Radiolabeled Peptides in Diagnosis and Tumor Imaging: Clinical Overview

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The authors briefly review radiopeptides currently approved for use in the United States. They present a short review of the peptide somatostatin's actions and also note the five somatostatin receptors (SSTRs) to which the peptide and its synthetic analogs octreotide, lanreotide, and vapreotide bind. The many conditions besides neuroendocrine tumors having SSTRs are listed. Labeled octreotide and the other two analogues have a strong affinity for SSTR2 and SSTR5, which thereby produce positive imaging. The various neuroendocrine tumors best imaged by somatostatin receptor scintigraphy (SRS) are discussed, and the exceptions (insulinoma and medullary thyroid carcinoma) are noted to be seen better with labeled VIP and ^{99m}Tc-dimethylsuccinic acid (DMSA), respectively. SRS and VIP receptor scintigraphy are also noted to image many non-neuroendocrine tumors, which often have appropriate receptors. Several of the currently emerging and very effective new imaging techniques are described. These include ^{99m}Tc-DMSA for medullary thyroid carcinoma, ^{18}F dihydroxyphenylalanine positron emission tomography, and C_{11}L 5-hydroxytryptophan positron emission tomography scanning for all neuroendocrine tumor, but especially carcinoid tumor, metastases. The special role of SRS in identifying gastric carcinoid tumors in hypergastrinemic patients is reviewed. Various pitfalls in interpreting SRS are presented and receptor-enhancing techniques described. Besides use of SRS (mainly Octreoscan, Mallinckrodt Medical, St Louis, MO) only for detecting and localizing primary tumors and metastases for staging, there are many additional special uses for clinical management of SRS-positive tumors. These include the intraoperative use of the handheld γ-detecting probe. A brief enumeration is given of the most promising of other non-SST G-protein–coupled receptors and ligands currently under development. Finally, we have posed a number of questions for which answers are needed in the immediate future to facilitate better imaging. Extrapolations of current knowledge and experience with radiolabeled peptide pharmaceutical imaging are converted to reasonable speculations of anticipated future developments in this field.

THE PAST FEW YEARS have witnessed the development of a virtual revolution in the art and technology of medical imaging. Nuclide-labeled peptides increasingly participate in this, but, of those compounds synthesized and studied, the only ones currently approved and available for clinical use in the United States are ^{111}In-diethylenetriamine pentaacetic acid–pentreotide (Octreoscan; Mallinckrodt Medical, St Louis, MO), ^{99m}Tc detreotide (P829; Neotect; Diatide, Inc, Londonberry, NH), and ^{99m}Tc-P280 (26 amino acids with high affinity for binding to glycoprotein IIb and IIIa fibrinogen receptors) (AcuTect; Diatide, Inc). Octreoscan is increasingly widely used. Neotect use has been much less and has been limited mainly to detecting pulmonary neoplasms not detected with Octreoscan. AcuTect, approved for imaging acute deep vein thrombosis, has had only limited use, and its clinical value has yet to be fully determined. A multitude of other peptide receptor–binding radionuclide compounds have been synthesized within the past few years and are currently in various stages of laboratory, in vivo, and clinical studies; they have not yet filtered down to general clinical use.[1] Therefore, as clinicians, our current use, experience, predominant interest, and comments are mainly concerned with the somatostatin analogues. These have been in use the longest and have led to accumulation of a vast body of data. Of course, the other newly appearing and rapidly expanding array of radionuclide peptide pharmaceuticals under development deserve close attention. Details of the more important and promising of these agents are presented in other articles in this issue.

