ANNALS OF SURGERY
Vol. 219, No. 3, 258–266

Splanchnic Neural Regulation of Somatostatin Secretion in the Isolated Perfused Human Pancreas

F. Charles Brunicardi,*† Dariush Elahi,* and Dana K. Andersen*‡

From the Department of Surgery and Medicine, State University of New York, Health Science Center at Brooklyn, Brooklyn, New York; the Department of Surgery-Veteran's Affairs Medical Center West Los Angeles and the University of California Los Angeles School of Medicine, Los Angeles, California;† and the Department of Surgery, University of Chicago Medical Center, Chicago, Illinois‡*

Objective

The somatostatin-secreting delta cells in the islets of Langerhans appear to be regulated by neural mechanisms that have not been defined clearly. In this study, the celiac neural bundle of the human pancreas was electrically stimulated in the presence and absence of selective neural antagonists.

Summary Background Data

The authors previously reported on studies of the splanchnic neural regulation of insulin, glucagon, and pancreatic polypeptide secretion. In these studies, alpha-adrenergic fibers appeared to have a predominant effect, strongly inhibiting the secretion of insulin, glucagon, and pancreatic polypeptide secretion. Cholinergic fibers appeared to stimulate strongly, although beta-adrenergic fibers weakly stimulated, the secretion of these hormones. Investigations of neural regulatory mechanisms governing human somatostatin release *in vitro* have not been previously reported.

Methods

Pancreata were obtained from eight cadaveric organ donors. The isolated perfused human pancreas technique was used to assess the regulation of somatostatin secretion by the various neural fibers contained within the celiac plexus. The secretory response of somatostatin was examined in the presence of 16.7 mmol/L glucose, with and without neural stimulation, and specific neural antagonists.

Results

The basal somatostatin secretion was 88 ± 26 fmol/g/min and increased 131 ± 23% ($n = 8$, $p < 0.01$) in response to 16.7 mmol/L glucose. The augmentation seen with glucose was inhibited 66 ± 22% ($n = 8$, $p < 0.05$) during celiac neural bundle stimulation. Alpha-adrenergic blockade resulted in a 90 ± 30% ($n = 6$, $p < 0.01$) augmentation of somatostatin release. Beta-adrenergic blockade caused a 13 ± 2% ($n = 6$, $p < 0.05$) suppression of somatostatin release. Complete adrenergic blockade resulted in a 25 ± 23% ($n = 5$, p = not significant) inhibition of somatostatin release. Cholinergic blockade resulted in a 40 ± 10% ($n = 6$, $p < 0.02$) suppression of somatostatin release.

Conclusions

The predominant effect of celiac neural bundle stimulation was inhibition of somatostatin secretion through an alpha-adrenergic effect. Beta-adrenergic fibers stimulate somatostatin secretion; cholinergic fibers have a negligible effect on somatostatin secretion. These data suggest that the splanchnic innervation of the pancreas has a potent regulatory role in somatostatin release in this *in vitro* human model.

The somatostatin-secreting delta cells in the islets of Langerhans appear to be regulated by neural mechanisms that have not been defined clearly. Animal studies yield conflicting results concerning these mechanisms. Vagal stimulation and acetylcholine have been shown to both inhibit[1-5] and stimulate[6-10] somatostatin secretion. Adrenergic agonists have also been shown to both stimulate and inhibit somatostatin secretion.[11-16] Human *in vivo* studies suggest that the postprandial rise in somatostatin plasma levels is regulated by cholinergic and not adrenergic mechanisms;[17-19] however, it is difficult to relate findings from *in vivo* studies specifically to the delta cell of the islet because somatostatin is released from many organs.[20]

To our knowledge, no investigation of neural regulatory mechanisms governing human somatostatin release *in vitro* has been previously reported. Using an *in vitro* human pancreas model, we previously reported on studies of the splanchnic neural regulation of insulin, glucagon, and pancreatic polypeptide secretion.[21,22] In these studies, alpha-adrenergic fibers appeared to have a predominant effect that strongly inhibited the secretion of insulin, glucagon, and pancreatic polypeptide secretion. Cholinergic fibers appeared to stimulate strongly, although beta-adrenergic fibers weakly stimulated, the secretion of these hormones. In this study, the isolated perfused human pancreas technique was used to assess the regulation of somatostatin secretion by the various neural fibers contained within the celiac plexus. The secretory response of somatostatin was examined in the presence of 16.7 mmol/L glucose, with and without normal stimulation, and specific neural antagonists.

MATERIALS AND METHODS

Pancreata were obtained from eight cadaveric organ donors after brain death caused by trauma (n = 3), subarachnoid hemorrhage (n = 4), or myocardial infarction (n = 1). The donors ranged from 16 to 71 years of age. Three were men, and five were women. There was no history of pancreatic disease in any of the donors.

We used an *in vitro* human pancreas model to examine the neural regulation of islet cell secretion. The details of the model were discussed previously.[21] All pancreata were harvested in a manner consistent with that of segmental pancreas transplantation.[23] The donors were free of pancreatic disease and had suffered brain death from various causes. However, all had undergone the stress of preharvest maintenance and had been exposed to preharvest medications. During the harvesting procedure, the splanchnic neural fibers adjacent to the splenic artery were isolated and preserved for subsequent neural stimulation.

