J. Steroid Biochem. Molec. Biol. Vol. 43, No. 1–3, pp 27–35, 1992
Printed in Great Britain.

0960-0760/92 $5.00 + 0.00

SOMATOSTATIN RECEPTORS IN HUMAN CANCER: INCIDENCE, CHARACTERISTICS, FUNCTIONAL CORRELATES AND CLINICAL IMPLICATIONS

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Summary—Somatostatin receptors (SS-R) have been identified in membrane homogenates or tissue sections from several hundred tumors. SS-R were found in most neuroendocrine tumors, i.e. GH and TSH producing pituitary tumors, endocrine gastroenteropancreatic (GEP) tumors, paragangliomas, pheochromocytomas, medullary thyroid carcinomas (MTC) and small cell lung carcinomas. SS-R were also expressed in a majority of malignant lymphomas, in several brain tumors (all meningiomas, most astrocytomas) and in breast tumors. The majority of tumors expressing SS-R are rather differentiated (i.e. astrocytomas vs glioblastomas), but exceptions exist (high grade malignant lymphomas). An inverse relationship exists between SS-R and receptors for epidermal growth factor (EGF-R) incidence in lung tumors, glial tumors and most breast tumors, whereas meningiomas express simultaneously both receptors. A minority of tumors (ovarian tumors, MTC, insulinomas) express a subtype of SS-R, characterized by low affinity for the octapeptide SS analog octreotide.

The function mediated by SS-R in human tumors may differ according to the tumor type. SS-R in pituitary and GEP tumor mediate hormone secretion inhibition with, in addition, possibly some antiproliferative effects. In meningiomas, however, activation of SS-R inhibits forskolin-stimulated adenylate cyclase activity, and weakly stimulates proliferation. Whereas SS-R seem to mediate antiproliferative effects in animal models and cell lines of lymphomas, breast and lung tumors, such an effect has not yet been convincingly documented in human primary tumors. The clinical implications of the presence of SS-R in tumors are manyfold: (1) as a predictive marker for efficient therapy with octreotide in pituitary and GEP tumors; (2) as a diagnostic marker: for pathobiochemical classification of tumors, using *in vitro* detection methods; for clinical evaluation using *in vivo* scanning techniques; (3) as a prognostic marker; and (4) as a potential radiotherapeutic target.

INTRODUCTION

Somatostatin (SS) belongs to the expanding family of small regulatory peptides which are often characterized by a wide spectrum of actions in various organs of the human body. One of the most prominent and well-documented roles of SS is its inhibition of hormone secretory processes, in particular in the pituitary (GH, TSH) and in the gastroenteropancreatic (GEP) system (Insulin, Glucagon, ViP, Secretin, etc ...) [1]. In addition, SS can modulate the neurotransmission in various brain regions [1]. All these SS actions seem to be mediated through specific SS receptors (SS-R) [2].

In recent years, two observations suggested that SS may also play a significant role in cancer:

(1) In numerous animal tumor models and cultured tumoral cell lines, SS and SS analogs were shown to inhibit tumor growth [3].
(2) SS receptors were shown to be expressed in a wide variety of primary human tumors and their metastases [4].

The present review will summarize the incidence of SS-R in human tumors and discuss their general chracteristics. It will also give some experimental evidence for the putative functions of these receptors in tumors and give an outlook of the clinical implications of tumoral receptors for a peptide, which may be

Proceedings of the Fourth International Congress on Hormones and Cancer, Amsterdam, The Netherlands, September 1991.

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considered paradigmatic among regulatory peptides in the field of cancer.

INCIDENCE OF SS-R IN HUMAN TUMORS

As seen in Table 1, a wide variety of human tumors express SS-R. One of the groups with the highest incidence of SS-R are neuroendocrine tumors [4]; most GH and TSH producing pituitary adenomas contain SS-R as does a significant proportion of endocrine hormone-producing GEP tumors; phaeochromo-cytomas and paragangliomas; some medullary thyroid carcinomas (MTC); and several small cell lung cancers (SCLC). Usually, these tumors have a high density of SS-R, but there is a great individual variability of receptor density: more than tenfold differences in SS-R density are not rare within individual tumor types. Most of the above mentioned tumors belong to the group of apudomas, i.e. tumors having the APUD cell as common origin.

