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REVIEW: Peptide-based Radiopharmaceuticals at a Glance

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ABSTRACT

Because of peptide receptors overexpression in many of the human tumors, the peptide receptors would be an attractive target for diagnostic imaging and radiotherapy. Accordingly, peptide-based radiopharmaceuticals were designed to bind to these receptors and be able to pursue their goals. Wide range of bifunctional chelating agents (BFCA) can be used for the convenient radiolabeling of bioactive peptides with different radionuclides. These advantages have led to producing a wide variety of peptide radiopharmaceuticals. A number of these peptides, such as bombesin, somatostatin, neurotensin, cholecystokinin/gastrin and vasoactive intestinal peptide have been able to have clinical applications in nuclear oncology. In this article we have tried to have an overview of peptide-based radiopharmaceuticals.

Introduction

The major advantages of peptides over antibodies are that they are not immunogenic, show rapid diffusion and target localization, and can be modified for metabolic and pharmacokinetic stability. One of the advantages of these compounds over small molecular compounds is that they are more tolerant of modifications required for proper labeling and strategies for optimizing pharmacokinetic (1, 2).

Tumor cells have receptors on their surface that are specific to the type of cancers and are selective for specific peptides. This peptide–receptor interaction can deliver radioactivity to the target tissue. Different receptors are over-expressed in certain types of tumors, and radiolabeled peptides attached to these receptors can be used to visualize tumor lesions (3-5). Several radiolabeled peptides are currently under investigation to determine their clinical potential as imaging and therapeutic agents for various cancers. Many of these peptides already have shown potential for clinical application primarily for imaging of thrombus, tumor, and infection/ inflammation (6, 7). The main emphasis in this article is on a brief overview of the development of peptide-based radiopharmaceuticals.

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Characteristics of peptides

Peptides have a number of distinct advantages over proteins and antibodies. These include: low toxicity and immune-genicity, easy preparation and radiolabeling, toleration of harsh conditions of chemical modification or radiolabeling, ability to attach BFCA at the C- or N terminus of the peptides, modifying rate and route of excretion, better tumor to background ratio, rapid clearance from blood and non-target tissues, and high affinity and penetration into the tumor tissue.

An important factor in designing of new peptide radiopharmaceuticals is the consideration of in vivo stability. Endogenous peptidases and proteases degrade Peptides in plasma rapidly, which is usually due to have a short biological half-life. Some methods that commonly used to prolong the biological half-life of peptides are: introduction of appropriate D-amino acids, use of unusual amino acids or side-chains, terminal-capping process, and cyclization (8-10).

The structure, solubility and function of peptides are characteristic of amino acid composition and their sequence. The route and rate of peptides excretion can be modified by introducing of specific hydrogen amino acids or specific lipophilic amino acids into the peptide chain without changing the binding properties. Lipophilic peptides are usually cleared from the body through the biliary liver, and hydrophilic peptides mainly excreted via the kidneys. Cyclization of peptides can increased receptor affinity and biological activity by restricting of conformational rotation (11-13). To prevent radionuclide from interfering with the binding region, a spacer function is incorporated between the chelating moiety and the binding site. Therefore, various techniques are available to modify the native peptides into clinically useful agents.

Radiolabeling of peptides

An ideal radiolabeling method is one in which the receptor binding properties and biological activity of the peptide remains constant and the radiolabeled peptide remains active during imaging (14). The methods improved for efficient and simple radiolabeling of peptides with different radionuclides are based on methods used for radiolabeling antibodies and proteins. However, the effect of radiolabeling on biological behavior is usually more profound in small peptides than antibodies and proteins (15). Site-specific radiolabeling is suitable for small peptides to prevent loss of binding affinity and biological activity. Methods have been developed, for radiolabeling peptides with ^{18}F, ^{123}I, ^{111}In, $^{66/67/68}Ga$, ^{64}Cu, and ^{99m}Tc (16, 17). Despite their good imaging characteristics, these radionuclides also have disadvantages that have been briefly presented in ***Table 1***.

Table 1. Some advantage and disadvantage of useful radionuclides.

