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Somatostatin Receptors in the Gastrointestinal Tract in Health and Disease

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The multiple actions of somatostatin are mediated by specific membrane-bound receptors present in all somatostatin target tissues, such as brain, pituitary, pancreas, and gastrointestinal tract. Three different types of tissues in the human gastrointestinal tract express somatostatin receptors: *(1)* the gastrointestinal mucosa, *(2)* the peripheral nervous system, and *(3)* the gut-associated lymphoid tissue, where the receptors are preferentially located in germinal centers. In all these cases, somatostatin binding is of high affinity and specific for bioactive somatostatin analogs.

Somatostatin receptors are also expressed in pathological states, particularly in neuroendocrine tumors of the gastrointestinal tract. Ninety percent of the carcinoids and a majority of islet-cell carcinomas, including their metastases, usually have a high density of somatostatin receptors. Only 10 percent of the colorectal carcinomas and none of the exocrine pancreatic carcinomas, however, contain somatostatin receptors.

The somatostatin receptors in tumors are identified with *in vitro* binding methods or with *in vivo* imaging techniques; the latter allow the precise localization of the tumors and their metastases in the patients. Since somatostatin receptors in gastroenteropancreatic tumors are functional, their identification can be used to assess the therapeutic efficacy of octreotide to inhibit excessive hormone release in the patients.

INTRODUCTION

Somatostatin (SS) is a cyclic 14-amino acid peptide with wide distribution in the body and multiple sites of action [1]. SS and another biologically active SS, SS-28, are processed through differential splicing from a pre-prosomatostatin precursor. Whereas SS was originally purified from hypothalamic tissue, it has since been identified in several other brain regions, in the peripheral nervous system, in the endocrine pancreas, in the thyroid, and in the gut.

SS is a very strong inhibitor of several key functions in the body [1]. It inhibits the secretion of growth hormone and thyrotropin; in the pancreas, it inhibits glucagon and insulin; in the brain, it exhibits a number of actions compatible with a role as neurotransmitter [2]. In lymphoid tissues, it inhibits immunoglobulin synthesis and lymphocyte proliferation. In the gastrointestinal system, SS is known to inhibit the secretion of all major gastrointestinal hormones, to inhibit gastric and intestinal motility, intestinal absorption, and gastric acid secretion.

SS induces these physiological effects by interacting with cell surface receptors in target tissues. The presence of high-affinity, specific SS receptors has been observed

Abbreviations: ECL: enterochromaffin-like GALT: gut-associated lymphoid tissue GEP: gastroenteropancreatic ICC: islet-cell carcinoma SS: somatostatin

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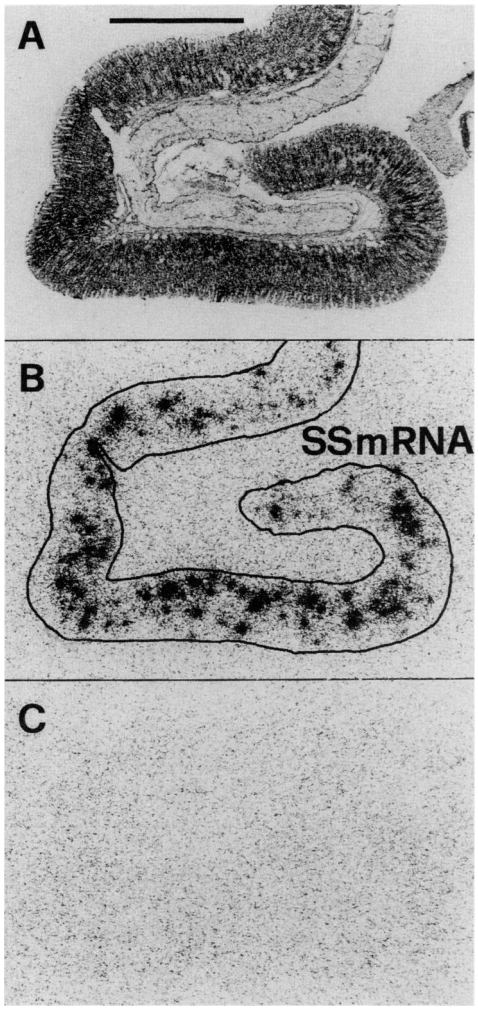

