Somatostatin: Diverse Physiological Roles and Therapeutic Implications*

GORDON C. WEIR, M.D.

Associate Professor of Medicine, Division of Endocrinology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

S. BONNER WEIR, PH.D

Research Associate, Division of Endocrinology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

In its brief lifetime as a known peptide, somatostatin has provided a truly remarkable story filled with surprising developments from unexpected quarters. The foundation was set in 1969, when Krulich and McCann[1] reported that fractions of a crude hypothalamic extract inhibited the secretion of growth hormone. In 1973, Guillemin's laboratory reported the sequence and synthesis of a fourteen amino acid peptide with the same inhibitory effect.[2,3] It occurs in both a cyclic and linear form, each displaying equal biological activity. Somatostatin was assigned as its name, but it is also commonly referred to as growth hormone release inhibitory factor (GHRIF) or somatotropin-release inhibiting factor (SRIF).

Characterization of somatostatin's biological activity proceeded rapidly once the synthetic peptide became available. It proved to be a potent inhibitor of thyroid stimulating hormone (TSH).[4] No effect was found upon prolactin or adrenocorticotropic hormone (ACTH) secretion except in the pathological situations of acromegaly[5] and Nelson's syndrome,[6] where inhibition has been described. The secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) is not inhibited by somatostatin.[7] There was great surprise when investigators in Seattle, working with baboons, found that somatostatin inhibited the secretion of two pancreatic hormones, insulin and glucagon,[8] and, as studies expanded to other organs, the inhibition of gastrin,[9] secretin,[10] gastric acid and pepsin secretion,[9] and secretin-stimulated exocrine pancreatic secretion[10] were described. Very little is known about the molecular mechanisms of somatostatin effects, but clues are being provided by the findings that inhibition of insulin secretion can be partially reversed by high calcium concentration[11] and by alpha adrenergic blockade with phentolamine.[12] Furthermore, somatostatin appears to interfere with calcium uptake by islets[13] and may inhibit tissue cyclic adenosine monophosphate (AMP) accumulation.[14] Both events are thought to be important in the secretory process.

Diabetes researchers became interested when it was shown that somatostatin infusions caused a fall of blood glucose in both normal subjects and diabetics.[15] In addition, somatostatin markedly slowed the development of ketoacidosis in insulin-deprived juvenile-type diabetics,[16] even though it did little to reverse established ketoacidosis.[17] Until then there was no convincing evidence that glucagon was anything

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more than a vestigial hormone, only continual debates about the theoretical relative contributions of insulin and glucagon to metabolic processes.

The widespread effects of insulin upon hepatic and peripheral tissues are well known, but glucagon's effects appear to be more limited. Although pharmacological amounts of glucagon can influence many organs, physiological concentrations act primarily on the liver, and probably have minor lipolytic effects on adipose tissue. Hepatic glycogenolysis and gluconeogenesis can both be stimulated by glucagon, thus leading to enhanced hepatic glucose output. It is also now clear that glucagon has a direct stimulatory effect upon hepatic ketogenesis.[18] The issue, however, is whether these effects are trivial and easily nullified by small amounts of insulin or whether they are physiologically important. Somatostatin has become a useful pharmacological tool to help answer these questions, because in addition to being able to block insulin and glucagon secretion, it has no known direct effect upon hepatic glucose output or peripheral glucose utilization. Several laboratories have now shown that the fall of blood glucose during a somatostatin infusion is secondary to a reduction of hepatic glucose output. The interpretation has therefore been made that inhibition of glucagon in these short-term experiments was more important than the inhibition of insulin. A similar fall in glucose was found in a diabetic with hypophysectomy, indicating that growth hormone inhibition did not have much influence.[15]

