Radiopharmaceuticals for Molecular Imaging

Yun-Sang Lee[*,1,2]

[1]*Department of Nuclear Medicine, Seoul National University College of Medicine, 28 Yongon-dong, Jongno-gu, Seoul 110-744, Korea*

[2]*Institute of Radiation Medicine, Medical Research Center, Seoul National University, 28 Yongon-dong, Jongno-gu, Seoul 110-744, Korea*

Abstract: Radiopharmaceuticals for molecular imaging involve careful consideration of the following two factors: radionuclide selection and specificity to the molecular target. In selecting a radionuclide, the specific decay mode, physical half-life, chemical properties, and method of production must be considered. For proper design of a radiopharmaceutical which targets a specific biological or disease process, structural features, including the size, charge, solubility, lipophilicity, and specific activity of the radiolabeled molecules, must be considered. Other factors, such as the rate of metabolism, plasma protein binding, and non-specific binding in non-target tissues, are also important in optimizing the *in vivo* behavior of radiolabeled molecules. There are several types of radiopharmaceuticals for molecular imaging that target a number of biochemical processes, such as blood flow or perfusion, metabolism, and specific receptors. With a better understanding of the properties of radiopharmaceuticals, including chemical, physical, and biological properties, radiopharmaceuticals can be properly used for molecular imaging of targets for biological or disease processes.

Keywords: Radiopharmaceutical, molecular imaging, PET, SPECT.

INTRODUCTION

Molecular imaging is an emerging technology that provides images to visualize specific molecular changes in various diseases in living species [1, 2]. Molecular imaging technology requires specific imaging modalities, such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), optical imaging, and scintigraphy. Each modality has merits and shortcomings; however, only scintigraphic technology can provide high sensitivity and specificity at tracer levels and directly visualize molecular events occurring in sub-millimolar levels [3]. The main tools for scintigraphy are positron emission tomography (PET) and single photon emission computed tomography (SPECT). PET and SPECT require a radio-labeled pharmaceutical (radiopharmaceutical) or the radionuclide.

Not all, but nearly all traditional radiopharmaceuticals used in nuclear medicine imaging are also of use in molecular imaging because the concept of a 'radiotracer,' which is commonly used in nuclear medicine, is a specific radiolabeled molecule that can trace the *in vivo* behavior of molecules and provide information about a specific biological process. A typical example by which to visualize a biological process involves ^{68}Ga-labeled Arg-Gly-Asp (RGD) peptide PET imaging, which targets angiogenesis (Fig. **1**). ^{68}Ga-1,4,7-triazacyclononae-1,4,7-triacitic acid-RGD (^{68}Ga-NOTA-RGD) has a high affinity and binds firmly to $\alpha_v\beta_3$ integrin, which is highly expressed during angiogenesis within the tumor vasculature [4]. Therefore, ^{68}Ga-NOTA-RGD can directly visualize integrin and angiogenesis through the measurement of ^{68}Ga-NOTA-RGD uptake during PET imaging. The ^{68}Ga-NOTA-RGD application is perfectly matched with the molecular imaging concept, and other radiopharmaceuticals, which are used for functional imaging in nuclear medicine, can be used for molecular imaging.

Molecular imaging technology using radiopharmaceuticals can be used for a broad range of applications, including drug development, pharmacokinetics, clinical investigations, and routine diagnostics.

Currently, molecular imaging technology has been varied by the development of new types of radiopharmaceuticals, such as radiolabeled multimodal imaging probes [5] and oligonucleotides including nucleic acid aptamers [6, 7]. Multimodal imaging probes, which are radiolabeled MR particles containing organic dyes, can provide scintigraphic, MR and optical signals (Fig. **2**). This combined technique can also provide more information and overcome the limitations of each modality. Radiolabeled oligonucleotides, for examples, radiolabeled RNA or DNA derivatives including nucleic acid aptamers, can be used for the measurement of the pharmacokinetics *in vivo* and evaluating the delivery of oligonucleotide derivatives to the target tissues. These newly developed radiopharmaceuticals or their technologies have been broadening the range of application of molecular imaging.

Herein we discuss important considerations for molecular imaging using radiopharmaceuticals and related applications.

