PLENARY LECTURE

Somatostatin Analogs: Future Directions

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SOMATOSTATIN is involved in the negative control of the normal function of a number of organ systems. One might call the peptide an inhibitory tissue (growth) factor, which mainly prevents local overreaction from a multitude of stimulatory factors. Long-term administration of somatostatin analogs in most instances only transiently inhibits physiological actions, either because of their desensitizing effects, or because of the compensatory reaction of local stimulatory factors which in most instances eventually have an overriding action. After administration of octreotide for 1 week, its stimulatory effect on intragastric pH is lost, while similarly, its inhibitory effects on pancreatic amylase, trypsin, and lipase secretion decrease considerably. Also, octreotide acutely blunts thyrotropin-releasing hormone (TRH)-stimulated thyrotropin (TSH) release, but long-term therapy does not affect thyroid function, probably because of local adaptation by other regulatory factors. However, this is not always the case, as long-term octreotide therapy relentlessly diminishes gallbladder contraction.

These considerations have consequences for the clinical use of somatostatin analogs. On the one hand, it makes them safe drugs with few side effects; most initial symptoms such as nausea, cramps, diarrhea, and fatty stools disappear spontaneously within 2 to 3 weeks as a consequence of local adaptation in the gastrointestinal tract and exocrine pancreas. Only gallstone formation is a long-term problem, although clinically symptomatic gallbladder disease occurs in about 1% of individuals per treatment year on octreotide. On the other hand, these mechanisms of local adaptation probably explain why the inhibitory effects of octreotide in functional gastrointestinal diseases (upper gastrointestinal bleeding, pancreatitis, diarrhea, and pancreatic fistula output) are only transient and rather short-lived, limiting the efficacy of the drug in these diseases.

Will it be possible to improve the efficacy of somatostatin analogs in the treatment of functional gastrointestinal diseases? There is little evidence that intermittent low-dose octreotide might prevent desensitization of somatostatin receptors or delay local adaptation. The use of the long-acting depot preparation of octreotide, which induces constant high circulating levels of the peptide for many weeks, will give an answer to these questions. Also, there is at present little evidence that somatostatin receptor subtype–specific analogs with a profile different from octreotide, such as BIM 23014 or RC-160, might improve the long-term effectiveness of therapy for bleeding, diarrhea, pancreatitis, or fistula output. Most studies so far suggest that the continuous infusion of somatostatin-14 has similar effects to octreotide on normal gastrointestinal function. However, with regard to the effect on insulin secretion, there might be an important difference. Octreotide was originally demonstrated, in monkeys, to inhibit growth hormone (GH) 45 times more potently than natural somatostatin, but insulin only 1.3 times more potently. Recently, it was demonstrated that the inhibitory actions of somatostatin on GH and insulin release are mediated by different somatostatin receptor subtypes. This selective effect of octreotide, which inhibits normal insulin release only transiently, has contributed to its minor effects on carbohydrate tolerance in humans. This also suggests that somatostatin receptor subtype–specific analogs with a different profile might cause hyperglycemia, limiting their day to day use in gastroenterology. The same limitation would apply to long-acting somatostatin analogs, which activate all receptor subtypes to a similar extent to natural somatostatin.

Octreotide does not cross the blood-brain barrier in humans. This limits its investigational use in brain disorders in which somatostatin regulation disturbances have been demonstrated. Nonpeptide somatostatin analogs that cross the blood-brain barrier remain to be developed.

The most successful use of (long-acting) octreotide so far is in the treatment of acromegaly. Effective control of GH secretion by the pituitary tumor and subsequent normalization of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor–binding protein 3 (IGFBP-3) levels occurs in the majority of patients. Elderly patients with small pituitary tumors are especially sensitive to octreotide. Therefore, octreotide has been proposed as a primary therapy in the treatment of elderly acromegalic patients. An important observation is that no loss of action, escape, or desensitization of somatostatin receptors seems to occur in the pituitary tumors of acromegalics, even after more than 10 years of therapy on 3 × 100 μg octreotide (in total >10,000 injections). This suggests a difference in the turnover, in the degree of internalization, and/or in the recruitment of the somatostatin receptors to the tumor cell membrane in human pituitary tumors, compared with the target cells of the normal gastrointestinal tract and the pancreas.

Somatostatin analogs are currently used with considerable success in the treatment of hormonal hypersecretion of metastasized carcinoids and islet cell tumors. Clinical improvement during octreotide therapy is mainly mediated via a direct inhibitory effect on hormone production by the tumor, but indirect non–tumor-mediated effects on intestinal fluid production and/or intestinal contractility also contribute to the subjective well-being of many patients.

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0026-0495/96/4508-1031$03.00/0

Somatostatin analogs thus contribute to the quality of life of patients with this type of metastasized endocrine tumor. However, surgery remains the primary treatment in such patients. Somatostatin receptor visualization of most tumors optimalizes the staging of these diseases and radioguided surgery assists in improving the outcome of surgical intervention.