These unexpected findings made it difficult to understand why patients with pancreatectomies were hyperglycemic. According to the results of the somatostatin experiments, the removal of both insulin and glucagon surgically should have led to hypoglycemia. One finding used to reconcile this puzzle was that insulin-deprived pancreatectomized dogs have abundant amounts of extra-pancreatic glucagon which is known to be primarily of gastric origin.[19] Humans, however, appear to have very little gastric glucagon.[20] The best explanation for the paradox appears to be that glucagon's effects are only transient; thus, a glucagon infusion leads to an increase of hepatic glucose output which lasts for about an hour.[21] Similarly, if glucagon is "removed" with somatostatin, there is a transient reduction in hepatic glucose output.[22] Therefore, during chronic somatostatin infusions, a fall of blood glucose is seen before hyperglycemia, which appears as insulin deficiency dominates.[22] These experiments and others have led some to say that glucagon's influence on blood glucose homeostasis is minor and that the hyperglycemia of diabetes is almost entirely secondary to insulin deficiency. The acceptance of a dominant role for insulin seems inescapable, but glucagon may still have important effects. Daily physiological events bear little relation to infusions of glucagon or somatostatin; glucagon concentrations do not remain constant during the day but fluctuate considerably, particularly with meals. Thus, if each one of these fluctuations led to a transient effect on blood glucose lasting for even 45 mintues, it is clear that glucagon's overall influence throughout the day could be substantial. Furthermore, there is abundant evidence that glucagon secretion is increased in diabetes.[23] To answer some of these critical questions, workers have given glucagon infusions and injections, trying to stay within the concentrations thought to be physiological.[24-26] There is agreement that glucagon has hyperglycemic effects when unopposed by insulin but disagreement that it causes deterioration of control during insulin therapy in diabetics. In addition, there is growing acceptance that endogenous insulin secretion in normal subjects can effectively counter the effects of artificially-raised plasma glucagon concentrations. Therefore, despite large amounts of recent work, there remains much disagreement about glucagon's importance in diabetes.

This rather elaborate background is necessary to understand somatostatin's possible usefulness as a therapeutic agent. Its ability to lower blood glucose is presumed to be mediated primarily via glucagon inhibition. Therefore the question of glucagon's contribution to the hyperglycemia of diabetes is of utmost importance. During debates about somatostatin's potential in diabetes a commonly raised question is, "Why worry about somatostatin? Why not give more insulin?" Somatostatin's advocates argue that following each meal there is a glucagon rise which drives blood glucose to unacceptable postprandial peaks even in so-called well-controlled diabetics. Aborting these glucagon rises with somatostatin would therefore minimize glucose excursions in a way unachievable with conventional insulin therapy. New data adding more confusion to these concepts is the finding that somatostatin can impair carbohydrate absorption by the gastrointestinal tract and may lower postprandial glucose by a mechanism independent of glucagon.[27]

As indicated above, much of the controversy about somatostatin centers on its possible effects

upon glucose control in diabetes. Even though data showing a connection between blood glucose and complications is not conclusive, there is enough circumstantial evidence to warrant the pursuit of optimal control. Another factor linked to complications is growth hormone. Even though large, well-controlled studies are still not available, the weight of evidence suggests that pituitary ablation has a beneficial effect upon diabetic retinopathy. Possibly important as well is the observation that plasma growth hormone levels are increased in diabetics, when control is poor[28] or during exercise.[29,30] Somatostatin therefore may possibly benefit diabetics through two mechanisms—control of blood glucose and suppression of growth hormone secretion.

Obviously much more work is needed before somatostatin's ultimate value as a therapeutic tool can be assessed and there are many hurdles which need to be overcome. Long-acting preparations must be developed, as injections before each meal are obviously impractical. A protamine-zinc somatostatin preparation has been found to increase the duration of action in rats[31] but has been unsuccessful in primates. There were early fears that inhibitory effects upon platelet function would lead to serious bleeding problems, but recent thorough studies have dispelled some of these anxieties.[32] Even though chronic suppression of growth hormone might help some diabetics, growth retardation in children would not be acceptable. Furthermore, it is possible that somatostatin's effects on the gastrointestinal tract will produce discomfort and maldigestion leading to nutritional deficiency. Efforts are underway to develop somatostatin analogues which will selectively suppress glucagon secretion and, although selectivity has not yet been accomplished, a D-tryptophan^8-somatostatin analogue has been synthesized which is eight times more potent than somatostatin in inhibiting growth hormone, insulin, and glucagon secretion.[33] In addition to its potential usefulness in diabetes, somatostatin may be of some benefit in the treatment of acromegaly,[5] peptic ulcer disease, and metastatic insulinomas and glucogonomas.

Another area of research has focused upon the localization of somatostatin. Immunohistochemical techniques, in particular immunofluorescence, have been very useful for accurate localization, and radioimmunoassay has permitted quantitation of somatostatin immunoreactivity. The major obstacle in the development of radioimmunoassays was the problem of labeling somatostatin. Labeling with ^{125}I of the tyrosine of the synthetic analogue l-tyrosinated somatostatin provided the breakthrough and several very specific, highly sensitive assay systems have become available through the research of Arimura et al[34] and by Y.C. Patel, MD and S. Reichlin, MD (unpublished data, 1975).

