Review
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Radiopharmaceuticals for somatostatin receptor imaging

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Abstract

The aim of this review is to summarize the developments and briefly characterize the somatostatin analogs which are currently used for somatostatin receptor imaging in clinical routine or in early phase clinical trials.

Somatostatin (sst) receptor targeting with radiolabeled peptides has become an integral part in nuclear oncology during the last 20 years. This integration process has been initiated in Europe with the introduction to the market of ^{111}In-DTPA-DPhe^{1}-octreotide [^{111}In-pentetreotide]. Introducing ^{99m}Tc in somatostatin receptor targeting radiopeptides resulted in much better image quality, higher sensitivity of tumor detection and lower mean effective dose for the examined patient. The next generation are ^{68}Ga labeled somatostatin analogs. Due to the spatial resolution of PET technique and increasing number of PET scanners, the PET or PET/CT technique became very important in somatostatin receptor imaging. Until up to a couple of years ago the analogs of somatostatin were constructed aiming at their agonistic behavior, expecting that their internalization with the receptor activated by the radiolabeled ligand and its retention within the tumor cell are crucial for efficient imaging and therapy. Recently it has been shown that the antagonists recognize more binding sites at the tumor cell membrane and hence offer an improved diagnostic efficacy, especially when the density of sst receptors is low. This approach may in future improve diagnostic value of somatostatin receptor imaging techniques. The developments in tracer design are followed by the improvements in imaging techniques. The new SPECT scanners offer resolution close to that of PET, which might open a new era for ^{99m}Tc and other SPECT radiotracers.

KEY words: somatostatin, sst, somatostatin receptors, sstr, agonist, antagonist, ^{99m}Tc-EDDA/HYNIC-Tyr^{3}-Octreotide, scintigraphy, imaging

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Introduction

Somatostatin (sst) receptor targeting with radiolabeled peptides has become an integral part in nuclear oncology during the last 20 years. This integration process has been initiated in Europe with the introduction to the market of ^{111}In-DTPA-DPhe^{1}-octreotide [^{111}In-pentetreotide] (Octreoscan® Mallinckrodt Medical, 1995) which was soon becoming the most important product for somatostatin receptor scintigraphy. It is in wide spread clinical use, although clinical drawbacks regarding sensitivity in tumor detection, image quality and patient exposure to relatively high effective doses of ionizing radiation have to be considered.

Major achievements of introducing ^{99m}Tc in somatostatin receptor targeting radiopeptides are much better image quality, higher sensitivity of tumor detection and lower mean effective dose for the examined patient [1–4]. Technetium-99m is considered to be a suitable radionuclide for somatostatin receptor scintigraphy (SRS). It is the workhorse of the nuclear medicine physician because of its short half-life (6 hrs.) and emission of gamma radiation with the energy of 141 keV. The wide availability and cost-effectiveness of ^{99m}Tc are of major importance for routine clinical applications. Several chelators were investigated to provide efficient and stable ^{99m}Tc-labeled somatostatin analogs with high affinity to somatostatin receptors, among them conjugates of 6-hydrazinonicotinamide (HYNIC) found their way to the clinics [5, 6]. Furthermore, [^{99m}Tc-ethylenediamine-N,N'-diacetic acid (EDDA)/HYNIC, Tyr^{3}]octreotide (^{99m}Tc-EDDA/HYNIC-TOC) is now available in a number of European countries and beyond (Tektrotyd, NCBJ RC POLATOM). The next generation of somatostatin analogs are tracers for PET or PET/CT somatostatin receptor imaging labeled with the radiometal ^{68}Ga (68 min). The commercially produced radionuclide generators ^{68}Ge/^{68}Ga are available for use in the clinics, independent of the cyclotrons. In combination with the spatial resolution of PET technique and increasing number of PET scanners, the technique became very attractive and ^{68}Ga labeled soma-

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tostatin analogs found their way to the clinic. Currently three major, clinically useful, ^{68}Ga labeled tracers for PET/CT imaging are available: ^{68}Ga-DOTA-Phe^{1}-Tyr^{3}-Octreotide (DOTATOC), ^{68}Ga-DOTA-Nal^{3}-Octreotide (DOTANOC), and ^{68}Ga-DOTA-Tyr^{3}-Octreotate (DOTATATE) [7].