The second group of human tumors frequently expressing SS-R are tumors of the nervous system [4]. More than 80% of the astrocytomas as well as a high percentage of neuroblastomas contain SS-R (Table 1). All meningiomas express a high density of SS-R.

Recently we identified a third group of tumors having a high incidence of SS-R: malignant lymphomas of the Hodgkin and non-Hodgkin type [5]. As seen in Fig. 1, the neoplastic follicles of the low grade non-Hodgkin lymphomas are particularly rich in SS-R.

Apart from the above mentioned tumor types usually showing a high incidence of SS-R, approximately half of the cases of breast cancer were shown to possess SS-R [4, 6]. Other tumors, such as colorectal cancers and ovarial tumors, displayed only a low incidence of SS-R (Table 1).

Table 1. Incidence of tumors expressing SS-R

Neuroendocrine tumors	Pituitary Adenomas, Carcinoids, Islet cell Ca, Paragangliomas, Pheochromocytomas, Medullary thyroid Ca, SCLC	High
Tumors of the nervous system	Astrocytomas, Neuroblastomas, Meningiomas	High
Lymphomas		High
Breat tumors		~50%
Ovarial Ca, Colon Ca		Low
Glioblastomas, NSCLC, Exocrine Pancreatic Ca, Prostata Ca		No receptors

Ca, carcinoma, SCLC, small cell lung carcinoma, and NSCLC, non-small cell lung carcinoma.

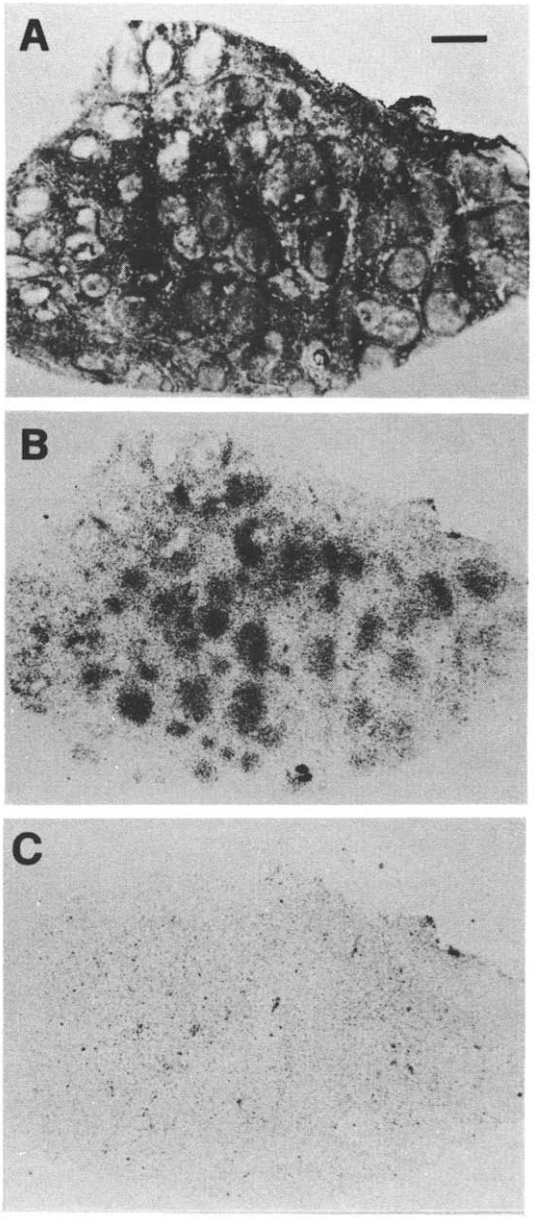


Fig. 1. SS-R in a low grade follicular B cell non-Hodgkin malignant lymphoma. (A) Hematoxylin-eosin stained section; (B) autoradiogram showing total binding of ^{125}I-[Tyr^3]-octreotide; and (C) autoradiogram showing non-specific binding of ^{125}I-[Tyr^3]-octreotide (in presence of 10^{-6} M [Tyr^3]-octreotide). Note the preferential labeling of the neoplastic follicles. Bar = 1 mm.

SS-R in the above mentioned tumors have been characterized as high affinity receptors specific for SS, comparable to the SS-R identified in healthy target tissues such as brain, pituitary or pancreas. In Fig. 2, the SS-R characteristics of a case of gastrinoma are depicted in a typical displacement experiment.

