Somatostatin and Analogues in the Treatment of Cancer

A Review

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Somatostatin is a naturally occurring cyclic tetradecapeptide that inhibits release of growth hormone and all gastrointestinal hormones. The beneficial effect of somatostatin in the treatment of certain hypersecretory disorders of hormone excess is well recognized; however its clinical usefulness has been limited in the past by its extremely short plasma half-life. The development of long-acting somatostatin analogues has provided clinically useful agents for treatment of hormone-producing tumors. In addition to well-known inhibiting effects on hormone release and actions, recent studies using experimental tumor models have demonstrated an antiproliferative effect of somatostatin and its analogues on growth of a variety of neoplasms. The exact role of somatostatin analogues in cancer therapy has yet to be established; however studies suggest that these agents could provide a useful and relatively nontoxic adjuvant therapy in the treatment of certain tumors. In this review, the oncologic application of somatostatin and possible mechanism of action are examined and current clinical and experimental studies are summarized.

SOMATOSTATIN WAS ISOLATED and characterized by investigators working in the laboratory of Guillemin at the Salk Institute[1] in 1973 following the original observations made by Krulich and coworkers[2] during a search for a growth hormone-releasing factor. Since the identification and purification of somatostatin-14 (Fig. 1), precursor forms of greater molecular weight have been recognized.[3-5] Somatostatin-28, or prosomatostatin, is a 28-amino acid polypeptide with somatostatin-14 making up the C-terminus[3] (Fig. 2). Preprosomatostatins are even larger precursor forms of 120 or more amino acids, with somatostatin-28 located at the C-terminus.[4] All of these forms exert biologic activity but differ in their relative potency.[6]

Somatostatin has been identified by a variety of immunocytochemical and radioimmunoassay techniques in multiple sites throughout the nervous system, including the cerebral cortex, cerebellum, hypothalamus, pituitary infundibular process, pineal gland, and spinal cord.[4,7] In the gastrointestinal tract, somatostatin has been found in the stomach (antrum, body, and fundus), the duodenum, jejunum, ileum, colon, and pancreas; the greatest amount is present in the stomach and pancreas.[3,4,7] More than 90% of the somatostatin immunoreactivity in the human gut is present within mucosal endocrine cells called D cells.[4,8] Muscle-layer somatostatin is located in nerves of the myenteric plexus.[4] Somatostatin in the pancreas is located in the D cells at the periphery of the islets of Langerhans.[4]

Somatostatin is characterized as a regulatory-inhibitory peptide with exocrine, endocrine, paracrine, and autocrine activity.[4] The general inhibitory function of somatostatin is wide ranging and affects a number of organ systems. Many have characterized it as the universal endocrine off-switch. Somatostatin inhibits the release of growth hormone and somatomedin C and all known gastrointestinal hormones.[3-8] Somatostatin also inhibits gastric acid secretion and motility, intestinal absorption, pancreatic bicarbonate and enzyme secretion, and selectively decreases splanchnic and portal blood flow in dogs and humans without affecting mucosal blood flow.[3-10]

Several clinical trials demonstrated impressive efficacy of somatostatin and its analogues in a variety of hypersecretory disorders resistant to standard therapy, including

Supported by grants from the National Institutes of Health (5R37 DK 15241, PO1 DK 35608), from the American Cancer Society (PDT-220), and in conjunction with the Walls Medical Research Foundation.

Dr. Parekh is a Visiting Scientist from the University of Witwatersrand, Johannesburg South Africa and is supported by a scholarship from the Medical Research Council and Michael and Janie Miller Foundation.

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Accepted for publication November 24, 1989.

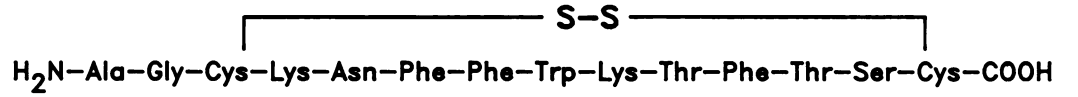

FIG. 1. Amino acid sequence of somatostatin-14.

acromegaly,[11,12] pancreatic ascites,[13] and pancreatic cholera.[14] They also proved useful in symptomatic treatment of gastrointestinal neoplasms of endocrine origin, including Zollinger–Ellison syndrome,[15–18] insulinoma,[19,20] VI-Poma (tumors resulting from hypersecretion of vasoactive intestinal peptide),[21–24] glucagonoma,[25,26] and carcinoid tumors.[17,27,28] Intriguing additions to the reported success of somatostatin in relieving symptoms produced by endocrine tumors have been reports of antiproliferative actions of somatostatin (both *in vivo* and *in vitro*) on various solid tumors, including breast,[29–33] prostate,[29,34–37] colon,[38–40] pancreatic,[6,29,41–43] and small cell lung carcinoma.[44,45]

The exact mechanism of the antitumor effect of somatostatin is not known, but some possibilities include one (or a combination) of the following: (1) a direct antiproliferative effect mediated through specific, high-affinity somatostatin receptors; (2) inhibition of secretion of gastrointestinal hormones thought to be important in tumor growth (that is, gastrin, secretin, cholecystokinin [CCK], and insulin); and (3) inhibition of release of growth hormone and other growth factors (that is, epidermal growth factor [EGF] and somatomedin C [IGF-I]).

Mascardo and Sherline[46] demonstrated direct antiproliferative effects of somatostatin by noting *in vitro* inhibition of EGF-induced DNA synthesis and cell replication by blocking centrosomal separation in gerbil fibroma and HeLa cells. Direct effects of somatostatin may be mediated through its interaction with specific somatostatin receptors found on normal cells and on cancer cells. Hierowski and colleagues[43] found that binding of somatostatin to its membrane receptors located on the pancreatic cancer cell line MIA PaCa-2 activates dephosphorylation of the EGF receptor, which prevents EGF-induced growth.

