# Receptor Affinity and Preclinical Biodistribution of Radiolabeled Somatostatin Analogs

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**Abstract.** *In this study, we investigated the relationship between affinity to somatostatin receptor subtype2 ($SSTR_2$) and uptake of radioactivity from a group of radiolabeled somatostatin analogues in somatostatin receptor-rich tissues of rats. Organs with a high density of somatostin receptors (namely the adrenals and pancreas bearing mainly $SSTR_2$; this receptor subtype is also the most abundant in somatostatin receptor-positive tumors) were chosen as markers of specific binding of the peptides in vivo. Accumulations of radioactivity in these organs 24 h and 48 h after intravenous administration of six $^{111}$In-labeled octreotide and octreotate derivatives with predominant affinity to $SSTR_2$ were correlated with affinity to $SSTR_2$ determined in vitro ($IC_{50}$ values). For correlation between adrenal uptake of radioactivity and $IC_{50}$, the best fit for exponential dependence was found; for that of pancreas, however, linear dependence was the most suitable. In cases where the values for the peptide with affinity to SSTR subtypes 2, 3 and 5, namely $^{111}$In- DOTA-Nal$^3$-octreotide were included in the group of studied agents, substantially less correlations were obtained. Our results showed that uptake of radioactivity in tissues with a high density of somatostatin receptors correlates with somatostatin receptor affinity of receptor-specific peptides; however, other factors (the affinity to particular receptor subtypes, the overall pharmacokinetic profile in the body etc.) may contribute to this observed relationship.*

Radiolabeled somatostatin derivatives represent important peptides for receptor-mediated diagnoses as well as radionuclide therapies directed against some tumor types and their metastases. Somatostatin receptors are integral membrane glycoproteins that are known to be expressed at a high density on neuroendocrine tumors as well as on tumors of the central nervous system, breast, lung and some others tissues (1, 2). Five different somatostatin receptors have been cloned ($SSTR_{1-5}$); unlike native somatostatin, which has a high affinity to all subtypes, most of the stable somatostatin analogs (octreotide and octreotate derivatives) have affinity predominantly for $SSTR_2$ (3, 4). As neuroendocrine tumors express relatively high levels of $SSTR_2$, they take up radiolabeled somatostatin analogs in a highly specific manner. While a number of somatostatin analogs have been constructed, the optimal structure of these peptides for clinical uses is still under debate. There are still improvements to be made in the field of SSTR targeting; however, a higher receptor affinity to SSTRs does not necessarily translate into more favorable characteristics of a somatostatin analog in peptide receptor-mediated radionuclide therapy (5). In patients, the pharmacokinetics of $^{111}$In-labelled DOTA-Tyr$^3$-octreotide (DOTA-TOC) and DOTA-Tyr$^3$-octreotate (DOTA-TATE) were found to be comparable (5), even though DOTA-TATE has a binding affinity more than nine fold higher for $SSTR_2$ in comparison with DOTA-TOC (4). The effect of receptor binding affinity on peptide uptake in SSTR-rich tissues is not yet completely understood. While a direct comparison of tumor distribution characteristics of different radiolabeled peptides in the same patient is not feasible for ethical reasons, the interpatient variability of uptake of radioactivity of tumors is known (2). In the past few years, our group has studied the pharmacokinetics of different radiolabeled octreotide and octreotate analogs to establish the binding distribution profiles of radiolabeled somatostatin analogs in preclinical experiments (6-9); these results have encouraged the further evaluation of factors affecting the suitability of individual somatostatin derivatives as vectors in targeted cancer diagnosis and treatment. SSTRs are also expressed in normal tissues, including the pancreas, adrenals, brain, thyroid and gastrointestinal tract (10, 11). Furthermore, the uptake of radioactivity by both tumors and the pancreas correlates with the rate of internalization of receptor-specific radiolabeled peptides into tumor cells (12). For this reason, organs bearing a high density of SSTRs (mostly $SSTR_2$),

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*Key Words:* Somatostatin analogs, $^{111}$In, receptor affinity, receptor-specific distribution.