However, there is a large group of neoplasms which do not express SS-R: it includes glioblastomas, non-SCLC (NSCLC), exocrine

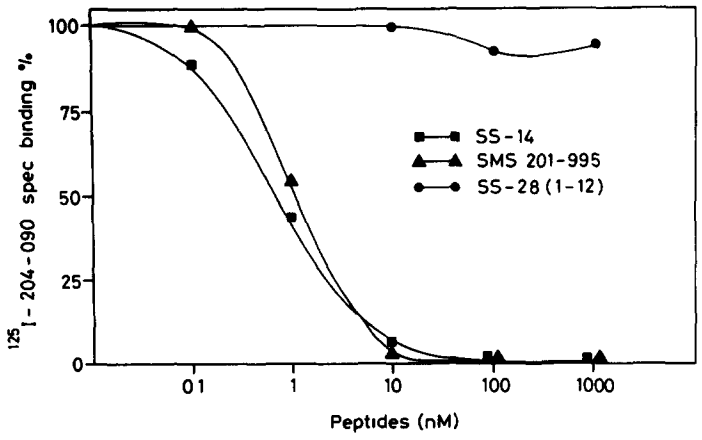


Fig. 2. SS-R in a human gastrinoma. Displacement curve of ^{125}I-[Tyr^3]-octreotide (=^{125}I-204–090) in tumor tissue sections incubated with 35,000 cpm/100 μl radioligand and increasing concentations of unlabeled octreotide (=SMS 201–995; ▲) or SS-14 (■) or the inactive SS analog SS-28 (1–12) (●).

pancreatic cancers, prostate cancers and most squamous cell carcinomas (Table 1).

In receptor positive cancers, SS-R are homogeneously distributed in the tumor tissue, whereas the surrounding, healthy tissue is usually lacking SS-R. Figure 3 shows the precise and homogeneous labeling of all tumor cell nests of a human carcinoid with an iodinated SS radioligand, whereas the non-tumoral surroundings are not labeled. Interestingly, however, there are tumors, in particular of the breast, that often display SS-R only in certain tumor regions, although the whole tumor appears to be histopathologically homogenous. Such a case is depicted in Fig. 4. This observation supports the idea that some breast tumors are composed of numerous different clones with variable biological properties. This has consequences in terms of the precise SS-R status in small samples of large breast tumors or for the therapeutic efficacy of SS analogs in such tumors.

GENERAL CHARACTERISTICS OF TUMORS EXPRESSING SS-R

Despite the fact that human tumors of very different origins are expressing SS-R, many of the SS-R containing tumors seem to have a number of common general features.

Firstly, SS-R positive tumors encompass most of the tumors of neuroendocrine origin. This is true for pituitary adenomas, islet cell carcinomas, carcinoids, phaeochromo-cytomas, MTC, paragangliomas, neuroblastomas and SCLC. In addition, a subgroup of breast tumors with neuroendocrine features is usually SS-R

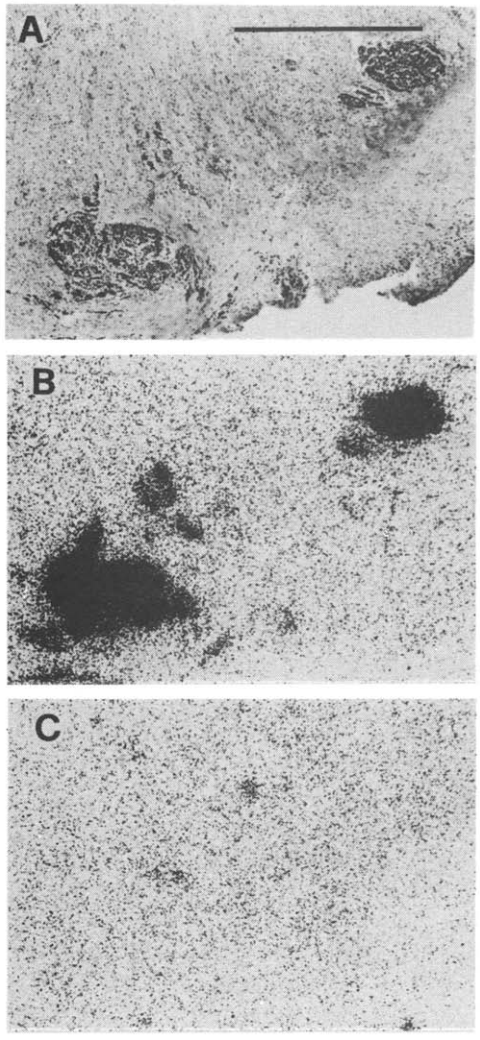


Fig. 3 SS-R in a human carcinoid. (A) Hematoxylin-eosin stained section showing several nests of tumor tissue. Bar = 1 mm; (B) autoradiogram showing total binding of ^{125}I-[Tyr^3]-octreotide. Tumor nests are selectively labeled; and (C) non-specific binding