FIG. 1. SS mRNA in healthy rat gastric mucosa. **A.** Hematoxylin-eosin stained section. Bar = 1 mm. **B.** Autoradiogram showing **SS mRNA,** using in situ hybridization. The limits of the mucosa are drawn in black. The dark regions are spots representing areas with high densities of hybridization signal. **C.** Autoradiogram showing the lack of hybridization signal when twentyfold excess of unlabeled probe is co-hybridized with the labeled probe.

in such tissues as the brain, pituitary, adrenal gland, endocrine and exocrine pancreas, gut, and lymphoid tissue. Through these specific SS receptors, SS has been shown to inhibit adenylate cyclase activity, resulting in a decrease in intracellular cyclic AMP, as well as a decrease of Ca^{2+} conductance and an increase of K^+ conductance. Most, if not all, of these functions appear to be mediated by pertussis toxin-sensitive GTP-binding proteins [3]. Moreover, in certain tissues, such as rat pancreatic acinar cells, SS was shown to stimulate a low-molecular-mass phosphoryl protein tyrosine phosphatase [4].

SS RECEPTORS IN THE GASTROINTESTINAL TRACT

SS as well as SS receptors are present in the healthy gastric mucosa. As shown in Fig. 1, SS mRNA is found abundantly by in situ hybridization techniques [5] in most layers of the rat gastric mucosa. In the same tissue, it is also possible to detect high numbers of SS receptors. These receptors are of high affinity, with a dissociation constant (K_D) in the nanomolar range, and they are specific for SS, since only

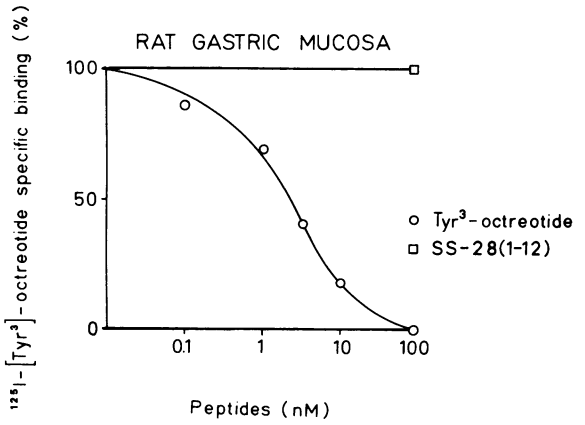

FIG. 2. Effect of SS analogs on SS binding in tissue sections from rat gastric mucosa. Displacement curve of ^{125}I-[Tyr^3]-octreotide in tissue sections incubated with 30,000 cpm/100 μl radioligand and increasing concentrations of [Tyr^3]-octreotide (○) or 100 nM of the biologically inactive SS analog SS-28 (1–12) (□).

biologically active SS analogs, but not inactive SS analogs or unrelated peptides, are able to displace SS radioligands, as shown in Fig. 2, for the gastric rat mucosa. Figure 3 shows an example of the distribution of these SS receptors in the rat gastric mucosa, using ^{125}I-[Tyr^3]-octreotide as radioligand. Many of these receptors are likely to be localized on parietal cells: indeed, high-affinity SS receptors were identified in a canine parietal cell preparation [6]; in this model, SS inhibits, dose

