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A selective analog for the somatostatin sst1-receptor subtype expressed by human tumors

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Abstract

Somatostatin mediates its actions through five different somatostatin receptor subtypes, sst1–sst5. Recently, the somatostatin analogs des-AA^{1,2,5}-[D-Trp^{8}, IAmp^{9}]somatostatin and des-AA^{1,5}-[Tyr^{2}, D-Trp^{8}, IAmp^{9}]somatostatin were synthesized and shown to be sst1-selective when tested in COS-7 cells transfected with each of the sst subtypes. In the present study, we tested the binding affinity and specificity of the iodinatable analog in primary human tumors expressing various sst subtypes, selected on the basis of in situ hybridization experiments. Des-AA^{1,5}-[Tyr^{2}, D-Trp^{8}, IAmp^{9}]somatostatin was found to have a high affinity, comparable to that of the natural somatostatin-28, for sst1-expressing tumors such as prostate cancers. However, it had no affinity for tumors expressing the sst2, sst3, or sst5 subtypes. For comparison, the somatostatin analogs octreotide or Tyr^{3}-octreotide have no affinity for sst1-expressing tumors, but high affinity for sst2- and sst5-expressing tumors and intermediate affinity for sst3-expressing tumors. These data represent the first characterization of a sst1-selective analog in human tumors; it may be of potential use in the therapy of sst1-expressing tumors as an antiproliferative agent, as well as providing a lead compound for the development of more potent sst1-selective radioligands for in vivo tumor scintigraphy. © 1998 Elsevier Science B.V.

Keywords: Somatostatin receptor subtype; Somatostatin sst1 receptor-selective analog; Tumors, human; Peptide receptor; Receptor autoradiography

1. Introduction

Somatostatin is a regulatory peptide with a wide range of actions in the brain, as well as in the gastrointestinal, endocrine, immune and vascular systems (Lamberts et al., 1991). These actions are mediated by different somatostatin receptor subtypes, sst1–sst5 (Hoyer et al., 1995; Reisine and Bell, 1995). In the last several years, it was shown that not only normal human tissues but also various human neoplasms were able to express somatostatin receptors and/or receptor mRNA (Reubi et al., 1992). It also became evident that individual neoplasms can express several subtypes of somatostatin receptors simultaneously, as do their healthy tissue counterparts (Greenman and Melmed, 1994; Kubota et al., 1994; Miller et al., 1995; Reubi et al., 1994, 1996; Schaer et al., 1997; Vikic-Topic et al., 1995).

Since the various sst subtypes appear to mediate the somatostatin actions through different second messenger systems, in particular related to tumor proliferation inhibition (Buscail et al., 1994, 1995; Reisine and Bell, 1995; Reubi and Laissue, 1995), it is interesting not only to identify the sst subtype expressed by a tumor, but also to develop subtype-selective analogs in order to have tools for a specific diagnostic or therapeutic targeting of these tumors (Krenning et al., 1995; Lamberts et al., 1991; Reubi, 1995).

A number of synthetic, stable somatostatin analogs have been developed by pharmaceutical companies during the last few years for the symptomatic therapy of selected tumors; the octapeptide somatostatin analog octreotide is the most widely known representative of such drugs and is particularly efficient in the treatment of neuroendocrine tumors (Lamberts et al., 1991). Compared to natural somatostatin, octreotide does not have a high affinity for all five human sst subtypes, since it prefers sst2, sst5, and, to a lesser extent, sst3, but has no affinity for sst1 and sst4 (Reisine and Bell, 1995). Fortunately, a large number of human tumors express sst2, providing therefore a rationale for the clinical use of octreotide in oncology. There are, however, several tumor types which do not, or rarely,

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express sst2, such as ductal pancreatic carcinomas (Buscail et al., 1996; Reubi et al., 1988) or primary hormone-sensitive prostate cancers (Reubi et al., 1995), both tumors being known, however, to often express sst1 (Buscail et al., 1996; Reubi et al., 1995). It is therefore of interest to develop somatostatin analogs with a selectivity for receptor subtypes different from sst2, such as sst1-selective analogs. Recently, the first sst1-selective analog des-AA^{1,2,5}-[D-Trp^{8}, IAmp^{9}]somatostatin and its iodinatable analog des-AA^{1,5}-[Tyr^{2}, D-Trp^{8}, IAmp^{9}]somatostatin (CH-288) were synthesized and shown to be of high affinity and selectivity for the sst1 subtype expressed in transfected COS-7 cells (Liapakis et al., 1996).