After renal harvesting, the pancreas was freed of surrounding structures and mobilized according to the technique described by Kelly et al.[23] After the colon was mobilized, the pancreatic resection began with the excision of the gastrolienal and lienorenal ligaments and transsection of the short gastric vessels. The pancreas and spleen were mobilized from the retroperitoneum and lifted medially, thus exposing the posterior surface of the pancreas. The splenic artery, splenic vein, and splanchnic neural trunk were identified and isolated along the posterior surface of the body of the pancreas. The splenic artery was cannulated with a 14-gauge catheter, and the pancreas was perfused *in situ* with cold lactated Ringer's solution. While the cold perfusion continued, the pancreas was transsected through the neck of the gland, and the spleen was dissected from the pancreas at the hilum with careful ligation of all vessels. The pancreatic duct was cannulated with an 18-gauge catheter, and the cut surface was oversewn. The splenic vein was cannulated with silastic tubing (6-mm outer diameter) containing multiple drain holes. The total dissection time was 20 to 25 minutes during which the gland was kept at 4 C. The gland was then transported in iced lactated Ringer's solution to the laboratory where single-pass perfusion was performed on the perfusion apparatus (AMBEC Two/Ten Perfuser, MX International, Aurora, CO).

The perfusion medium was a Krebs-Ringer's bicarbonate buffer containing 3.9 mmol/L glucose, 1% human serum albumin (NYBCEN, New York, NY), and 3% T-70 dextran (Sigma, St. Louis, MO). The medium was gassed with 95% O_2 and 5% CO_2 and heated to 37 C. After rewarming and equilibration with a 30-minute

Supported by a grant from the National Institutes of Health (DK 39950).

Address reprint requests to Charles Brunicardi, M.D., UCLA School of Medicine, Department of Surgery, Room 72-215 CHS, Los Angeles, CA 90024.

Accepted for publication June 21, 1993.

basal perfusion, sequential 16-minute test periods were performed, separated by 14-minute basal periods. The total length of perfusion was 178 ± 15 minutes and ranged from 106 to 220 minutes. Flow rates were adjusted to maintain a perfusion pressure of 50 to 60 cmH_2O and ranged from 1.0 to 1.2 mL/g/min. Aliquots of venous effluent (6 to 9 mL) containing Trasylol, 500 kIU/mL (FBA Pharmaceuticals, New Haven, CT) were collected on ice by splenic vein catheter drainage, immediately assayed for glucose, and then frozen at −20 C for subsequent radioimmunoassay of hormones.

Each test period contained either (1) 16.7 mmol/L glucose alone (n = 8) or 16.7 mmol/L glucose in combination with (2) bipolar electrical stimulation (10 V, 5 ms, 10 Hz; model 104-A laboratory stimulator, American Electronic Laboratories, Colmar, PA) of the splanchnic neural fibers (n = 8) or (3) neural stimulation and 4 μmol/L phentolamine (Ciba Geigy, Summit, NJ; n = 6); (4) neural stimulation and 6 μmol/L propranolol (Eli Lilly, Indianapolis, IN; n = 6); (5) neural stimulation, phentolamine, and propranolol (n = 5); or (6) neural stimulation and 5 μmol/L atropine (Elkins-Sinn, Cherry Hill, NJ; n = 6), in random order. The 14-minute basal period allows sufficient time for hormone secretion to return to the baseline level; however, to minimize the effect of one stimulation on the subsequent stimulation, randomization of the infusions was performed. Not all preparations received every test substance or intervention. Comparisons were made only when appropriately controlled test periods were completed in each perfusion. The perfusates were prepared fresh in perfusion media immediately before each study and delivered through a side arm into the arterial port. The viability of the preparation for the length of the extended perfusion was documented by basal and stimulated hormone secretion at the end of the perfusion period in response to 16.7 mmol of glucose, by periodic arteriovenous oxygen differences, and by histologic examination of the pancreas.

Perfusate and effluent glucose levels were determined by the glucose oxidase method (Beckman glucose analyzer, Fullerton, CA). Immunoreactive somatostatin (IRS) was measured using antibody SL-7.[24] The antibody was made in rabbits against synthetic somatostatin conjugated to bovine serum albumin and is specific for the central region of somatostatin, with a 75% cross reactivity with somatostatin-28. The 50% inhibitory dose for the radioimmunoassay using this antibody was 20 fmol per tube, and the minimal detection limit was 2 fmol per tube. The interassay coefficient of variation was 8%, and the intra-assay variation was 11%.

Statistical analyses were performed comparing stimulated basal periods by paired Student's t test. A p value less than 0.05 was considered significant. The integrated somatostatin responses were calculated as the weighted mean increase or decrease from basal values using the trapezoidal rule. The integrated area was then divided by the total time of the period (16 minutes) to determine the mean difference from the basal level in femtomoles per gram per minute for somatostatin secretion. If more than one stimulation with identical stimulants was performed in a single preparation, the mean responses were calculated, and comparisons between test periods were then carried out by paired analyses. The data are presented as the mean ± the standard error of the mean.

As a result of the large variation in basal and stimulated values observed in the eight preparations, these and all subsequent data are depicted graphically as the per cent of the basal level. Calculations of augmentation or inhibition of responses, and the significance thereof, were performed on the actual integrated response of somatostatin during the time interval examined. This study was reviewed and approved by Institutional Review Boards of the State University of New York-Brooklyn Health and Science Center. Informed consent was obtained from the next of kin of each donor subject.

RESULTS

IRS Response to 16.7 mmol/L Glucose

The somatostatin response to 16.7 mmol/L glucose is shown in Figure 1. The upper panel depicts the glucose square wave created by raising the glucose concentration through the side-arm infusion from a basal value of 70 mg/dL to an elevated value of 300 mg/dL for 16 minutes. The basal somatostatin secretion was 88 ± 27 fmol/g/min and increased 12 ± 3.2 fmol/g/min in response to 16.7 mmol/L glucose ($n = 8$, $p < 0.01$). This represented a 131 ± 23% basal level as depicted in Figure 1. Although there appeared to be a mild rebound effect immediately after the stimulation period, the effect was not significant.