*Address correspondence to this author at the Department of Nuclear Medicine, Seoul National University College of Medicine, 28 Yongon-Dong, Jongno-Gu, Seoul 110-744, Korea; Tel: +82-2-740-8906; Fax: +82-2-745-7690; E-mail: wonza43@snu.ac.kr

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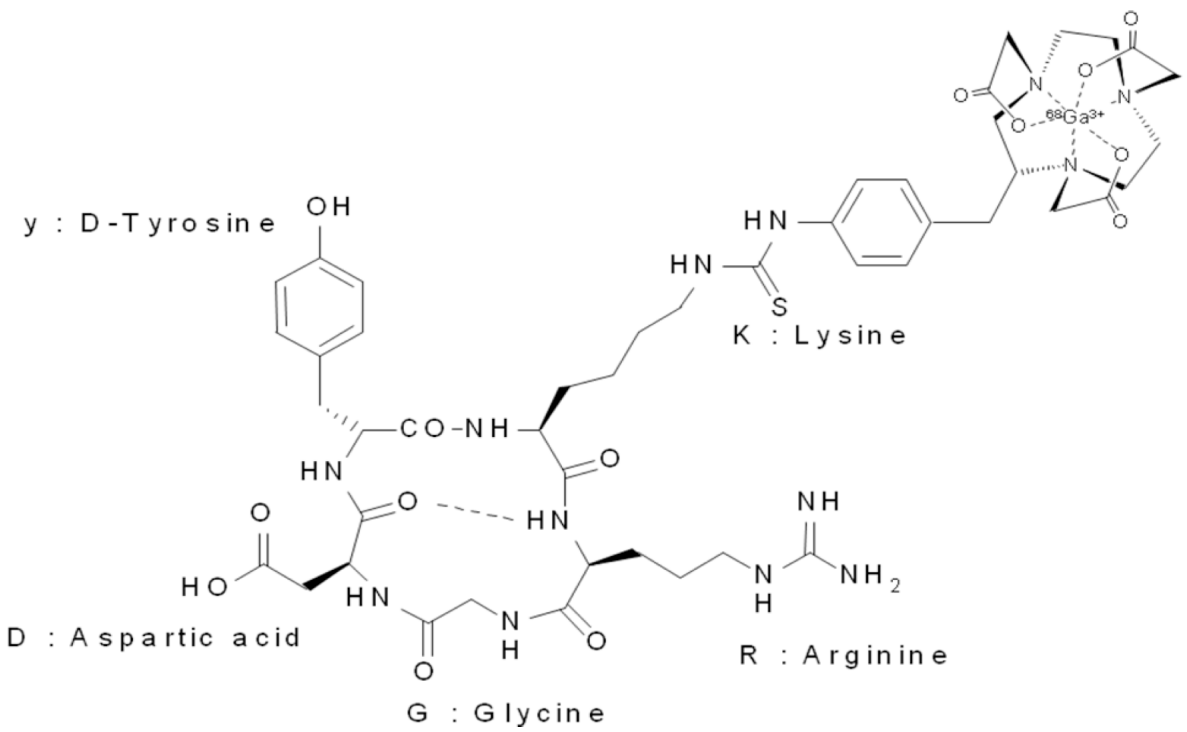

Fig. (1). The chemical structure of ^{68}Ga-NOTA-RGD contains the Arg-Gly-Asp amino acid sequence.

GENERAL CONSIDERATIONS

To select a radiopharmaceutical or develop a new radiopharmaceutical for a specific biological target or disease, one must consider several factors. First, the choice of the radionuclide is very important because of the different time domain of each biological or disease process and the difference in each radionuclide half-life. The second factor is related to the specificity of each biological or disease target, including the size or charge of the molecule, the affinity, the specific activity, the lipophilicity, the stability, and the metabolism of the radiolabeled compounds. Moreover radiopharmaceuticals, intended for human use, should be sterile, pyrogen-free, safe, and efficacious for specific indications. Therefore, quality control procedures including physicochemical, radiochemical or biological test should be carried out for each radiopharmaceutical after synthesis.

RADIONUCLIDE SELECTION

A number of radionuclides are listed in Table **1**, all of which are diagnostic radionuclides, and emit a positron or gamma photon. Each radionuclide has a specific decay mode, a physical half-life, chemical properties, and a production method. The decay mode and physical half-life is independent of any physicochemical condition, is characteristic for a given radionuclide, and cannot be changed with any other method, such as a physicochemical modification. Therefore, one must select which radionuclide is adequate for the target for the biological process or disease which is to be visualized, characterized, or measured. For example, technetium has two radioisotopes, ^{94m}Tc and ^{99m}Tc (Table **1**). ^{94m}Tc has a 52 min half-life and a positron decay mode, while ^{99m}Tc has a 6 hr half-life and a gamma decay mode. If the target process occurs in a period of 1 hour, one can select ^{94m}Tc or ^{99m}Tc to obtain the data from PET or SPECT; however, if the target process occurs in a period of 1 day, one would have to select ^{99m}Tc and the data could only be obtained from SPECT.