In regard to the great clinical potential of such compounds, the aim of the present study was to characterize the binding affinity and specificity of des-AA^{1,5}-[Tyr^{2}, D-Trp^{8}, IAmp^{9}]somatostatin in somatostatin receptor-expressing primary human tumors. We have therefore selected from our collection of primary human tumors, characterized previously for their sst-subtype content (Reubi et al., 1994; Schaer et al., 1997), those expressing abundantly and preferentially one of the sst subtypes. Using cryostat sections of these tumors, we have then performed competition experiments with the universal somatostatin ligand ^{125}I-[Leu^{8}, D-Trp^{22}, Tyr^{25}]somatostatin-28 (^{125}I-[LTT]-SS-28) (Reubi et al., 1981) using in vitro receptor autoradiographical methodologies.

2. Materials and methods

2.1. Selection of sst-subtype expressing tumors

The tumors used for testing the binding characteristics of des-AA^{1,5}-[Tyr^{2}, D-Trp^{8}, IAmp^{9}]somatostatin were chosen from the large collection of somatostatin receptor-positive human tumors available at the Division of Cell Biology, Institute of Pathology, University of Berne, on the basis of the following criteria.

(1) High density of somatostatin receptors measured with the universal ligand ^{125}I-[LTT]-SS-28 using receptor autoradiography (Reubi, 1985; Reubi et al., 1990).

(2) Preferential abundance of one of the sst mRNAs, identified with in situ hybridization methodologies, as reported previously (Reubi et al., 1994; Schaer et al., 1997): these tumors were characterized by a positive in situ hybridization signal for one of the sst mRNAs, while mRNAs for the other sst subtypes were undetectable.

The following tumors were selected for the study: three sst1-expressing hormone-dependent prostate carcinomas; one sst1-expressing leiomyosarcoma; one sst1-expressing gastroenteropancreatic tumor; one sst2-expressing gastroenteropancreatic tumor; one sst2-expressing breast carcinoma; two sst2-expressing growth hormone-producing pituitary adenomas; three sst3-expressing inactive pituitary adenomas; one sst3-expressing breast carcinoma; three sst5-expressing growth hormone-producing pituitary adenomas; two sst2 + sst5-expressing growth hormone-producing pituitary adenomas; one sst3 + sst5-expressing pituitary adenoma.

2.2. Somatostatin receptor autoradiography

Twenty-micron thick cryostat sections of the tissue samples were processed for somatostatin receptor autoradiography as described in detail previously (Reubi et al., 1990). The radioligand used was the somatostatin analog ^{125}I-[LTT]-SS-28, known to specifically label somatostatin receptors (Reubi et al., 1981). The ligand was iodinated, purified on a high-pressure liquid chromatography column,