IRS Response to Splanchnic Nerve Stimulation

The IRS response to bipolar electrical stimulation (10 V, 5 ms, 10 Hz) of the splanchnic neural fibers during 16.7 mmol/L glucose perfusion is shown in Figure 2. The IRS response to 16.7 mmol/L glucose was inhibited 66 ± 22% ($n = 8$, $p < 0.05$) by nerve stimulation. This effect was observed throughout the perfusion period.

IRS Response to Splanchnic Nerve Stimulation and Phentolamine Infusion

The response of IRS to electrical stimulation of the splanchnic neural fibers during the combined perfusion

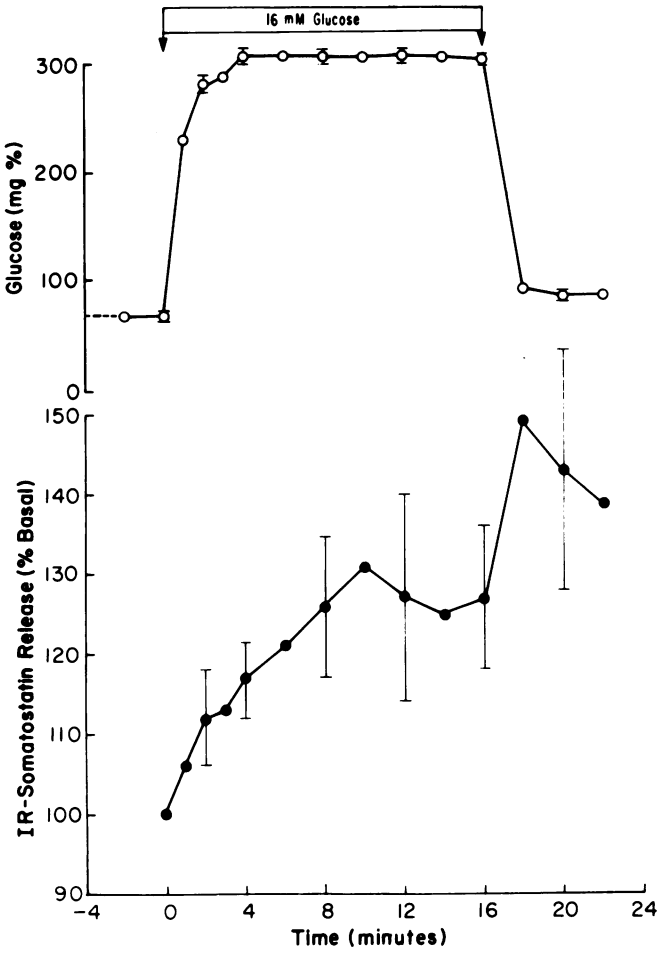

Figure 1. IRS response to high glucose. The IRS response to 16.7 mmol/L glucose (G) is shown. The upper panel depicts the glucose square wave created by raising the glucose concentration through the side-arm perfusion. The lower panel depicts the IRS response. The basal IRS level was 88 ± 27 fmol/g/min. In response to G, somatostatin secretion was stimulated 131 ± 23% (n = 8, $p < 0.01$) above the basal level. The mean ± standard error of the mean (SEM) of the values are shown.

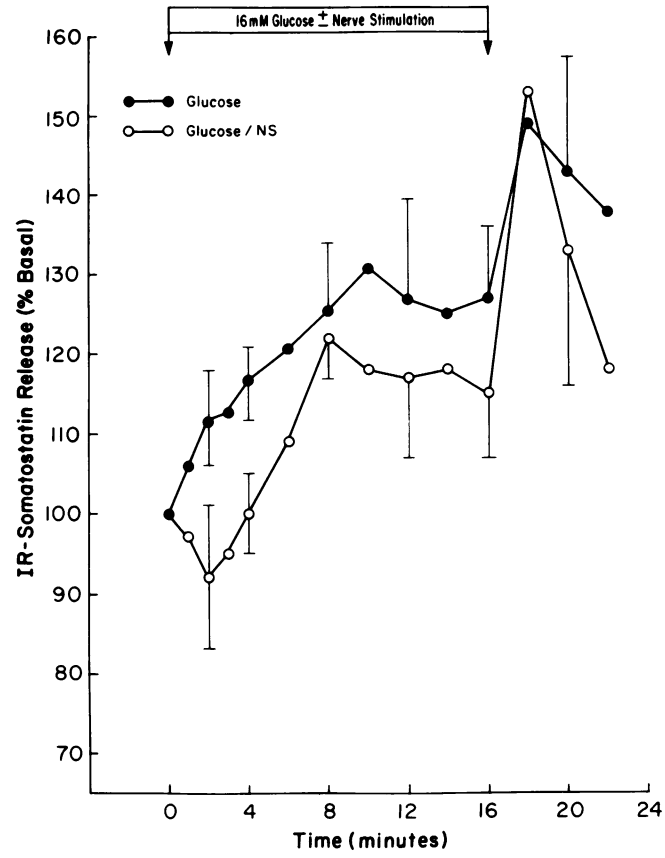

Figure 2. IRS response to splanchnic nerve stimulation. The IRS response to bipolar electrical stimulation (10 V, 5 ms, 10 Hz) of the splanchnic neural fibers (NS) during 16.7 mmol/L glucose (G) perfusion is shown. The panel compares the IRS release seen with NS and G (open circles) to the IRS release seen with G alone (closed circles). The integrated response of IRS was inhibited 66 ± 22% (n = 8, $p < 0.05$) by NS by comparison with that seen with G alone. The mean ± SEM of the values are shown.

with 4 μmol/L phentolamine and 16.7 mmol/L glucose is shown in Figure 3. Alpha-adrenergic blockage was reversed during the inhibition of glucose-induced IRS release by nerve stimulation; this represented an augmentation of 90 ± 30% (n = 6, $p < 0.05$) above the response of IRS to glucose alone and 151 ± 50% (n = 5, $p < 0.05$) above the response of IRS to glucose and nerve stimulation alone.