Radionuclide	Advantages	Limitation
^{99m}Tc	Easy availability and low cost Reasonable half-life of 6h 140 KeV γ-emission Absence of α and β radiations Excellent imaging characteristics	Not suitable for delayed imaging studies
^{123}I	159 KeV γ-emission 13h half-life Good imaging characteristics	High cost Limited availability
^{111}In	171 and 245 KeV γ-emission 2.8 days half-life Useful for acquiring delayed images	High cost Limited availability Suboptimal nuclear characteristics

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Table 1. Continued

^{64}Cu	Emission of β^- (573 KeV) and β^+ (655 KeV) Suitable for imaging and radiotherapy Half-life of 12.7 days Can be produced using generator system	Limited availability Costly production and shipment Suboptimal characteristic for PET imaging
$^{66/67/68}Ga$	Suitable for γ-scintigraphy and PET imaging	High cost Limited availability
^{18}F	Can be produced in high quantity High resolution and sensitivity Low radiation dose to patients The half-life of 110 min permits both radiopharmaceutical preparation and imaging studies	High cost Limited availability Cyclotron-produced radionuclide

Peptide-based radiopharmaceuticals as diagnostic imaging and therapeutic agents

Recently, several peptide-based radiopharmaceuticals have been improved for imaging of tumors and other diseases (18, 19). A number of these peptides are currently on clinical trial and are showing potential for imaging of thrombi, tumors, and infection/inflammation. In the following ***Table 2***, we will present briefly some of these radiopharmaceuticals.

Table 2. A number of peptide-based radiopharmaceuticals that are on clinical trial.

Application	Peptide	Some Pharmacokinetic characteristic	Ref
Thrombus imaging	^{99m}Tc-apcitide	Good imaging of venous thrombi Rapid blood clearance and renal excretion in human	20-22
	^{99m}Tc-TP-1201	High binding to thrombin-activated Rapid blood clearance and renal excretion in human	23
	^{99m}Tc-TP850	Rapid blood clearance Good imaging of deep venous thorombosis (DVT) and pulmonary embolism (PE)	24, 25
Neuroendocrine origin tumors	^{111}In-DTPA-octreotide	High and specific binding to somatostatin receptors (SSRTs) High accumulation in kidneys	26
	^{111}In-DOTA-lanreotide	High affinity for various human tumor cells High uptake in primary human tumors including: neuroendocrine tumors, intestinal adenocarcinomas, lymphomas, prostate and lung cancers.	27, 28
	[^{18}F]FP-Gluc-TOCA	Good visualization of tumors in a patient with PET Low uptake in the liver and intestine	29
$\alpha_V\beta_3$ integrin	[^{18}F]Galacto-RGD	Suitable for imaging of $\alpha_V\beta_3$ expression with tumor Rapid blood clearance and excretion via renal pathway	30
	[^{18}F]-cycloRGD	$\alpha_V\beta_3$ receptor specific uptake in the tumor poor tumor-to-nontarget organs uptake ratios	31
CCK receptors	^{99m}Tc-HYNIC-sCCK$_8$	Rapid uptake in CCK-B receptor-positive tissues Low retention in the kidneys	32
	^{99m}Tc-DTPA-CCK$_8$	Rapid uptake in the liver Specific uptake in the brain, pancreas and stomach	33
Infection/Inflammation Imaging	^{99m}Tc-EC-for-MLFK	High binding to granulocytes Unsuitable for imaging infection in the abdominal region	34
	^{99m}Tc-TP765	High specificity for neutrophils Rapid blood clearance	35

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Conclusion

Obviously, radiolabeled peptides have become an important class of imaging agents for the detection of a wide range of human tumors and for imaging infection, inflammation, and thrombosis, thus they have great potential for a broad range of applications in nuclear medicine. A large number of radiolabeled peptides have already exhibited potential clinical applications. Examples include the FDA-approved ^{99m}Tc-depreotide for imaging lung cancer, and ^{111}In-Octreoscan for imaging somatostatin receptor-expressing tumors. In addition, ^{99m}Tc-HYNIC-octreotide, ^{99m}Tc-RP-527, and ^{123}I-VIP have shown promise for imaging several human tumors.

Additionally, the diagnostic applications of peptides, the progress of macrocyclic chelators, such as DOTA allows site-specific labeling to be performed not only with different radio-metals for diagnosis but also with therapeutic radionuclides; the ability of MAG_3 to form stable complexes with ^{99m}Tc and $^{186/188}$Re, has paved the way for therapeutic application of peptides.

According to the available documents and evidences, peptide-based radiopharmaceuticals have a high potential in the diagnosis and treatment of many human diseases, and in the future we will see further improvement and development of this type of radiopharmaceuticals.

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Conflicts of interest

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Authors' contributions

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