The clinical usefulness of native somatostatin is limited greatly by its short plasma half-life (1 to 3 minutes in humans).[6] Somatostatin analogues were developed that are long-acting and more potent than native somatostatin-14. The first such analogue was SMS 201–995 (SANDOSTATIN® [octreotide acetate]) (Fig. 3). SMS 201–995 is a synthetic octapeptide with a prolonged circulating half-life of approximately 41 to 58 minutes in humans when administered intravenously.[6] The elimination half-life of SMS 201–995, when given subcutaneously, is even longer (approximately 113 minutes in healthy volunteers).[47–49] This analogue was found to be three times more potent than native somatostatin in suppressing glucose-stimulated insulin secretion and 19-times more potent than native somatostatin in inhibiting growth hormone secretion.[48] In recent years, major strides were made in the synthesis of newer, longer-acting analogues specifically designed for antitumor activity. Schally[29] and Cai and coworkers[50] synthesized more than 300 analogues using solid-phase methods. These octapeptide 'superanalogues' are more potent and have longer durations of action than either native somatostatin or SMS 201–995.

The somatostatin analogues have a wide therapeutic index and seem to be free of major side effects.[29,48,51] Most of the reported side effects are gastrointestinal in nature and include minor nausea, bloating, diarrhea, constipation, or steatorrhea. Currently SMS 201–995 is approved only for the control of symptoms associated with metastatic carcinoid or VIP-secreting tumors; however use of these analogues may prove beneficial in the future as novel adjuvant agents in cancer chemotherapy. The success of somatostatin in treating the hypersecretory disorders of patients with endocrine tumors has been documented extensively in many clinical trials.[13–22] This review will focus specifically on the oncologic application of somatostatin and its analogues in the treatment of endocrine and non-endocrine solid tumors.

Breast Cancer

Immunoreactive somatostatin-14 is found in human breast milk in a concentration 10 times higher than in plasma.[52] Somatostatin in milk possesses bioactivity as demonstrated by its ability to inhibit basal- and prostaglandin-induced release of growth hormone from anterior pituitary cell cultures in a fashion that is parallel to that of synthetic somatostatin-14.[52] Somatostatin activity also was demonstrated in human breast cancers. Using receptor autoradiography, Reubi and coworkers[53] demonstrated the presence of high-affinity somatostatin receptors in 3 of 39 breast cancers. The presence of somatostatin recep-

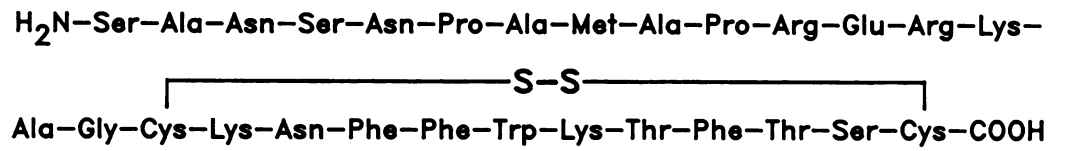

FIG. 2. Amino acid sequence of somatostatin-28.

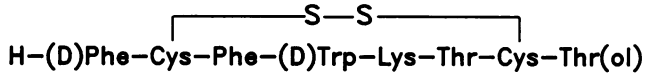

FIG. 3. Amino acid sequence of long-acting somatostatin octapeptide analogue (SMS 201-995).

tors did not correlate with the age of the patient or with the number of estrogen and progesterone receptors. Spring-Mills and colleagues[54] demonstrated somatostatinlike immunoreactivity in a majority of human breast cancers studied. These findings of somatostatinlike activity in breast milk and specific high-affinity somatostatin receptors in human breast tissue led several investigators[31,33] to speculate that the role of somatostatin may be that of an autocrine or paracrine factor linked to control of breast cell proliferation.

Scambia and coworkers[33] studied *in vitro* effects of somatostatin-14 and the long-acting somatostatin analogue, SMS 201–995, on three human breast cancer cell lines (CG5, T 47 D, and ZR 75-1). They found a dose-dependent inhibition of growth of all three lines with either native somatostatin-14 or SMS 201–995. Significant inhibition was noted in CG5 cell growth at a concentration of 0.01 nmol/L (nanomolar) of SMS 201–995. Maximal inhibition (40%) occurred with a concentration of 100 nmol/L. The effects were less pronounced with T 47 D and ZR75-1. A significant inhibition in growth (approximately 10% compared to untreated control cells) was not noted until a concentration of 10 nmol/L of somatostatin was used. Further increases in the concentration of somatostatin failed to produce additional inhibition. Although not mentioned in their studies (and not specifically measured), one possible explanation for the increased inhibitory effect of somatostatin on CG5 compared to T 47 D and ZR75-1 may be the presence of somatostatin receptors. CG5 is a variant of another breast cancer cell line, MCF-7, which has a single class of high-affinity somatostatin receptors. Using the MCF-7 cell line, Setyono-Han and colleagues[31] studied *in vitro* antiproliferative effects of somatostatin-14, somatostatin analogue, SMS 201–995, and another long-acting somatostatin analogue, CGP 15–425. All three agents inhibited growth of MCF-7 with maximal inhibition of cell proliferation noted at a concentration of 10 nmol/L (approximately 75% inhibition). These two studies suggest a direct inhibitory effect of somatostatin on breast tumor cells.

