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# SOMATOSTATIN RECEPTORS IN MALIGNANT TISSUES

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**Summary**—High affinity somatostatin receptors (SS-R) have been identified in membrane homogenates or tissue sections from several hundred human tumors. SS-R were found in most tumors originating from SS target tissues, i.e. GH- and TSH-producing pituitary tumors, endocrine gastroenteropancreatic (GEP) tumors (including metastases) and brain tumors, including gliomas and neuroblastomas. SS-R were also expressed in several tumors originating from various other tissues, i.e. breast and small cell lung carcinomas, some colorectal cancers, and medullary thyroid carcinomas. In general, most of the SS-R+ tumors are well-differentiated and/or have neuroendocrine features. They often have low or absent epidermal growth factor receptor (EGF-R) expression. In some tumors (i.e. breast tumors) SS-R are not homogeneously distributed, making SS-R autoradiography a particularly useful tool for assessing SS-R status. SS-R are functional in pituitary and GEP tumors where they mediate hormone secretion inhibition. In these and in the other SS-R+ tumors, SS-R may also mediate antiproliferative effects of SS, as evidenced in animals where growth of SS-R+ tumor xenografts is inhibited by SS analogs. For diagnosis, SS-R+ tumors and metastases can be localized *in vivo* by scanning techniques after $^{123}$I-labelled SS analog injection.

## INTRODUCTION

During the last decade, it has been established that the various actions of somatostatin (SS) in experimental animals and in man are mediated through specific, high affinity SS receptors (SS-R). Such receptors are located in all SS target tissues, such as the anterior pituitary, the endocrine and exocrine pancreas, the gastrointestinal tract and the central nervous system (CNS).

More recently, it has become evident that not only healthy tissues but also several types of malignant tissues contain SS-R. The aim of this review is to summarize the incidence and distribution of SS-R in human tumors, demonstrate that they are functional, describe some common characteristics shared by SS-R+ tumors and provide evidence that they can be detected not only with *in vitro* methodologies such as homogenate binding and receptor autoradiography on tumor samples, but also with *in vivo* imaging techniques in the patients.

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## DISTRIBUTION AND INCIDENCE OF SS-R

Methodologies used for this purpose include *in vitro* receptor binding on homogenate and receptor autoradiography on tissue sections, using preferentially as radioligands an SS-28 analog or an SS octapeptide analog ($^{125}$I-labeled Tyr$^3$-SMS 201-995) [1]. As shown in Table 1, a large variety of human tumors contain SS-R. For instance, most GH- and TSH-producing pituitary adenomas contain SS-R. These receptors have the same biochemical characteristics as healthy pituitary receptors [2]. However, there is a more than 10-fold variability in

Table 1. Incidence of SS-R in human tumors

| | | |
|---|---|---|
| Pituitary adenomas—GH | 42/43 | 98% |
| —TSH | 2/2 | |
| —inactive | 6/15 | 40% |
| Carcinoids | 66/81 | 82% |
| Islet cell carcinomas | 31/35 | 89% |
| Neuroblastomas | 15/23 | 65% |
| Glial tumors—astrocytomas | 14/17 | 82% |
| —glioblastomas | 1/45 | 2% |
| Meningiomas | 54/55 | 98% |
| Med. thyr. carcinomas | 9/26 | 35% |
| Pheochromocytomas | 4/7 | 57% |
| Glomus tumors | 7/9 | 78% |
| Breast tumors | 72/356 | 20% |
| (large tumors | 33/72 | 46%) |
| Lung tumors—SCLC | 4/7 | 57% |
| —NSCLC | 0/17 | 0% |
| Ovarian carcinomas | 2/47 | 4% |
| Colorectal tumors | 3/26 | 11% |

receptor density among different tumor samples. Usually the majority of pituitary tumors have an SS-R density considerably higher than the corresponding healthy tissue. Interestingly, a relatively high SS-R incidence is detected in endocrine-inactive pituitary adenomas, a remarkable observation in view of a potential diagnostical and therapeutical approach for these poorly characterized tumors [3].

A very high incidence of homogeneously distributed SS-R is found in most hormone-producing gastroenteropancreatic (GEP) tumors, such as carcinoids or islet cell carcinomas (Table 1). We have also demonstrated that all metastases of SS-R+ GEP tumors are positive [1, 4]. Such homogeneous biological properties of primary and metastatic lesions with regard to SS-R have important therapeutic as well as diagnostic consequences. The primary as well as its metastases should be equally sensitive to SS therapy; all metastases derived from an SS-R+ primary GEP tumor should be detectable with *in vivo* imaging techniques (see below) in the patient.