Until up to a couple of years ago the analogs of somatostatin were constructed aiming at their agonistic behavior, expecting that their internalization with the receptor activated by the radiolabeled ligand and its retention within the tumor cell are crucial for efficient imaging and therapy. Recently it has been shown that the antagonists recognize more binding sites at the tumor cell membrane and hence offer an improved diagnostic efficacy, especially when the density of sst receptors is low. The feasibility of using somatostatin receptor antagonists in clinical settings has been proven already [8]. This approach may in future improve diagnostic value of somatostatin receptor imaging techniques.

The developments in tracer design are followed by the improvements in imaging techniques. The new SPECT scanners offer resolution close to that of PET, which might open a new era for ^{99m}Tc and other SPECT radiotracers.

The aim of this review is to summarize the developments and briefly characterize the somatostatin analogs which are currently used for somatostatin receptor imaging in clinical routine or in early phase clinical trials.

Octreotide and its analogs

The development of somatostatin analogs reflected the increasing knowledge of the role of somatostatin. It has been shown that sst-expressing tumors can be treated with somatostatin or synthetic analogs to either reduce hypersecretion of hormones and/or inhibit tumor growth [9]. However, because somatostatin undergoes rapid *in vivo* enzymatic degradation, somatostatin analogs which are more resistant to *in vivo* degradation have been developed [10–12]. The molecule was modified in various ways, by introduction of D-amino acids and shortening of the molecule to the bioactive core sequence resulting in improved biological characteristics. The first synthesized somatostatin analogue was octreotide (Sandostatin, SMS 201-995), with the high affinity to sst2 and less affinity to sst5 and sst3. It has been used since 1983 for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NET) and hormone-secreting pituitary tumors [13]. Later the other eight amino acid-containing somatostatin analogs such as lanreotide (BIM23014) and vapreotide (RC-160) have been synthesized [14]. Newer developments aimed at somatostatin analogs with selective affinity to a wider somatostatin receptor subtypeprofile, such as pasireotide (SOM230) with affinity to somatostatin receptors subtypes 1, 2, 3 and 5 [15].

The first somatostatin analogue labeled with a radionuclide and used for the localization of NET by SRS was [^{123}I,Tyr^{3}]-octreotide. However, due to several drawbacks like time-consuming and difficult labeling procedure, high cost, intestinal accumulation of activity rapidly cleared via the liver and biliary system, which made image interpretation difficult and limited its clinical utility. In consequence, ^{123}I was replaced with ^{111}In, which was bound to octreotide by diethylenetriamine pentaacetic acid (DTPA) as a chelator [16]. Since then ^{111}In-DTPA-D-Phe^{1}-octreotide (^{111}In-pentetreotide) has been broadly used to visualize neuroendocrine tumors expressing somatostatin receptors [17].

Although SRS with ^{111}In-pentetreotide is very effective, the method is hampered by various factors, such as the necessity of a tumor to background ratio of at least 2: 1, relatively low spatial resolution particularly for small tumors, and the lack of precise quantification of receptor density and radionuclide biodistribution. The energy of ^{111}In is relatively high, which results in suboptimum image resolution and a relatively high patient exposure to ionizing radiation. Moreover, ^{111}In obtained from cyclotron is expensive and not easy to attain in several countries.

For these reasons researches on establishing new radiopharmaceuticals based on somatostatin analogs labeled with ^{99m}Tc for SPECT and with ^{68}Ga for PET were undertaken.

Modeling somatostatin analogs for labeling with radiometals

The development of radiolabeled peptides for successful receptor targeting requires consideration of several factors, such as the high uptake in the target and low in non-target tissues, the clearance from the body, the excretory pathway and the *in vivo* stability of the radiopeptide. The radiolabeled peptides which successfully went through all tests, including toxicological studies, and with well-established preparation method, may enter clinical studies in humans [18–20].