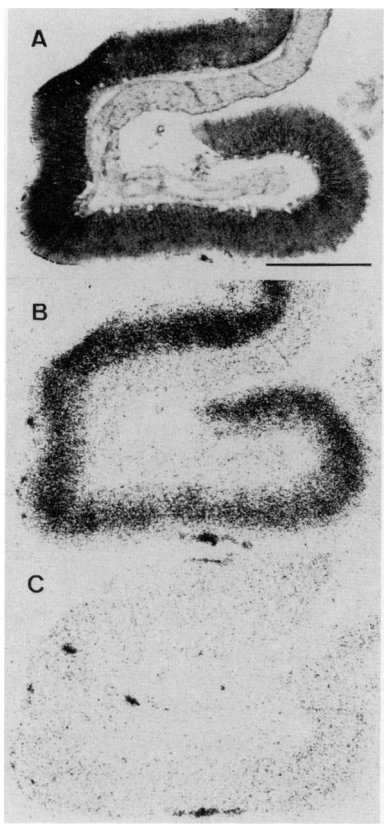

FIG. 3. SS receptors in the rat gastric mucosa. **A.** Hematoxylin-eosin stained section. Bar = 1 mm. **B.** Autoradiogram showing total binding of ^{125}I-[Tyr^3]-octreotide. **C.** Autoradiogram showing nonspecific binding of ^{125}I-[Tyr^3]-octreotide, in presence of 10^{-6}M unlabeled [Tyr^3]-octreotide. SS receptors are located in the major part of the mucosa.

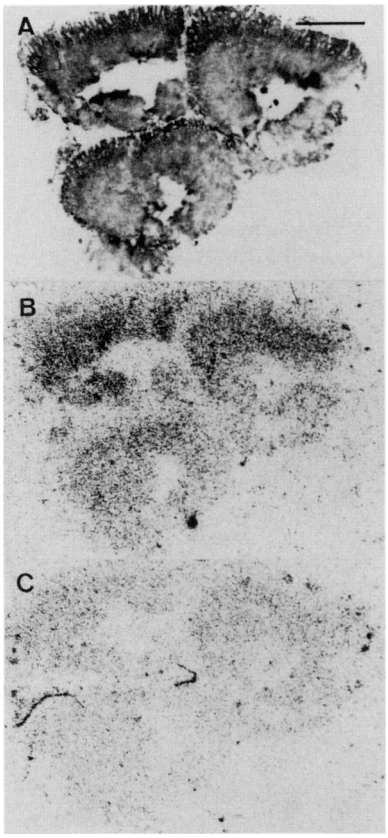

FIG. 4. SS receptors in a biopsy of human gastric mucosa. (Tissue was obtained from F. Halter.) **A.** Hematoxylin-eosin stained section. Bar = 1 mm. **B.** Autoradiogram showing total binding of ^{125}I-[Tyr^3]-octreotide. **C.** Autoradiogram showing nonspecific binding of ^{125}I-[Tyr^3]-octreotide (in the presence of 10^{-6}M [Tyr^3]-octreotide).

dependently, parietal cell activity stimulated by various secretagogues [6,7]. According to other functional studies, however, SS receptors are also likely to be localized in other cell types of the gastric mucosa, such as the gastrin-producing cells and the histamine-producing enterochromaffine-like (ECL) cells [8,9; see also papers by Makhlouf and by Soll, in this symposium]. We have recently had strong evidence that high-affinity SS receptors are located on ECL cells [10]; indeed, the ECL tumors originating spontaneously, or after H_2-receptor blocker (loxtidine) treatment, in the stomach of the mastomys mouse express a high density of SS receptors. Since these tumors are highly differentiated and contain ECL cells exclusively, it is probable that healthy mucosal ECL cells would also express SS receptors. These data imply, therefore, an important role of SS in the gastric physiology, in particular through regulation of histamine secretion.

In addition to the above-mentioned membrane-bound SS receptors, cytosolic SS receptors were also reported [11] in gastric mucosa. Their role remains unclear.