Several *in vivo* investigations corroborated the *in vitro* findings of somatostatin-induced inhibition of breast cancer. Rose and coworkers[30] studied the effects of somatostatin-14 and a long-acting somatostatin analogue, L 362,823, on the growth of mammary carcinomas induced by N-nitrosomethylurea in female rats. Pergolide, an agent that suppresses serum prolactin, had no effect on tumor growth, but when it was combined with a 7-day treatment of somatostatin-14 (20 μg/hour *via* osmotic minipump), tumor surface areas decreased significantly. Once somatostatin treatment was stopped, the tumors underwent regrowth despite the continuation of pergolide. Similar findings were noted when the experiment was repeated using the long-acting somatostatin analogue, L 362,823 (5 μg/hour *via* osmotic minipump). Neither pergolide nor L 362,823 were effective as single agents. When L 362,823 was administered for 7 days in combination with pergolide, tumor regression again was noted. With cessation of L 362,823, however, immediate tumor regrowth was found. These findings suggest a cytostatic effect of somatostatin on this chemically induced mammary carcinoma.

In another model of chemically induced rat mammary cancer, Klijn and colleagues[55] studied the effects of different dosages (0, 0.05, 0.2, 1.0, 5.0, and 20 μg) of somatostatin analogue SMS 201–995 administered twice daily for 3 weeks to rats with dimethylbenzanthracene-induced tumors. They found a similar bell-shaped dose-response curve as noted in *in vitro* studies from their laboratory.[31] Maximal tumor inhibition (83%) was noted with SMS 201–995 (0.2 μg, twice daily).

Weber and coworkers[32] recently reported on the effect of SMS 201–995 on the growth of estrogen-dependent (MCF-7) and estrogen-independent (BT-20) human breast cancer that was xenografted in nude mice. SMS 201–995 (4 μg, twice daily) significantly decreased MCF-7 tumor volume and prolonged tumor doubling time compared to controls. A much higher dosage of SMS 201–995 (50 μg, twice daily) was required to produce a modest, but significant, prolongation of BT-20 tumor doubling time and a decrease in the calculated growth increment. The volume of the BT-20 tumor was not affected by SMS 201–995.

The mechanism by which somatostatin inhibits growth of breast cancer in experimental studies is not known. *In vitro* studies demonstrate a direct effect of somatostatin possibly mediated through specific somatostatin receptors.[31,33] Also somatostatin may act indirectly by inhibiting release of growth factors known to stimulate human breast cancer cells. EGF and IGF-I stimulate growth of breast cancer *in vitro*, and several breast cancer lines, including MCF-7, have specific receptors for EGF or IGF-I.[22,56] Somatostatin and its analogues reduce levels of these growth factors, which may contribute to the antiproliferative effect seen in experimental studies.

Lung Cancer

Human small cell lung cancer accounts for 20% to 25% of all lung cancer.[57] It is a rapidly growing tumor char-

acterized by early metastasis and ectopic hormone production.[58,59] Advances in multidrug chemotherapeutic regimens modestly improved survival, but the prognosis is still dismal.[60] Taylor and colleagues[45] demonstrated somatostatin receptors on human small cell lung cancer cells, a finding that provides a possible clue for a growth-regulatory function for somatostatin. To test this hypothesis, a somatostatin analogue, BIM-23014 C, was used to treat the human small cell lung cancer cell line, NCI-H69.[45] *In vitro* studies demonstrated inhibition of tumor cell proliferation (59% of untreated controls) with a concentration of 10 nmol/L of BIM-23014 C. *In vivo* growth was assessed by injecting NCI-H69 cell suspension subcutaneously into the flanks of nude mice. Treatment was initiated with BIM-23014 C (500 μg/injection, twice daily) administered intraperitoneally in one group, subcutaneously around the tumor in a second group, and in a remote subcutaneous location in a third group. The mean tumor lag time was delayed in mice treated by intraperitoneal and remote subcutaneous injections, but inhibition of tumor growth at 48 days was dramatic with subcutaneous administration around the tumor. Discontinuing treatment by any route resulted in an acceleration of tumor growth that was similar to the findings of Rose and coworkers[30] in breast cancer. These results would certainly suggest a direct cytostatic effect of somatostatin on NCI-H69 tumor growth, rather than a cytotoxic effect. Consideration must be given also to an indirect effect of somatostatin on tumor growth.

Cuttitta and colleagues,[61] Moody and coworkers,[62] and others[63–66] demonstrated bombesinlike immunoreactivity and a high density of bombesin-binding sites in a number of cell lines of human small cell lung cancer, as well as in resected surgical specimens of tumor. These findings suggest that bombesin may function as an autocrine growth factor. We showed stimulation of growth of NCI-H69 xenografts in nude mice that were treated with bombesin.[67] Somatostatin inhibits the release of bombesin and could affect tumor growth indirectly by this mechanism. Milhoan and colleagues,[44] working in our laboratory, examined the effect of another long-acting somatostatin analogue, MK-678, on NCI-H69 growing in nude mice. Treatment with MK-678 (300 μg/kg, three times daily) for 46 days resulted in a significant decrease in tumor area (51%), DNA content (64%), and RNA content (55%), as compared to control values. Tumor protein and weight were not significantly reduced. Although the degree of tumor inhibition varies between studies, the data of Milhoan and coworkers[44] and Taylor and colleagues,[45] showing inhibition of NCI-H69 with different somatostatin analogues, suggest a possible role for these agents in the adjuvant therapy for human small cell lung cancer.

Colon Cancer

Three experimental studies examined the effect of somatostatin on growth of colon cancers.[39,68,69] Certain colon cancers have gastrin receptors and studies using established tumor models demonstrated stimulation of tumor growth by gastrin or its analogues.[68,69] In our laboratory, Singh and coworkers[39] showed that SMS 201–995 inhibited pentagastrin-induced growth of MC-26, a murine colon cancer that is positive for gastrin receptors. Also from our laboratory, Milhoan and colleagues[40] demonstrated significant growth inhibition of two human colon cancers (RIP and DRUM) xenografted in nude mice by the long-acting somatostatin analogue, MK-678 (300 μg/kg, administered three times daily intraperitoneally), and by α-difluoromethylornithine. Alpha-difluoromethylornithine is an irreversible inhibitor of ornithine decarboxylase that catalyzes the first and rate-limiting step in polyamine biosynthesis. Polyamines are essential for cell growth and differentiation and levels are elevated in rapidly dividing tissues. The addition of α-difluoromethylornithine to the MK-678 analogue inhibited growth of both RIP and DRUM tumors to a greater extent than either agent alone, a finding that suggests different mechanisms of action.