Particularly for the well-characterized somatostatin receptors, the design of a peptide and its synthetic pathway was possible in order to produce metabolically stabilized peptide analogs which preserved most of the biological activity of the original molecule and high affinity for the corresponding receptor. They could be labeled with various radionuclides for both diagnosis and therapy, while the choice of radiolabeling approach depended on the radionuclide properties and characteristics of the chelator. As a common feature it is required that the labeling protocols allow very high labeling yield, radiochemical purity and specific activity and the peptide retains the affinity for the receptors.

Peptides can be radioiodinated by electrophilic substitution and this reaction can take place at an amino acid residue of the peptide which contains aromatic rings, e.g. tyrosine or histidine. Such approach is known as a direct radiolabeling. In contrast, the radioactive metal ions such as ^{111}In, ^{99m}Tc, ^{68}Ga are generally more difficult to attach and require an indirect radiolabeling approach. The indirect methods link radio-metals to peptides using bifunctional chelators (BFCs) [21]. BFCs consists of two functional groups, which serve different purposes; one binds the chelator to the peptide and the second one chelates the metal ion [22]. These functional groups are responsible for stable binding between the peptide and radiometal and its resistance against radiolysis under physiological conditions. The BFC can be attached to the peptide via a spacer, which is also a pharmacokinetic modifier. In addition, the BFCs should not alter the biological properties and receptor affinity and specificity of the peptide [23, 24]. Metallic radionuclides present various chemistries, hence there is no universal BFC to chelate all radiometals. Several BFCs are used depending on the choice of radionuclide since the size, charge, and electron configuration of the radiometal will determine the coordination number required of a BFC [25] (Figure 1).

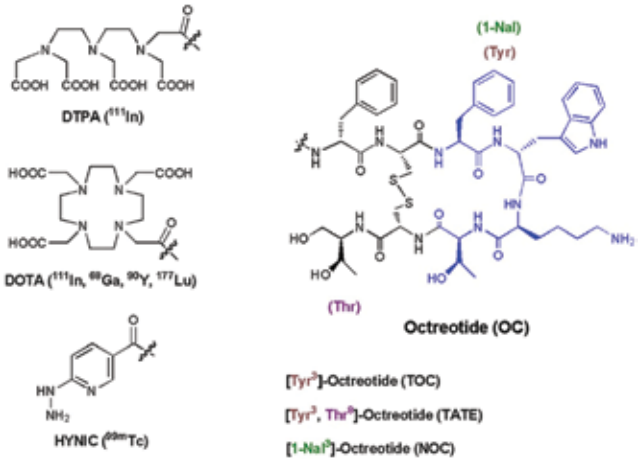

Figure 1. Octapeptides, chelators, and radiometals for imaging and targeted radionuclide therapy of neuroendocrine tumors in patients [1] (This research was originally published in JNM. Valentina Ambrosini et al. Radiopeptide Imaging and Therapy in Europe. J Nucl Med 2011; 52: 42S–55S © by the Society of Nuclear Medicine and Molecular Imaging, Inc.)

Chelators for ^{99m}Tc labeling of somatostatin analogs

The radionuclide widely used for radiolabeling is technetium (^{99m}Tc) which decays by gamma emission (energy 141 keV) with a physical half-life of 6.02 hours to technetium-99 which is regarded as quasi stable.

Several somatostatin analogs have emerged carrying a variety of chelators utilized for efficient ^{99m}Tc labeling of biomolecules including small peptides [25–28], among them propylene amine oxime [29], open chain or cyclic tetraamines [30, 31].

The HYNIC core with N-hydroxysuccinimidyl hydrazinonicotinamide (NHS-HYNIC, HYNIC) has become one of the most popular and effective BFCs used for ^{99m}Tc labeling of somatostatin analogs [32]. It has initially been developed for radiolabeling of polyclonal immunoglobulin [33], and was then recommended for preparation of hydrazino-modified proteins and synthesis of ^{99m}Tc-protein conjugates [34] and chemotactic peptides [35] and HYNIC as bifunctional chelator (BFC) was introduced for ^{99m}Tc labeling of octreotide and TOC (Tyr^3-octreotide) with high efficiency [36, 37].