Table I. *List of the peptides used*.

| Name of peptide | Abbreviation | Sequence |
|---|---|---|
| DTPA-octreotide† | DTPA-OC | DTPA-*D*Phe-Cys-Phe-*D*Trp-Lys-Thr-Cys-Thr-ol |
| DOTA-octreotide† | DOTA-OC | DOTA-*D*Phe-Cys-Phe-*D*Trp-Lys-Thr-Cys-Thr-ol |
| DOTA-Tyr$^3$-octreotide† | DOTA-TOC | DOTA-*D*Phe-Cys-Tyr-*D*Trp-Lys-Thr-Cys-Thr-ol |
| DOTA-Tyr$^3$-octreotate‡ | DOTA-TATE | DOTA-*D*Phe-Cys-Tyr-*D*Trp-Lys-Thr-Cys-Thr-COOH |
| DOTAGA-Tyr$^3$-octreotate† | DOTAGA-TATE | DOTAGA-*D*Phe-Cys-Tyr-*D*Trp-Lys-Thr-Cys-Thr-COOH |
| DOTA-t-GA-Tyr$^3$-octreotate† | DOTA-t-GA-TATE | DOTA-t-GA-*D*Phe-Cys-Tyr-*D*Trp-Lys-Thr-Cys-Thr-COOH |
| DOTA-Nal$^3$-octreotide‡ | DOTA-NOC | DOTA-*D*Phe-Cys-Nal-*D*Trp-Lys-Thr-Cys-Thr-ol |

DTPA, Diethylenetriaminepentaacetic acid; DOTA, tetraazacyclododecanetetraacetic acid; DOTAGA or DOTA-t-GA, 2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraaza-cyclododecane-1-yl)glutaric acid which is bound to the peptide in two different ways (9); Nal, 1-naphthyl-alanine; †Kindly supplied by H.R. Maecke, University Medical Center, Freiburg, Germany; ‡Purchased from PiChem, Graz, Austria.

namely the adrenals and pancreas, serve as an endogenous model system to profile the specific binding of peptides to $SSTR_2$ in *in vivo* conditions; this receptor subtype is also most abundant in human SSTR-expressing malignancies.

The aim of this study was to determine whether there is a correlation between *in vitro* receptor affinity of various $^{111}$In-labeled somatostatin derivatives and the uptake of radioactivity of normal SSTR-rich organs (namely the adrenals and pancreas). This will allow for the assessment of other parameters that may affect prospects for the use of such peptides in radionuclide diagnoses and therapies.

## Materials and Methods

*Peptides under study*. A list of somatostatin analogs used and their suppliers is shown in Table I.

*Radiolabeling*. Radiolabeling was performed by adding approximately 0.5 mCi $^{111}InCl_3$ (Amersham, UK) in 50-100 μl 40 mM HCl to 200 μl 0.4 M acetate buffer (pH 5) with 0.24 M gentisic acid and 10 μg of peptide. After incubation at 90-95˚C for 25 min, the quality of the product was determined by gradient HPLC analysis.

*Determination of radiochemical purity*. A volume of 30 μl 0.1% trifluoroacetic acid (TFA) and 10 μl $10^{-3}$ M diethylenetriamine-pentaacetic acid (DTPA) were added to 2 μl of labeled peptide solution. HPLC gradient elution analysis was performed on a Pharmacia-LKB system with a Gradient Master GP 962 (UOCHB, Prague, Czech Republic) equipped with a LichroCART 125-4 HPLC Cartridge Purospher RP 18e, 5 μm (Merck, Darmstadt, Germany) with a UV monitor and an analyzer monitoring radioactivity using 0.1% TFA as mobile phase A and $CH_3CN$ as phase B. The gradient used was as follows: 0-5 min 0% B, 5-25 min 0-30% B, 25-30 min 30% B, 30-35 min 30-100% B, 35-40 min 100% B. The flow rate was 1 ml/min.

*Animals*. Animal studies were carried out using male Wistar rats weighing 190-260 g (BioTest, Konarovice, Czech Republic). The animals were fasted overnight before experiments (to empty the bowels) but had free access to water. All animal experiments were approved by the Ethics Committee of the Faculty of Pharmacy, Charles University, Hradec Kralove.

*Biodistribution in rats*. Radiolabeled agents diluted with a saline to concentration of the peptide 1 μg/ml were administered to rats intravenously in a volume of 0.2 ml. During the course of experiments, the animals were placed singly in cages (four animals in each time intervals after dosing were used). At various time points after injection, the carotid artery was exposed under ether anesthesia and a blood sample was collected into a glass tube containing dry heparin. The rats were then sacrificed and dissected. The organs of interest were weighed and assayed for radioactivity using a 1480 Wizard 3 automatic gamma counter (Wallac OY, Turku, Finland).