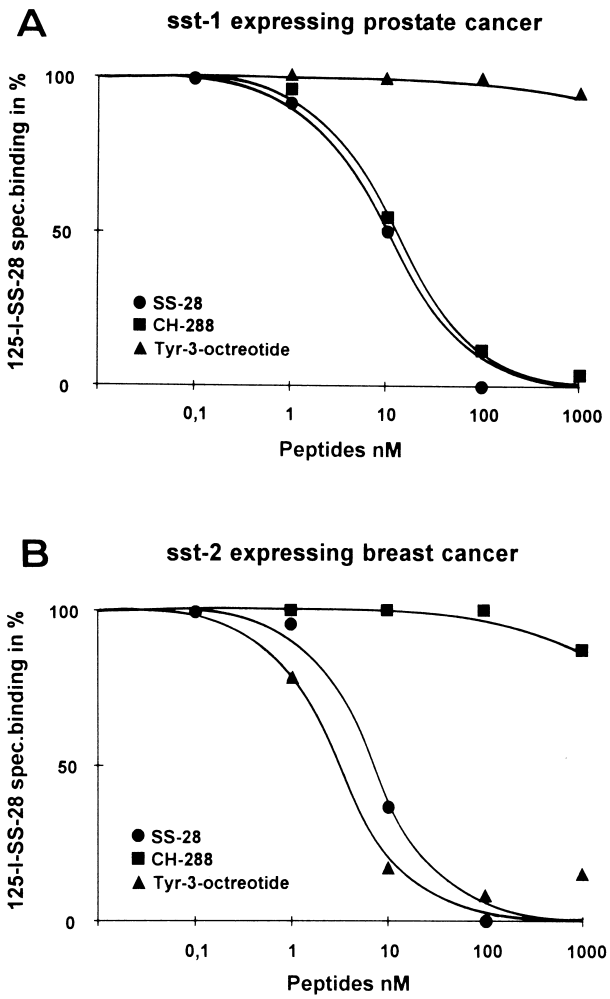

Fig. 1. Displacement curve of ^{125}I-[LTT]-SS-28 in tissue sections from a sst1-expressing hormone-dependent prostate carcinoma (A) and from a sst2-expressing breast carcinoma (B). Tissue sections were incubated with 30 000 counts/min per 100 μl of radioligand and increasing concentrations of unlabeled somatostatin-28 (SS-28: ●), des-AA^{1,5}-[Tyr^{2}, D-Trp^{8}, IAmp^{9}]somatostatin (CH-288: ■), and Tyr^{3}-octreotide (▲). Each point represents the absorbance of binding measured in at least two sections. Notice that, in the sst1-expressing tumor, SS-28 and CH-288 displaced the radioligand with similar high affinity whereas Tyr^{3}-octreotide was inactive; in the sst2-expressing tumor, SS-28 and Tyr^{3}-octreotide displaced the radioligand with high affinity whereas CH-288 was inactive.

and characterized in standard binding assays, as described previously (Reubi et al., 1981).

For autoradiography, tissue sections were mounted on precleaned microscope slides and stored at −20°C for at least 3 days to improve adhesion of tissue to the slide. Sections were then incubated for 2 h at ambient temperature in the presence of the iodinated ligand (0.15×10^6–0.30×10^6 dpm/ml; spec. activity: 2000 Ci/mmol). The incubation solution was 170 mmol/l Tris–HCl buffer (pH 8.2) containing 1% bovine serum albumin, bacitracin (40 μg/ml), and $MgCl_2$ (10 mmol/l) to inhibit endogenous proteases. Incubated sections were washed twice for 5 min each time in cold incubation buffer containing 0.25% bovine serum albumin, then in buffer alone, and dried quickly. Finally, the sections were apposed to ^{3}H-Hyperfilms (Amersham, Little Chalfont, UK) and exposed for 1 week in X-ray cassettes.

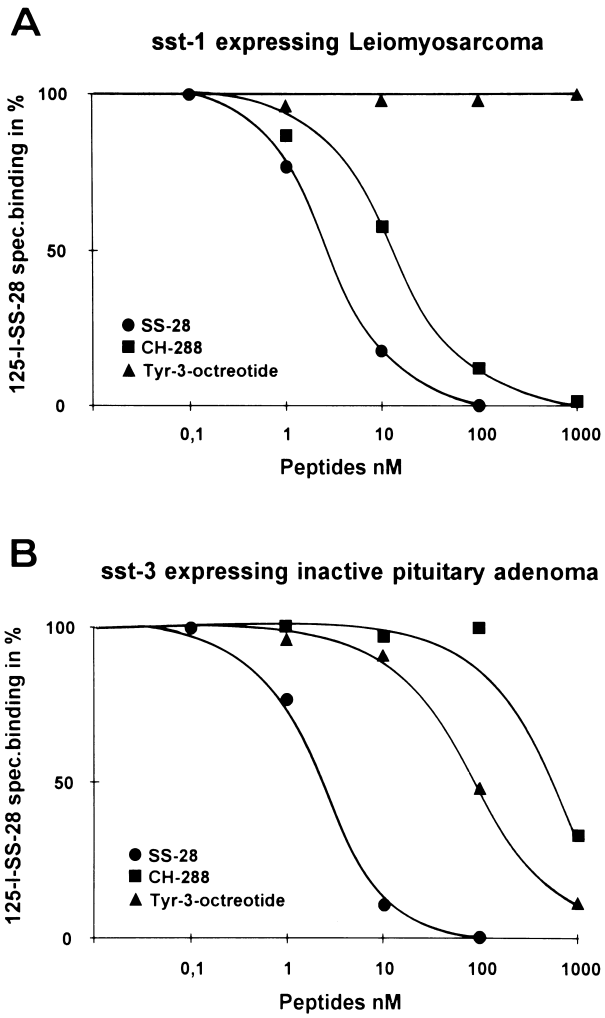

Fig. 2. Displacement curve of ^{125}I-[LTT]-SS-28 in tissue sections from a sst1-expressing leiomyosarcoma (A) and from a sst3-expressing inactive pituitary adenoma (B). Tissue sections were incubated with 30000 counts/min per 100 μl of radioligand and increasing concentrations of unlabeled somatostatin-28 (SS-28: ●), des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin (CH-288: ■), and Tyr^3-octreotide (▲). Each point represents the absorbance of binding measured in at least two sections. Notice that, in the sst1-expressing tumor, SS-28 and CH-288 displaced the radioligand with high affinity whereas Tyr^3-octreotide was inactive; in the sst3-expressing tumor, SS-28 displaced the radioligand with high affinity whereas CH-288 was inactive, and Tyr^3-octreotide was moderately active.