Study of potential structures by LC-MS confirmed that HYNIC may function as a monodenate or a bidentate chelator [38, 39]. Therefore, ^{99m}Tc-labeling is performed in the presence of one or more coligands, which saturate the hexacoordinate coordination sphere of the Tc(V) core with donor groups such as amine, carboxylate or hydroxyl [39].

Initially tricine (N-[Tris(hydroxyl-methyl)-methyl]glycine) was used as co-ligand for ^{99m}Tc to complete the ^{99m}Tc-HYNIC core [40]. It was assumed that the ^{99m}Tc species is coordinated by two tricine molecules and the terminal N-atom of the hydrazine group of HYNIC in the resulting ^{99m}Tc-HYNIC-protein complex [41]. Detailed HPLC analysis indicated that the complex can reversibly adopt various forms, depending on temperature, reaction time and pH. Replacement of tricine by other co-ligands such as ethylenediamine-N,N'-diacetic acid (EDDA) resulted in more stable complexes and lower number of isomers [42, 43]. Changing the coligand can significantly affect the lipophilicity of the complex and allows for modification of its biodistribution. Several studies have been published on the ^{99m}Tc labeling of octreotide via HYNIC in combination with different co-ligands [44, 45]. ^{99m}Tc-HYNIC-TOC after labeling with ^{99m}Tc using tricine and EDDA as co-ligands retained its receptor affinity as determined *in vitro* in rat brain cortex membranes and showed favorable biodistribution *in vivo* in tumor bearing animals [37, 38]. In animal models, the tracer accumulation ratio in the tumor compared with kidneys and liver was higher than in case of ^{111}In-DTPA-octreotide [46].

The first ^{99m}Tc-HYNIC-TOC (with tricine as co-ligand) scintigraphy in comparison with ^{111}In-octreoscan was published by Bangard et al. in 2000 [5]. Favorable influence of EDDA on biodistribution of the ^{99m}Tc-HYNIC-TOC in clinical trials was presented. When using this tracer, higher target/non-target ratios were obtained and more lesions were detected than with the use of ^{111}In-octreotide [47].

Promising pre-clinical results were obtained also with the conjugates obtained by coupling an open-chain tetraamine chelator (N_4 chelator) of the ^{99m}Tc-Demotate series (e.g. [^{99m}Tc-N_4^0,Tyr^3] octreotate, ^{99m}Tc-Demotate 1) [48, 49] or with [^{99m}Tc-N_4^{0-1},Asp^0,Tyr^3] octreotate, ^{99m}Tc-Demotate 2, during a pre-clinical comparison with [^{111}In]DOTA-TATE in the detection of sst_2-positive tumors [50]. ^{99m}Tc-labeled octreotide analogs have been developed and clinically evaluated for SPECT imaging, such as HYNIC-TOC [51], HYNIC-TATE [52–54] and ^{99m}Tc-Demotate 1 [55, 56].

The verification of the diagnostic efficacy of ^{99m}Tc-EDDA/HYNIC-TOC and ^{99m}Tc-EDDA/HYNIC-TATE was performed by direct comparison of SRS using both tracers in the uniform group of 12 patients with confirmed GEP-NET [57]. Both ^{99m}Tc-EDDA/HYNIC-TOC and ^{99m}Tc-EDDA/HYNIC-TATE were found to be useful radiopharmaceuticals for SRS-SPECT, in neuroendocrine tumors, especially those expressing sst2. Similar number of metastatic lesions was detected using either agent, 85% correlation was found when analyzing each of metastases individually. No significant differences were observed in the uptake of these agents in the tumors and in the kidneys. The uptake of ^{99m}Tc-HYNIC-TOC in the liver was higher than in the case of ^{99m}Tc-HYNIC-TATE, but the ratio of uptake in the lesion to background was comparable. Somewhat higher lipophilicity of ^{99m}Tc-HYNIC-TOC might have an impact on the detection of metastases located in lymph nodes and in the liver; however, as seen in Figure 2, the excellent images of tumors located in these difficult locations can be obtained with ^{99m}Tc-EDDA/HYNIC-TOC.