Native somatostatin (SST) was discovered, identified, and named just over 3 decades ago.[2] Its physiologic and pharmaceutical effectiveness is very brief, approximately 2 minutes after intravenous injection. This peptide and its subsequently synthesized longer-acting analogues (eg, octreotide, and lanreotide) have many predominantly inhibitory hormonal functions throughout the gastrointestinal tract and nervous system, as well as direct and indirect antineoplastic effects. These include inhibition of various trophic growth factors and hormones, angiogenesis, and stimulation of apoptosis and the reticuloendothelial system. Many of the actions of these and other peptides depend on an affinity for specific cell membrane surface receptors that, once bound to these ligands, transfer them to within the cell (internalization) and eventually to the perinuclear and nuclear location, where they persist for relatively long periods. Hence, once firmly labeled, the radioligand is thereby useful for imaging and therapy.

There are five known human somatostatin receptors (SSTRs). SST has an affinity for all five receptors, but the three main SST analogues—octreotide, lanreotide, and vapreotide—bind mainly with SSTR2 and SSTR5.[3-5] Past experience has been with octreotide, unlabeled (cold) and labeled, in imaging and in treatment of neuroendocrine tumors (NETs). The density of SSTRs has determined the efficacy of both radioligand imaging and therapy. Recently, special molecular studies, such as reverse transcriptase–polymerase chain reaction, have demonstrated considerable heterogeneity of receptor endowment in different tumors and within different areas of individual tumors.[2] Even though almost all NETs are well endowed with SSTRs, such studies suggest that SSTRs are also expressed to a varying degree in significant percentages by many common tumors. These have included small-cell lung cancer, carcinoma of the breast, prostate, colon, kidney, ovary, liver, and thyroid, Hodgkin's and non-Hodgkin's lymphoma, and various nervous system tumors, in addition to pituitary NETS. In particular, pituitary NETS include tumors secreting growth hormone and

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thyroid-stimulating hormone and a minority of prolactin-producing and nonfunctioning pituitary tumors.[6,7]

SSTRs are also present on activated lymphocytes, in inflammation and granulation tissue (including that associated with recent surgery), sarcoidosis, tuberculosis, rheumatoid arthritis, Crohn's disease, celiac disease, Hashimoto's thyroiditis, Grave's disease, Weggener's granulomatosis, aspergilosis, systemic lupus erythematosis, Henoch-Schönlein purpura, and some benign cavernous hemangiomas, as well as a number of other conditions.[1,8-10]

Cold octreotide and other SST analogues have been widely used and have been approved for more than a decade for controlling NET-associated endocrine syndromes. Furthermore, although unapproved, effective use of these congeners has also been used by many clinicians in a number of other conditions. These have included control of bleeding upper gastrointestinal tract varices, postgastrectomy dumping syndrome, chemotherapy-induced diarrhea, enterocutaneous and pancreatic and billiary fistula, human immunodeficiency virus–associated secretory diarrhea, diarrhea of graft vs host disease, and a number of other less common nonneoplastic diseases. More recently, direct and indirect antitumor effects of cold octreotide and other SST analogues have been noted and partially elucidated.[11]

After more than a decade of experience with radiolabeled SST analogues localizing primary and metastatic NETs expressing SSTRs, somatostatin receptor scintigraphy (SRS) has become the main and preferred imaging technique for NETs, and recently, clinical trials of targeted radiotherapy with similar radionuclide-labeled peptide ligands have been under way. This is discussed in other sections of this issue.[12]

The biologic and pharmacologic side effects of cold SST analogues are usually mild, and the drugs are very well tolerated. The analogue dose to which the isotope label is conjugated for SRS is so small as to rarely exert any biologic effect, and the label itself has no noticeable effect other than its intended imaging of the receptor-bearing tissue for which it has an affinity. Efficacy vs adverse effects of therapeutic radioligands seems promising.