To determine the effect of SSTR blockade on a given peptide distribution profile, two groups of animals (n=4) were pretreated with an intravenous injection of 0.1 mg/kg octreotide (Sandostatin, Novartis International AG, Basel, Switzerland) 15 min before the peptide administration.

*Statistical analysis*. Data are shown as the mean±standard deviation. GraphPad Prism (version 5.02, La Jolla, CA, USA) was used for curve fitting.

## Results

The distribution profiles of the peptides under investigation in rats after intravenous administration were generally similar. Rapid clearance of radioactivity from the blood and SSTR-negative organs were observed for all agents. Conversely, a high level of uptake of radioactivity with very slow radioactivity wash out was observed for the kidney and SSTR-expressing tissues (the adrenals, pancreas and gastrointestinal tract). For longer time intervals (from 2 to 48 h) uptake of radioactivity in other organs and tissues was only marginal. Accumulation of radioactivity in SSTR-rich organs was significantly reduced by pretreatment with non-labeled somatostatin. An example of the distribution profile of radioactivity and the effect of the receptor blockade on radioactivity in selected organs after $^{111}$In-DOTA-TOC administration is shown in Table II. Radioactivity in the blood and the liver was very low for longer time intervals (from 2 to 48 h) and practically unaffected by SSTR blockade. The pretreatment of animals with somatostatin

Table II. *Uptake of radioactivity from $^{111}$In-DOTA-TOC in selected organs of control and somatostatin receptor-blocked (sandostatin pretreated) rats. Activity of each organ is expressed as percentage of injected activity per gram. Data are the mean±SD of four animals.*

| | The point after administration | | | | | | |
|---|---|---|---|---|---|---|---|
| | 5 min | 60 min | 120 min | 120 min | 24 h | 48 h | 48 h |
| Organ | | | | Sandostatin pretreated | | | Sandostatin pretreated |
| Blood | 0.760±0.049 | 0.096±0.011 | 0.022±0.003 | 0.024±0.003 | 0.002±0.000 | 0.002±0.002 | 0.002±0.002 |
| Plasma | 1.442±0.161 | 0.171±0.031 | 0.040±0.004 | 0.041±0.008 | 0.004±0.001 | 0.004±0.003 | 0.002±0.001 |
| Pancreas | 6.888±3.162 | 13.13±2.13 | 12.19±1.36 | 2.558±0.812 | 4.926±0.768 | 4.271±0.584 | 0.873±0.231 |
| Liver | 0.208±0.021 | 0.102±0.034 | 0.071±0.015 | 0.058±0.007 | 0.053±0.005 | 0.065±0.008 | 0.055±0.005 |
| Adrenals | 9.847±3.875 | 16.16±1.86 | 18.51±3.55 | 2.430±1.275 | 13.16±1.87 | 12.51±1.38 | 2.649±0.735 |
| Kidney | 8.307±2.541 | 2.024±0.309 | 2.061±0.815 | 2.378±0.149 | 1.941±0.110 | 2.402±0.663 | 2.457±0.238 |
| Lung | 0.697±0.087 | 0.226±0.048 | 0.128±0.004 | 0.046±0.004 | 0.062±0.011 | 0.065±0.018 | 0.031±0.026 |
| Heart | 0.363±0.036 | 0.062±0.010 | 0.022±0.002 | 0.016±0.004 | 0.008±0.001 | 0.009±0.002 | 0.006±0.003 |
| Spleen | 0.240±0.033 | 0.084±0.021 | 0.050±0.015 | 0.026±0.004 | 0.050±0.035 | 0.053±0.011 | 0.031±0.005 |
| Stomach | 1.264±0.424 | 1.512±0.279 | 1.829±0.628 | 0.236±0.150 | 0.998±0.290 | 0.889±0.109 | 0.198±0.047 |
| Intestine | 0.576±0.212 | 0.469±0.024 | 0.553±0.085 | 0.131±0.033 | 0.293±0.020 | 0.287±0.021 | 0.060±0.018 |
| Colon | 0.338±0.048 | 0.444±0.126 | 0.375±0.059 | 0.136±0.045 | 1.084±0.182 | 0.472±0.070 | 0.296±0.192 |
| Testes | 0.104±0.009 | 0.043±0.005 | 0.017±0.001 | 0.014±0.003 | 0.007±0.001 | 0.007±0.002 | 0.005±0.001 |
| Skin | 0.463±0.046 | 0.110±0.006 | 0.051±0.006 | 0.030±0.004 | 0.026±0.002 | 0.021±0.004 | 0.013±0.002 |
| Muscle | 0.168±0.011 | 0.026±0.004 | 0.009±0.001 | 0.007±0.001 | 0.003±0.001 | 0.004±0.001 | 0.004±0.001 |
| Thyroid | 0.799±0.150 | 0.296±0.027 | 0.190±0.018 | 0.065±0.011 | 0.079±0.013 | 0.081±0.011 | 0.032±0.011 |
| Brain | 0.032±0.002 | 0.007±0.002 | 0.003±0.001 | 0.002±0.001 | 0.002±0.000 | 0.003±0.001 | 0.002±0.000 |
| Fat | 0.350±0.088 | 0.046±0.008 | 0.026±0.005 | 0.014±0.005 | 0.011±0.004 | 0.013±0.002 | 0.010±0.006 |
| Femur | 0.364±0.035 | 0.412±0.086 | 0.341±0.046 | 0.143±0.034 | 0.288±0.063 | 0.241±0.037 | 0.111±0.021 |