Shrinkage of tumor (metastases) during octreotide therapy has been reported in 10% to 20% of carcinoid and vasoactive intestinal polypeptide (VIP)-oma patients, but this shrinkage is temporary and transient. Control of tumor growth occurs in about half of the patients for a period of 8 to 16 months, but eventually all patients escape from somatostatin analog therapy with regard both to hormonal hypersecretion and to tumor growth. It is not evident at present whether this escape is the consequence of desensitization, structural changes in the somatostatin receptors on these tumors, the selection of rapidly growing clones of dedifferentiated tumor cells lacking these receptors, or a mixture of these phenomena. Somatostatin receptor scintigraphy can be used to find answers to this. The four main questions concerning the use of somatostatin analogs in gastroenteropancreatic tumors are as follows:

(1) which mechanism(s) are responsible for the loss of efficacy of octreotide in the control of hormonal hypersecretion and tumor growth;
(2) is it possible to control tumor growth with radiotherapy with radionuclide-coupled somatostatin analogs, and if so, at what stage should this procedure be performed;
(3) at what stage should chemotherapy and/or chemoembolization of liver metastases be considered, especially with regard to the points raised under 1 and 2; and
(4) is there a place for novel somatostatin receptor subtype–specific analogs?

Recent evidence suggests that most, if not all, antihormonal and antimitotic actions of somatostatin are mediated via receptor subtypes 2 and 5, making octreotide, BIM 23014, and RC-160 the most optimal analogs in the treatment of carcinoids and most islet cell tumors. Only in the case of insulinomas is there evidence that receptor subtypes are present that do not or only minimally bind octreotide and RC-160. For such tumors, the development of analogs with an alternative binding profile is of some importance.

Somatostatin analogs inhibit the growth of a variety of tumors in different animal models. Somatostatin receptors have been found on many human breast, thyroid, prostatic, and other adenocarcinomas, on brain tumors such as meningiomas, and on hematological malignancies.

What are the consequences for practical oncology? Little is known at present concerning the potential value of (high-dose?) octreotide therapy in patients with inoperable neuroendocrine tumors, breast cancer, malignant lymphomas, and meningiomas. Octreotide directly inhibits hormone release and cell growth in most cultured human neuroendocrine tumors, but a different effect was observed in cultured human meningiomas; octreotide inhibited adenylyl cyclase activity in these tumor cells, but stimulated their growth. Octreotide probably interferes with the inhibitory autocrine growth control of meningioma cells. Despite the direct antimitotic effects of somatostatin analogs on (monoclonal) breast cancer cell lines, the nonhomogeneous distribution of somatostatin receptors in many human breast cancer specimens suggests that treatment with somatostatin analogs might only affect parts of these tumors. The differential antimitotic and antihormonal effects of natural somatostatin, octreotide, and RC-160, the variable presence of different somatostatin receptor subtypes on different human tumor types, as well as the as yet undefined pathophysiological significance of the presence of somatostatin receptors on tumor vascularization, have to be investigated further. These considerations mean that a place for somatostatin analog treatment in patients with inoperable somatostatin receptor–positive cancer is not established yet. However, there seems little doubt that somatostatin receptor scintigraphy can enhance the quality of clinical trials of somatostatin analogs by selecting those patients whose tumors express somatostatin receptors. In this regard it seems important that the direct antiproliferative action of octreotide on cultured tumor cells is additive to that exerted by different cytostatic drugs.

The main questions in the field of oncology, which need to be addressed further are as follows:

(1) what is the biological significance of the heterogeneous distribution of somatostatin receptors on adenocarcinomas?
(2) Does somatostatin analog therapy result in the selection of preferentially growing somatostatin receptor–negative tumor cells?
(3) Is it possible to induce, using somatostatin analogs, a consistent lowering of IGF-1 bioactivity in the circulation, as well as that of other hormones that have been implicated in tumour growth?
(4) Which human cancers are controlled by their intracellular cyclic adenosine monophosphate (cAMP) levels? Is somatostatin analog therapy, which inhibits the adenylate cyclase activity of such tumor cells, risky and contraindicated?

A number of small peptides have been identified, which are widely distributed over the human body, and are potent and important regulators of biological processes in normal tissues, as well as in the growth of certain cancers (eg, bombesin, substance P, vasoactive intestinal polypeptide [VIP], cholecystokinin, and gastrin). The recent development of somatostatin analogs for the diagnosis and treatment of a variety of cancers will be repeated in the near future with other small peptides and their analogs. Despite the broad range of physiological actions of somatostatin, its analogs control hormonal hypersecretion by endocrine tumors that express receptors for this peptide or analog without important side effects. As mentioned earlier, the high density of somatostatin receptors on tumors (and on groups of activated immune cells), as well as the availability of potent and stable somatostatin analogs as radioligands, made it possible to develop an in vivo technique for their visualization. Somatostatin receptor scintigraphy represents the first example of the clinical use of a small peptide

as an efficient in vivo diagnostic tool for the presence of peptide receptors. Apart from its localizing merits, a positive scan often predicts a favorable response to octreotide therapy. Recently, VIP receptor scintigraphy and substance P receptor scintigraphy have been successfully developed for the visualization of gastrointestinal cancer, as well as chronic immune diseases. Small peptides such as somatostatin may be considered a powerful alternative to monoclonal antibodies and their fragments.

Radiolabeled chelated somatostatin analogs are already more than a theoretical option. However, there is considerable variability in uptake of radioactivity between tumors. Experimental studies show that it might be possible to transiently upregulate somatostatin receptor expression, increasing their uptake of radioactivity. Radiotherapy with radionuclide-coupled stable somatostatin analogs is the most promising use of these compounds in palliative oncology.