In addition to pituitary and GEP tumors, other tumors, also classified as apudomas with neuroendocrine differentiation, have been shown to have SS-R; this is the case for most glomus tumors, for a large percentage of phaeochromocytomas and for a subpopulation of medullary thyroid carcinomas (Table 1).

Since SS plays a role in the CNS, we might expect that some CNS tumors will contain SS-R (Table 1). Indeed, not only neuron-derived tumors such as neuroblastomas but also glial-derived tumors (astrocytomas, oligodendrogliomas) have SS-R [5]. Of particular interest is the fact that highly undifferentiated glial tumors (glioblastomas) do not express SS-R as compared to differentiated glial tumors. An intriguing group of tumors with a very high incidence of SS-R are meningiomas [6]: these tumors do not originate from an established SS target; to date, unfortunately, a role for SS-R in these tumors has not been found [7].

Finally, a number of other tumors originating from various tissues not established as SS targets have been shown to have SS-R. One group consists of breast tumors [8, 9], which show a 20% incidence in the 356 cases studied (Fig. 1). However, when samples 10 times larger were evaluated, a higher incidence of 46% is found in 72 tumors (Table 1) [9]. This difference may be related to an important observation: in more than half of the breast tumor cases, the SS-R are not homogeneously distributed in the tumor tissue but regions with high or low SS-R density are found in a single sample [9]. This may have consequences since tumor regions with few or no SS-R may not respond to SS treatment. A second group of tumors is represented by lung tumors [10], where small lung cell carcinomas (SCLC), classified as apudomas with neuroendocrine features, have SS-R, but non-SCLC have no SS-R. Finally, ovarian carcinomas and colorectal tumors seldom express SS-R (Table 1).

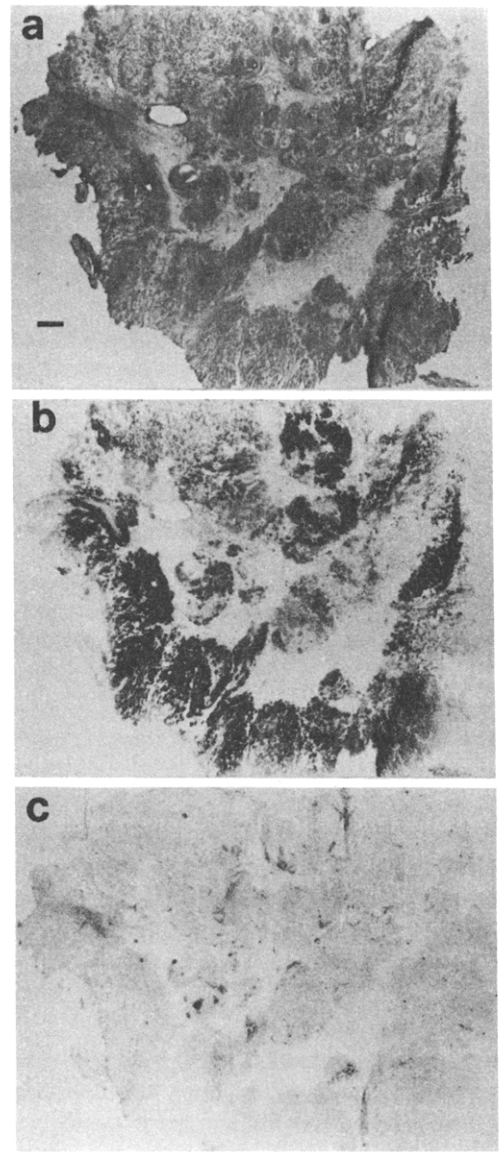


Fig. 1. SS-R in a breast carcinoma. (a) Hematoxylin-eosin stained section. (b) Autoradiogram showing total binding of $^{125}$I-labeled Tyr$^3$-octreotide. (c) Autoradiogram showing non-specific binding (in the presence of 1 $\mu$M Tyr$^3$-octreotide); bar = 1 mm.