These techniques led to an unexpected and important discovery in late 1974 when Dubois in France, using immunofluorescence, found somatostatin immunoreactivity in discrete cells of the islets of Langerhans in several species.[35] This finding was rapidly confirmed in isolated islets with a specific radioimmunoassay.[36] Somatostatin was also found scattered throughout the gastrointestinal tract with unusually large amounts in the gastric antrum,[37] and in addition was found in numerous extrahypothalamic areas of the central nervous system,[36,38] with especially large concentrations in the septum and preoptic area, the thalamus, and the cortex. The highest concentration of somatostatin in the hypothalamus has been localized to the median eminence and the arcuate nucleus.[38] Definitive proof that extrahypothalamic material with somatostatin immunoreactivity is identical to hypothalamic somatostatin awaits amino acid sequence determination. The material does appear to have biological activity, however, as extracts of frog pancreas with a high content of somatostatin immunoreactivity have been found to inhibit growth hormone secretion.[39]

Immunofluorescent techniques were also used to show that the cells containing somatostatin immunoreactivity in islets and gut were of the D-type.[40] D cells comprise about 5% to 10% of the mammalian islet cell population and tend to occur in close proximity to glucagon-containing A cells. In the mouse and rat, for instance, A and D cells form a rim of tissue around a central core of B cells.[41] In the horse, however, there is a central mass of A and D cells with peripheral cells being B cells, and in man A and D cells occur together next to capillary walls. The physiological importance of this distribution is as yet unknown, but it seems likely that there is some unique interaction between A and D cells.

An exception to the above pattern is found in birds which have a population of islets, called light islets, with D cells and B cells, but almost no A cells.[42] There are also, however, dark islets containing both A and D cells and few B cells. Birds are also unique because their pancreases contain high concentrations of glucagon and somatostatin compared to mam-

mals,[43,44] but the significance of this can only be speculated upon.

It was assumed by many that normal islet D cells contained gastrin, largely because the cells of gastrin-containing tumors of the Zollinger-Ellison syndrome have D-cell-like morphology. Some workers have found gastrin immunoreactivity in islet tissue,[45] but a recent thorough study has been unable to confirm this.[46] Thus, the origin of the gastrin-containing cells of the Zollinger-Ellison syndrome remains undiscovered.

There has been discussion about whether somatostatin in extrahypothalamic cells is synthesized in situ or taken up following secretion by the hypothalamus. The latter possibility seemed less likely because of somatostatin's instability in blood and the finding that the concentration of somatostatin in islets is comparable to that found in the hypothalamus. Recent studies in the angler fish indicate that somatostatin is synthesized in islets. The angler fish is unique as it has enormous (100 to 200 mg) islets which can easily be dissected free and contain no pancreatic exocrine tissue. Immunohistochemical studies have shown that approximately 30% of the cells contain somatostatin, 20% contain glucagon, and 35% contain insulin. Islets were incubated with the labeled amino acids ^{3}H-tryptophan and ^{35}S-cystine, and islet proteins were separated with column chromatography (P-10) and polyacrylamide gel electrophoresis (pH 9.5). Clear peaks of radioactivity were found in fractions containing the largest quantity of somatostatin immunoreactivity.[47] Synthetic cyclic somatostatin migrated into the same fractions. Thus there is now good evidence that somatostatin is synthesized in situ in islet tissue and there is also preliminary evidence that there is a larger precursor form of somatostatin (prosomatostatin). Precursor forms have been described for a number of other peptides including insulin and glucagon.

There is currently great interest in defining the characteristics of the secretory control of somatostatin as this should help solve some of the puzzles about its physiological role. Data is fragmentary, but studies by G. Patton and co-workers[48] and E. Samols and co-workers[49,50] in the isolated perfused canine and rat pancreas now show that somatostatin secretion can be stimulated by glucagon and arginine. The present interpretation is that glucagon probably has a direct influence upon the D cell, and that the arginine effect may be indirect, acting via local secretion of glucagon by the A cell.

Somatostatin's contribution to the pathophysiology of diabetes has yet to be elucidated, but some provocative information is available. Following the induction of diabetes in rats with the B-cell toxin, streptozotocin, a significant increase of islet somatostatin content was found using radioimmunoassay techniques.[51] This author has observed (unpublished data, 1976) that increased somatostatin in extracts of whole rat pancreas has been found with streptozotocin, as well as with alloxan, a different B-cell toxin. With immunofluorescent techniques it has been possible to show both hypertrophy and hyperplasia of islet D cells not only in streptozotocin diabetic rats but also in tissue from two juvenile-type human diabetics.[52] These findings may be a secondary phenomenon related to the hypersecretion of glucagon, or perhaps the hyposecretion of insulin known to occur in diabetes, or to some other factor. The critical question is whether there is increased islet somatostatin secretion leading to reduced insulin secretion. Also, even though diabetics secrete excessive amounts of glucagon which contribute to hyperglycemia, they might secrete even more glucagon were it not for D-cell secretion of somatostatin. Therefore, the D-cell hypertrophy could have either a beneficial or detrimental influence upon diabetes.