The SST analogue and its ^{111}In label used in Octreoscan are bound preferentially to SSTR2 and SSTR5 and, to a lesser extent, SSTR3 and SSTR1. ^{111}In-emitted γ rays provide the imaging. Of course, a lack of affinity for SSTR1, 3, and 4 results in the failure of Octreoscan to image those tumors in which one or a combination of these receptor types predominate. NeoTect binds with affinity to SSTR2, 5, and 3 and hence sometimes images tumors (particularly in the lung) not detected by Octreoscan.[13]

NETs studied in relation to SRS have been mainly carcinoid, gastrinoma, Vasoactive intestinal peptide secreting tumors (VIPoma), glucagonoma, pheochromocytoma with related paraganglianomas, insulinoma, pituitary NETs, Merckel cell cancer, and other rarer NETs. SRS is the preferred first choice for imaging and localizing all gastroenteropancreatic NETs except insulinoma, in which fewer than 50% will image on OctreoScan because of the preponderance of SSTR3 and VIPR1 and 2 in these tumors.[9,11,14] It has been reported that the majority of insulinomas will be detected by I^{125}-VIP or, more recently, by ^{99m}Tc-labeled VIP.[14,15] VIP receptors are widely distributed, particularly in the gastrointestinal tract, and recent experimental experience suggests the promise of usefulness for labeled VIP in detecting some cancers in the gastrointestinal tract, thyroid, breast, uterus, and bone.[4,14,15]

Octreoscan has successfully imaged and localized approximately 85% of all carcinoids. SRS is well established as the best initial test for localizing and indicating the extent of metastases of gastrinoma, and, particularly when it is coupled with endoscopic ultrasound (EUS), will image more than 90% of the lesions in the pancreas.[9] False-positive localization can be imaged because of density of SSTRs in normal thyroid, breast, granulomatous lung tissue, accessory spleen, operative sites, parapelvic renal cysts, and various other conditions that express receptors as indicated previously, and also as the result of deviation from proper procedural techniques.[8] It must be emphasized that interpretation of the SRS finding must be evaluated in relation to the clinical picture. Single photon emission computed tomography imaging, in addition to the planar images, is essential.[16] Octreotide has replaced secretin and calcium infusion tests in diagnosis of gastrinoma, and it also replaces arginine infusion for diagnosis of glucagonoma. Pentagastrin and epinephrine-provocative tests have also been largely replaced by Octreoscan in diagnosing carcinoid tumor causing carcinoid syndrome. The nonspecific blood serum neuroendocrine tumor marker, chromogranin A, however, persists as a most useful laboratory aide for corroborating the diagnosis of NET and for following tumor progress. Its split fragment, pancreastatin, awaits verification of its usefulness as a NET progression marker.

In regard to insulinoma, because Octreoscan is suboptimal for diagnosing and localizing and because labeled VIP is not yet generally available, conventional computed tomography and magnetic resonance imaging scanning and EUS are more likely to be successful. Occasionally, selective angiography with hepatic venous sampling is still necessary to supplement these modalities in diagnosing and localizing a rare insulinoma.

SRS is helpful, although suboptimal, in imaging pheochromocytoma-paraganglianoma, in which ^{123}I-metaiodobenzylguanidine (MIBG) will more often successfully image a primary tumor and metastases.[17] Imaging of medullary thyroid carcinoma (MTC), although sometimes suboptimal with SRS, is more successful with labeled MIBG. ^{99m}Tc-dimethylsuccinic acid (DMSA) has been shown to have an even greater success in imaging MTC, with a sensitivity of 69%. The combination of SRS and ^{99m}Tc-DSMA has a sensitivity of 84%.[4] Metastatic MTC may have a higher percentage of SSTR2s. A comparison of the overall effectiveness of SRS sensitivity with that of conventional imaging methods for localizing primary and metastatic NETs demonstrated that SRS is superior by 50%.[4]

Among its many applications SRS has been demonstrated to be highly specific and fairly sensitive in identifying gastric carcinoid tumors in patients with hypergastrinemic states. This is particularly important in the presence of Zollinger-Ellison syndrome (ZES) in which localization of increased isotope uptake in the epigastrium could be caused by concurrent gastric carcinoid tumor.[18] Furthermore, it is predicted that when combined with esophagogastroduodenoscopy and biopsy, SRS will help earlier identification of patients with pernicious anemia who are developing gastric carcinoid tumors.