In Poland, ^{99m}Tc-EDDA/HYNIC-TOC(^{99m}Tc-Tektrotyd) is the most frequently used tracer in scintigraphic visualization of neuroendocrine tumors. A radiopharmaceutical kit for technetium-99m labeling is manufactured at National Centre for Nuclear Research (NCBJ RC POLATOM), Poland. ^{99m}Tc-Tektrotyd was granted marketing authorization in Poland on April 29, 2004.

Gallium-68 labeled somatostatin analogs for PET imaging

The next generation of somatostatin analogs are tracers for PET or PET/CT labeled with ^{68}Ga, because of its suitable radiophysical properties: its positron yield is high, with 89% of all disintegrations, its half-life of 68 min matches the pharmacokinetics of

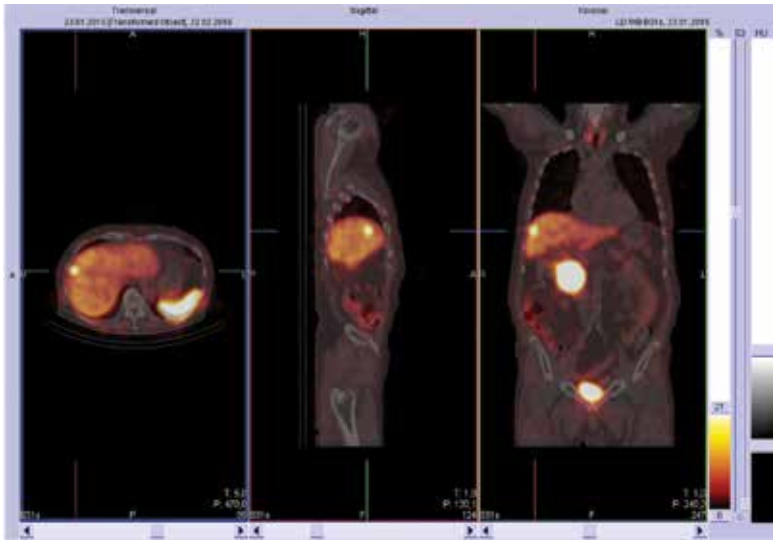

Figure 2. Somatostatin receptor positive lesion at the head of the pancreas, adjacent to the duodenum. Somatostatin receptor positive metastasis in the liver. SRS SPECT/CT with ^{99m}Tc-EDDA/HYNIC-TOC at 4 h p.i. Image kindly provided by Prof. dr. Ingo Brink, Potsdam, Germany

many peptides and other small molecules owing to a fast blood clearance, quick diffusion and target localization [58]. The commercially produced radionuclide generators ^{68}Ge/^{68}Ga are available for use in the clinics. The long half-life of the mother radionuclide ^{68}Ge (270.8 days) allows the exploitation of the generator for over 6 months and due to the rapid ingrowth of the daughter ^{68}Ga, the generators can be eluted every 3 hours. The most widely used BFC for ^{68}Ga is DOTA (1,4,7,10-tetraazacyclododecane, 1,4,7,10-tetraacetic acid). Currently three major, clinically useful, ^{68}Ga labeled tracers for PET/CT imaging are available: ^{68}Ga-DOTA--Phe^{1}-Tyr^{3}-Octreotide (DOTA-TOC), ^{68}Ga-DOTA-Nal^{3}-Octreotide (DOTA-NOC), and ^{68}Ga-DOTA-Tyr^{3}-Octreotate (DOTA-TATE) [7]. These three tracers present some differences in pharmacokinetics but more importantly, their affinity to sstr subtypes varies. Whereas ^{68}Ga-DOTA-TATE is sst2-selective, with the highest binding affinity of any sst2 receptor-binding peptide, ^{68}Ga-DOTA-TOC binds to sst2 with high affinity and to sst5 with reasonable affinity and ^{68}Ga-DOTA-NOC has high affinity to sst2, sst3 and sst5 [59, 60].