IRS Response to Splanchnic Nerve Stimulation and Propranolol Infusion

The response of IRS to electrical stimulation of the splanchnic neural fibers during combined perfusion with 6 μmol/L propranolol and 16.7 mmol/L glucose is shown in Figure 4. Beta-adrenergic blockade resulted in further suppression of the IRS response than to the level seen with nerve stimulation. In the presence of propranolol, IRS release was inhibited 13 ± 2% (n = 5, $p < 0.01$) by comparison with glucose alone and 8 ± 2% (n = 4, $p < 0.025$) by comparison with glucose and nerve stimulation.

IRS Response to Splanchnic Nerve Stimulation with Phentolamine and Propranolol Infusion

The response of IRS to electrical stimulation of the splanchnic neural fibers during combined perfusion with 4 μmol/L phentolamine, 6 μmol/L propranolol, and 16.7 mmol/L glucose is shown in Figure 5. Total sympathetic blockade resulted in a mild inhibition of IRS release. In the presence of phentolamine and propranolol, IRS release was inhibited 25 ± 23% (n = 5, p = not sig-

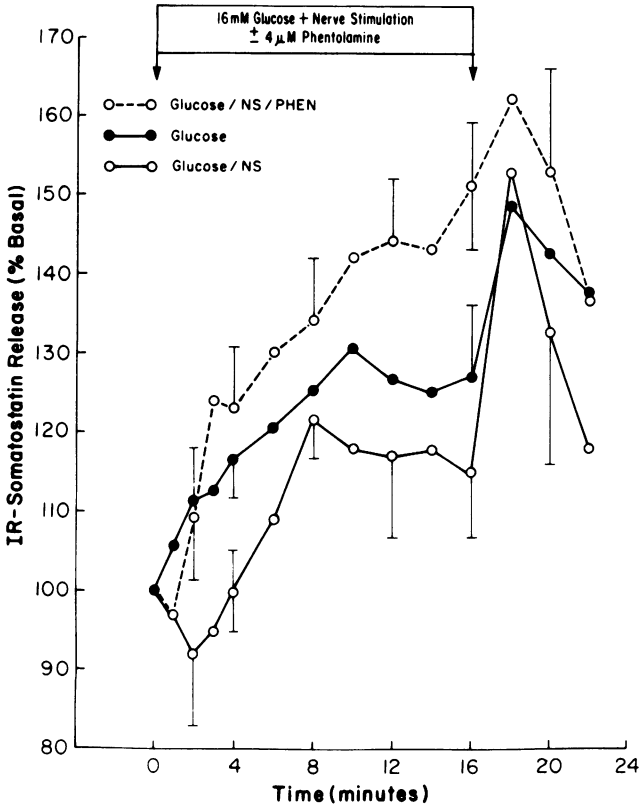

Figure 3. IRS response to splanchnic nerve stimulation and phentolamine infusion. The IRS response to electrical stimulation of the splanchnic neural fibers (NS) during 4 μmol/L phentolamine and 16.7 mmol/L glucose (G) perfusion is shown. The panel compares IRS release seen with phentolamine, NS, and G (open circles, dashed lines) with the IRS release seen with NS and G alone (closed circles, solid lines) with the IRS release seen with G alone (closed circles). The inhibition of IRS by NS was reversed by phentolamine resulting in a 90 ± 30% (n = 6, $p < 0.05$) increase in the IRS release by comparison with G alone and a 151 ± 50% (n = 5, $p < 0.05$) increase by comparison with G and NS alone.

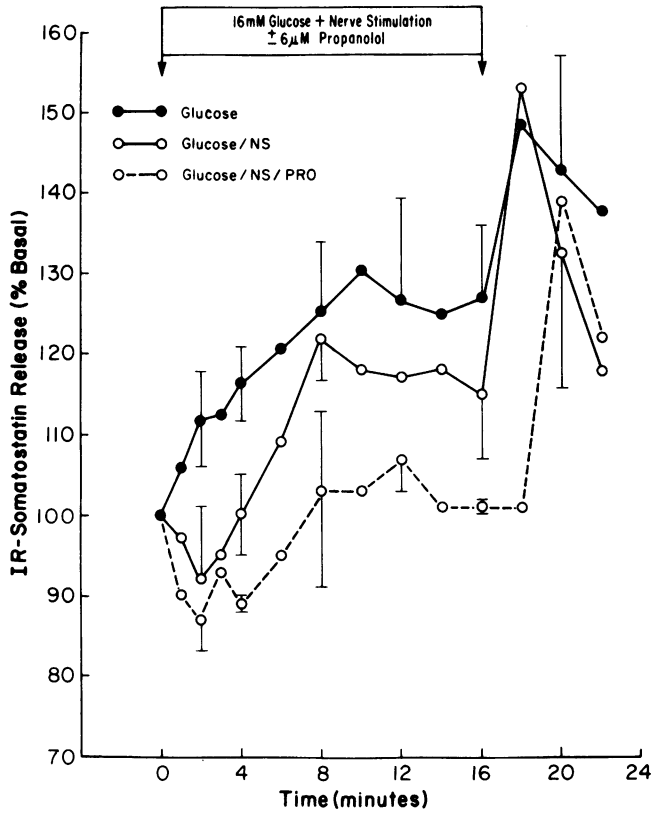

Figure 4. IRS response to splanchnic nerve stimulation and propranolol infusion. The IRS response to electrical stimulation (10 V, 5 ms, 10 Hz) of the splanchnic neural fibers (NS) during 6 mmol/L propranolol and 16.7 mmol/L glucose (G) perfusion is shown. The panel compares the IRS release seen with propranolol, NS, and G (open circles, dashed lines) with the IRS release seen with NS and G (open circles, solid lines) with the IRS release seen with G alone (closed circles). The addition of G and NS during propranolol infusion further suppressed the IRS release by 13 ± 2% (n = 5, $p < 0.01$) by comparison with G alone and 8 ± 2% (n = 4, $p < 0.025$) by comparison with G and NS alone.

nificant) by comparison with the response seen with glucose alone and was augmented 50 ± 22% (n = 4, p = NS) by comparison with glucose and nerve stimulation.