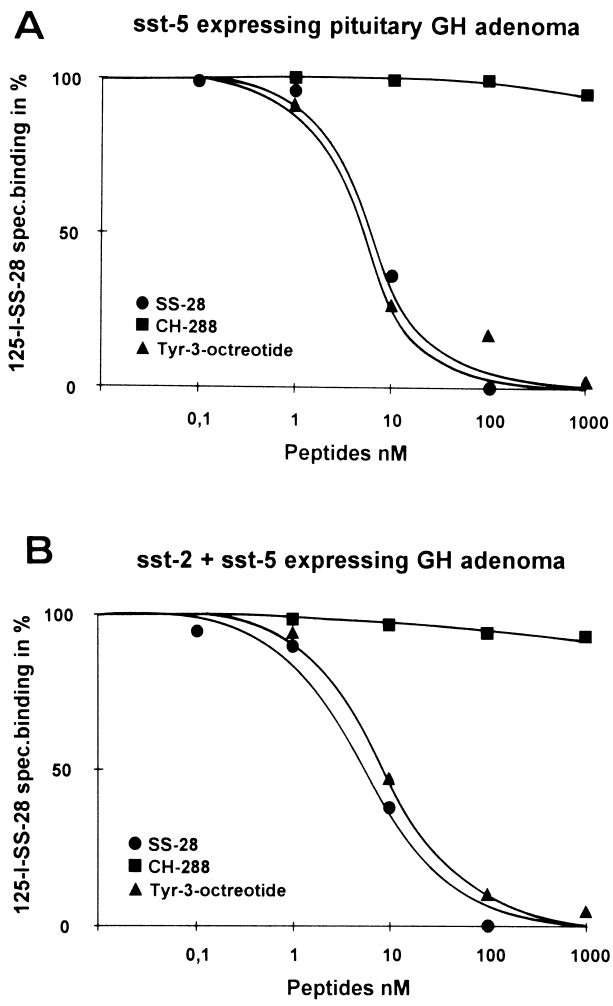

Fig. 3. Displacement curve of ^{125}I-[LTT]-SS-28 in tissue sections from a sst5-expressing growth hormone-producing pituitary adenoma (A) and from a sst2 + sst5-expressing growth hormone-producing pituitary adenoma (B). Tissue sections were incubated with 30000 counts/min per 100 μl of radioligand and increasing concentrations of unlabeled somatostatin-28 (SS-28: ●), des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin (CH-288: ■), and Tyr^3-octreotide (▲). Each point represents the absorbance of binding measured in at least two sections. Notice that in both tumors, SS-28 and Tyr^3-octreotide displaced the radioligand with high affinity whereas CH-288 was inactive.

In all cases, displacement experiments were performed in successive tissue sections by use of increasing concentrations of the following compounds: somatostatin-28, octreotide, Tyr^3-octreotide, des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin. Nonspecific binding was considered as the residual binding in presence of 100 nM unlabeled somatostatin-28. The autoradiograms were quantified using a computer-assisted image-processing system previously described (Reubi et al., 1990).