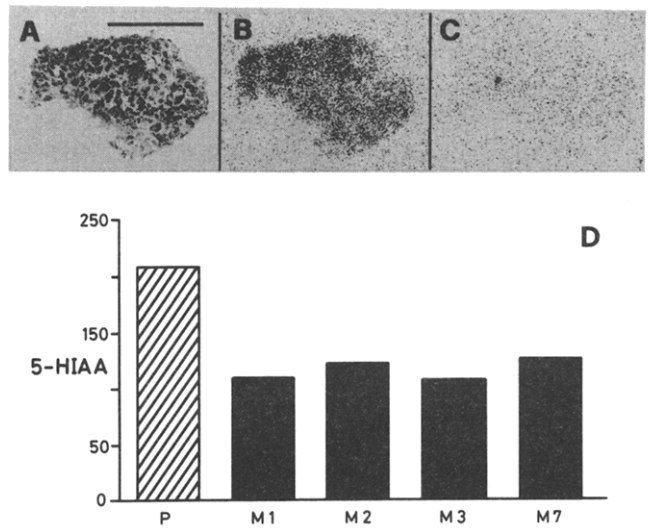


Fig. 2. Presence of SS-R in a carcinoid tumor responsive *in vivo* to chronic octreotide therapy. (A) Hematoxylin stained section. Bar = 1 mm. (B) Autoradiogram showing total binding of $^{125}$I-labeled Tyr$^3$-octreotide. (C) Autoradiogram showing non-specific binding. (D) 5-HIAA levels (mg/24 h) in the patient before (P) and during octreotide therapy (after 1, 2, 3 and 7 months).

## FUNCTIONALITY OF TUMORAL SS-R

SS-R in human pituitary adenomas and GEP tumors are likely to be functional and mediate SS inhibition of hormone secretion. The following studies support this view:

(1) In 11 GH-secreting pituitary adenomas, a good correlation between SS-R content and *in vivo* GH inhibition by octreotide is observed [11].
(2) In one TSH adenoma, SS-R mediating TSH inhibition were found [12].
(3) In 31 cases of GEP tumors, a highly significant correlation was found between the SS-R status and the ability of octreotide to inhibit *in vivo* hormone secretion [13]. An example of such a correlation is seen in Fig. 2 in a carcinoid patient excreting 5-hydroxyindolacetic acid (5-HIAA).
(4) In two SS-R+ gastrinomas grown in culture, octreotide could consistently inhibit gastrin secretion [14].

Therefore, SS-R in pituitary and GEP tumors are the likely molecular basis for hormone inhibition by SS and therefore relevant for the therapeutic efficacy of octreotide. No data exist about the functionality of SS-R in other human tumors. However, there is extensive data in animal tumor models and cultured tumor cell lines, i.e. breast tumors, SCLC and GEP tumors, that SS or octreotide have an antiproliferative action, with a 50% growth inhibition being reported [15–17] (Table 2). Antiproliferative effect of SS on meningiomas in culture could not be consistently observed [7].

In summary, the analysis of pituitary and GEP tumor tissue for SS-R seem to be important for predicting responsiveness to therapy with octreotide. However, the lack of data showing the antisecretory or antipoliferative effects of octreotide in other SS-R+ human tumors, such as breast carcinomas or SCLC, makes it more difficult at the moment to predict

Table 2

| Tumor type | SS-R incidence | SS-R-mediated SS action | Clinical efficacy of Sandostatin® | Prognostic value of tumoral SS-R |
|---|---|---|---|---|
| Pituitary adenomas | High | GH/TSH hormone secretion | + | |
| GEP tumors | High | GI hormone secretion (Antiproliferation in SS-R+ animal tumors) | + | |
| Breast tumors | Up to 50% (non-homogeneous) | (Antiproliferation in SS-R+ animal tumors) | ? | + |
| SCLC | 4/7 | (Antiproliferation in SS-R+ animal tumors) | ? | |
| CNS tumors | | | | |
| Neuroblastomas | >50% | ? | ? | + |
| Meningiomas | High | Antiproliferation *not* demonstrated | | |

with this test the clinical efficacy of SS analogs in these tumors.

## COMMON CHARACTERISTICS OF SS-R+ TUMORS

As seen in Table 1, a wide variety of tumor types contain SS-R. Do these SS-R+ tumors have some common characteristics? The first feature seen regularly in most of these tumors is their neuroendocrine differentiation: it is found in pituitary and GEP tumors, in other apudomas, in brain tumors, in SCLC and in a subpopulation of breast cancers. The second common feature is the relatively higher differentiation grade of SS-R positive vs negative tumors: for instance, the few receptor negative carcinoids all belong to the undifferentiated, atypical carcinoid type [4]. Undifferentiated glial tumors [7] as well as exocrine pancreatic carcinomas are lacking in SS-R. SS-R+ neuroblastomas have a better Shimada histopathological pattern and no N-myc amplification compared to SS-R− cases [18]. Finally, we consistently find an inverse correlation between the presence of SS-R and of epidermal growth factor receptors (EGF-R) in most tumor samples from pituitary, GEP, lung, glial or breast tumors [7, 10, 19].