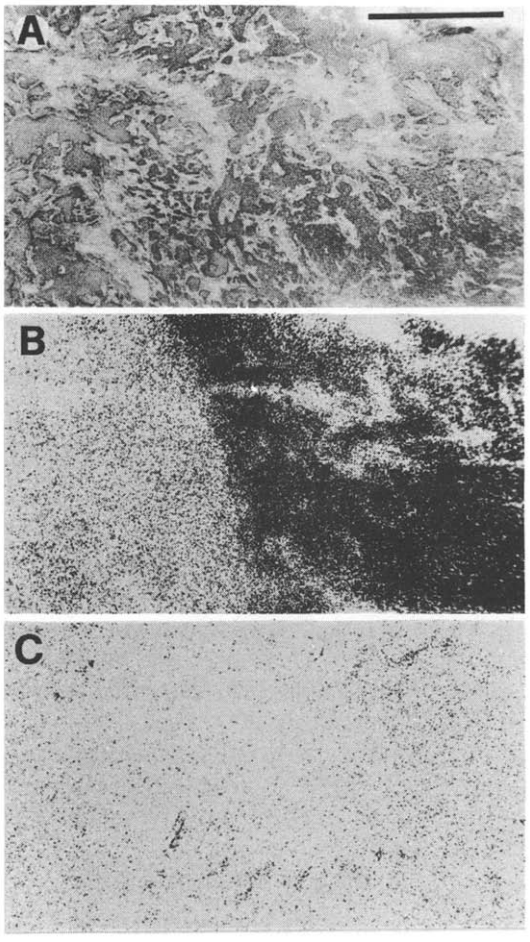


Fig. 4. SS-R non-homogeneously distributed in human breast tumor. (A) Hematoxylin-eosin stained section; (B) autoradiogram showing total binding of ^{125}I-[Tyr^3]-octreotide; and (C) non-specific binding.

positive [7]. The same may apply to the SS-R positive colonic and ovarian carcinomas since it is known that a small percentage of those tumors also have neuroendocrine features.

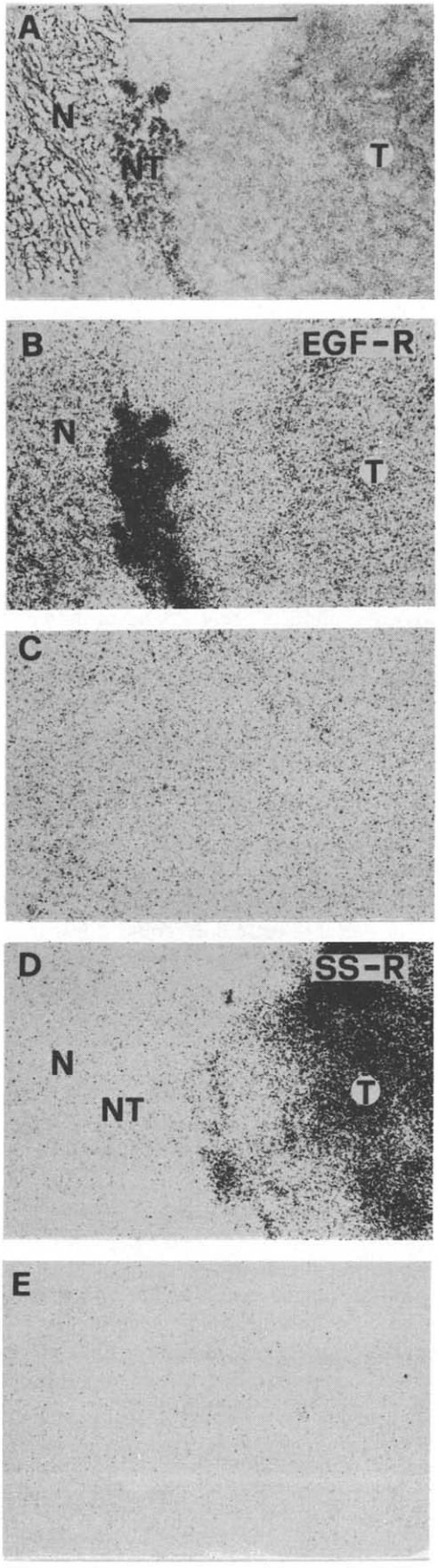
Secondly, the majority of SS-R containing tumors belong to rather well-differentiated tumors. This is true for most of the neuroendocrine tumors. It is worth mentioning that the well-differentiated carcinoids express SS-R in the great majority of the cases, whereas the less differentiated, "atypical carcinoids" often lack SS-R [8]. In a case of a MTC we observed two different areas within the excised tumor sample, a well-differentiated tumor area containing calcitonin and SS-R, and an undifferentiated SS-R negative part [9]. Analogous observations have been made in glial tumors, where SS-R are often expressed by astrocytomas I-III, but not by the undifferentiated glioblastomas [4]. At least one exception to this general trend exists, namely the malignant lymphomas, which often contain SS-R, even in high density, in the undifferentiated high grade tumor types [5]. This particularity may be linked to the fact that SS-R in normal human lymphoid tissue are preferentially located in activated, proliferating lymphoid cells within germinal centers (Reubi and Laissue, unpublished).