Improving the sst receptor affinity profile and the *in vitro* and *in vivo* stability of somatostatin analogs

Radiolabeled pansomatostatin-like analogs are expected to enhance the diagnostic sensitivity and to expand the clinical indications of currently applied sst2 receptor specific radioligands. The search for other somatostatin-based peptides having affinity for a broader range of somatostatin receptor subtypes and hence might target a broader spectrum of tumors but also a higher net tumor uptake resulted in the development of several new compounds showing high affinity to sst2, sst3 and sst5 [61]. The modification at position 3 of octapeptide, replacing tyrosine by the unnatural amino acid 1-naphtyl-alanine resulted in ^{111}In-DOTA-NOC (1-Nal^{3}-octreotide) [60], which than gained clinical interest for PET/CT of NETS when labeled with ^{68}Ga [62]. However, the application of similarly developed ^{111}In-DOTANOC-ATE (1-Nal^{3}-Thr^{8}-octreotide), and ^{111}In-DOTABOC-ATE (Bz-Thi^{3}-Thr^{8}-octreotide) remained limited [63]. Fani et al. (2010) reported the development of bicyclic somatostatin analogs with affinity to sst2, sst3 and sst5, such as AM3 (DOTA-)Tyr-cyclo(DAB-Arg-cyclo(Cys-Phe--D-Trp-Lys-Thr-Cys)) which showed fast background clearance and high tumor to non-tumor ratios which might be ideal for imaging with short lived radionuclides such as ^{68}Ga [64]. Pan-somatostatin radiopeptides with high affinity binding for all five receptor subtypes have also been developed. The first such peptide, KE108 (Tyr-cyclo(DAB--Arg-Phe-Phe-D-Trp-Lys-Thr-Phe)), was modified by Tyr as a prosthetic group for iodination NH_2-terminally [65], it was then coupled with DOTA, resulting in the analogue ^{111}In-KE88 [66]. This analogue was able to bind with high affinity to all five receptor subtypes (sst1-sst5) but was efficiently internalized only in sst3 expressing cells. It did not appear to offer multi-subtype imaging properties, since the *in vitro* internalization and *in vivo* uptake in sst2 tumors was very low, compared with sst3 tumors.

In the last years, not only octapeptides but also a native somatostatin-14 (SS14) was considered for ligand development. The native SS14 and its DTrp^{8} analogue were functionalized with the universal chelator DOTA and radiolabeled with ^{111}In. Both compounds showed a pansomatostatin affinity profile with the respective hsst1-5 IC50 values in the lower nanomolar range. In addition, the DTrp^{8} analogue behaved as an agonist for sst2 and sst3 since it stimulated receptor internalization. This analogue also localized in experimental tumors which selectively expressed sst2 (both of rat and human origin), hsst3 and hsst5 [67]. Furthermore, Maina et al. (2014) [68] evaluated the somatostatin mimic [DOTA]LTT-SS28 {[(DOTA)Ser^{1},Leu^{8},D-Trp^{22},Tyr^{25}]SS28} and its ^{111}In radioligand. [DOTA]LTT-SS28 exhibited a pansomatostatin-like profile binding with high affinity to all five hsst1-hsst5 subtypes (IC50 values in the lower nanomolar range). [DOTA]LTT-SS28 behaved as an agonist at hsst2, hsst3, and hsst5, efficiently stimulating internalization of the three receptorsubtypes. Significant and specific uptake was observed in HEK293-hsst2-, HEK293-hsst3-, and HEK293-hsst5-expressing tumors (4.43 ± 1.5, 4.88 ± 1.1, and < 3% ID/g, respectively, with

values of < 0.5% ID/g during receptor blockade), indicating that the somatostatin mimic [^{111}In-DOTA]LTT-SS28 shows promise for multi-sst1-sst5 targeted tumor imaging. These studies revealed the feasibility of structural modifications to enhance metabolic stability in order to achieve higher tumor uptake, such as amino acid replacements and changes of ring size.

The significance of *in vivo* stability of radiopeptide is a key element of successful tumor targeting for cancer visualization and therapy in patients. It has been revealed that the action of a single peptidase (i.e. neutral endopeptidase, NEP) is responsible for the rapid *in vivo* breakdown of intravenously administered radiopeptides from at least the somatostatin, bombesin, and gastrin peptide families. Most importantly, this phenomenon can be overcome by enhancing their supply and accumulation at tumor sites through the mere co-injection of a protease inhibitor, such as phosphoramidon [69]. This approach may result in increased diagnostic sensitivity and therapeutic efficacy being the potential strategy for translation into clinical practice [70, 71].