These common features of neuroendocrine and high-grade differentiation linked to a poor expression of EGF-R suggest that SS-R+ tumors are a relatively homogeneous population despite a wide distribution among tumors originating from several target tissues. Preliminary data in breast tumors and neuroblastomas exist, suggesting that the presence of SS-R may, in the future, represent a marker for those tumors with a more favorable prognosis [18, 20].

## *IN VIVO* LOCALIZATION OF SS-R+ TUMORS

Another very attractive application of the knowledge that many human tumors have a high density of SS-R is the possibility of diagnosing and localizing these tumors *in vivo* in the patient [21]. This is achieved by i.v. injection of $^{123}$I-labeled Tyr$^3$-octreotide in patients suspected of having SS-R+ tumors; such tumors are then localized with planar and ECT images obtained with a $\gamma$-camera [22]. With this method, total binding, not specific binding, of the ligand to the tumor is measured. However, several lines of evidence clearly demonstrate that the hot spots identified with this method represent SS-R-containing tumors:

(1) In a rat tumor model containing SS-R, systemic injection of non-radioactive octreotide abolishes the hot spots seen on the tumor site after $^{123}$I-labelled Tyr$^3$-octreotide injection [23].
(2) There is a highly significant correlation between the incidence of SS-R+ positive tumors measured with *in vitro* methods and the incidence of such tumors detected with *in vivo* imaging [21, 24].

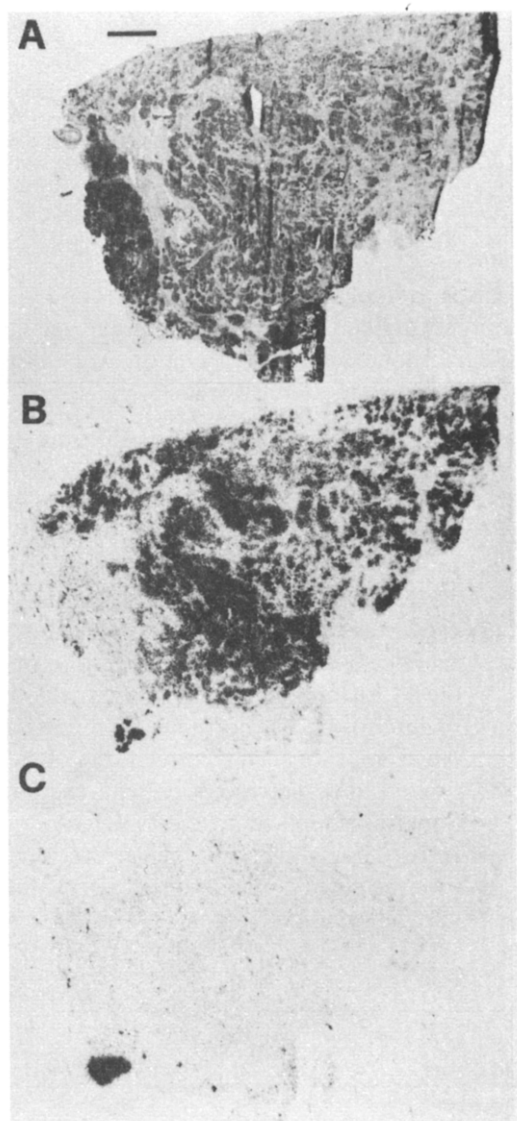


Fig. 3. SS-R in an insulinoma tumor visualized previously *in vivo* in the patient with $\gamma$-camera scintigraphy. (a) Hematoxylin-eosin stained section; bar = 1 mm. (b) Autoradiogram showing total binding of $^{125}$I-labeled Tyr$^3$-octreotide. (c) Autoradiogram showing non-specific binding (in the presence of 1 $\mu$M Tyr$^3$-octreotide).

Moreover, we have confirmed recently that in all cases with positive scans who later underwent operative biopsies, the hot spots corresponded to SS-R+ positive tumors, as measured with *in vitro* binding techniques (Fig. 3). Moreover, in two positively scanned gastrinomas, we could show that these SS-R-containing tumors set into culture could be inhibited by octreotide in their gastrin release [14]. These arguments clearly demonstrate the specificity of the *in vivo* imaging method. It confirms, moreover, the *in vitro* findings that several tumors and their metastases contain high densities of SS-R. The fact that they are measurable *in vivo* in the patient opens up very promising new avenues for diagnosis and, ultimately, for therapy.

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