The listed radionuclides are divided into the following five groups: organic elements (C, N, and O), an alkali metal (Rb), halogens (F and I), metals (Ga and In), and transition metals (Cu and Tc). The organic radionuclides are ^{11}C, ^{13}N and ^{15}O. All of these radionuclides are isotopes of natural elements, therefore radiopharmaceuticals labeled with ^{11}C, ^{13}N or ^{15}O are indistinguishable from their natural counterparts biochemically. The alkali metallic radionuclide is ^{82}Rb, which has the same properties of potassium and is widely used for myocardial PET imaging [8]. The halogen radionuclides are ^{18}F, ^{123}I, ^{124}I, and ^{125}I. The ^{18}F atom closely mimics the hydrogen atom based on size, and therefore the C-^{18}F bond shows a similar biologic behavior with the C-H bond. There are three radioisotopes for iodine (^{123}I, ^{124}I, and ^{125}I). ^{123}I emits a gamma photon, and in the last 20 years a number of radiopharmaceuticals have been developed based on ^{123}I for SPECT. ^{125}I also emits a gamma photon, but it has a 60 day physical half-life and is not affordable to humans, therefore ^{125}I is used only for *in vitro* and *in vivo* animal studies. ^{124}I is a PET version of ^{123}I. Theoretically, all the ^{123}I-labeled radiopharmaceuticals are substituted by ^{124}I-labeled radiopharmaceuticals. Metallic radionuclides are ^{67}Ga, ^{68}Ga, and ^{111}In. Gallium is located in group 13 (IIIA) in the periodic table, likes 3^+ ionic form, and needs a specific chelating agent, such as 1,4,7-triazacyclononae-1,4,7-triacitic acid (NOTA; Fig. **3**). ^{67}Ga and ^{111}In emit a gamma photon and are used for SPECT. ^{68}Ga emits a positron and is used for PET. ^{68}Ga is produced by a cost-effective generator, and can be eluted 3 or 4 times per day. The transition metallic radionuclides include ^{62}Cu, ^{64}Cu, ^{94m}Tc, and ^{99m}Tc. ^{99m}Tc emits a gamma photon, and ^{62}Cu, ^{64}Cu, and ^{94m}Tc emit a

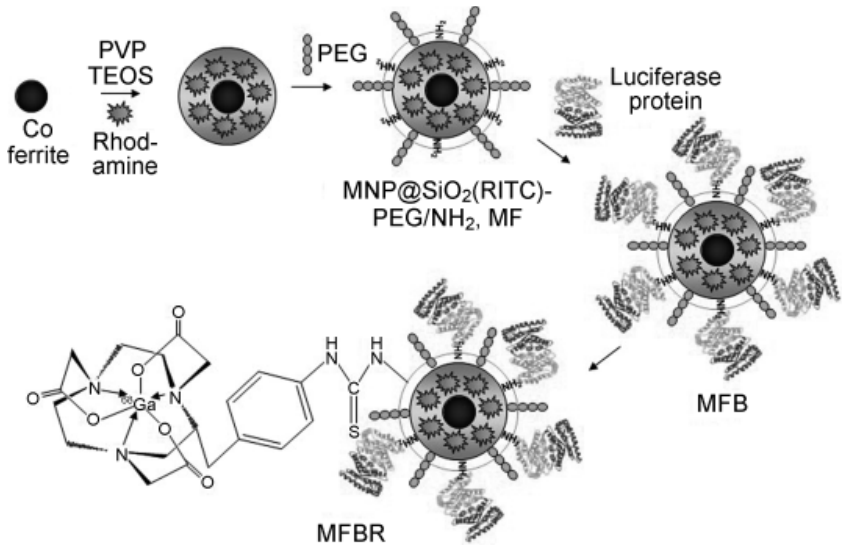

Fig. (2). Schematic diagram of the synthesis of magnetic-fluorescent-bioluminescent-radioisotopic particle (MFBR particle).