IRS Response to Splanchnic Nerve Stimulation with Atropine Infusion

The response of IRS to electrical stimulation of the splanchnic neural fibers during combined perfusion with 5 μmol/L atropine and 16.7 mmol/L glucose is shown in Figure 6. Cholinergic blockade resulted in an inhibition of IRS release. During atropine infusion, the IRS response was inhibited 40 ± 10% (n = 6, $p < 0.02$) by comparison with glucose alone, and it was inhibited 73 ± 6% (n = 3, p = not significant) by comparison with glucose and nerve stimulation.

DISCUSSION

In the 19th century, Claude Bernard[25] punctured the floor of the fourth ventricle and demonstrated alterations in glucose regulation. Since then, the neural regulation of islet cell secretion has been extensively studied.[26-30] It is therefore well accepted that the islets are highly innervated and that innervation plays an important regulatory role in islet hormone release.[31]

In examining the splanchnic neural regulation role of insulin, glucagon, and pancreatic polypeptide in the perfused human pancreas, we previously demonstrated that alpha-adrenergic fibers inhibit, cholinergic fibers strongly stimulate, and beta-adrenergic fibers mildly stimulate hormone secretion.[21,22] Electrical stimulation of the entire celiac bundle, however, affected the secretion of these three hormones in different ways. Glucose-stimulated insulin secretion was strongly inhibited by ce-

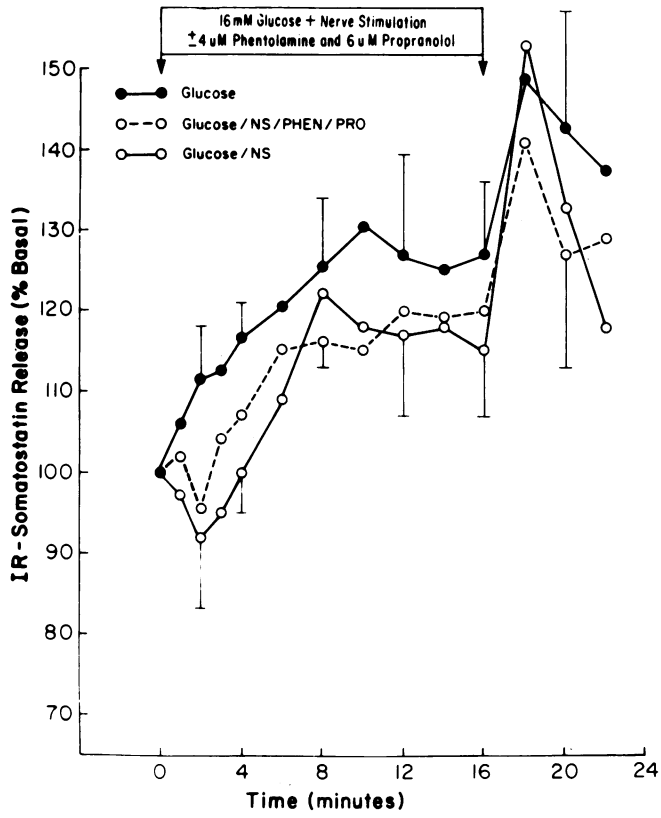

Figure 5. IRS response to splanchnic nerve stimulation, phentolamine, and propranolol infusion. The IRS response to electrical stimulation of the splanchnic neural fibers (NS) during 4 mmol/L phentolamine, 6 mmol/L propranolol, and 16.7 mmol/L glucose (G) perfusion is shown. The panel compares IRS release seen with phentolamine, propranolol, NS, and G (open circles, dashed lines) with the IRS release seen with NS and G (open circles, solid lines) with the IRS release seen with G alone (closed circles). G plus NS during phentolamine and propranolol infusion resulted in a mild augmentation 50 ± 22% (n = 4, p = NS) of IRS by comparison with G and NS and 25 ± 23% (n = 5, p = NS) inhibition of IRS release by comparison with that seen with G alone.