The presence of SS receptors cannot only be demonstrated in the gastric mucosa of experimental animals, but also in man. Figure 4 shows SS receptors in the mucosa of a biopsy taken from a human stomach. The number of SS receptors appears to be lower in human than in rat gastric mucosa; however, a greater variability in receptor density is observed in human than in rat tissue. Technical reasons may, in part, be responsible for that fact, since the conditions for obtaining human samples may sometimes be suboptimal.

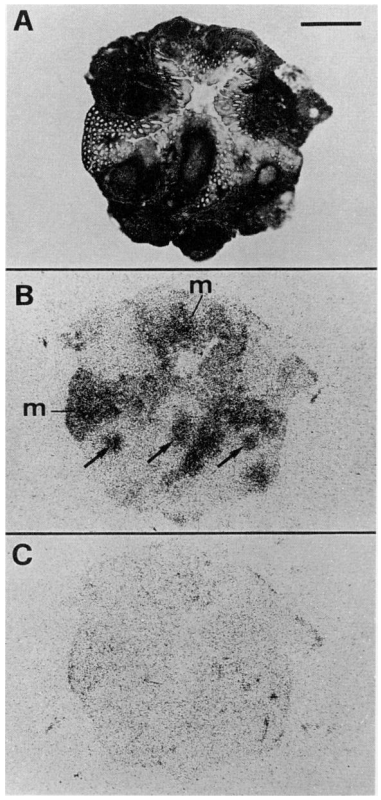

FIG. 5. SS receptors in an appendix from a child. (Tissue was obtained from J. Gebbers.) **A.** Hematoxylin-eosin stained section showing lymphatic follicles with germinal centers and intestinal mucosa. Bar = 1 mm. **B.** Autoradiogram showing total binding of ^{125}I-[Tyr^3]-octreotide. Germinal centers are labeled *(arrows)* as well as intestinal mucosa (**m**). **C.** Nonspecific binding.

High-affinity SS receptors are also found in the lower human gastrointestinal tract. They can be identified, for instance, in the mucosa of the ileum, jejunum, and colon [12,13]. Their function there is not well established; they may mediate the SS inhibition of peptide secretion from endocrine cells, as described for most other parts of the gastrointestinal tract. More specifically, they may inhibit the intestinal fluid secretion induced by various peptides (VIP, glucagon) in the jejunum and the colon [14–16]. As expected, SS receptors are not only found in the mucosa but also in the plexus myentericus and plexus submucosus [12], where SS has been shown to inhibit cholinergic transmission [17]. Moreover, SS receptors are localized in the gut-associated lymphoid tissue, as recently reported [12], and are shown in an example in Fig. 5. In this study, we have evaluated SS receptors in four human gut-associated lymphoid tissues, namely, palatine tonsils, ileal Peyer patches, vermiform appendix, and colonic solitary lymphatic follicles, using receptor autoradiography on tissue sections incubated with ^{125}I-[Tyr^3]-octreotide [12]. All four tissues were somatostatin receptor-positive; the receptors were preferentially located in the germinal centers, with the luminal part of the center more strongly labeled than the basal part. The corona of the follicles and the primary follicles without germinal centers did not display somatostatin receptors. The receptors were of high affinity and specific for somatostatin. Displacement by nanomolar concentrations of somatostatin-14, somatostatin-28, and octreotide was observed, as well as GTP dependency. These data suggest strongly that the germinal centers of the gut-associated lymphoid

TABLE 1
Incidence of Somatostatin Receptors in Various Gut Tumors

Tumor Type	Presence of SS Receptors (% of Positive Cases)
GEP tumors	
a. Islet-cell carcinomas	
Insulinomas	8/11 (72)
Vipomas	7/8 (87)
Gastrinomas	5/5 (100)
Glucagonomas	3/3 (100)
GRF-omas	4/4 (100)
Non-functioning ICC	4/4 (100)
b. Carcinoids	66/81 (81)
Exocrine pancreatic carcinomas	0/12 (0)
Colonic carcinomas	3/26 (11)

tissue (GALT) are a site of action of somatostatin; possibly it mediates antiproliferative effects and inhibits immunoglobulin synthesis in the activated lymphoid cells [12]. The human gut, therefore, represents a multi-faceted target for somatostatin action, in which at least three different tissues, namely, mucosa, nerve plexus, and lymphoid tissue, are involved.