Smith and Solomon[38] studied cell lines from three human colon cancers (CXI, X56, and HT29). The growth of these tumors *in vivo* was examined in nude mice using X56 and CXI. Three dosages of somatostatin-14 (33, 100, and 300 μg/kg) were injected subcutaneously twice daily. The growth of X56 was not affected by any dosage of somatostatin. Somatostatin-14 (100 and 300 μg/kg) significantly reduced tumor volume, weight, protein, and DNA content of CXI after 20 days of treatment. The experiment was repeated using a tumor load of CXI that was five times larger. Somatostatin (100 μg/kg) decreased the final tumor volume and DNA content only, whereas somatostatin (300 μg/kg) significantly decreased all measurements of growth.

This study and the previous study by Milhoan and coworkers[40] demonstrate the variable effects of somatostatin-14 and a long-acting analogue, MK-678, on growth of human colon cancer. Three of the four colon cancers were inhibited by administration of somatostatin. Again the exact mechanism for this action cannot be determined specifically. We speculated that a possible mechanism may be an indirect effect on gastrin release or a modulation of gastrin receptors that are present on the colon cancers. As previously noted, Singh and colleagues[39] demonstrated that administration of SMS 201–995 blocked pentagastrin-induced stimulation of MC-26 colon cancer. Gastrin receptors were found to be down regulated in tumors after treatment with somatostatin, which suggests that tumors

were made less responsive to the trophic effect of pentagastrin. Smith and Solomon[38] found that pentagastrin (1000 μg/kg) increased the protein and DNA content of the X56 tumor and stimulated all measurements of CXI growth (tumor volume, weight, and DNA and protein content). Although somatostatin was not combined with pentagastrin treatment in the *in vivo* studies, another human colon cancer (HT29) was studied *in vitro*. Gastrin-17 (400 pmol/L [picomolar]) significantly stimulated HT29 cell proliferation and somatostatin-14 (400 pmol/L) decreased cell proliferation. Somatostatin, when combined with gastrin, inhibited the gastrin-induced proliferation of cells (34% reduction in cell counts), compared to the HT29 tumor that was treated with gastrin alone.

Exocrine Pancreatic Cancer

Adenocarcinoma of the pancreas is common and fatal; it has an overall 5-year survival rate of 1% to 2% and a median survival time of 2.5 months.[29] The only effective treatment is surgical resection, which is possible only in the infrequent case of localized tumor. Radiotherapy and chemotherapy offer no real advantages.[29]

Experimental studies showed an antiproliferative effect of somatostatin and its analogues on the growth of pancreatic cancer. Redding and Schally[41] reported a significant reduction in tumor weight (51%) and volume (67%) in Wistar/Lewis rats bearing the acinar pancreatic tumor DNCP-322 after a 21-day administration of somatostatin analogue [L-5-Br-Trp^8] somatostatin-14 (30 μg, twice daily). In the second experiment, Syrian golden hamsters bearing a ductal adenocarcinoma were treated with [L-5-Br-Trp^7]somatostatin-14 (20 μg, twice daily) for 30 days with resultant diminished tumor weight and significantly decreased tumor volume compared to controls.

Upp and coworkers[42] in our laboratory demonstrated inhibition of two human pancreatic cancers (SKI and CAV) maintained as nude mouse xenografts by the administration of somatostatin analogue SMS 201–995 (100 μg/kg, IP, three times daily). SKI, a CCK receptor-positive tumor whose growth was stimulated by caerulein[70] and CAV, a CCK-receptor-negative tumor whose growth was not stimulated, both were inhibited to a similar degree by SMS 201–995. Tumor growth of SKI and CAV also was inhibited when treatment was delayed 21 days after tumor implantation.

The exact role that gastrointestinal hormones play in the growth of pancreatic cancer is not known. Townsend and colleagues[71] found that growth of the hamster pancreatic cancer, H2T, was stimulated significantly by administration of caerulein, a CCK analogue, in combination with secretin. As noted above, we also showed significant growth stimulation with caerulein of a human pancreatic cancer (SKI) that has CCK receptors.[70] The inhibitory effect of somatostatin on pancreatic cancer may be due partially to its ability to inhibit the release or action of CCK and secretin. This response could explain the effect seen in SKI but would not explain the inhibition seen in CAV, which does not possess CCK receptors and is not affected by exogenous caerulein.[70]

Other factors (*e.g.*, EGF) may be important in growth of pancreatic cancer. *In vitro* studies by Hierowski and coworkers[43] and Liebow and colleagues[72] demonstrated receptors for somatostatin and EGF in a cell line from an undifferentiated human pancreatic cancer (MIA PaCa-2). Epidermal growth factor stimulates *in vitro* growth of this cancer. Somatostatin reverses the stimulatory effect of EGF by activating dephosphorylation of the EGF receptor.

Prostate Cancer

The endocrine treatment for advanced prostatic cancer is well established and is based on androgen dependence.[34] Investigators studied the effect of two long-acting somatostatin analogues (RC-160 and RC-121), combined with a luteinizing hormone-releasing hormone agonist ([D-Trp^6]-LH-RH), on the growth of the hormone-dependent prostatic cancer, Dunning R-3327H.[35] [D-Trp^6]-LH-RH, when given alone, suppressed pituitary and gonadal function and inhibited growth of Dunning R-3327H tumor. The combination of [D-Trp^6]-LH-RH and a long-acting somatostatin analogue (RC-121 or RC-160) was more effective in inhibiting tumor growth than either agent alone. A possible explanation suggested by the authors for the enhanced effect seen with combination treatment is that the somatostatin analogues inhibit release of growth hormone and prolactin, which are thought to be important for growth of the normal prostate and possibly play a role in proliferation of malignant cells. Whatever the mechanism, this study suggests that inhibition of hormonally sensitive prostatic cancers may be enhanced with the combination of somatostatin analogues.