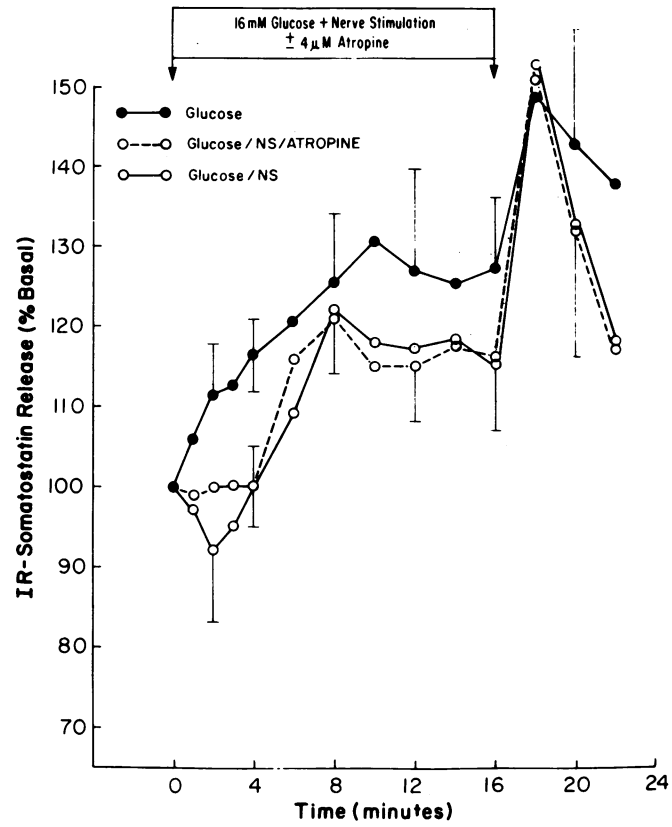

Figure 6. IRS response to splanchnic nerve stimulation and atropine infusion. The IRS response to electrical stimulation of the splanchnic neural fibers (NS) during 5 mmol/L atropine and 16.7 mmol/L glucose (G) perfusion is shown. The panel compares IRS release seen with atropine, NS, and G (open circles, dashed lines) with the IRS release seen with NS and G (open circles, solid lines) with the IRS release seen with G alone (closed circles). G and NS during atropine infusion resulted in a 40 ± 10% (n = 6, $p < 0.02$) suppression of IRS by comparison with G alone and a 73 ± 66% (n = 3, p = not significant) suppression by comparison with NS and glucose alone.

liac neural bundle stimulation; glucagon and pancreatic polypeptide were strongly stimulated. In this single-pass perfusion system, the differences in hormone secretion were attributed either to a direct neural effect or to an indirect hormonal effect, perhaps caused by alterations in intraislet somatostatin levels.

The neural regulation of the somatostatin-secreting delta cells of the islet has not been clearly delineated. The results of studies on the regulatory mechanisms governing the neural control of somatostatin secretion in numerous animal models have been contradictory. Sympathetic stimulation was reported to both augment and inhibit somatostatin release.[11-16] Vagal stimulation and acetylcholine both inhibited[1-5] and stimulated[6-10] somatostatin secretion. In the isolated canine pancreas model, alpha-adrenergic agonism caused an inhibition of somatostatin secretion, and beta-adrenergic agonism caused an increase in somatostatin secretion. In the isolated porcine pancreas model, vagal stimulation inhibited somatostatin secretion.

In vivo human studies suggest that somatostatin is primarily under vagal control.[17-19] It is difficult to interpret human *in vivo* studies of neural regulation of somatostatin secretion because the hormone is released from many organs.[20] This is the first study, to our knowledge, in which an analysis of the individual effects of alpha-adrenergic, beta-adrenergic, and cholinergic mediation of somatostatin release was done in an *in vitro* human pancreas model. The basal secretory rate of somatostatin in this model was 80 ± 26 fmol/g/min. In response to 16.7 mmol/L glucose perfusion, somatostatin secretion was significantly stimulated. This response is consistent with previous studies in which glucose-stimulated somatostatin secretion was observed.[24,32-34] In a previous study, we observed parallel responses of somatostatin

and insulin to 16.7 mmol/L glucose perfusion and reciprocal responses of pancreatic polypeptide and glucagon.[35] The stimulation of somatostatin secretion by glucose was consistent with a possible inhibitory role of this hormone on pancreatic polypeptide and glucagon secretion during high-glucose perfusion. Although paracrine effects have never been demonstrated in any pancreas model, potential intraislet regulation of peptide secretion must be considered. These data support the hypothesis that somatostatin plays a regulatory role in the secretion of glucagon and pancreatic polypeptide within the islet.[36,37]

Bipolar electrical stimulation of the entire celiac neural bundle resulted in an inhibition of somatostatin release. The neural stimulation chosen was based on previous studies in animal models, especially the studies on the isolated perfused pig pancreas. This stimulation should result in a broad stimulation of all splanchnic fibers. The net effect of combined stimulation of different neural fibers on somatostatin secretion suggests a predominant alpha-adrenergic effect. The somatostatin response to combined neural stimulation parallels that of insulin, whereas glucagon and pancreatic polypeptide were stimulated by combined celiac neural bundle stimulation. These responses could be related in part to paracrine effects and to the direct effect of neurotransmitters on glucagon and pancreatic polypeptide secretion.

Alpha-adrenergic blockade with phentolamine infusion during nerve stimulation resulted in an augmentation of somatostatin secretion by comparison with that seen with glucose. This response was most likely the result of combined cholinergic and beta-adrenergic stimulation in the presence of a high-glucose infusion. It is possible, but unlikely, that the augmentation is related to changes in blood flow because the perfusion pressure and flow rate remained constant during the experiment; however, changes in intrapancreatic blood flow have been noted with certain stimuli[38,39] and could not be ruled out in this study. The fact that all four islet hormones are stimulated by alpha-adrenergic blockade in this human model supports the hypothesis that alpha-adrenergic fibers play an inhibitory role in the regulation of islet cell function in the pancreas.[12,21,22,40]

Beta-adrenergic blockade with propranolol infusion resulted in further inhibition of somatostatin secretion by comparison with that seen with glucose, suggesting that the beta-adrenergic fibers stimulate delta cell secretion. The potency of the beta-adrenergic fibers is unique for the delta cell because insulin, glucagon, and pancreatic polypeptide are only mildly augmented by beta-adrenergic stimulation in the *in vitro* human model.[21,22] Beta-adrenergic stimulation resulted in the stimulation of somatostatin secretion in different animal models[6,18,31,34] and was attributed to receptors of the β_1 subgroup.[40]

