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Recent Advances in ^{99m}Tc Radiopharmaceuticals

Yasushi Arano*

Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675, Japan

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When ^{99m}Tc was first applied to radiopharmaceuticals for diagnostic nuclear medicine, major efforts were focused on the development of ^{99m}Tc complexes for excretory organs such as the liver and kidney. Over the past 30 years, a significant advance was made in technetium chemistry and radiopharmaceutical design. Now, ^{99m}Tc radiopharmaceuticals for measuring regional cerebral and myocardial blood flow are available in clinical studies. More recently, transporter functions of the brain can also be visualized with ^{99m}Tc radiopharmaceuticals. In this manuscript, recent advances in ^{99m}Tc radiopharmaceuticals will be briefly reviewed.

1. Introduction

Technetium-99m (^{99m}Tc) is one of the most desirable radionuclides in diagnostic nuclear medicine, due to an emission of a gamma ray of optimal energy (140 keV), a suitable half-life (6 h), and availability from ^{99}Mo-^{99m}Tc generator systems. In addition, development of ^{99m}Tc radiopharmaceuticals for tumor imaging paves the way for therapeutic radiopharmaceuticals with high energy beta emitters ^{186}Re and ^{188}Re since chemical properties of Tc are close to those of Re.

Technetium (Z = 43) is situated in the middle of the second-row transition series and does not have stable isotopes, which retarded the development of its chemistry. At the initial stage of ^{99m}Tc radiopharmaceutical development, major efforts were focused on imaging excretory organs such as the liver and kidney, since it was thought that Tc is a foreign substance and should be recognized as such by the body. In 1982, Yokoyama et al. reported that a ^{99m}Tc complex of glucosone bis (thiosemicarbazone) (Figure 1A) showed an uptake into normal brain in laboratory animals.[1, 2] They also reported that ^{99m}Tc-dithiosemicarbazone complexes appended with a tertiary or a quarternary amine group showed myocardial uptake.[1, 3] Meanwhile, the Davison and Jones group demonstrated that pentavalent oxotechnetium (5+) forms a five-coordinated mononuclear complex of high stability with a N_2S_2 ligand (Figure 1B).[4] These findings encouraged further efforts to develop ^{99m}Tc radiopharmaceuticals for brain and myocardial functions. In this paper, progress in developing ^{99m}Tc radiopharmaceuticals will be briefly reviewed.

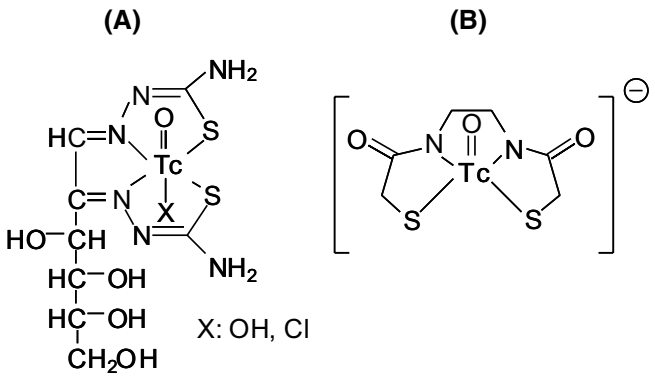

Figure 1. ^{99m}Tc complexes that paved the way for currently available ^{99m}Tc radiopharmaceuticals. (A) ^{99m}Tc-dithiosemicarbazone derivative of glucose, (B) oxo^{99m}Tc(V) complex containing a ^{99m}TcON_2S_2 core.

*Corresponding author. E-mail: arano@p.cbiba-u.ac.jp. FAX: +81-43-226-2897.

2. ^{99m}Tc Radiopharmaceuticals for Perfusion Imaging

2.1. Regional cerebral blood flow. To determine regional cerebral blood flow, coordination molecules (ligands) are requested to provide ^{99m}Tc complexes that can penetrate the intact blood-brain barrier (BBB) in response to the blood flow. A variety of ligands were developed that form mononuclear, neutral, lipophilic and stable ^{99m}Tc complexes. These include diaminodithiolate (DADT or BAT),[5] bis(thiosemicarbazone) derivatives (DTS),[6] propylene amine oxime (PnAO),[7] as illustrated in Figure 2. Although all ^{99m}Tc complexes penetrated the intact BBB with significant initial brain uptake, they were also marked by rapid washout from the brain, due to a lack of an appropriate functional group that fixed the ^{99m}Tc complexes in the brain. Since radioiodinated compounds with amine derivatives such as [^{123}I]*N*-isopropyliodoamphetamine ([^{123}I]IMP) and [^{123}I]*N,N,N'*-trimethyl-*N*'-(2-hydroxy-3-methyl-5-iodobenzyl)-1,3-propane diamine ([^{123}I]HIPDM)[8] demonstrated significant brain uptake and retention sufficient for external imaging, initial efforts were made to append an amine group to the neutral and lipophilic mononuclear ^{99m}Tc complexes. Although this chemical modification provided ^{99m}Tc complexes of longer residence time in the brain (e.g. an *N*-piperidinylethyl derivative of ^{99m}Tc-DADT), this resulted in the formation of two ^{99m}Tc complexes with different biological characteristics,[9] which were identified as *syn* and *anti* isomers. This hampered further efforts to develop cerebral perfusion agents based on this molecular design.