Antagonists vs agonists

All compounds described so far have agonistic properties, which were considered mandatory because of the ability of these compounds to induce internalization of the peptide-receptor complex. Presented studies have been based on the development of radiolabeled somatostatin agonists, assuming that the internalization of the receptor after radioligand binding is critical for efficient retention of the tracer in tumor cells, allowing for efficient imaging and therapy. The molecular-pharmacologic investigations showed that efficient internalization is usually provided by agonists [72]. Recent developments have indicated that receptor antagonists may be as good as or even better than agonists for such purposes. Ginj et al. (2006) showed that high-affinity somatostatin receptor antagonists that poorly internalize into tumor cells can, in terms of in vivo uptake in animal tumors, perform equally good or better than corresponding agonists, which highly internalized into tumor cells. They provided potentially even better tumor visualization than agonists. The same tendency was seen for both sst2 and sst3 selective analogs, suggesting that this observation may be valid for more than just one particular G-protein-coupled receptor. The study demonstrated that the sst antagonists are preferable for *in vivo* tumor targeting [73]. The first clinical evaluation of SRS with an antagonist confirmed the pre-clinical data, as it showed higher tumor uptake of the antagonist ^{111}In-DOTA-sst2-ANT (p-NO_2-Phe--cyclo(D-Cys-Tyr-D-Trp-Lys-Thr-Cys)D-Tyr-NH_2) compared with the agonist ^{111}In-DTPA^0-octreotide and improved tumor-to-background ratios, in particular tumor-to-kidney [74].

One of the first reports describing ^{68}Ga- and ^{64}Cu-labeled sst2 antagonists indicated the high potential of these radiopeptides in PET/CT [75]. Translational aspects related to peptide receptor radionuclide therapy (PRRT) and imaging with antagonist were also addressed. In the pre-clinical evaluation the increased tumor uptake, prolonged residence time, favorable differential washout and optimized peptide mass improved the therapeutic index of ^{177}Lu-OPS201, the sst antagonist compared with ^{177}Lu-DOTATATE. The authors suggested that due to the larger density of binding sites at tumor cell membrane the interruption of sst-analogs before PRRT may not be needed when using radiolabeled antagonists [76]. The new family of antagonist tracers may even present a better imaging and therapy option. Indeed, the results of first clinical trials revealed the superior detection of liver metastasis with the use of sst antagonist ^{68}Ga-OPS202 compared with the agonist ^{68}Ga-DOTATOC [77] and in diagnostics and therapy of NETs in a THERANOSTIC pair combination with the ^{177}Lu labeled counterpart [78]. Further clinical trials are planned.

A novel instrumentation

The superiority of PET/CT over SPECT/CT results from the differences in spatial resolution. Exciting developments in the field of SPECT/CT have taken place over the last years. Namely the utilization of semiconductor CZT detectors have advanced the SPECT technology, mainly in cardiac imaging [79]. As a result, lower activities can be applied, the patient's camera time is reduced and the spatial resolution is improved.

Moreover, technological advances and improved algorithms nowadays allow for quantitative data analysis of SPECT/CT images and enable the calculation of standard uptake values for SPECT tracers [80, 81]. Recently GE Healthcare introduced its Discovery™ NM/CT 670 CZT, the first commercially-available general purpose SPECT/CT system powered by CZT technology. This novel whole body system combines CZT detectors and quantitative SPECT/CT with a spatial resolution as low as in the 3 mm range. Such devices hold the potential to pave the way for new applications of (established) SPECT tracers, especially in cases where SPECT data is used for therapy planning [82]. The use of ^{99m}Tc-EDDA/HYNIC-TOC in therapy planning of patients with neuroendocrine tumors could be one such application. The first ^{99m}Tc-sst antagonists were tested pre-clinically and are on the way to the clinic.

Summary

The studies related to the role of antagonist represent the recent most favorable innovation in molecular imaging and PRRT of NETs. Taking into account the progress in design of ligands and in instrumentation and the availability of ^{99m}Tc and other radionuclides, there is still space for SPECT and PET technique and for further developments in imaging strategies.

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