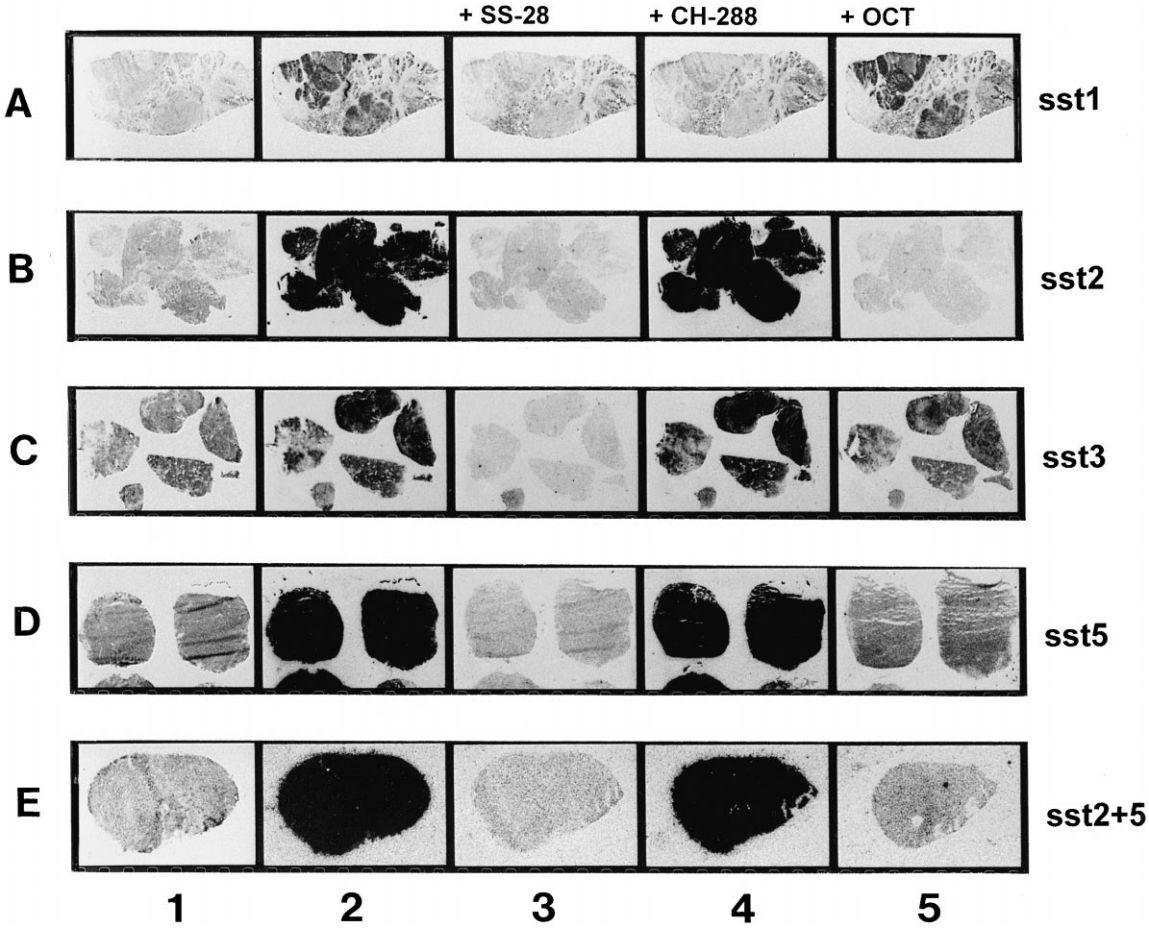

Fig. 4. Series of autoradiograms showing the differential binding characteristics of SS-28, des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin and octreotide in various sst-expressing tumors. A = sst1-expressing prostate carcinoma. B = sst2-expressing growth hormone-producing pituitary adenoma. C = sst3-expressing inactive pituitary adenoma. D = sst5-expressing growth hormone-producing pituitary adenoma. E = sst2 + sst5-expressing growth hormone-producing pituitary adenoma. Lane 1: Hematoxylin–eosin stained sections. Lane 2: Autoradiograms showing total binding of ^{125}I-[LTT]-SS-28. All tumors are strongly somatostatin receptor-positive. Lane 3: Autoradiograms showing displacement of ^{125}I-[LTT]-SS-28 by 100 nM unlabeled SS-28 in all tumors. Lane 4: Autoradiograms showing displacement of ^{125}I-[LTT]-SS-28 by 100 nM des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin. Full displacement is observed in the sst1-expressing prostate tumor (A), but no displacement is seen in all the other tumors. Lane 5: Autoradiograms showing displacement of ^{125}I-[LTT]-SS-28 by 100 nM octreotide. No displacement is seen in tumor A, but full displacement in tumors B and E, and incomplete displacement in tumors C and D.

2.3. Radiolabeling of des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin

The des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin was synthesized as described previously (Liapakis et al., 1996). It was iodinated using the lactoperoxidase method, and purified using a C-18 reverse-phase high pressure liquid chromatography column by Anawa (Wangen, Switzerland). The specific activity of the radioligand was 2000 Ci/mmol. The radioligand was used in receptor autoradiography

Table 1
Relative binding potencies of CH-288 in comparison to somatostatin-28 in selected human tumors expressing distinct sst subtypes

	Relative potency of CH-288 (vs. SS-28 = 1.0)
(A) sst_1-expressing tumors[a] (prostate carcinoma, sarcoma, gastroenteropancreatic tumor)	0.75
(B) sst_2-expressing tumors[a] (growth hormone-producing adenoma, breast carcinoma, gastroenteropancreatic tumor)	< 0.001
(C) sst_3-expressing tumors[a] (inactive pituitary adenoma)	0.0027
(D) sst_5-expressing tumors[a] (growth hormone-producing adenoma)	0.0013
(E) sst_2 + sst_5-expressing tumors (growth hormone-producing adenoma)	< 0.001

n = at least three tumors per group (except group E, $n = 2$).
[a]Selected human tumors expressing preferentially one subtype, as identified with in situ hybridization for sst1, sst2, sst3, and sst5 mRNA (see Section 2). IC_{50} of SS-28 for the various tumors tested was 4.5 ± 0.9 nM (mean ± S.E.M.) except for prostate cancer (9.5 ± 0.6 nM; mean ± S.E.M.).

studies of various sst1-expressing tumors (prostate cancers, leiomyosarcomas, gastroenteropancreatic tumors) according to the same protocol, as described above with ^{125}I-[LTT]-SS-28.