Considering the increasing importance of immuno-neuroendocrine interactions [18], it may be speculated that these three SS receptor-containing tissues are, in fact, integrated within a SS regulatory system of a higher hierarchy. The studies by Felten et al. [19] and Fehér et al. [20] show an extensive noradrenergic and somatostatinergic innervation of the lymphoid tissue, including the GALT. Therefore, it is conceivable that the peripheral nervous system, including SS-containing nerve fibers, plays an integrative role for immuno-neuroendocrine functions.

SS RECEPTORS IN HUMAN TUMORS

Remarkably, SS receptors have been observed not only in normal SS target tissues, but also in several types of human cancer [21]. The receptors occur in most neuroendocrine neoplasms and also in tumors of the central nervous system, breast, and lung; they are, in addition, expressed by most lymphomas and renal cell cancers. The presence of SS receptors may be, for certain tumor types, a pathobiochemical marker of predictive value for the efficacy of SS analog therapy [22], while, in others, it may be of prognostic significance [23]. Moreover, these SS receptors can be visualized *in vivo* with gamma-camera scanning techniques, making possible the precise localization of primary and metastatic tumor sites [24,25].

SS Receptors in Hormone-Producing Gastroenteropancreatic Tumors

A very high incidence of homogeneously distributed SS receptors is found in most hormone-producing gastroenteropancreatic (GEP) tumors [26,27] (Table 1). Eighty-one percent of the carcinoids tested ($n = 81$) were SS receptor-positive. A typical case, with high density of receptors located preferentially in the tumor cells, is shown in Fig. 6, where it can be observed that the receptor density in the carcinoid tumor cells is much higher than in the surrounding healthy mucosa (see also Fig. 4). Interestingly, the presence of SS receptors in a tumor may be related to its

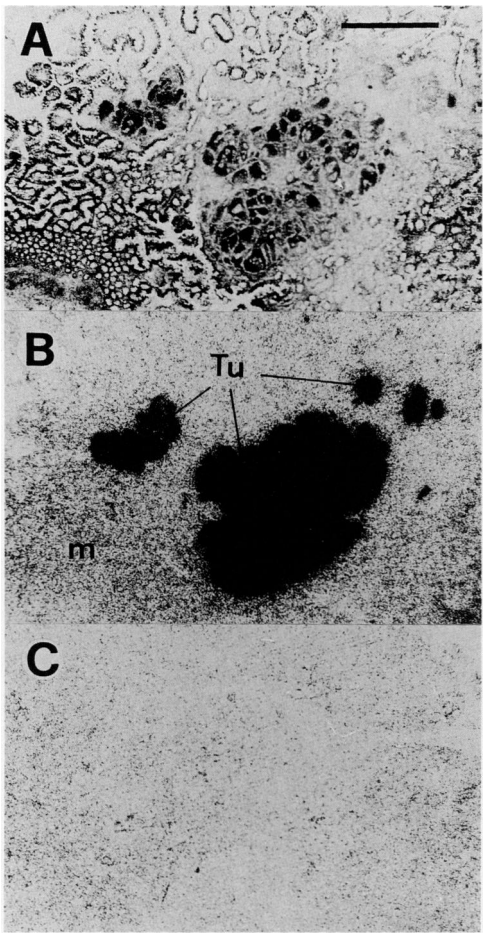

FIG. 6. SS receptors on intestinal carcinoid tumor. (Tumor was obtained from L. Kvols.) **A.** Hematoxylin-eosin stained section. Bar = 1 mm. **B.** Autoradiogram showing total binding of ^{125}I-[Tyr^3]-octreotide. **Tu** tumor; **m,** mucosa. **C.** Autoradiogram showing nonspecific binding (in the presence of 10^{-6}M [Tyr^3]-octreotide). Notice the very high receptor density in the tumor compared to the low density in the mucosa.