Thirdly, an inverse relationship is frequently seen between the presence of SS-R and of epidermal growth factor (EGF)-R in several types of tumors. SS-R negative NSCLC and glioblastomas are in most instances EGF-R positive, whereas SS-R positive SCLC or astrocytomas usually lack EGF-R [10, 11]. A similar tendency is found in breast tumors. It should, however, be noticed that in the vicinity of SS-R positive breast tumor samples EGF-R positive normal breast tissue can be found, while the tumoral tissue remains EGF-R negative [6]. The inverse correlation between SS-R and EGF-R strongly suggests that SS-R positive tumors are usually more differentiated, less aggressive tumors with possibly a better prognosis than their SS-R negative counterparts. The meningiomas, however, represent an exception since all tumor samples express simultaneously SS-R and EGF-R [11]. Interestingly, in many cases, the two receptors are not necessarily located on identical cellular entities, as seen in Fig. 5. There, SS-R are located in high density over the tumor tissue only, whereas necrotic tissues and the necrobiotic tumor area have no SS-R. On the contrary, EGF-R are only weakly expressed in the "resting" tumor area, but intensely in the more aggressive and proliferating part of the tumor near the necrotic zone. Therefore, even in tumors expressing both receptors simultaneously, SS-R seem preferentially located in the less aggressive region of the tumor [11].

Thus, several common characteristics of SS-R positive tumors can be identified, such as neuroendocrine features, differentiation state or inverse correlation with EGF-R. However, exceptions are regularly observed, such as SS-R positive high grade lymphomas or SS-R and EGF-R positive meningiomas.

EVIDENCE FOR SS-R SUBPOPULATION IN SELECTED TUMORS

It has been reported that, in rat and human brain, subpopulations of SS-R exist. For example, pharmacological evidence for such SS-R subpopulations is provided by the differential affinity for the SS analog octreotide



(high affinity = SS_1; low affinity = SS_2) as compared to SS-14 or SS-28, in various brain regions [12, 13]; functional correlates for these subtypes exist as observed by the differential response of the adenylate cyclase activity to SS and SS analogs [14] in various brain regions.