3. Results

To test the selectivity of des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin to bind to sst1 receptors, the ability of this peptide to inhibit ^{125}I-[LTT]-SS-28 binding in sst1-, sst2-, sst3-, sst5-, sst2 + sst5-, and sst3 + sst5-expressing human tumors was tested in competition studies. All the selected tumors were strongly labeled with ^{125}I-[LTT]somatostatin-28 radioligand and this labeling was displaced by unlabeled somatostatin-28 in the nanomolar range (Figs. 1–4); nonspecific labeling (in presence of 10^{-7} M somatostatin-28) was below 15% of total binding. In these experiments, the two somatostatin analogs Tyr^3-octreotide and des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin had different types of displacement curves depending on the sst expressed by the respective tumors. Fig. 1 shows that in a sst1-expressing prostate cancer des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin (code-named CH-288) has a high binding affinity similar to that of somatostatin-28, whereas Tyr^3-octreotide is inactive. Conversely, in a sst2-expressing breast cancer, des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin is completely inactive, whereas Tyr^3-octreotide and somatostatin-28 have similar high affinity. Fig. 2 also shows in a case of a leiomyosarcoma expressing preferentially sst1 that des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin completely displaces ^{125}I-[LTT]-SS-28 in the nanomolar range, whereas Tyr^3-octreotide is inactive. Conversely, in the sst3-expressing inactive pituitary adenoma, des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin

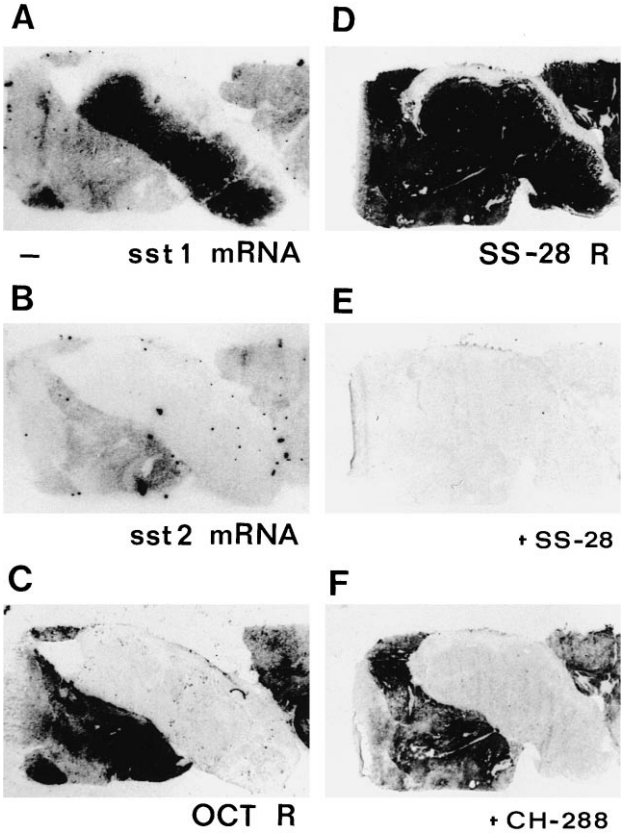

Fig. 5. Specificity of des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin for sst1 receptors in a mixed sst1/sst2-expressing gastroenteropancreatic tumor. A: Autoradiogram showing sst1 mRNA abundant in the middle part and moderate in the peripheral parts of the tumor. Bar = 1 mm. B: Autoradiogram showing sst2 mRNA in the peripheral parts of the tumor but its absence in the middle part. C: Autoradiogram showing total binding of the sst2-selective ^{125}I-Tyr^3-octreotide: No labeling is seen in the middle part, moderate labeling is present in the peripheral parts. D: Autoradiogram with total binding of ^{125}I-[LTT]-SS-28 showing somatostatin receptors equally present in the middle and peripheral parts of the tumor. E: Autoradiogram with nonspecific binding of ^{125}I-[LTT]-SS-28 (in presence of 10^{-6} M SS-28). F: Autoradiogram showing displacement of ^{125}I-[LTT]-SS-28 by 10^{-6} M des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin. Displacement is complete in the sst1-expressing middle part and partial in the sst1/sst2-expressing peripheral parts.