differentiation state: for instance, most of the SS receptor-negative carcinoids belong to the less differentiated atypical carcinoids [27]; these are often bronchial carcinoids, whereas intestinal carcinoids usually are receptor-positive. Also, most of the islet-cell carcinomas (ICC) have SS receptors (Table 1). Whereas all gastrinomas, glucagonomas, GRF-omas, and non-functioning ICC tested possess SS receptors, 87 percent of vipomas, and 72 percent of insulinomas were receptor-positive. Here again, a high density of SS receptors is located in tumor tissue, well delimited from surrounding tissue. Carcinoid and ICC SS receptors have the same biochemical characteristics as SS receptors in healthy target tissues.

We have demonstrated that virtually all metastases of SS receptor-positive GEP tumors are positive. Such homogeneous biological properties of primary and metastatic lesions in regard to SS receptors have important therapeutic and diagnostic consequences. The primary tumor, as well as its metastases, should be equally sensitive to somatostatin therapy. This concept led us to develop a method of analyzing the SS receptor status in patients with GEP tumors by measuring SS receptors with autoradiography on small-needle biopsies from liver metastases [27]. By this method, the functionality of these tumoral SS receptors can be investigated;

in 31 cases of GEP tumors, a highly significant correlation was found between the SS receptor status and the ability of octreotide to inhibit *in vivo* hormone secretion [27; see also paper by Kvols et al. in this symposium]. Interestingly, some of these tumors, in particular insulinomas, may bear an SS receptor subtype [27]. Such SS receptor subtypes have been identified pharmacologically in the rat and the human brain by mean of their differential affinity for certain somatostatin analogs [28–30]. Octreotide, for example, can differentiate between two SS receptor types, one having a high affinity for octreotide (SS_1-R), the other a low affinity for octreotide (SS_2-R). The ratio between SS_1-R and SS_2-R varies among brain regions. Whereas a majority of brain structures contain mainly SS_1-R, the substantia nigra contains mainly SS_2-R. In turn, a majority of receptor-positive GEP tumors expressed the SS_1-R subtype, but some tumors expressed the SS_2-R subtype. Those tumors included one-third of insulinomas: they had SS receptors with low affinity for octreotide and high affinity for SS-14 and SS-28, and their insulin release was inhibited only by SS-14 and SS-28, but not by octreotide, *in vitro* as well as *in vivo* [31]. In carcinoids, less than 10 percent of the SS receptor-positive cases were expressing SS_2-R. Recently, the cloning and sequencing of genes encoding three different SS receptor subtypes (SSTR1, SSTR2, and SSTR3) has been reported [32,33]. Preliminary studies in the brain tissue suggest that SSTR1 and SSTR2 could correspond to the pharmacologically identified SS_2 and SS_1 receptor subtypes, respectively [34,35]. The presence of SS receptor subtypes on tumors may have clinical implications. Indeed, those tumors with SS_2-R subtypes may react poorly, therapeutically, to octreotide, and they will not be visualized *in vivo* with radiolabeled octreotide. The knowledge of SS receptor subtypes may lead to the development of subtype-specific somatostatin analogs to be used for selected and new indications.

Therefore, SS receptors in GEP tumors are the probable molecular basis for hormone release inhibition by SS and, as such, relevant to the therapeutic efficacy of octreotide. Additional functions of SS may, however, be mediated by SS receptors in these tumors: there are data from animal tumor models and cultured tumor cell lines, i.e., in SS receptor-positive insulinomas or carcinoids, demonstrating that SS or octreotide has an antiproliferative action, with a 50 percent growth inhibition being reported [36,37]. In patients with GEP tumors, however, such an antiproliferative effect of chronic SS analog therapy and its exact site of action remain difficult to evaluate. Recently, in pituitary tumor cells, it was possible to observe a dissociation between antiproliferative and antihormonal effects of SS [38]. Both effects may be mediated by different SS receptor subtypes.