Another radiopharmaceutical technique has been developed for imaging NETs which does not require affinity for specific receptors. This technique involves the labeling of a metabolic precursor of a specialized chemical product of a tumor. Thereby the isotope label will become concentrated in the endocrine tumor cell and hence facilitate imaging. This mechanism, when applied to carci-

noid tumors, consists of positron emission tomography (PET) scanning with use of ^{11}C-L-5-hydroxytryptophan (5HTP) or ^{18}F-dihydroxyphenylalanine (DOPA). 5HTP is the precursor for serotonin and hence is concentrated and metabolized to the active amine in the tumor cell. Because NETs exemplify the amine precursor uptake and decarboxylation concept, they all have the ability to take up amine precursors, and therefore labeled DOPA will be taken up by almost all NETs, especially carcinoids. Each of these experimental PET scanning techniques has been shown to be specific and often positive, even when SRS has been negative. Favorable preliminary reports of patient studies with these techniques suggest them as alternatives for imaging Octreoscan-negative NETs.[19,20]

CAVEATS

It must be borne in mind that there is poor correlation of the intensity of scintigraphy with actual tumor size because the intensity of imaging is more related to the density of receptors present in the tumor and often also in the peritumoral blood vessels. In addition, multiple tumor metastases will often have significant isotope uptake in only some of the growths. Furthermore, loss of receptors may occur after dedifferentiation of tumor cells or after chemotherapy. Hence, negative imaging could falsely suggest tumor regression.[8] Additionally it must be borne in mind that the intensity of imaging is unrelated to endocrine function of the tumor, so that the severity of the clinical syndrome that may be associated with any given functioning neuroendocrine tumor, such as carcinoid syndrome, ZES, glucagonoma, VIPoma, or pheochromocytoma-associated syndromes, has no bearing on the intensity of SRS imaging. A co-registered PET scan showing active uptake in areas of cold Octreoscan may help establish a tumor status.

Additional problems in interpretation, as indicated previously, are posed by the uptake of ligand by a multitude of inflammatory, granulomatous, and nonneoplastic conditions, in addition to normal organs. Physiologic uptake of ligand by normal organs may result in significant background radiation that can obscure imaging of small, or even large, tumors in those organs.[8]

ENHANCING LIGAND UPTAKE

Several manipulations have been used to enhance ligand uptake. In vitro and in vivo pretreatment studies with cold octreotide in patients with small-cell lung carcinoma and carcinoid tumors increased the tumor uptake of radiolabeled ligand but decreased uptake in liver, spleen, and kidney.[21-23] Although 50% to 100% of small-cell lung carcinoma tumors express SSTRs, the receptors expressed may not be predominantly those for which SST analogues have a strong affinity. And it must again be emphasized that most NETs express more than 1 SSTR.

Another technique that sometimes enhances ligand uptake by upregulating receptors seems to be prolonged treatment with SST analogues. This certainly has not been clearly established, although it has been demonstrated in a few instances, both in vivo and in vitro.

Another newly developed strategy to increase expression of SSTR2 in cancer cells has been the use of gene transfer techniques to upregulate the receptor. This certainly offers the promise of enhanced radioligand imaging and therapy and is a potentially useful addition to the future peptide pharmaceutical armamentarium.[24]

ADDITIONAL USES AND REFINEMENT IN SRS

The usefulness of SRS has extended beyond just detecting and localizing primary tumors and includes

1. Imaging metastases for staging.[25]
2. Monitoring progression or regression of disease in response to medical treatment or completeness of surgery or ablation.
3. Selection of best candidates for liver transplantation.

On the basis of demonstration of appropriate receptors, SRS also shows a number of predictive uses.