Table III. *Affinity profiles for human somatostatin receptor subtype 2 (SSTR2, $IC_{50}$ values) and selected biodistribution data (in % dose/gram tissue) of the peptides with predominant affinity to SSTR2.*

| | | Adrenals | | Pancreas | | Kidney-to-adrenals | Muscle-to-adrenals |
|---|---|---|---|---|---|---|---|
| Peptide | $IC_{50}$ (nM) (ref) | 24 h | 48 h | 24 h | 48 h | 24 h | 24 h |
| $^{111}$In-DTPA-OC | 22† | 1.20±0.32 | 0.06±0.21 | 0.53±0.05 | 0.33±0.05 | 1.512 | 0.00167 |
| $^{111}$In-DOTA-OC | 14† | 3.51±0.03 | 2.23±0.85 | 2.03±0.19 | 1.37±0.31 | 0.87 | 0.00095 |
| $^{111}$In-DOTA-TOC | 14† | 3.41±0.46 | 4.1±0.85 | 2.20±0.20 | 1.30±0.22 | 0.943 | 0.00059 |
| $^{111}$In-DOTA-TATE | 1.5† | 10.44±2.60 | 9.39±2.27 | 2.97±0.25 | 3.05±0.34 | 0.272 | 0.00019 |
| $^{111}$In-DOTA-GATATE | 1.1‡ | 14.40±1.87 | 13.0±1.78 | 4.69±0.09 | 3.35±0.13 | 0.524 | 0.00028 |
| $^{111}$In-DOTA-t-GA-TATE | 5.2‡ | 8.37±1.12 | 6.93±0.52 | 3.16±0.38 | 2.87±0.09 | 0.940 | 0.00024 |

†Taken from Reubi JC *et al*. (3); ‡taken from Laznicek M *et al*. (17).

significantly reduced (by about five fold) accumulation of radioactivity in the adrenals and pancreas, indicating that these organs can serve as appropriate models for uptake of radioactivity in tumors with a high density of SSTRs. Renal radioactivity was not significantly changed by SSTR blockade. The main route of excretion of radioactivity was *via* the kidneys for all peptides studied.

Values of receptor affinities for the human $SSTR_2$, radioactivity accumulation in the adrenals and pancreas at 24 h and 48 h after dosing, kidney-to-adrenal and muscle-to-adrenal ratios of the peptides exhibiting predominant affinity for the $SSTR_2$ are summarized in Table III. Receptor affinity values were taken from the literature (3, 17). In cases where the receptor affinity for a given radiolabeled peptide was not available in the literature, the receptor affinity for the parent peptide (without the radiolabel) was used as a substitute, as the differences between the receptor affinity of labeled *versus* non-labeled peptides are typically insignificant.