Table 1. Useful Radionuclides for Molecular Imaging

Radioisotopes	Atomic Number	Physical Half-Life	Decay Mode (%)	γ-Ray Energy (MeV)	Production
^{11}C	6	20.4 min	β^+ (100)	0.511	Cyclotron
^{13}N	7	9.96 min	β^+ (100)	0.511	Cyclotron
^{15}O	8	2.03 min	β^+ (100)	0.511	Cyclotron
^{18}F	9	109.8 min	β^+ (97)	0.511	Cyclotron
^{62}Cu	29	9.76 min	β^+ (97), EC (3)	0.511	Cyclotron
^{64}Cu	29	12.8 hr	β^+ or β^-, EC	0.511	Cyclotron
^{67}Ga	31	3.3 days	EC (100)	0.093, 0.184, 0.300	Cyclotron
^{68}Ga	31	68 min	β^+ (89), EC(11)	0.511	Generator
^{82}Rb	37	75 sec	β^+ (95), EC(5)	0.511	Generator
^{94m}Tc	43	52 min	β^+ (72), EC(28)	0.511	Cyclotron
^{99m}Tc	43	6.0 hr	IT(100)	0.140	Generator
^{111}In	49	2.8 days	EC(100)	0.171, 0.245	Cyclotron
^{123}I	53	13.2 hr	EC(100)	0.159	Cyclotron
^{124}I	53	4.2 days	β^+ (23), EC(77)	0.511	Cyclotron
^{125}I	53	60 days	EC(100)	0.035	Reactor

positron. Like metallic elements, transition metals also require chelating agents. After making a complex between a metal or transition metal and a chelator, the complex has a chemical structure that affects the shape of the entire molecular structure. Therefore, metal or transition metal radiolabeling is preferred for large molecules, such as peptides, proteins, or antibodies, than small molecules. For preparation of metal- or transition metal-labeled radiopharmaceuticals, one must find the proper chelating agent for each metal or transition metal. For example, for ^{68}Ga labeling, NOTA is a better chelator than 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA; Fig. **3**), and the ^{68}Ga-NOTA complex is more stable than the ^{68}Ga-DOTA complex. The ^{68}Ga-NOTA complex is formed under room temperature; in contrast, the ^{68}Ga-DOTA complex is formed under condition of heat [9, 10].

The method for production of radionuclides is also an important factor in radionuclide selection. The method for production of the radionuclide is related to the cost of radionuclide production and the availability of the radionuclide.

THE SPECIFICITY CONCERN

The main purpose of using radiopharmaceuticals for molecular imaging is to specifically visualize or characterize biological or disease processes at the molecular or cellular level. To maintain specificity, the radiopharmaceutical should be designed carefully for the structural requirements in a molecule in order to optimize target specificity and the pharmacokinetic and pharmacodynamic behavior of the radiopharmaceutical to meet the demands of the imaging technique. The structural features that affect the

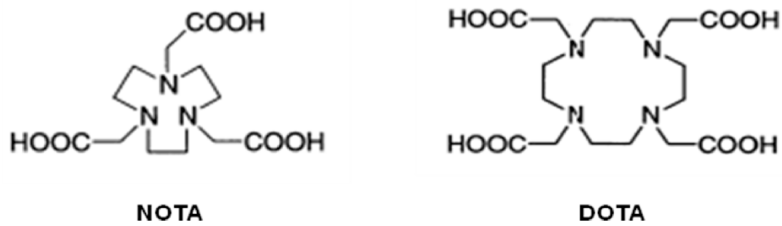

Fig. (3). Chemical structures of NOTA and DOTA.

physicochemical properties are the size, charge, solubility, lipophilicity, and specific activity (SA) of the radiolabeled molecules. Other factors, such as the rate of metabolism, plasma protein binding, and non-specific binding in non-target tissues, are also important to optimize the *in vivo* behavior of radiolabeled molecules.

Size and Charge

The molecular size or mass of a radiopharmaceutical is one of the major properties of the molecule that determines the rate of clearance from the circulation and localization *in vivo*. Small organic molecules or small peptides, natural or synthetic, are cleared from the circulation and localized to the target tissue rapidly, thus providing a much higher target-to-background ratio. In contrast, large molecules, such as large peptides, proteins, and antibody, have a longer clearance and localization time than small molecules. The molecular size also affects the distribution pattern of radiopharmaceuticals *in vivo*, e.g., larger molecules are not filtered by the kidneys. Such information regarding the range of molecular weights of the desired radiopharmaceutical is essential for a given biological or disease process investigation.