An understanding of somatostatin's physiologic importance may help us make sense of what is occurring in disease states. There is good reason to think that somatostatin's effects are exerted locally. It seems no accident that cells containing somatostatin are located in close proximity to cells capable of responding to somatostatin. Because of this proximity and because of somatostatin's instability in blood, it would seem inefficient for this peptide to be transported through the circulation to distant organs. Unfortunately, it has not yet been possible to measure physiological levels of somatostatin in plasma. Local secretory mechanisms are probably important in many organs, but islets are particularly intriguing. There is now good evidence that local secretion by autonomic nerve terminals of norepinephrine and acetylcholine can influence both glucagon and insulin secretion.[53] Some data suggest that local insulin secretion suppresses glucagon release from A cells[54] and there is now reason to suspect that glucagon may stimulate insulin release,[55] that somatostatin may inhibit the secretion of insulin and glucagon, and that glucagon may stimulate somatostatin secretion. The potential interactions which take place in islet interstitial spaces may be extraordinarily complex and

difficult to clarify. Another possible way in which different islet cells could communicate is through gap junctions. Small molecules have been shown to move from the cytoplasm of one cell into the cytoplasm of another through these structures. Gap junctions have been described as occurring between B cells, and also between A and B cells,[56] but thorough studies of possible D-cell gap junctions are not yet available. Suggestions have also been made that there may be important electrical interactions between islet cells.

Even though one can make many speculations about the possible importance of somatostatin in islets and the gastrointestinal tract, no definitive effects have been elucidated. There is, however, evidence that somatostatin exerts a physiological influence on the pituitary. Injections of somatostatin antiserum into rats led to increases in growth hormone and TSH secretion, presumably by neutralizing somatostatin in the hypothalamic-hypophyseal portal circulation.[57,58] The finding that somatostatin is distributed throughout extrahypothalamic areas of the central nervous system raises important questions about somatostatin's possible role as a neurotransmitter. There is also much curiosity about the evolution and embryology of somatostatin, particularly since its presence is found in such diverse areas as the central nervous system, pancreatic islets, and gut. It is worth noting that another peptide, substance P, has recently been found in various parts of the brain including the hypothalamus, and the gut.[7]

It was predictable that a "somatostatinoma" would eventually be found, and O. P. Ganda and associates[59] indicate that it has been. A 46-year-old woman with an eight-year history of well-documented diabetes mellitus was found to have a pancreatic islet cell tumor during a cholecystectomy. Clinically there was no evidence of its being an insulinoma, glucagonoma, or a tumor of either the Zollinger-Ellison or pancreatic cholera (Verner-Morrison) type. Ultrastructurally the majority of the cells appeared to be of the D-type. The somatostatin content of the tumor was remarkably high (301 ng/mg of tissue), and the content of insulin, glucagon, gastrin, and vasoactive intestinal peptide was negligible.

Pathologically the tumor was judged to be a low-grade malignancy, and metastatic tissue was found in one of the 38 resected lymph nodes. Remarkably, following surgical removal of the entire tumor, glucose values returned to normal and have remained so for 16 months (a recent fasting blood sugar was 73 mg/100ml and two-hour postprandial was 70 mg/100ml). We hypothesized that the patient was diabetic because of the continued secretion of large amounts of somatostatin by her tumor. As mentioned above, experimental infusions of somatostatin in normal subjects produce a fall of blood glucose; this drop, however, is only transitory, lasting for a few hours; with a longer infusion, hyperglycemia develops. Studies of insulin, glucagon, and growth hormone secretion in response to an arginine infusion were done prior to surgery and the response of each hormone appeared to be diminished, as one might expect with chronic somatostatin exposure. Unfortunately, it was not possible to repeat the study following surgery. When a patient is found to have an apparently non-functioning pancreatic tumor of the islet cell type, especially if diabetes is also present, the possibility of a somatostatinoma should be considered.

Somatostatin has proved to be infinitely more interesting than anyone might have imagined at the time of its discovery in 1973. Current interest in this unique peptide is focused upon its potential role in the pathophysiology and therapy of diabetes mellitus. It is probable that somatostatin also will come to occupy an increasingly prominent place in such diverse disciplines as cell biology, the neurosciences, endocrinology, and gastroenterology.

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