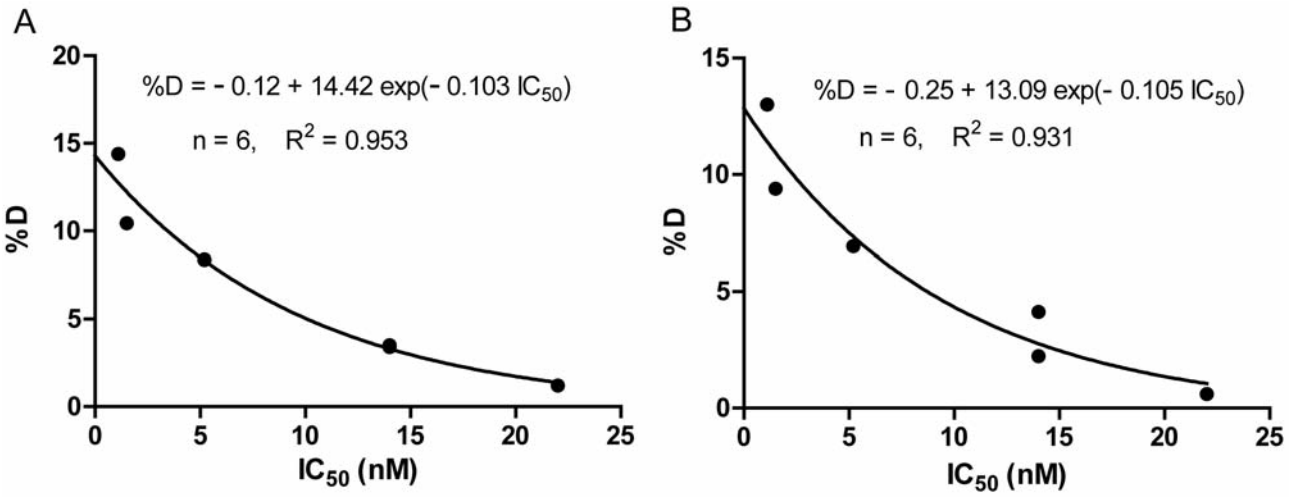


Figure 1. *Non-linear regression analysis of the correlation between the uptake of radioactivity into the adrenals of rats (%D/g) at 24 h (A) and 48 h (B) after administration and somatostatin receptor affinity as represented by the $IC_{50}$ value for somatostatin analogs presented in Table III.*

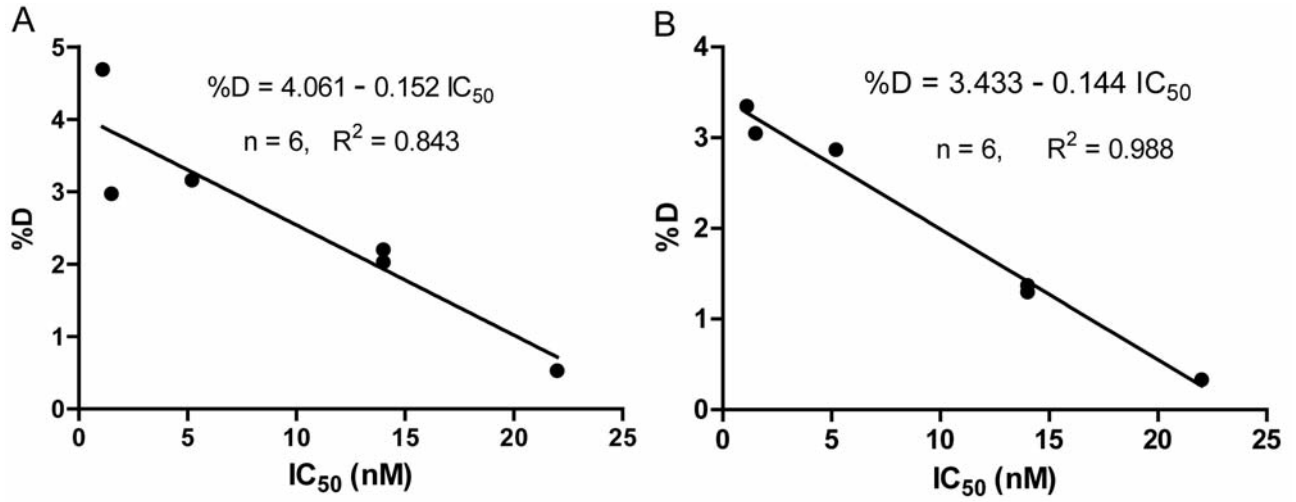


Figure 2. *Linear regression analysis of the correlation between the uptake of radioactivity into the pancreas of rats (%D/g) at 24 h (A) and 48 h (B) after administration and somatostatin receptor affinity as represented by the $IC_{50}$ value for somatostatin analogs presented in Table III.*