The majority of the numerous human tumors tested up to now expressed a SS-R with a high affinity for octreotide (SS_1). Nevertheless, we have observed that a restricted number of SS-R-containing tumors expressed the SS-R subtype SS_2 described above, defined as having a low affinity for octreotide, i.e. at least two orders of magnitude lower than SS-14 or SS-28. This receptor subtype has been observed in a small percentage (< 10%) of pituitary adenomas, carcinoids, glial tumors, meningiomas or breast tumors. A higher incidence of SS_2 receptors was found, however, in insulinomas [15]. Moreover, we could demonstrate that this SS_2 subtype was functional since in those insulinomas cultured *in vitro*, the insulin release was inhibited by SS-14 and SS-28, but not by octreotide [16]. In addition, these insulinomas were not visualized *in vivo* using a ^{123}I-[Tyr^3]-octreotide as tracer [16] (see below). Conversely, insulinomas with a SS_1 receptor subtype reacted normally to octreotide in terms of insulin inhibition and were visualized *in vivo* as expected. Approximately half of the MTCs [9] had also a SS-R subtype with low affinity for octreotide (SS_2). Furthermore, all SS-R positive ovarian tumors displayed this same SS_2 receptor subtype. They can be labeled with SS-14 or SS-28 radioligand (Fig. 6) but not with [Tyr^3]-octreotide radioligand [17]. Clearly, therefore, some peripheral tumoral tissues have also the potential, as does the healthy brain, to express the SS_2 receptor subtype.

These findings have a number of clinical consequences: first, tumors with only SS_2

Fig 5 SS-R and EGF-R are simultaneously expressed in a human meningioma. (A) Hematoxylin-eosin stained section showing the tumor (T) on the right, a necrosis (N) on the left and a more actively proliferating and partly necrotic area of the tumor (NT) in the middle. Bar = 1 mm; (B) autoradiogram showing total binding of ^{125}I-EGF. Low receptor density is found in the tumor (T) and the necrosis (N) but high receptor density in the necrobiotic tumor area (NT) in the middle; (C) autoradiogram showing non-specific binding of ^{125}I-EGF; (D) autoradiogram showing total binding of ^{125}I-[Tyr^3]-octreotide in a section adjacent to A. High SS-R density is seen in the tumor (T) but no receptors are found, neither in the necrosis (N) nor in the necrobiotic tumor (NT); and (E) autoradiogram showing non-specific binding of ^{125}I-[Tyr^3]-octreotide.

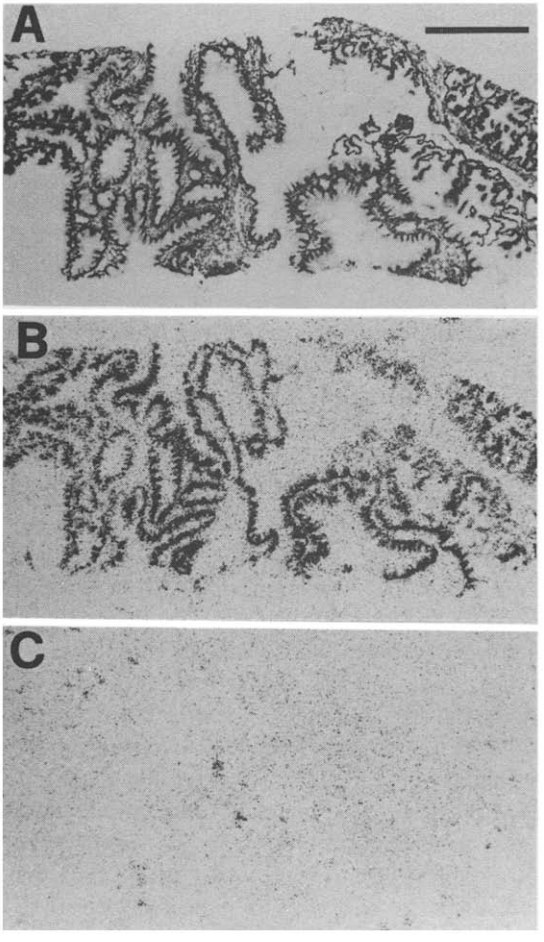


Fig. 6. SS-R in a human ovarian tumor of borderline malignancy. (A) Hematoxylin-eosin stained section Bar = 1 mm; (B) autoradiogram showing total binding of ^{125}I-[Leu^8,DTrp^{22},Tyr^{25}]-SS 28 Note the labeling of the neoplastic epithelial cells, and (C) autoradiogram showing non-specific binding. Note that this tumor cannot be labeled with ^{125}I-[Tyr^3]-octreotide

receptors will not be visualized *in vivo*, neither with ^{123}I-[Tyr^3]-octreotide nor with ^{111}In-[DTPA,DPhe^1]-octreotide as tracer [16]; secondly, tumors expressing SS_2 receptors will not or only poorly respond to a conventional octreotide therapy [16]; this may be one of the reasons why insulinomas and MTCs often react poorly to conventional doses of octreotide [16]; very high doses of octreotide are required to elicit a reaction in some potentially responsive tumors. This means that for the *in vivo* visualization or successful therapy of such SS_2 receptor containing tumors other types of SS analogs (based on a structure different from that of octreotide) will have to be developed. Since additional SS-R subtypes are likely to exist and to be expressed in certain tumors, new SS analogs may be found which allow us to identify and treat a larger number of human tumors [18].