Endocrine Tumors

Somatostatin analogues demonstrated impressive efficacy in the control of symptoms from hormone excess produced by endocrine tumors resistant to standard therapies. Somatostatin has been used in the treatment of the Zollinger–Ellison syndrome of glucagonoma, of VIPoma, of insulinoma, and of carcinoid tumors. The role of somatostatin in the symptomatic treatment of endocrine tumors recently was reviewed extensively.[73–76]

Recent experimental and anecdotal clinical reports suggest that somatostatin may inhibit the growth of endocrine tumors. Experimental *in vivo* studies have been reported for a rat pituitary tumor, 7315a,[77] hamster in-

sulinoma,[20] and a small cell lung cancer.[45] We also studied the effects of SMS 201-995 in small cell lung cancer[44] and in BON, a human carcinoid tumor growing in nude mice.[78]

Lamberts and colleagues[77] studied the effect of the somatostatin analogue, SMS 201-995, on a transplantable prolactin and ACTH-secreting rat pituitary tumor, 7315a. Rats were injected twice daily with SMS 201-995 (2 or 20 μg/kg) for 30 days. Administration of both doses of the somatostatin analogue significantly decreased tumor area and weight. Reubi[20] reported the effects of SMS 201-995 (200 μg/kg/day for 36 days) on a transplantable hamster insulinoma with high-affinity somatostatin receptors. There was a 50% reduction in tumor volume and 40% reduction in tumor weight compared to control animals. In a second experiment, the effects of SMS 201-995 on the growth of an established insulinoma was studied. After 16 days of tumor growth, hamsters bearing the insulinoma tumor were treated with SMS 201-995 (2 or 25 μg/kg/day). Treatment caused a reduction in tumor volume of 33% at the lower dose and of 52% at the higher dose. These findings suggest that the antiproliferative effect of somatostatin was mediated through its receptor.

We examined the effect of somatostatin on a transplantable human carcinoid, BON, that was established in nude mice.[78,79] In the first study, we treated 12 male mice bearing BON xenografts with either SMS 201-995 (300 μg/kg) or saline. At the end of 6 weeks, the tumors were excised and weighed and plasma serotonin was measured. SMS 201-995 significantly reduced plasma serotonin levels and inhibited the growth of BON. In the second experiment, the effect of SMS 201-995 (300 μg/kg) and SMS 201-995 combined with α-difluoromethylornithine (2% in drinking water) was examined on the growth of BON. Both SMS 201-995 and α-difluoromethylornithine inhibited the growth of BON, and the combination of the two inhibited BON to a greater extent than either agent alone. This finding suggests that somatostatin may play a useful role in multiagent chemotherapy.

These studies clearly demonstrate that somatostatin analogue, in a widely ranging dosage (2 μg/kg to 300 μg/kg), inhibits the growth of transplantable endocrine tumors in experimental tumor models. The mechanism of somatostatin's antiproliferative action has not been clarified. Somatostatin may modulate tumor growth by a direct action on somatostatin receptors as demonstrated by Reubi[20] or by an inhibition of release of endogenous hormones that modulate tumor growth in hormone-responsive cancers. Both of these actions (that is, suppression of hormone release and direct suppression of tumor growth) may interact to produce the total antiproliferative effect of somatostatin. Further studies will be needed to clarify the mode of action of the antiproliferative effect of somatostatin in endocrine tumors.

While the experimental studies reviewed above suggest an antiproliferative action of somatostatin, its effects in patients have been variable. Somatostatin analogues were used primarily for symptomatic control in patients with advanced tumors (the majority with extensive liver metastasis). The reported effects of somatostatin on tumor often are based on small experience and usually rely on serial computed tomography or liver scans (Table 1). In-

TABLE 1. *Summary of Antiproliferative Effects of Somatostatin Analogue, SMS 201-995, on Endocrine Tumors in Clinical Studies*

Investigators	Tumor*	Dosages of SMS 201-995 Duration of Treatment	Effect on Tumor
Shepherd and Senator[80]	Gastrinoma (1)	1 year	Initial shrinkage of tumor
Kvols et al.[28]	Malignant carcinoid (13)	150 μg tid, 18 months	Apparent shrinkage of hepatic metastasis in 3 patients
Souquet et al.[17]	Gastrinoma (2) carcinoid (1)	100 μg bid, 8 months	Tumor progression
Kraenzlin et al.[23]	VIPoma (1)	50 μg bid, 14 months	Shrinkage of hepatic metastasis
Juby et al.[22]	VIPoma (1)	50 μg bid, 24 months	Tumor size stable during treatment period
Clements and Elias[24]	VIPoma (1)	50 μg daily, 9 months	Shrinkage of hepatic metastasis
Altimari et al.[26]	Glucogonoma (1)	50 μg bid, 8 months	No effect
Boden et al.[25]	Glucagonoma (1)	50 μg bid, 8 months	No effect
Williams et al.[49]	VIPoma (4) gastrinoma and/or glucagonoma (6) carcinoid (1)	50 μg bid, 18 to 38 months	Tumor progression
Wiedenmann et al.[81]	Carcinoid (1)	100 μg bid, 7 months	Shrinkage of hepatic metastasis

* Number of patients in parentheses.

terpretation of an antiproliferative effect is complicated further in some studies by multiple therapeutic sallies, including chemotherapy and embolization of the hepatic artery. The reported effects of somatostatin analogues on inhibition of tumor growth have been modest or absent. Kraenzlin and colleagues[23] first reported that SMS 201–995 produced shrinkage of a hepatic metastasis in a patient with a VIPoma. In a later study with a long-term follow-up in four patients with VIPomas, Williams and colleagues[49] could not demonstrate a tumor suppression with somatostatin. Studying the effects of various chemotherapeutic regimens in patients with endocrine tumors is further complicated by the fact that these tumors are relatively rare and tumor growth is usually slow, indolent, and unpredictable. Endocrine tumors are infrequent, and this makes the successful evaluation of the role of somatostatin analogues extraordinarily difficult. However consideration of such a study is warranted in solid, nonendocrine tumors, such as pancreatic or breast cancer.