In 1984, Fair et al. synthesized and characterized a technetium complex of PnAO as a neutral complex with a square pyramidal structure.[10] Volkert et al. found that ^{99m}Tc-PnAO passively penetrated the intact blood-brain-barrier in laboratory animals with a first-pass efficiency of 80%, followed by rapid washout

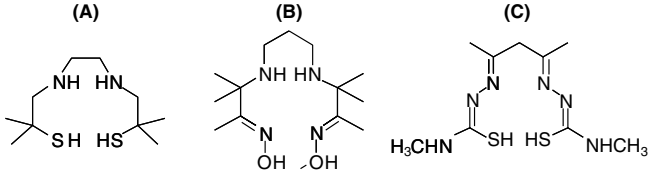

Figure 2. Presentative N_2S_2 ligands that provide neutral, lipophilic and stable mononuclear ^{99m}Tc complexes that cross the intact blood-brain barrier. (A) diaminodithiolate (DADT or BAT), (B) propylene amine oxime (PnAO), and (C) pentane-2,4-dione bis(thiosemicarbazone).

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from the brain.[7] Following a series of structure-distribution studies of ^{99m}Tc complexes of PnAO derivatives, Neirinckx et al. selected *d,l*-diastereoisomer of hexamethyl propyleneamine oxime (HM-PAO) (Figure 3A).[11] ^{99m}Tc-HM-PAO showed rapid uptake in the brain, followed by high residence times of radioactivity in the brain up to 24 h post-injection, due to rapid conversion of lipophilic ^{99m}Tc-HM-PAO to more hydrophilic secondary complexes. Further studies showed that intracerebral glutathione (GSH) would be involved in the conversion of ^{99m}Tc-HM-PAO to hydrophilic forms, which would account for the retention of this ^{99m}Tc complex in brain and other cells.[12]

Meanwhile, Walovitch et al. reported that ^{99m}Tc complex of *N,N'*-1,2-ethanediylbis-L-cysteine diethylester (ECD) (Figure 3B) exhibited high uptake and retention of baboon brain.[13] Metabolic studies suggested that the brain retention of ^{99m}Tc-ECD would be caused by rapid metabolism to a polar monoester-monoacid metabolite that is trapped in the brain. Although high initial brain uptake was observed with ^{99m}Tc-D,D-ECD isomer, rapid elimination from the brain was observed, suggesting enzyme-mediated hydrolysis of the ester in ^{99m}Tc-ECD. Clinical studies showed that ^{99m}Tc-ECD provided diagnostic information comparable to that obtained by PET brain perfusion agent.

2.2. Myocardial Perfusion Agents. In a search for ^{99m}Tc radiopharmaceuticals that provide diagnostic information compatible to those of ^{201}Tl, efforts were made to synthesize cationic ^{99m}Tc complexes with appropriate lipophilicity so that the complexes can reflect myocardial blood flow. The first cationic ^{99m}Tc chelate that exhibited significant myocardial uptake in animals was ^{99m}Tc complexes of *trans*-$[^{99m}Tc(DIARS)_2X_2]^+$, where DIARS represents the *o*-phenylenebis(dimethylarsine) ligand and X represents chloride or bromide,[14] as shown in Figure 4A. To reduce lipophilicity of the complex and replace harmful arsine to another atom, they utilized 1,2-bis(dimethylp hosphino)ethane (DMPE) as a ligand for a ^{99m}Tc (III) cationic complex, *trans*-$[^{99m}Tc(DMPE)_2Cl_2]^+$ (Figure 4B).[15] This cationic complex, however, was reduced to neutral ^{99m}Tc(II) form, $[^{99m}Tc(II)(DMPE)_2Cl_2]^0$,[16] which facilitated elimination of the complex from myocardium.