FUNCTIONS MEDIATED BY SS-R IN TUMORS

As we could demonstrate in various recent studies, the SS-R detected on human tumors have, in addition to a role as pathobiochemical markers of those tumors, also a specific function. However, the SS function mediated by SS-R may vary as a function of the tumor type.

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

(1) In 11 GH-secreting pituitary adenomas, a positive correlation between SS-R content measured in surgically removed tumors and *in vivo* GH inhibition by a single application of 100 μg of octreotide was observed [19].
(2) In TSH-secreting adenomas, SS-R-mediated TSH inhibition was found [20].
(3) In 31 cases of GEP tumors, a highly significant correlation was found between the SS-R status measured in small needle biopsy of the metastases, and the ability of long-term octreotide treatment to inhibit *in vivo* hormone secretion [8].
(4) In two SS-R positive gastrinomas grown in culture, octreotide could consistently inhibit gastrin secretion [16]. Octreotide had no effect on the hormone output of SS-R negative GEP tumors grown in culture.

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. To date, there is no conclusive evidence that SS-R present in those human tumors also mediate an antiproliferative action of SS. However, several studies using *in vivo* animal models and *in vitro* cultured cell lines from several tumor types suggest that there is such an effect. One recent study in GEP tumors indicates that SS may play an antiproliferative role in human tumors: indeed, a SS-R positive human carcinoid, transplanted into a nude mouse and retaining his original carcinoid characteristics, was shown to be inhibited in its growth by 50% after 2 weeks of octreotide therapy [2].

Several other animal and cell culture studies suggest that a direct antiproliferative effect of SS, mediated by SS-R, takes place in certain tumors [3, 22]. For instance, both *in vitro* and *in vivo* growth inhibition by the SS analog somatuline was observed in a SS-R positive SCLC cell line [23]. Conversely, in SS-R negative DMBA-induced breast tumors no growth inhibitory effect of SS was observed [24]. Nevertheless, when the growth of a tumor is strongly growth factor dependent, an indirect *in vivo* growth inhibition by SS can take place, despite the absence of tumoral SS-R. In those cases, exogenous SS will act on SS-R located on healthy SS targets (pituitary, pancreas), as shown for the IGF- and insulin-dependent Swarm chondrosarcoma [25].

We have recent evidence that at least in one tumor type, the meningioma, the high density of SS-R present in this neoplasm does not mediate tumor growth inhibition [26]. The SS-R present in meningiomas are functional since SS and SS analogs can inhibit forskolin-stimulated adenylate cyclase activity. In this type of tumor an increase in c-AMP levels induced a significant tumor growth inhibition, as measured by [^{3}H]thymidine incorporation. Therefore, the addition of SS to cultures of meningiomas resulted in a slight but significant growth stimulation of the tumor cells, but not in growth inhibition [26].

These examples show that SS-R in human tumors are likely to mediate SS actions. There is convincing evidence that they mediate SS inhibition of hormone secretion in pituitary and GEP tumors. They may also mediate antiproliferative effects of SS in certain tumors (breast tumors, SCLC), although definite proof of cytostatic activity in primary human tumors is still lacking. Finally, they may mediate growth proliferation in selected tumors, such as meningiomas.