Conclusions

Somatostatin analogues represent a novel approach from traditional chemotherapeutic regimens in the treatment of certain cancers. The obvious advantages of somatostatin treatment include a wide range of inhibitory and antiproliferative actions with few side effects. The exact mechanism of somatostatin's antitumor effect is unknown. It may act directly by interaction with specific somatostatin receptors known to be present on membranes of a variety of tumors, or indirectly by inhibiting release of growth factors known to stimulate neoplastic growth. Whatever the mechanism, somatostatin therapy may offer an additional period of symptom-free living in selected patients with solid neoplasms and in those patients with hypersecretory disorders from endocrine tumors. Somatostatin may prove to be a salient addition to cancer chemotherapy.

References

1. Brazeau P, Vale W, Burgus R, et al. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science 1973; 179:77–79.
2. Krulich L, Dhariwal APS, McCann SM. Stimulatory and inhibitory effects of purified hypothalamic extracts on growth hormone release from rat pituitary *in vitro*. Endocrinology 1968; 83:783–790.
3. Lucey MR. Endogenous somatostatin and the gut. Gut 1986; 27: 457–467.
4. Newman JB, Lluis F, Townsend CM Jr. Somatostatin. *In* Thompson JC, Greeley GH Jr, Rayford PL, Townsend CM Jr, eds. Gastrointestinal Endocrinology. New York: McGraw-Hill Book Co, 1987, pp 286–299.
5. Reichlin S. Secretion of somatostatin and its physiologic function. J Lab Clin Med 1987; 109:320–326.
6. Longnecker SM. Somatostatin and octreotide: literature review and description of therapeutic activity in pancreatic neoplasia. Drug Intell Clin Pharm 1988; 22:99–106.
7. Reichlin S. Somatostatin (first of two parts). N Engl J Med 1983; 309:1495–1501.
8. Reichlin S. Somatostatin (second of two parts). N Engl J Med 1983; 309:1556–1563.
9. Price BA, Jaffe BM, Zinner MJ. Effect of exogenous somatostatin infusion on gastrointestinal blood flow and hormones in the conscious dog. Gastroenterology 1985; 88:80–85.
10. Tyden G, Samnegard H, Thulin L, et al. Circulatory effects of somatostatin in anesthetized man. Acta Chir Scand 1979; 145:443–446.
11. Lamberts SWJ, Uitterlinden P, del Pozo E. SMS 201–995 induces a continuous decline in circulating growth hormone and somatomedin-C levels during therapy of acromegalic patients for over two years. J Clin Endocrinol Metab 1987; 65:703–710.
12. Williams G, Burrin JM, Ball JA, et al. Effective and lasting growth-hormone suppression in active acromegaly with oral administration of somatostatin analogue SMS 201–995. Lancet 1986; 2: 774–777.
13. Ellison EC, Garner WL, Mekhjian HS, et al. Successful treatment of pancreatic ascites with somatostatin analog (SMS 201–995). Gastroenterology 1986; 90:1405(Abst).
14. Santangelo WC, O'Dorisio TM, Kim JG, et al. Pancreatic cholera syndrome: effect of a synthetic somatostatin analog on intestinal water and ion transport. Ann Intern Med 1985; 103:363–367.
15. Ellison EC, O'Dorisio TM, Elkammas E, et al. Long-acting somatostatin analog inhibits calcium and secretin stimulated gastrin release in the Zollinger-Ellison syndrome. Gastroenterology 1986; 90:1405(Abst).
16. Ellison EC, O'Dorisio TM, Sparks J, et al. Observations on the effect of a somatostatin analog in the Zollinger-Ellison syndronme: implications for the treatment of apudomas. Surgery 1986; 100: 437–444.
17. Souquet J-C, Sassolas G, Forichon J, et al. Clinical and hormonal effects of a long-acting somatostatin analogue in pancreatic endocrine tumors and in carcinoid syndrome. Cancer 1987; 59: 1654–1660.
18. Vinik AI, Tsai S, Moattari AR, Cheung P. Somatostatin analogue (SMS 201–995) in patients with gastrinomas. Surgery 1988; 104: 834–842.
19. Osei K, O'Dorisio TM. Malignant insulinoma: effects of a somatostatin analog (compound 201–995) on serum glucose, growth, and gastro-entero-pancreatic hormones. Ann Int Med 1985; 103: 223–225.
20. Reubi JC. A somatostatin analogue inhibits chondrosarcoma and insulinoma tumour growth. Acta Endocrinologica 1985; 109:108–114.
21. O'Dorisio TM, Gaginella TS, Mekhjian HS, et al. Somatostatin and analogues in the treatment of VIPoma. Ann NY Acad Sci 1988; 527:528–535.
22. Juby LD, Burke DA, Axon ATR. Somatostatin analogue SMS 201–995 long term therapy for vipoma. Postgraduate Med J 1987; 63:287–289.
23. Kraenzlin ME, Ch'ng JLC, Wood SM, et al. Long-term treatment of a VIPoma with somatostatin analogue resulting in remission of symptoms and possible shrinkage of metastases. Gastroenterology 1985; 88:185–187.
24. Clements D, Elias E. Regression of metastatic VIPoma with somatostatin analogue SMS 201–995. Lancet 1985; 1:874–875.
25. Boden G, Ryan IG, Eisenschmid BL, et al. Treatment of inoperable glucagonoma with the long-acting somatostatin analogue SMS 201–995. N Engl J Med 1986; 314:1686–1689.
26. Altimari AF, Bhoopalam N, O'Dorsio T, et al. Use of a somatostatin analog (SMS 201–995) in the glucagonoma syndrome. Surgery 1986; 100:989–995.
27. Ahlman H, Ahlund L, Dahlstrom A, et al. Use of a somatostatin analogue in association with surgery and hepatic arterial embolisation in the treatment of the carcinoid syndrome. Br J Cancer 1987; 56:840–842.