The charge on a radiopharmaceutical determines its solubility in various solvents. Radiopharmaceuticals with a greater charge have a greater solubility in aqueous solution. Non-charged molecules tend to be more soluble in organic solvents and lipids. The charge of radiopharmaceuticals also determines the characteristics of the distribution pattern *in vivo*. For example, ^{99m}Tc-*hexakis*isobutylisonitrile (^{99m}Tc-MIBI), which is a positively charged complex, is accumulated at the myocardium like potassium ion [11]. In contrast, ^{99m}Tc-mercaptoacetyl-Gly-Gly-Gly (^{99m}Tc-MAG_3), which is a negatively charged complex, is accumulated in the kidneys [12]. Several types of radiopharmaceuticals have a charge after radiolabeling, and this phenomenon occurs after the complex-forming reaction between the metal or transition metal and the chelator because of the various oxidation states of the metal or transition metal and the charge derived from the chelator molecules containing nitrogen, oxygen, or sulfur atoms. For example, a well-known chelator for ^{99m}Tc labeling, diaminedithiol (N_2S_2), can form ^{99m}Tc-N_2S_2 as a neutral complex. However, dimethyl derivatives of N_2S_2 can form a positive complex after labeling of ^{99m}Tc [13].

Solubility and Lipophilicity

For injection in an animal model or humans, radiopharmaceuticals should be prepared in aqueous solution in the pH range compatible with the pH of blood. The ionic strength or osmolality of the agents should also be appropriate for blood. The solubility of radiopharmaceuticals in aqueous solution is influenced by the charge, the size, the mass, the shape, and the lipophilicity of radiopharmaceuticals.

Lipophilicity, denoted by Log P or Log D, is the affinity of a molecule or moiety for a lipophilic environment, and a fundamental physicochemical property of each compound [14]. Lipophilicity also plays an important role in the absorption, distribution, and elimination of drug molecules. Normally, polar compounds exhibit high water solubility and fast clearance through the kidneys, and often highly polar compounds, such as charged compounds, cannot penetrate the blood-brain barrier (BBB). In general, only the neutral, lipophilic molecules can pass through the BBB and enter the brain.

Specific Activity

Generally, SA is defined as the amount of radioactivity per unit mass of an element, molecule, or compound, which implies that the mass represents the combined mass of radioactive species and the non-radioactive counterpart. The SA units are expressed as Ci/g, Ci/mol, or Gbq/mol. The SA of radiopharmaceuticals is very important for molecular imaging studies since SA is a measure of the number of radioactive probe molecules which are bound to the target system, and that can give a radioactive signal in a given mass of radiopharmaceuticals. The proper SA of a given radiopharmaceutical depends on the concentration of target molecules, such as specific receptors, enzymes, proteins or genes, present in a given cell or tissue. Normally, neuroreceptor or gene imaging studies need very high SA (2-10 Ci/μmol), and enzyme-mediated studies need a 100-1000-fold lower SA [15]. SA is related to the purity of a radiopharmaceutical and the half-life of an attached radionuclide. For example, even if we could get a highly pure radiopharmaceutical, that contains no other chemical and non-radioactive species, at the zero time point, after spending one half-life ($T_{1/2}$), the remaining radioactive species would be one-half of a given mass of the radiopharmaceutical. After spending 8 times the half-life, the remaining radioactive species would be only 0.4% of a given mass of the radiopharmaceutical (Fig. **4**). Therefore, a low SA radiopharmaceutical, which contains a larger amount of non-radioactive species than radioactive species, is not proper for receptor or gene imaging because the number or concentration of target molecules is limited and an extremely smaller amount of radioactive species than non-radioactive species may not occupy the binding site of the target systems. To increase the SA, if possible, we should purify the radiopharmaceutical after the radiolabeling procedure or reduce the amount of precursor for radiolabeling.