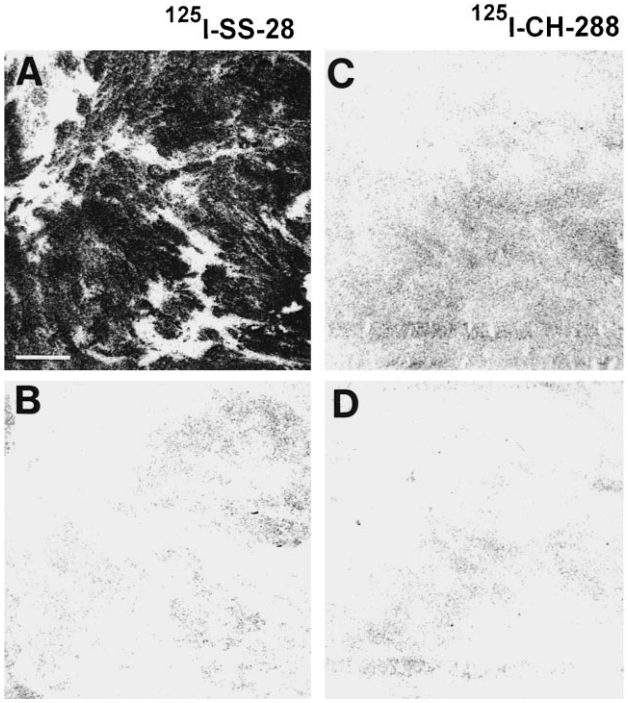

Fig. 6. Visualization of a sst1-expressing prostate carcinoma with the universal radioligand ^{125}I-[LTT]-SS-28 (A, B) and comparison with the ^{125}I-radiolabeled sst1-selective des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin (C, D). A: Autoradiogram showing total binding of ^{125}I-[LTT]-SS-28. Notice the strong labeling of all the tumoral structures. B: Autoradiogram showing nonspecific binding (in presence of 10^{-6} M SS-28). C: Autoradiogram showing total binding of ^{125}I-labeled des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin. D: Nonspecific binding (in presence of 10^{-6} M des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin). Comparison of the strong labeling by ^{125}I-[LTT]-SS-28 with the weak labeling by ^{125}I-labeled des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin shows the poor ability of the iodinated sst1-selective compound to bind to this sst1-expressing tumor.

does not displace the ligand at 100 nM concentrations, whereas Tyr^3-octreotide is moderately active. In the sst5- and sst2 + sst5-expressing growth hormone-producing pituitary adenomas of Fig. 3, des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin is inactive in both cases, whereas Tyr^3-octreotide and somatostatin-28 have similar high affinities. Des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin is also completely inactive in a sst3 + sst5-expressing pituitary adenoma (data not shown).

Fig. 4 illustrates in a selection of receptor autoradiograms the displacement profile of ^{125}I-[LTT]-SS-28 by 100 nM of somatostatin-28, des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin, and octreotide in tumors expressing different sst subtypes. In the sst1-expressing prostate cancer, the ^{125}I-[LTT]-SS-28 labeling localized in the tumor cells is completely displaced by somatostatin-28 or des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin, but not by octreotide. In the sst2-, sst5-, and sst2 + sst5-expressing growth hormone-producing pituitary adenomas, the labeling on the tumor cells is abolished by somatostatin-28, but not by des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin; in presence of octreotide, binding is abolished in the sst2-expressing tumor, whereas residual binding is observed in the sst5- and sst2 + sst5-expressing tumors. In the sst3-expressing inactive pituitary adenoma, the labeling is abolished by somatostatin-28, but not by des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin, and only partially by octreotide. Fig. 5 represents a particularly striking proof of the selectivity of des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin for sst1 receptors in a tumor expressing sst1 and sst2 receptors in two different topographical regions. Indeed, the medial part of this tumor contains only sst1 receptors according to the in situ hybridization data, and is not labeled by ^{125}I-Tyr^3-octreotide, whereas both lateral parts express sst1 and sst2 as seen by in situ hybridization and by ^{125}I-Tyr^3-octreotide binding: Des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin displaces completely ^{125}I-[LTT]-SS-28 only in the medial part, whereas it displaces only partly ^{125}I-[LTT]-SS-28 in both lateral parts. Table 1 shows in summary that des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin has binding characteristics very close to that of somatostatin-28 in sst1-expressing tumors; on the other hand, it is several orders of magnitude less potent than somatostatin-28 in those tumors expressing sst2, sst3, or sst5.