28. Kvols LK, Moertel CG, O'Connell MJ, et al. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. N Engl J Med 1986; 315:663–666.
29. Schally AV. Oncological applications of somatostatin analogues. Cancer Res 1988; 48:6977–6985.
30. Rose DP, Gottardis M, Noonan JJ. Rat mammary carcinoma regressions during suppression of serum growth hormone and prolactin. Anticancer Res 1983; 3:323–326.
31. Setyono-Han B, Henkelman MS, Foekens JA, Klijn JGM. Direct inhibitory effects of somatostatin (analogues) on the growth of human breast cancer cells. Cancer Res 1987; 47:1566–1570.
32. Weber C, Merriam L, Koschitzky T, et al. Inhibition of growth of human breast carcinomas in vivo by somatostatin analogue, SMS 201–995, treatment of nude mouse xenografts. Surgery 1989; 106:416–422.
33. Scambia G, Panici PB, Baiocchi G, et al. Antiproliferative effects of somatostatin and the somatostatin analog SMS 201–995 on three human breast cancer cell lines. J Cancer Res Clin Oncol 1988; 114:306–308.
34. Schally AV, Comaru-Schally AM, Redding TW. Antitumor effects of analogs of hypothalamic hormones in endocrine-dependent cancers. Proc Soc Exp Biol Med 1984; 175:259–281.
35. Schally AV, Redding TW. Somatostatin analogs as adjuncts to agonists of luteinizing hormone-releasing hormone in the treatment of experimental prostate cancer. Proc Natl Acad Sci USA 1987; 84:7275–7279.
36. Zalatnai A, Paz-Bouza JI, Redding TW, Schally AV. Histologic changes in the rat prostate cancer model after treatment with somatostatin analogs and D-Trp-6-LH-RH. The Prostate 1988; 12:85–98.
37. Murphy WA, Lance VA, Moreau S, et al. Inhibition of rat prostate tumor growth by an octapeptide analog of somatostatin. Life Sci 1987; 40:2515–2522.
38. Smith JP, Solomon TE. Effects of gastrin, proglumide, and somatostatin on growth of human colon cancer. Gastroenterology 1988; 95:1541–1548.
39. Singh P, Le S, Townsend CM Jr, et al. A long acting somatostatin analog (SRIF) (201–995) and proglumide (PGL) inhibit the trophic and gastrin receptor (GR) regulatory effects of pentagastrin (PG) on mouse colon cancer (MC-26) cells in vivo. Gastroenterology 1986; 90:1636(Abst).
40. Milhoan RA, Milhoan LH, Trudel JL, et al. Somatostatin and α-difluoromethylornithine (DFMO) have additive inhibitory effects on growth of human colon carcinoma (HCC) in vivo. Biomed Res 1988; 9:30(Abst).
41. Redding TW, Schally AV. Inhibition of growth of pancreatic carcinomas in animal models by analogs of hypothalamic hormones. Proc Natl Acad Sci USA 1984; 81:248–252.
42. Upp JR Jr, Olson D, Poston GJ, et al.Inhibition of growth of two human pancreatic adenocarcinomas in vivo by somatostatin analog SMS 201–995. Am J Surg 1988; 155:29–35.
43. Hierowski MT, Liebow C, du Sapin K, Schally AV. Stimulation by somatostatin of dephosphorylation of membrane proteins in pancreatic cancer MIA PaCa-2 cell line. FEBS Lett 1985; 179: 252–256.
44. Milhoan RA, Trudel JL, Lawrence JP, et al. Somatostatin inhibits growth of human small cell lung carcinoma in vivo. Surg Forum 1988; 39:438–439.
45. Taylor JE, Bogden AE, Moreau J-P, Coy DH. In vitro and in vivo inhibition of human small cell lung carcinoma (NCI-H69) growth by a somatostatin analogue. Biochem Biophys Res Commun 1988; 153:81–86.
46. Mascardo RN, Sherline P. Somatostatin inhibits rapid centrosomal separation and cell proliferation induced by epidermal growth factor. Endocrinology 1982; 111:1394–1396.
47. Davies RR, Miller M, Turner SJ, et al. Effects of somatostatin analogue SMS 201–995 in normal man. Clin Endocrinol 1986; 24: 665–674.
48. Bauer W, Briner U, Doepfner W, et al. SMS 201–995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 1982; 31:1133–1140.
49. Williams G, Anderson JV, Williams SJ, Bloom SR. Clinical evaluation of SMS 201–995. Long-term treatment in gut neuroendocrine tumours, efficacy of oral administration, and possible use in non-tumoural inappropriate TSH hypersecretion. Acta Endocrinologica 1987; suppl 286:26–36.
50. Cai R-Z, Szoke B, Lu R, et al. Synthesis and biological activity of highly potent octapeptide analogs of somatostatin. Proc Natl Acad Sci USA 1986; 83:1896–1900.
51. Lamberts SWJ, Koper JW, Reubi J-C. Potential role of somatostatin analogues in the treatment of cancer. Eur J Clin Invest 1987; 17: 281–287.
52. Werner H, Amarant T, Millar RP, Fridkin M, Koch Y. Immunoreactive and biologically active somatostatin in human and sheep milk. Eur J Biochem 1985; 148:353–357.
53. Reubi JC, Maurer R, von Werder K, et al. Somatostatin receptors in human endocrine tumors. Cancer Res 1987; 47:551–558.
54. Spring-Mills EJ, Stearns SB, Numann PJ, Smith PH. Immunocytochemical localization of insulin- and somatostatin-like material in human breast tumors. Life Sci 1984; 35:185–190.
55. Klijn JGM, Setyono-Han B, Bakker GH, Foekens JA. Effects of somatostatin analog (SMS-A) treatment (sandostatin) in experimental and human cancer. Eur J Cancer Clin Oncol 1986; 22: 727.
56. Lippman ME, Dickson RB, Kasid A, et al. Autocrine and paracrine growth regulation of human breast cancer. J Steroid Biochem 1986; 24:147–154.
57. Erisman MD, Linnoila RI, Hernandez O, et al. Human lung small-cell carcinoma contains bombesin. Proc Natl Acad Sci USA 1982; 79:2379–2383.
58. Abe K, Kameya T, Yamaguchi K, et al. Hormone-producing lung cancers. Endocrinologic and morphologic studies. *In* Becker KL, Gazdar AF, eds. The Endocrine Lung in Health & Disease. Philadelphia: WB Saunders, 1984, pp 549–595.
59. Gazdar AF. The biology of endocrine tumors of the lung. An overview. *In* Becker KL, Gazdar AF, eds. The Endocrine Lung in Health & Disease. Philadelphia: WB Saunders, 1984, pp 448–459.
60. Catane R, Lichter A, Lee YJ, Brereton HD, Schwade JG, Glatstein E. Small cell lung cancer: analysis of treatment factors contributing to prolonged survival. Cancer 1981; 48:1936–1943.
61. Cuttita F, Carney DN, Mulshine J, et al. Bombesin-like peptides can function as autocrine growth factors in human small-cell lung cancer. Nature 1985; 316:823–826.
62. Moody TW, Bertness V, Carney DN. Bombesin-like peptides and receptors in human tumor cell lines. Peptides 1983; 4:683–686.
63. Yoshizaki K, de Bock V, Takai I, et al. Bombesin-like peptides in human small cell carcinoma of the lung. Regul Pept 1986; 14: 11–20.
64. Sorenson GD, Bloom SR, Ghatei MA, et al. Bombesin production by human small cell carcinoma of the lung. Regul Pept 1982; 4: 59–66.
65. Walsh JH, Reeve JR Jr. Mammalian bombesin-like peptides: neuromodulators of gastric function and autocrine regulators of lung cancer growth. Peptides 1985; 6:63–68.
66. Wood SM, Wood JR, Ghatei MA, et al. Bombesin, somatostatin and neurotensin-like immunoreactivity in bronchial carcinoma. J Clin Endocrinol Metab 1981; 53:1310–1312.
67. Alexander RW, Upp JR Jr, Poston GJ, et al. Effects of bombesin on growth of human small cell lung carcinoma in vivo. Cancer Res 1988; 48:1439–1441.
68. Upp JR Jr, Singh P, Townsend CM Jr, Thompson JC. The clinical significance of gastrin receptors in human colon cancers. Cancer Res 1989; 49:488–492.
69. Winsett OE, Townsend CM Jr, Glass EJ, Thompson JC. Gastrin stimulates growth of colon cancer. Surgery 1986; 99:302–307.
70. Upp JR Jr, Singh P, Townsend CM Jr, Thompson JC. Predicting response to endocrine therapy in human pancreatic cancer with cholecystokinin receptors. Gastroenterology 1987; 92:1677(Abst).
71. Townsend CM Jr, Franklin RB, Watson LC, et al. Stimulation of pancreatic cancer growth by caerulein and secretin. Surg Forum 1981; 32:228–229.