SS Receptors in Other Gastrointestinal Tumors

Unfortunately, SS receptors seem not to be expressed frequently in undifferentiated pancreatic and colonic carcinomas. We have not identified any SS receptors in the 12 human exocrine pancreatic carcinomas tested [39]. We and others have, however, found a small percentage of primary human colonic cancers to be SS receptor-positive [13,21,40]. The lack of SS receptors in pancreatic carcinomas may be a possible explanation for the inefficacy of octreotide in the treatment of these tumors [41].

It is interesting to note that some, but not all [42], of the animal and human transplanted tumors or cell lines derived from exocrine pancreatic and colonic carcinomas may have high densities of functional SS receptors [36,39].

IN VIVO LOCALIZATION OF SS RECEPTOR-POSITIVE TUMORS

The high density of SS receptors in many human tumors offers attractive possibilities for their detection *in vivo*. This result can be achieved by intravenous injection of ^{123}I-[Tyr^3]-octreotide or ^{111}In-DTPA-octreotide in patients suspected of having SS receptor-positive tumors [24,25,37,43]; such tumors are then localized with planar and ECT images obtained by means of a gamma camera. With this method, hot spots representing radioligand binding on SS receptor-positive tumors are visualized; the hot spots thus identified represent SS receptor-containing tumors, since there is a highly significant correlation in human tumors between the frequency of SS receptor positivity found by *in vitro* methods and by *in vivo* imaging. Indeed, most growth hormone and thyrotropin-secreting pituitary adenomas, most carcinoids and islet-cell carcinomas, all meningiomas, most glomus tumors, and many neuroblastomas, as well as several breast tumors and small-cell lung carcinomas, including their metastases, have also been visualized *in vivo* [37]. Moreover, we have recently confirmed that, in virtually all tumor patients with receptor-positive scans who later underwent operative biopsies, the hot spots identified *in vivo* corresponded to SS receptor-positive tumors, as measured with *in vitro* binding techniques [37]. These findings clearly demonstrate the specificity of the *in vivo* imaging method and confirm the *in vitro* findings that several tumors and their metastases contain high densities of SS receptors. The *in vivo* labeling of tumors, in particular of the SS receptor-dense GEP tumors, opens very promising new avenues for diagnosis and, ultimately, for therapy.

CONCLUSIONS

SS receptors in the gastrointestinal tract, localized in various different tissues and cell types, are mediating the extremely complex and not yet fully understood multiple functions of SS in this organ. Eventually, future research may discover that these different functions are mediated by selective SS receptor subtypes; as a consequence, subtype-specific analogs may be developed with selective therapeutic indications. This process, in turn, may enlarge the present clinical applications of SS analogs in SS receptor-positive tumors and in non-malignant pathologies, both as diagnostic and as therapeutic tools.

More generally, the discovery of SS receptors in gastrointestinal tumors and their clinical implications suggest that other peptide receptors may also play a role as tumor markers. We already know that a large number of peptide receptors, i.e., gastrin, bombesin, VIP, CCK, or tachykinin receptors, can be expressed by gastrointestinal tumor cell lines or primary tumors; it can be foreseen that a similar development, as in the SS field, may occur in relation to one or the other of these peptides. Ideally, high expression of a peptide receptor should be identified in tumors lacking SS receptors, i.e., colonic or pancreatic carcinomas, in order to complete the diagnostic spectrum. As a prerequisite, small-sized and stable analogs of these peptides need to be developed in order to make available successful markers for these putative peptide receptors, not only for *in vitro* studies, but also for the *in vivo* visualization of the tumors in patients.

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