Receptor autoradiography was also performed with ^{125}I-labeled des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin in all sst1-expressing tumors. The labeling of the tumor tissue was negative or at the limit of detection in all cases, with the best results being found in the sst1-expressing prostate cancer shown in Fig. 6. However, the comparison with the strong labeling obtained with ^{125}I-[LTT]-SS-28 in adjacent sections demonstrates that ^{125}I-radiolabeled des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin is not an adequate radioligand.

4. Discussion

The present results show that the des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin has a high affinity and a high selectivity for sst1-expressing human tumors. Indeed, the binding affinity of this analog in sst1-expressing prostate cancers is comparable to that of the natural ligand somatostatin-28. Conversely, its binding affinity is very low in all the other sst-expressing tumors, including sst2-, sst3-, and sst5-expressing tumors. The selectivity of this analog in human tumors agrees well with the data reported by Liapakis et al. (1996) on transfected COS-7 cells. For comparison and as internal control, octreotide and Tyr^3-octreotide, which are known to preferentially bind to sst2 and sst5, and to a lesser extent to sst3 (Bruns et al., 1994), showed, as expected, binding characteristics completely different from those of des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin, i.e., a high binding affinity for sst2- and sst5-expressing tumors, a moderate affinity for sst3- and no affinity for sst1-expressing tumors.

The high sst1 selectivity of des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin was observed in all types of tumors tested, showing a high binding affinity in sst1-expressing tumors such as prostate cancers, some hormone-producing gastroenteropancreatic tumors, and some sarcomas, but low affinity in sst2-, sst3-, and/or sst5-expressing tumors such as pituitary adenomas and breast cancers. Unfortunately, no tumors expressing solely sst4 could be identified and included in this study; it should be noticed that tumors expressing exclusively the sst4 subtype have extremely rarely been reported in the literature, even in studies using polymerase-chain reaction amplification methods (Greenman and Melmed, 1994; Kubota et al., 1994; Miller et al., 1995; Vikic-Topic et al., 1995). Therefore, for the time being, we can only speculate that des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin has a low affinity for sst4-expressing human tumors, based on the data by Liapakis et al. (1996) showing a lack of affinity of this analog for sst4 expressed in COS-7 cells. Since recent preliminary studies by Patel (1997) seem however not to confirm this low affinity binding to sst4, further investigations will be necessary to clear this issue.

The presence of a Tyr in the des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin molecule opens the possibility to iodinate the compound and to use it as specific sst1 tracer. Unfortunately, the present data on the visualization of sst1-expressing tumors with ^{125}I-des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin are disappointing in this regard. This may be explained either by the rapid degradation of this radioligand by peptidases present in human tissues or by the observation of Reisine and Rivier (unpublished data) that the iodination of this compound was considerably decreasing its binding affinity for sst1, implicating that only tissues expressing an extremely high density of sst1 receptors (i.e., sst1-transfected COS-7 cells) may be identi-

fied with this radioligand (Liapakis et al., 1996). The fact that human tumors do not usually express sst1 receptors in an extremely high density, may explain the poor labeling obtained with ^{125}I-des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin in sst1-expressing tumors. A different strategy of radiolabeling this molecule, not involving iodination of Tyr^2 and therefore not affecting the binding properties of this analog, might therefore be tried in the future.

This study represents the first demonstration of a somatostatin analog which binds selectively and with high affinity to sst1 receptors expressed in human tumors. These data have a number of implications: (1) Des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin may be a tool to understand the pathophysiology of sst1-expressing human tumors, such as prostate cancers or exocrine pancreatic carcinomas; Buscail et al. (1994) have already suggested, using tumor cell lines, that sst1 may be involved in the mediation of the antiproliferative action of somatostatin. (2) Des-AA^{1,5}-[Tyr^2, D-Trp^8, IAmp^9]somatostatin may be a lead compound for the development of adequately labeled radioligands, which may be used clinically for the in vivo diagnosis or for the radiotherapy of sst1-expressing tumors, i.e., prostate cancers (Reubi et al., 1995), in a similar way as octreotide-like compounds are presently used for sst2- (and sst5)-expressing tumors (Krenning et al., 1995; Lamberts et al., 1991; Reubi and Laissue, 1995). The fact that, in comparison to sst2, only a low proportion of the sst1 subtype is internalized after agonist binding (Hukovic et al., 1996; Nouel et al., 1997) may, however, represent a potential disadvantage for the above-mentioned clinical indications. Finally, this class of sst1-selective analogs may also be of potential use for long-term therapy, as an adjunct to octreotide in tumors expressing multiple subtypes such as sst1, sst2, and sst5 receptors (Schaer et al., 1997).

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