Combined perfusion with phentolamine and propranolol during splanchnic nerve stimulation and 16.7 mmol/L glucose perfusion resulted in a weak but insignificant inhibition of somatostatin secretion by comparison with that seen with glucose alone. The response seen during splanchnic nerve stimulation during beta-adrenergic and alpha-adrenergic blockade would suggest that cholinergic stimulation had little effect on somatostatin secretion. That was supported by the response seen during splanchnic nerve stimulation and atropine infusion, that is, the somatostatin response was essentially unchanged compared with that observed during splanchnic nerve stimulation alone. This result corroborates the minimal effect observed by direct cholinergic stimulation and is consistent with a potent, overriding alpha-adrenergic effect. Although the mild inhibition did not achieve statistical significance in this study, vagal stimulation and acetylcholine infusion were shown to result in a significant inhibition of somatostatin secretion in the isolated perfused pig pancreas.[40] The inhibitory response was believed to be the result of the activation of classic postganglionic cholinergic nerve fibers impinging on muscarinic cholinoreceptors. In the isolated perfused rat pancreas, acetylcholine infusion strongly stimulated insulin and glucagon secretion; it had no effect on somatostatin secretion.[3] Furthermore, the weak effect of the cholinergic fibers is unique for the delta cell because cholinergic stimulation had a potent stimulatory effect on the secretion of the other islet hormones.[21,22] The cholinergic regulation of somatostatin release may be species specific, and it is not a principal factor in the human pancreas.

Our results indicate that, in the isolated perfused human pancreas, splanchnic innervation plays an important regulatory role in somatostatin secretion. These data suggest that the predominant splanchnic neural effect on the delta cell is an alpha-adrenergic response that results in the inhibition of somatostatin secretion. Beta-adrenergic fibers stimulate somatostatin secretion, and cholinergic fibers have little effect on somatostatin secretion. By comparison with insulin, glucagon, and pancreatic polypeptide secretion, these findings suggest that the strong stimulatory role of the beta-adrenergic fibers and the weak inhibitory effect of the cholinergic fibers are unique for the delta cell. This suggests that the splanchnic innervation of the islet has a differential effect on islet cell secretion.

Although the influences of the individual alpha-adrenergic, beta-adrenergic, and cholinergic fibers on somatostatin release have been quantified in this study, the precise mechanism of the neural regulation of islet cell function remains unclear. Neural fibers may communicate

directly with islet cells, and the presence of these fibers has been observed histologically within the islets.[41,42] Somatostatin release has also been shown to be mediated by the ambient degree of insulin release, glucagon release, or both.[20,33,37,43] Therefore, the neural regulation of delta cell function may rely on endocrine or paracrine effects mediated by the response of the beta cells to direct neural inhibition or stimulation. Alpha-adrenergic stimulation may also result in reduced total islet blood flow as a result of local arteriolar vasoconstriction, and neurally mediated redistribution of islet blood flow may result in altered pancreatic hormone release. Although the mechanisms of action of the neural regulation of somatostatin release await further definition, it appears that the splanchnic innervation of the human pancreas has a potent regulatory role on somatostatin secretion. Neural control of delta cell hormone release is a potent form of regulation in the human pancreas.

Acknowledgment

The authors thank Dr. Tadataka Yamada for performing the somatostatin radioimmunoassays for this study.

