Unger RH (1976) Response of pancreatic immunoreactive somatostatin to arginine. Life Sci 19: 1957–1960
67. Patton GS, Ipp E, Dobbs RE, Orci L, Vale W, Unger RH (1977) Pancreatic immunoreactive somatostatin release. Proc Natl Acad Sci USA 74: 2140–2143
68. Pearse AGE, Polak JM (1978) The diffuse neuroendocrine system and the APUD concept. In: Bloom SR (ed) Gut hormones. Churchill Livingstone, Edinburgh London New York, p 33–39
69. Porte D, Pupo AA (1969) Insulin response to glucose: Evidence for a two pool system in man. J Clin Invest 48: 2309–2319
70. Randle PJ, Ashcroft SJH, Gill JR (1968) Carbohydrate metabolism and release of hormones. In: Dickens F, Randle PJ, Whelan WJ (eds) Carbohydrate metabolism and its disorders, vol 1. Academic Press, London New York, p 427–447
71. Redding TW, Coy DH (1974) The disappearance, distribution and excretion of ^{125}I-tyrosine^{1}-growth hormone release inhibiting hormone in mice, rats and man. 56th Meeting of the American Endocrine Society, Atlanta, Georgia, A198
72. Rehfeld JF (1978) Gastrointestinal hormones and somatostatin release. Gastroenterology 75: 540–541
73. Rehfeld JF, Larsson L-I, Goltermann NR, Schwartz TW, Holst JJ, Jensen SL, Morley JS (1980) Neural regulation of pancreatic hormone secretion by the C-terminal tetrapeptide of CCK. Nature 284: 33–38
74. Rouiller D, Schusdziarra V, Harris V, Unger RH (1978) Physiological role of CCK, secretin and GIP in pancreatic and gastric somatostatin release. Clin Res 26: 721A
75. Samols E, Tyler JM, Marks V (1972) Glucagon – Insulin interrelationships. In: Lefebvre P, Unger RH (eds) Glucagon. Pergamon, New York, p 151–173
76. Samols E, Weir GC (1979) Adrenergic modulation of pancreatic A, B, and D cells. J Clin Invest 63: 230–238
77. Samols E, Weir GC, Ramseur R, Day JA, Patel YC (1978) Modulation of pancreatic somatostatin by adrenergic and cholinergic agonism and by hyper- and hypoglycemic sulfonamides. Metabolism 27 [Suppl 1]: 1219–1221
78. Schauder P, McIntosh C, Arends J, Arnold R, Frerichs H, Creutzfeldt W (1977) Somatostatin and insulin release from rat pancreatic islets in response to D-glucose, L-leucine, α-ketoisocaproic acid or D-glyceraldehyde: evidence for a regulatory role of adenosine – 3',5'-cyclic monophosphate. Biochem Biophys Res Commun 75: 630–635
79. Schauder P, McIntosh C, Arends G, Arnold R, Frerichs H, Creutzfeldt W (1976) Somatostatin and insulin release from isolated rat pancreatic islets stimulated by glucose. FEBS Lett 68: 225–227
80. Schauder P, McIntosh C, Arends J, Frerichs H (1979) Effect of fasting on the release of insulin and somatostatin from perfused islets of Langerhans. Diabetes 28: 204–207
81. Schauder P, McIntosh C, Panten U, Arends J, Arnold R, Frerichs H, Creutzfeldt W (1977) Dynamics of somatostatin release from isolated rat pancreatic islets. FEBS Lett 81: 355–358
82. Schauder P, McIntosh C, Panten U, Arends J, Arnold R, Frerichs H, Creutzfeldt W (1978) Dynamics of somatostatin and insulin release from isolated rat pancreatic islets. Evidence for intra-islet interactions between B cells and D cells. Metabolism 27 [Suppl 1]: 1211–1214
83. Schauder P, McIntosh C, Schindler B, Panten U, Frerichs H (1978) Comparison of α-ketoisocaproic acid and glucose in rats: effects on insulin and somatostatin release and on islet cAMP content. Mol Cell Endocrinol 11: 51–61
84. Schusdziarra V, Dobbs RE, Harris V, Unger RH (1977) Immunoreactive somatostatin levels in plasma of normal and alloxan diabetic dogs. FEBS Lett 81: 69–72
85. Schusdziarra V, Harris V, Arimura A, Unger RH (1979) Evidence for a role of splanchnic somatostatin in the homeostasis of ingested nutrients. Endocrinology 104: 1705–1708
86. Schusdziarra V, Harris V, Conlon JM, Arimura A, Unger RH (1978) Pancreatic and gastric somatostatin release in response to intragastric and intraduodenal nutrients and HCl in the dog. J Clin Invest 62: 509–518
87. Schusdziarra V, Harris V, Unger RH (1979) Half-life of somatostatin-like immunoreactivity in canine plasma. Endocrinology 104: 109–110
88. Schusdziarra V, Ipp E, Harris V, Dobbs RE, Raskin P, Orci L, Unger RH (1978) Studies on the physiology and pathophysiology of the pancreatic D cell. Metabolism 27 [Suppl 1]: 1227–1232
89. Schusdziarra V, Rouiller D, Arimura A, Unger RH (1978) Antisomatostatin serum increases levels of hormones from the pituitary and gut, but not from the pancreas. Endocrinology 103: 1956–1959
90. Schusdziarra V, Rouiller D, Harris V, Conlon JM, Unger RH (1978) The response of plasma somatostatin-like immunoreactivity to nutrients in normal and alloxan diabetic dogs. Endocrinology 103: 2264–2273
91. Schusdziarra V, Rouiller D, Harris V, Unger RH (1979) Gastric and pancreatic release of somatostatin-like immunoreactivity during the gastric phase of a meal. Effects of truncal vagotomy and atropine in the anesthetized dog. Diabetes 28: 658–663
92. Schusdziarra V, Zysnar E, Rouiller D, Boden G, Brown JC, Arimura A, Unger RH (1980) Splanchnic somatostatin: A hormonal regulator of nutrient homeostasis. Science 207: 530–532
93. Sehlin J, Täljedal I-B (1974) Transport of rubidium and sodium in pancreatic islets. J Physiol (Lond) 242: 505–515
94. Sehlin J, Täljedal I-B (1974) Sodium uptake by microdissected pancreatic islets: effects of ouabain and chloromercuribenzene-p-sulphonic acid. FEBS Lett 39: 209–213
95. Seino S, Sakurai H, Seino Y, Tsuda K, Tanigawa K, Kuzuya H, Goto Y, Imura H (1980) Starvation-induced changes of somatostatin, glucagon, and insulin secretion from the isolated perfused rat pancreas. Diabetes 29: 323–325
96. Shapiro B, Berelowitz M, Pimstone BL, Kronheim S, Sheppard M (1979) Tissue and serum somatostatin-like immunoreactivity in fed, 15-h-fasted, and 72-h-fasted rats. Diabetes 28: 182–184
97. Sheppard M, Shapiro B, Pimstone BL, Kronheim S, Berelowitz M, Gregory M (1979) Metabolic clearance and plasma disappearance time of exogenous somatostatin in man. J Clin Endocrinol Metab 48: 50–53
98. Spiess J, Rivier JE, Rodkey JA, Bennett CD, Vale W (1979)