1. Anticipated response to treatment with cold STS analogues.
2. Suitability of a given tumor for radioligand therapy.
3. Need for aggressive surgery, chemotherapy, or both (as in the instance of a progressing tumor with sparse endowment of receptors).

It is reasonable to anticipate that these uses will be extended to include a number of more common non-NET tumors. Such a use might be the introduction of the handheld γ-detecting probe for intraoperative localization of occult NETs, which has been an additional use and refinement in SRS.[26]

The usefulness of this technique has led to its further development and growing widespread application.[27] This has facilitated the intraoperative detection of small or even microscopic occult or mesenteric primary tumors as well as metastases, and it has also been used in determining the completeness of resection at the time of surgery. This radioguided surgical technique has been extended to use ^{99m}Tc-DMSA in detecting tiny metastases too small for palpation by the surgeon's finger. Similarly, with ^{123}I-MIBG, this technique has detected small nonpalpable neuroblastomas.[28] Demonstration of the presence of SSTRs in most human breast cancer has led to a successful pilot trial of the handheld γ detector using ^{125}I-lanreotide to determine the completeness of lumpectomy and predicting the presence of tumor in axillary lymph nodes thought to be negative on routine histology.[29]

OTHER POTENTIALLY USEFUL ISOTOPES, LIGANDS, AND RECEPTORS

All 5 of the SSTRs are G-protein–coupled receptors. However, there are many other G-protein–coupled receptors of potential use for imaging and treatment.[30,31] For imaging tumors a partial list of such receptors already used includes those binding a large variety of peptide hormones, such as the mammalian bombesin peptide (GRP), substance P, cholecystokinin A and B/gastrin, α-MSH and neurotensin, VIP, calcitonin, and, finally, for imaging infection and inflammation, vitronectin and interleukin 2 and 8.[1,11,32] Further discussion of many of these peptides and their receptors is presented in later articles in this issue.

In addition to those radioisotopes already in use and mentioned previously, a number of other potentially useful diagnostic and therapeutic labels are also currently being studied: ^{188}Re, ^{161}Tb, ^{64}Cu, ^{177}Lu, and ^{67}Ga.

QUESTIONS THAT NEED TO BE ANSWERED FOR FURTHER PROGRESS IN IMAGING

1. In tumors and in nonneoplastic tissue from which they are expressed, what is the function of each type of SSTR?

2. What is the mechanism of SSTR upregulation and downregulation in response to SST analogue treatment and to other influences: continuous or intermittent?
3. What are the possible enhancements in efficacy of combinations of labeled STS analogues with other labeled peptide ligands?
4. What benefits might result from the combination of SRS with other imaging techniques?
5. What is the ability of gene therapy to convert nonimaging tumors to positive imaging?

NEEDS AND PROMISES FOR THE IMMEDIATE FUTURE

The door of opportunity for the diagnostic and therapeutic use of labeled peptides has been opened partway, enough to provide more than a glimpse of the potential for these radiopharmaceuticals. It is reasonable to anticipate the development of radioligands that will bind to each one of the SSTRs, as well as those that will bind to other peptide receptors. This will result in a better and broader spectrum of imaging for both tumors and nonneoplastic diseases and will also pave the way for more effective and wider application of various radiopeptide therapeutic modalities. Gene therapy for upregulating receptors will be further developed and enhance the effective application of radioisotope-labeled peptides. Combinations of these pharmaceuticals with cytotoxic drugs will also find useful application.

CONCLUSIONS

SRS and the newer labeled peptide receptor–binding ligands significantly augment our diagnostic ability. However, at present no single available scintigraphic technique can image all primary and metastatic NET sites. Currently most complete results are achieved by combining SRS with common imaging techniques, including ^{18}F-fluorodeoxyglucose PET scanning. VIP scintigraphy, ^{18}F DOPA, and ^{11}C-L-5HTP PET scanning, when they become available, will add considerably to the armamentarium for diagnosing NETs. Additional benefits will come from use of some of the other labeled peptides still in development.

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