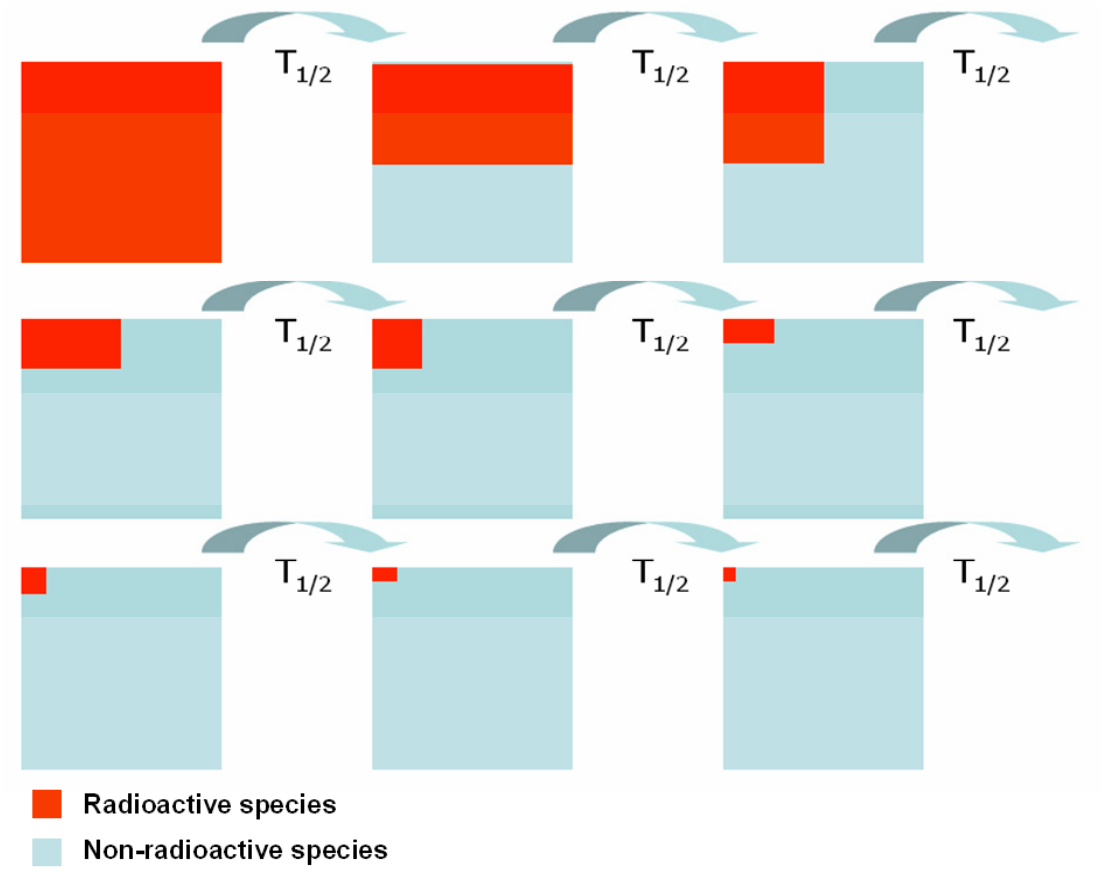

Fig. (4). SA is related to the physical half-life of the attached radionuclide.

For preparation of the radiopharmaceutical, the amount of each component to be added for the radiolabeling procedure or after purification should be known. This information is particularly important in tracer level investigations and can help better understand the image or quantification data.

Stability and Metabolism

The stability of a radiopharmaceutical is one of the major concerns in radionuclide labeling chemistry and molecular imaging. The radiopharmaceuticals for molecular imaging should be stable *in vitro* and *in vivo*. Temperature, pH, and light affect the stability of many compounds and the optimal range of these physicochemical conditions must be established for the preparation and storage of radiolabeled compounds. *In vivo*, metabolically decomposed radiopharmaceuticals cause an undesirable biodistribution of radioactivity and decrease the quality of the image, which contains mixed images from the radioactivity of the intact radiolabeled molecule and metabolic fragments. Therefore, for the design of a radiopharmaceutical, radionuclide labeling should be in a metabolically stable position and an intact radiolabeled molecule should be formed a metabolically stable structure. Metabolism in the blood may decrease the delivery of the radiopharmaceutical to the target site, and at or near the target site, and may decrease the specific binding to the molecular target. Furthermore, the quantification of the molecular target concentration based of kinetic modeling may be complicated if the metabolic products are also trapped at the target site. Therefore, the relative concentration of the intact radiopharmaceutical and all the metabolic products must be measured to get a meaningful interpretation of the imaging data.