Isolation and characterization of somatostatin from pigeon pancreas. Proc Natl Acad Sci USA 76: 2974–2978
99. Stagner JI, Samols E, Weir GC (1980) Sustained oscillations of insulin, glucagon, and somatostatin from the isolated canine pancreas during exposure to a constant glucose concentration. J Clin Invest 65: 939–942
100. Stewart JK, Steiner RA, Barber J, Koerker DJ, Goodner CJ, Game GC (1977) Effects of active immunisation against somatostatin on secretion of growth hormone and insulin in adolescent male baboons. Program of 59th Annual Meeting of the Endocrine Society, 348A
101. Taniguchi H, Utsumi M, Hasegawa M, Kobayashi T, Watanabe Y, Murakami K, Seki M, Tsutou A, Makimura H, Sakoda M, Baba S (1977) Physiologic role of somatostatin. Insulin release from rat islets treated by somatostatin antiserum. Diabetes 26: 700–702
102. Tannenbaum GS, Epelbaum J, Colle E, Brazeau P, Martin JB (1978) Dissociation of effects of somatostatin antiserum on growth hormone and insulin secretion. Metabolism 27 [Suppl 1]: 1263–1267
103. Unger RH, Ipp E, Schusdziarra V, Orci L (1977) Hypothesis: physiologic role of pancreatic somatostatin and the contribution of D-cell disorders to diabetes mellitus. Life Sci 20: 2081–2086
104. Wasada T, Pietri A, Raskin P, Dobbs R, Unger RH (1980) Effect of free fatty acids (FFA) on the gastric and pancreatic secretion of somatostatin-like immunoreactivity. Diabetes 29 [Suppl 2]: 9A
105. Weir GC, Samols E, Day JA, Patel YC (1978) Glucose and glucagon stimulate the secretion of somatostatin from the perfused canine pancreas. Metabolism 27 [Suppl 1]: 1223–1226
106. Weir GC, Samols E, Loo S, Patel YC, Gabbey KH (1979) Somatostatin and pancreatic polypeptide secretion: effects of glucagon, insulin, and arginine. Diabetes 28: 35–40
107. Zern RT, Foster LB, Blalock JA, Feldman JM (1979) Characteristics of the dopaminergic and noradrenergic systems of the pancreatic islets. Diabetes 28: 185–189

Received: September 9, 1980

K. Hermansen
2nd University Clinic of Internal Medicine
Kommunehospitalet
DK-8000 Aarhus C
Denmark