References

1. Holst JJ, Jensen SL, Knuhtsen S, et al. Effect of vagus, GIP, and HCl on gastrin and somatostatin release from perfused pig antrum. Am J Physiol 1983; 244:G515–G522.
2. Holst JJ, Jensen SL, Nielsen OV, et al. Oxygen supply, oxygen consumption, and endocrine and exocrine secretion of the isolated perfused porcine pancreas. Acta Physiol Scand 1980; 109:7–13.
3. Kimura H, Katagiri K, Ohno T, et al. Effect of acetylcholine and new cholinergic derivative on amylase output, insulin, glucagon and somatostatin secretions for perfused isolated rat pancreas. Horm Metab Res 1982 14:356–360.
4. Samols E, Stagner JI, Weir GC. Autonomic function and control of pancreatic somatostatin. Diabetologia 1981; 20:338–392.
5. Uvnas-Wallensten K, Roovete A, Johansson C, et al. Decreased release of somatostatin into the portal vein following electrical stimulation in the cat. Acta Physiol Scand 1980; 109:393–399.
6. Hermansen K. Secretion of somatostatin from the normal and diabetic pancreas. Studies in vitro. Diabetologia 1980; 19:492–504.
7. Hermansen K, Christensen SE, Orskov H. Characterization of somatostatin release from the pancreas. The role of calcium and acetylcholine. Diabetologia 1979; 16:261–266.
8. Honey RN, Weir GE. Acetylcholine stimulates insulin, glucagon and somatostatin release in the perfused chicken pancreas. Endocrinology 1980; 107:1065–1068.
9. Kaneto A, Sato H, Kaneko T, et al. Stimulation of somatostatin, pancreatic polypeptide, glucagon and insulin secretion by acetylcholine infused intrapancreatically in dogs. Biomed Res 1981; 2: 57–66.
10. Wasada T, Dobbs RE, Harris V, et al. Effect of 2-deoxy-D-glucose on plasma somatostatin levels in conscious dogs. Endocrinology 1981; 108:1222–1227.
11. Honey RN, Schwarz JA, Mathe CJ, et al. Insulin, glucagon, and somatostatin secretion from isolated perfused rat and chicken pancreas-duodenum. Am J Physiol 1980; 238:E150–E156.
12. Itoh M, Gerich JE. Adrenergic modulation of pancreatic somatostatin, insulin and glucagon secretion: evidence for differential sensitivity of islet A, B, and D cells. Metabolism 1982; 31:715–720.
13. Samols E, Weir G. Adrenergic modulation of pancreatic A, B, and D cells. Alpha-adrenergic suppression and beta-adrenergic stimulation of somatostatin secretion, alpha-adrenergic stimulation of glucagon secretion in the perfused dog pancreas. J Clin Invest 1979; 63:230–238.
14. Sorenson RL, Elde RP, Seybold V. Effect of norepinephrine on insulin, glucagon and somatostatin secretion in isolated perfused rat islets. Diabetes 1979; 28:899–904
15. Roy MW, Jones MS, Miller RE. Pancreatic somatostatin secretion is suppressed by splanchnic nerve stimulation. Diabetologia 1981; 20:102–105.
16. Ahren B, Veith RC, Paquette TL, et al. Sympathetic nerve stimulation versus pancreatic norepinephrine infusion in the dog: 2. Effects on basal release of somatostatin and pancreatic polypeptide. Endocrinology 1987; 121:332–339.
17. Epstein S, Berelowitz M. The lack of adrenergic effects of somatostatin-like immunoreactivity in normal man. Neuropeptides 1981; 2:53–58.
18. Glaser B, Vinik I, Valtyason G, et al. Truncal vagotomy abolishes the somatostatin response to insulin-induced hypoglycemia in man. J Clin Endocrinol Metab 1981; 52:823–825.
19. Lucey MR, Wass JAH, Fairclough P, et al. Autonomic regulation of postprandial plasma somatostatin, gastrin, and insulin. Gut 1985; 26:683–688.
20. Reichlin S. Somatostatin. N Engl J Med 1983; 309:1495–1501.
21. Brunicardi FC, Goulet RJ, Sun YS, et al. Splanchnic neural regulation of insulin and glucagon release in the isolated perfused human pancreas. Am J Surg 1987; 153:34–40.
22. Brunicardi FC, Druck P, Seymour NE, et al. Splanchnic neural regulation of pancreatic polypeptide release in the isolated human pancreas. Am J Surg 1989; 159:50–57.
23. Kelly WD, Lillihei RC, Merkel FK, et al. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 1967; 651:827–37.
24. Gerich J, Greene K, Hara M, et al. Radioimmunoassay of somatostatin and its application in the study of pancreatic somatostatin secretion in vitro. J Lab Clin Med 1979; 93:1009–1017.
25. Bernard C. Chiens rendus diabetiques. Comptes Rendus des Seances de la Societe de Biologie et de ses Filiales (Paris) 1849; 1:60.
26. Langerhans P. Contributions to the Microscopic Anatomy of the Pancreas. Baltimore: Johns Hopkins Press, 1937.
27. Zunz E, LaBarre J. Contribution a l'étude des variations physiologiques de la sécrétion interne du pancreas. Arch Int Physiol Biochim Biophys 1927; 29:265–80.
28. Wilenko GG. Uber den einfluss des adrenalins auf den respiratorischen quotienten and die wirkungsweise des adrenalins. Biochem Z 1912; 42:44–58.
29. Sergeyeva MA. Microscopic changes in the islands of Langerhans produced by sympathetic and parasympathetic stimulation in the cat. Anat Rec 1940; 77:297–317.
30. Kaneto A, Kosaka K, Nakas K. Effects of stimulation of the vagus nerve on insulin secretion. Endocrinology 1967; 80:530–6.
31. Woods SC, Porte D Jr., Neural control of the endocrine pancreas. Physiol Rev 1974; 54:596–619.
32. Ipp E, Dobbs RE, Arimura A, et al. Release of immunoreactive somatostatin from the pancreas in response to glucose, amino acids, pancreozymin-cholecystokinin, and tolbutamide. J Clin Invest 1977; 60:760–765.
33. Brunicardi FC, Druck P, Sun YS, et al. The neural and hormonal regulation of somatostatin secretion in the isolated perfused pancreas. Gastroenterology 1986; 90:1360.

34. Hermansen K. Effects of substance P and other peptides on the release of somatostatin, insulin, and glucagon in vitro. Endocrinology 1980; 107:256–261.
35. Brunicardi FC, Druck P, Sun Y, et al. Regulation of pancreatic polypeptide secretion in the isolated perfused human pancreas. Am J Surg 1988; 155:63–69.
36. Klaff LJ, Taborsky GJ Jr. Role of pancreatic somatostatin in determining glucagon response to arginine and morphine. Am J Physiol 1987; 252:E751–E755.
37. Brunicardi FC, Watt P, Colonna J, et al. Paracrine regulation of islet cell secretion in the isolated perfused human pancreas. Surg Forum 1991; 42:232–334.
38. Meyer HH, Vetterbain F, Schmidt G, et al. Measurement of blood flow in pancreatic islets of the rat: effect of isoproterenol and norepinephrine. Am J Physiol 1982; 242:E298–E304.
39. Jansson L, Hellerstrom C. Stimulation by glucose of the blood flow to the pancreatic islets of the rat. Diabetologia 1983; 24:45–50.
40. Holst JJ, Jensen SL, Knuhtsen S, et al. Autonomic nervous control of pancreatic somatostatin secretion. Am J Physiol 1983; 245: E542–E548.
41. Sternini C, DiGiorgio R, Brunicardi FC, et al. CGRP immunoreactivity in the mammalian pancreas. Species differences. Ann N Y Acad Sci 1992; 657:487–490.
42. Esterhuizen AC, Spriggs TLB, Lever JD. Nature of islet cell innervation in the cat pancreas. Diabetes 1968; 17:33–36.
43. Samols E, Stagner JI. Islet somatostatin-microvascular, paracrine, and pulsatile regulation. Metabolism 1990; 39:55–60.