72. Liebow C, Hierowski M, duSapin K. Hormonal control of pancreatic cancer growth. Pancreas 1986; 1:44–48.
73. Krejs GJ. Proceedings of a Symposium. Gastrointestinal endocrine tumors: diagnosis and management. Role of somatostatin analogue SMS 201–995. Am J Med 1987; 82(Suppl 5B):1–99.
74. Bloom SR, Greenwood C. Proceedings of somatostatin '85. Chemical, physiological, and clinical advances. Scand J Gastroenterol 1986; 21(Suppl 119):1–274.
75. Maton PN, Gardner JD, Jensen RT. Use of long-acting somatostatin analog SMS 201–995 in patients with pancreatic islet cell tumors. Dig Dis Sci 1989; 34:28S–39S.
76. Gorden P, Comi RJ, Maton PN, Go VLW. Somatostatin and somatostatin analogue (SMS 201–995) in treatment of hormone-secreting tumors of the pituitary and gastrointestinal tract and non-neoplastic diseases of the gut. Ann Internal Med. 1989; 110: 35–50.
77. Lamberts SWJ, Reubi J-C, Uiterlinden P, et al. Studies on the mechanism of action of the inhibitory effect of the somatostatin analog SMS 201–995 on the growth of the prolactin/adrenocorticotropin-secreting pituitary tumor 7315a. Endocrinology 1986; 118:2188–2194.
78. Allen E, Evers BM, Townsend CM Jr, et al. Somatostatin analog (201–995) and α-difluoromethylornithine (DFMO) inhibit growth of human carcinoid tumor. Surg Forum 1989; 40:22–24.
79. Upp JR Jr, Alexander RW, Poston GJ, et al. Inhibition of a human malignant carcinoid growing in nude mice. Gastroenterology 1987; 92:1643(Abst).
80. Shepherd JJ, Senator GB. Regression of liver metastases in patient with gastric-secreting tumour treated with SMS 201–995. Lancet 1986; ii:574.
81. Wiedenmann B, Rath U, Radsch R, Becker F, Kommerell B. Tumor regression of an ileal carcinoid under the treatment with the somatostatin analogue SMS 201–995. Klin Wochenschr 1988; 66: 75–77.