We next tested whether there were any correlations between adrenal and pancreatic uptake of radioactivity *in vivo* that related to affinity to $SSTR_2$. Radioactivity uptake of organ decreased with increasing $IC_{50}$; an appropriate model should take into account that adrenal and pancreatic uptake of radioactivity has lower and upper limits. Accordingly, the uptake value must be positive for any $IC_{50}$ and should ultimately reach zero for very low receptor affinity values. The upper limit is dependent on the possible mechanisms that determine maximal adrenal and pancreatic accumulation of agents under study. Sigmoidal and exponential dependences of organ accumulation of radioactivity on $IC_{50}$ values were thus the first choice. In our study, the best fit for exponential decrease (Figures 1) for the adrenals and linear decrease for pancreas (Figures 2) were found.

Recently, a promising radiopeptide, DOTA-NOC, with an improved SSTR-binding profile (a high binding affinity for $SSTR_2$, $SSTR_3$ and $SSTR_5$) was described (13). The values for $^{111}$In-DOTA-NOC are presented in Table IV. If these results with $^{111}$In-DOTA-NOC are included in the relationship between *in vitro* receptor affinity and uptake of radioactivity *in vivo*, a much lower correlation coefficient is obtained.

Uptake of radioactivity in the adrenals and pancreas 24 hours and 48 hours after dosing is in this case described by equations 1 to 4:

Adrenals, 24 h after administration:

$$\%D = -4.27 + 20.19\, e^{-0.0642\, IC_{50}} \quad n=7 \quad R^2=0.780 \qquad \text{(Eqtn. 1)}$$

48 h after administration:

Table IV. *Affinity profiles for human SSTR2 ($IC_{50}$) and selected biodistribution data of somatostatin analog $^{111}$In-DOTA-NOC with high affinity to SSTR2, 3 and 5.*

| | | Adrenals | | Pancreas | | Kidney-to-adrenals | Muscle-to-adrenals |
|---|---|---|---|---|---|---|---|
| Peptide | $IC_{50}$ (nM) (ref) | 24 h | 48 h | 24 h | 48 h | 24 h | 24 h |
| $^{111}$In-DOTA-NOC | 2.9† | 18.51±5.68 | 14.44±2.72 | 6.01±1.25 | 4.38±0.60 | 0.119 | 0.00032 |

†Taken from Wild D *et al*. (13).

$\%D = -3.145 + 16.90\ e^{-0.0698\ IC_{50}}$ n=7 $R^2$=0.843 (Eqtn. 2).
Pancreas, 24 h after administration:
$\%D = 4.71 - 0.329\ IC_{50}$ n=7 $R^2$=0.698 (Eqtn. 3)
48 h after administration:
$\%D = 3.80 - 0.164\ IC_{50}$ n=7 $R^2$=0.873 (Eqtn. 4),
where %D is percentage of dose administered.

The values for radioactivity uptake of $^{111}$In-DOTA-NOC by both the adrenals and pancreas clearly lie above the curve (or line) describing the dependence for the other peptides.

There are also other parameters that determine the efficacy of radiolabeled receptor-specific peptides for cancer diagnosis and treatment. The most important of these are probably dose limiting organ-to-target ratio and background-to-target ratio. Because the kidney is the most critical organ in tumor radionuclide therapy, the values of kidney-to-adrenals ratios are included in Tables III and IV. The values of muscle-to-adrenals ratios were selected as being representative of the background/target ratio (Tables III and IV).