SOURCES OF ENDOGENOUS SS INTERACTING WITH TUMORAL SS-R

In order to be functional, tumoral SS-R need a sufficient supply of endogenous SS. In healthy humans, SS is produced in various tissues, including the nervous system, the endocrine pancreas and the gastrointestinal tract [1]. It is not clearly established to which extent SS-R positive tumors, in particular those situated outside the SS producing or target tissues, will receive a sufficient SS supply, considering the very short half life of natural SS. Our own studies demonstrate that, although human tumors may be able to synthesize a sufficient amount of SS, SS is by far not detected in all SS-R positive tumors [27]. For instance, the SS-R positive meningiomas have neither SS mRNA, detectable by *in situ* hybridization, nor SS, detectable by radio-immunoassay [27]. This suggests that these tumors are fully dependent of physiological SS sources, synthetized in distant tissues. There is therefore no evidence for an autocrine feedback mechanism of SS in such tumors. However, some tumors are known to be the sites of SS synthesis: all MTCs, most pheochromo-cytomas and some GEP tumors have often extremely high amounts of SS mRNA as well as immunoassayable SS [27, 28]. An example of high SS mRNA expression in a MTC is shown in Fig. 7. *In situ* production provides sufficient SS for SS-R-mediated actions in the tumor. However, a SS-R downregulation or even complete suppression of SS-R production may be induced if such a high, chronic, sustained SS production is provided by the tumor itself. Exogenous supply of SS, i.e. in the form of stable SS analogs, may be useful in SS-R positive tumors in particular in those lacking a potential to synthetize SS.

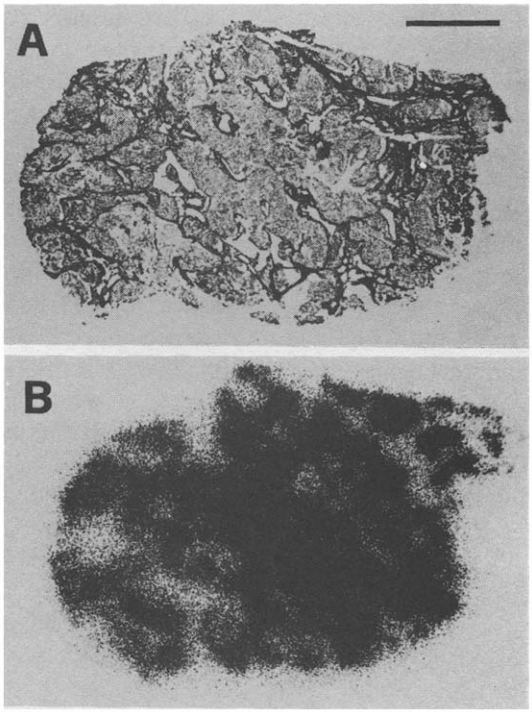


Fig. 7. SS mRNA in a human MTC. (A) Hematoxylin-eosin stained section Bar = 1 mm; and (B) autoradiogram showing SS mRNA using *in situ* hybridization.

CLINICAL IMPLICATIONS

The presence of SS-R in a large variety of human tumors has a number of clinical implications. *In vitro* detection of those receptors may be useful for the pathobiochemical characterization of various tumor types and subtypes, especially since SS-R positive tumors often display neuroendocrine features and a high differentiation grade. *In vivo* detection of these receptors, using radiolabeled octreotide analogs and γ-camera scintigraphy (see paper by Lamberts), is extremely useful for the localization of SS-R positive tumors, the evaluation of the metastatic disease and, for lymphomas, for the staging of the disease [29, 30].

Since these receptors have been shown to be functional, their presence may be predictive for a successul octreotide treatment in those types where an octreotide therapy is indicated (pituitary adenomas; GEP tumors) [8].

Recently, we could demonstrate in two types of human tumors that the SS-R status may also have a predictive value for the prognosis of the tumor. In a retrospective study involving 110 breast cancer patients, we found 17 (15%) of the tumors to be SS-R positive [31]. In this group of patients no significant relationship was observed between the presence of SS-R and lymph node status, or age of the patients. However, the disease-free survival probability for patients with SS-R positive tumors was significantly higher. In the 17 patients with SS-R positive breast tumors the 5 year disease-free survival was 82%, compared with 46% for the 83 patients with SS-R negative tumors [31].

Furthermore, we have shown in a preliminary study with neuroblastomas that there was an inverse relationship between the presence of SS-R and N-myc oncogene expression [32]. The presence of SS-R in about 50% of tumors seemed to correlate with a favorable prognosis [32].

As a future clinical perspective we should finally mention the possibility of using tumoral SS-R as a radiotherapeutical target. For this purpose, a SS analog linked to an adequate β-emitting isotope would be needed. However, a careful evaluation of the ratio between the beneficial effects of the radiotherapy in destroying the tumor tissue and the destruction of SS-R containing physiological targets will be a prerequisite.

Acknowledgements—We thank Mrs U. Horisberger and B. Waser for excellent technical assistance.

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