Protein Binding

It is a well-known phenomenon that almost all drugs, radioactive or not, can bind specifically or non-specifically to plasma proteins, cell membranes, and other components present in the blood to variable degrees. Protein binding is greatly influenced by a number of factors, such as the charge on the radiopharmaceutical molecule, pH, the nature of the protein, and the concentration of anions in the plasma. Non-specific binding to albumin and other plasma proteins is correlated positively and linearly with increasing lipophilicity [16]. Protein contains hydroxyl, carboxyl, and amino groups which determine their configuration in the protein structure and the extent and strength of protein binding to the radiopharmaceutical. Metal complexes can exchange the metal ions with proteins because of the stronger affinity of the metal for the protein. This process is called "trans-chelation" and leads to *in vivo* metabolism of the complex. For example, ^{67}Ga-citrate exchanges ^{67}Ga with transferrin to form ^{67}Ga-transferrin in the plasma [17].

Protein binding affects the tissue biodistribution and plasma clearance of a radiopharmaceutical and its uptake by the interest target system. Therefore, the extent of protein binding of any new radiopharmaceutical should be determined before its clinical use.

Table 2. Frequently Used Radiopharmaceuticals for Molecular Imaging

Biochemical Process	Specific Target	Imaging Agent	Target Organ or Disease	References
Blood flow	Simple diffusion	^{99m}Tc Red blood cell	GI bleeding, ventricle	[20]
		[^{13}N]Ammonia	Ventricle	[21]
Perfusion	Perfusion	^{82}Rb, [^{15}O]Water	Myocardium, brain	[8, 22]
		^{99m}Tc-MIBI, ^{201}Tl	Myocardium	[11, 23]
		^{99m}Tc-HMPAO	Brain	[24]
		^{99m}Tc-MAG$_3$ ^{99m}Tc-DTPA ^{99m}Tc-DMSA	Kidney	[12, 25, 26]
Metabolism				
Glucose	Hexokinase	[^{18}F]FDG	Tumors, brain, myocardium	[18]
Amino acids	Protein synthesis	[^{11}C]Methionine [^{18}F]FMT	Tumors	[27, 28]
DNA synthesis	Thymidine kinase	[^{11}C]Thymidine [^{18}F]FLT	Tumors	[29, 30]
Lipids	Choline kinase	[^{11}C]Choline [^{18}F]Choline [^{11}C]Acetate	Tumors	[31-33]
Angiogenesis	$\alpha_v\beta_3$ integrin	^{68}Ga-NOTA-RGD [^{18}F]Galacto-RGD	Tumors	[4, 19]
Hypoxia	Acidic pH and reductive potential	[^{18}F]FMISO [^{18}F]FAZA ^{64}Cu-ATSM	Hypoxia in tumor	[34-36]
Apotosis	Phosphatidylserine	^{99m}Tc-Annexin-V [^{124}I]Annexin-V	Lung tumors	[37, 38]
Tumor receptors	Estrogen receptor	[^{18}F]Fluoroestradiol	Endometrial cancer	[39]
	Somatostatin receptor	^{68}Ga-DOTA-TOC ^{111}In-Octreotide ^{99m}Tc-TOC, ^{99m}Tc-TATE	Neuroendocrine Tumors	[40-42]
Neuroreceptors				
Dopamine metabolism	Aromatic amino acid decarboxylase	[^{18}F]FDOPA	Movement disorder	[45]
Dopamine receptor	Dopamine D2 receptor	[^{11}C]Raclopride [^{123}I]IBZM	Movement disorder	[46, 47]
Dopamine reuptake	Dopamine presynaptic transporter	[^{18}F]FP-CIT [^{123}I]-β-CIT	Movement disorder	[48, 49]
Reporter gene imaging	HSV1-TK	[^{18}F]FHBG	Gene therapy	[50]
	Dopamine D2 receptor	[^{18}F]FESP	Gene therapy	[51]
	Sodium/iodide symporter	^{123}I	Gene therapy	[52]
Amyliod binding	β-Amyloid	[^{11}C]PIB	Alzheimer dementia	[53]
Macrophage	Peripheral benzodiazepine receptor	[^{11}C]PK11195	Neuroinflammation	[56]

FREQUENTLY USED RADIOPHARMACEUTICALS FOR MOLECULAR IMAGING

There are several types of radiopharmaceuticals for molecular imaging for targeting a number of biochemical processes, such as blood flow or perfusion, metabolism, and specific receptors (Table **2**). Each radiopharmaceutical focuses on specific target of each biochemical or biological process. For example, [^{18}F]FDG can target the enzyme, hexokinase, and specifically assess the glucose metabolism *in vivo* [18]. In the same manner, one who wants to investigate tumor angiogenesis can focus on the specific target, such as $\alpha_v\beta_3$ integrin, and can adopt ^{68}Ga-NOTA-RGD or [^{18}F]galacto-RGD to visualize angiogenesis [4, 19].