## Discussion

Radiolabeled somatostatin analogs are promising modalities in the management of neuroendocrine tumors. The uptake of these agents by tumor cells through SSTR-mediated internalization enables *in vivo* targeting for peptide receptor radionuclide diagnosis and therapy. In the present study, the influence of the receptor binding affinity of $SSTR_2$ for somatostatin analogs *in vitro* ($IC_{50}$ values) on *in vivo* uptake of radioactivity in tissue with a high density of SSTRs (the normal adrenals and pancreas) was analyzed in a rat model. In an attempt to generalize *in vitro*/*in vivo* correlations, we tested a variety of somatostatin analogs that bind predominantly to $SSTR_2$. The relative uptake of radioactivity by the adrenals and pancreas is dependent on the proportion of accumulation of radioactivity in these organs (organ blood flow multiplied by the amount of agent extracted from the organ) and the total radioactivity that escapes from the bloodstream by all routes (excretion by the glomerular filtration being a predominant pathway, given by the glomerular filtration rate multiplied by free peptide fraction in blood).

The negative correlation observed between the uptake of radioactivity in the adrenals or the pancreas and $IC_{50}$ values reveals that a higher receptor affinity (lower $IC_{50}$ value) results in a higher uptake in the adrenals and pancreas for peptides with a strong affinity for $SSTR_2$. For mathematical evaluations, an exponential decrease of adrenal uptake with increasing $IC_{50}$ is probably the most appropriate curve-fitting method. For the pancreas, however, the best correlation was as a linear relationship between the uptake of radioactivity and $IC_{50}$ values. This linear dependence does not provide a generally valid description, however, as it predicts negative values for uptake of radioactivity for the pancreas for agents with low receptor affinities. The accuracy of this model is limited by the receptor affinity values used in this study. There are additional factors that can further affect our observed correlations. For instance, receptor binding affinities were obtained from different literature sources and may therefore be burdened with errors (for some compounds, only the values for parent non-radiolabeled peptides were available). It is also probable that not only receptor binding affinity, but non-receptor interactions of the peptide with non-specific binding sites located in the immediate vicinity of the receptor may alter equilibrium binding constants and internalization. Furthermore, in some cases, the rate of endocytosis of the peptide receptor complex may be the rate-limiting step in the uptake of these agents. Moreover, the cell type, as well as the origin of the SSTRs, might play role in the rate of internalization (14). Plasma-protein binding properties for individual peptides may also be different and affect both the extraction ratio in the adrenals and pancreas, as well as the rate of elimination from the body.

When radiolabeled DOTA-NOC derivatives were taken into account, much weaker correlations were obtained. Uptake of radioactivity by the adrenals and pancreas were significantly higher for DOTA-NOC derivatives than would be expected from the results obtained for the other analogs. The reason for this is likely due to the significant binding affinity of radiolabeled DOTA-NOC for receptor subtypes other than $SSTR_2$.

Factors other than receptor affinity may also play an important role in the evaluation of radiolabeled somatostin derivatives. Of note, nephrotoxicity is possible due to renal reabsorption and retention of the peptides, which may limit

the tumor dose in receptor-targeted radiotherapy (15, 16). The kidney-to-adrenals and muscle-to-adrenals ratios have a general downward trend with decreasing $IC_{50}$ values. Whereas the essential pharmacophore of somatostatin analogs responsible for SSTR binding is the $Phe_7$-Trp-Lys-$Thr_{10}$ fragment of somatostatin, retention of radioactivity in the kidney is mediated by the megalin/cubilin system in the proximal tubules, which is responsible for a great part of the interaction of the agents under study with the endocytic system in the kidney (16).

Only very minor amounts of radioactivity were detected at later time intervals (2-48 h after dosing) in the blood, muscles and other organs not bearing SSTRs, due to rapid clearance of radioactivity from these tissues; very high adrenal-to-muscle ratios suggested no significant risk of radiation damage to non-target organs and tissues.

In conclusion, we found statistically significant correlations between the receptor affinities of selected radiolabelled somatostatin analogs ($IC_{50}$ values for $SSTR_2$) and the uptake of peptide radioactivity in SSTR-rich tissues in rats. Accumulation of radioactivity in these organs is probably affected not only by specific binding to $SSTR_2$, but also by peptide binding to other SSTRs, peptide lipophilicity and, perhaps, also by the rate of peptide receptor binding and consequent internalization, as the rate of decrease of radioactivity in the blood was found to be relatively rapid. The results of the present study demonstrate that it is possible to predict how radiolabled peptides will accumulate in SSTR-rich tissues based solely on *in vitro* SSTR affinity, even though more parameters should be taken into account for a complete model.

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