Blood flow and perfusion imaging are utilized mostly in the evaluation of heart, brain, bone, and renal applications. The radiopharmaceutical uptakes are through several different mechanisms, but the major contribution of signals derives from

the blood flow and high first-pass extraction efficiency [8, 11, 12, 20-26].

Metabolism imaging using radiopharmaceuticals provides important information of the hyperactivity of tissues or cells *in vivo*. Almost all the radiopharmaceuticals for metabolism imaging have developed with slight structural modification of natural molecules, e.g., ^{11}C- or ^{18}F-labeled radioactive analogues of carbohydrates, amino acids, nucleotides, and lipids [18, 27-33].

Angiogenesis is an important process on which tumors depend to maintain growth and is subjected to regulation by growth factors, such as vascular epithelial growth factor (VEGF), inhibitors, and integrins. For imaging of angiogenesis, ^{68}Ga-NOTA-RGD and [^{18}F]galacto-RGD PET imaging of $\alpha_v\beta_3$ integrin have been studied to exploit their binding to RGD containing components on extracellular matrix which are upregulated in the tumor vasculature [4, 19].

Tumor hypoxia is assessed by ^{18}F labeled misonidazole ([^{18}F]FMISO) PET imaging, which is useful for effective external beam radiation therapy [34]. ^{18}F-fluoroazomycin arabinoside ([^{18}F]FAZA) and ^{64}Cu-diacetyl-bis(N^4-methylthiosemicarbazone; ^{64}Cu-ATSM) are also used for imaging of tumor hypoxia [35, 36]. Cells undergoing programmed death, or apoptosis, externalize important subcellular components, including phospohphatidylserine (PS) as potential markers of apoptosis. Naturally-occurring annexin V is known to be bound to exposed PS. ^{99m}Tc or ^{124}I labeled annexin V were studied for imaging of apoptosis [37, 38].

Tumor-related specific receptor, such as estrogen and somatostatin receptor (ER and SSTR), can be imaged by ^{18}F labeled estradiol and radiolabeled octreotide derivatives [39-42]. ^{68}Ga-DOTA-Tyr^3-octreotide (^{68}Ga-DOTA-TOC) is used for direct imaging of SSTR, and evaluates the therapeutic effect of the peptide receptor radiotherapy (PRRT) of neuroendocrine tumors with ^{90}Y- and ^{177}Lu-DOTA-Tyr^3-Thr^8-octreotide (^{177}Lu-DOTA-TATE) [43].

To explore subtypes of cholinergic, adrenergic, histaminergic, serotoninergic, dopaminergic, and benzodiazepine receptors and transporters in humans, neuroreceptor imaging studies have been flourished to study dementia, epilepsy, movement disorders, and pain pathways, and to direct central nervous system (CNS) drug development [44]. Each radiopharmaceutical has a specific target, such as neurotransmitter metabolism, receptor activity, and reuptake site activity [45-49].

Reporter gene imaging is an emerging technology based on molecular biology and can reveal the locations of gene products and the efficacy of gene therapy [50-52]. As previously mentioned, for imaging of receptor or reporter gene, radiopharmaceuticals should be maintained the high SA because of the limited number or concentration of receptors or gene products.

Accumulation of plaques and beta amyloid in the brain is a histopathologic hallmark for the diagnosis of Alzheimer's disease. The use of ^{11}C labeled Pittsburgh compound B (PIB) has enabled accurate classification of patients with versus without Alzheimer's disease and other neurodegenerative diseases [53].

A major feature of acute or chronic neuroinflammation is the activation of microglial cells. During the early 1980s, it was discovered that increased binding of PK11195 (an isoquinoline) is a hallmark of microglial activation [54]. Their binding site is the peripheral benzodiazepine receptor (PBR; the new nomenclature is translocator protein, TSPO [55]), therefore neuroinflammation is assessed by targeting of PBR using [^{11}C]PK11195 [56].

CONCLUSION

Molecular imaging using radiopharmaceuticals has provided great opportunities to explore human diseases at the levels of compartments, organs, tissues, or even genes. Radiopharmaceutical represents any radiolabeled molecule intended for human use, and should be sterile, pyrogen-free, safe for human use, and efficacious for specific indications. With a better understanding of the properties, including the chemical, physical, and biological properties of each radiopharmaceutical, these radiopharmaceuticals can be properly used for molecular imaging of targets for biological or disease processes.

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