During these studies, it was also found that besides the ^{99m}Tc(III) complex, DMPE also formed $[^{99m}Tc(I)(DMPE)_3]^+$ (Figure 4C) and $[^{99m}Tc(V)O_2(DMPE)_2]^+$ (Figure 4E) complexes.[17] This stimulated further efforts to develop ^{99m}Tc cationic complexes for myocardial blood flow. Kelly et al. synthesized cationic and lipophilic ^{99m}Tc complex of diphosphine ligand, 1,2-bis[bis(2-ethoxyethylene)phosphino]ethane (tetrofosmin) with a $^{99m}TcO_2$ core as shown in Figure 4F.[18] This complex is now approved as a radiopharmaceutical for myocardial blood flow.

Another type of cationic ^{99m}Tc complex was developed by Jones et al. who prepared organometallic ^{99m}Tc(I) hexakis(isonitrile) complexes.[19] The Tc(I) oxidation state is particularly advantageous because of the kinetic inertness inherent in its low-spin d_6 configuration. After extensive structure-distribution studies of the isonitrile derivatives, hexakis(2-methoxy-isobutylisonitrile; MIBI) technetium(I) shown in Figure 4D was found to improve the biodistribution properties when compared with the prototype compound, hexakis(*t*-butylisonitrile) technetium(I), due to rapid clearance of radioactivity from the liver and lung. This could be attributed to the metabolism of the ether groups in MIBI ligand to hydrophilic hydroxyl groups. Further studies showed that the fundamental myocellular uptake mechanism of ^{99m}Tc-MIBI involves passive distribution across plasma and mitochondrial membranes and that at equilibrium ^{99m}Tc-MIBI is sequestered within mitochondria by the large negative transmembrane potentials.[20]

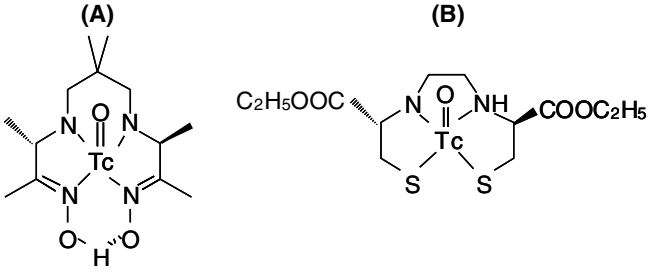

Figure 3. Clinically applied ^{99m}Tc radiopharmaceuticals for brain perfusion. (A) ^{99m}Tc-L,L-ECD and (B) ^{99m}Tc-HM-PAO.

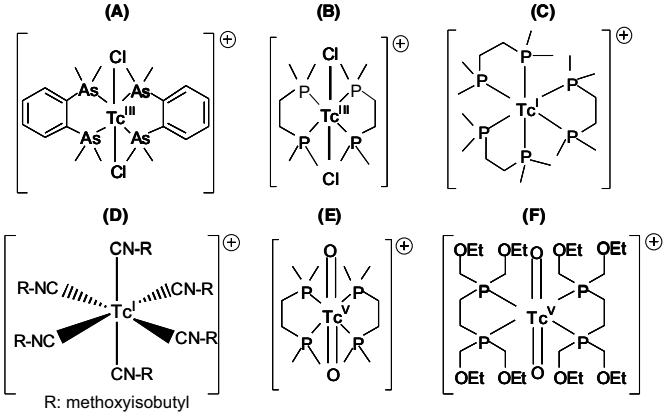

Figure 4. ^{99m}Tc cationic complexes for measuring myocardial perfusion. (A) $[^{99m}Tc(III)(DIARS)_2Cl_2]^+$, (B) $[^{99m}Tc(III)(DIMPE)_2Cl_2]^+$, (C) $[^{99m}Tc(I)(DMPE)_3]^+$, (D) $[^{99m}Tc(I)MIBI]^+$, (E) $[^{99m}Tc(V)O_2(DMPE)_2]^+$ and (F) $[^{99m}TcO_2(tetrofosmin)]^+$.

3. ^{99m}Tc Radiopharmaceuticals for Targeted Imaging

A large number of organic compounds labeled with ^{11}C, ^{18}F and ^{123}I have been designed and synthesized as radiopharmaceuticals for imaging of receptors, transporters and enzymes activites. Owing to the progress in technetium chemistry, recent efforts have been directed toward the development of ^{99m}Tc radiopharmaceuticals for targeted imaging.

To develop ^{99m}Tc compounds for targeted imaging, a stable and neutral ^{99m}Tc chelate was conjugated to a compound that possesses a specific localization mechanism to target tissues (e.g. receptors, transporters and enzymes). This approach is analogous to the strategy employed for proteins and peptide labeling with ^{99m}Tc. When the chemical design is further applied to small molecular weight compounds, strategic replacement of ^{99m}Tc chelating moiety at sterically tolerant sites of mother molecules plays a critical role in order to minimize the loss of the original bioactivity. ^{99m}Tc complexes for dopamine transporter imaging, simultaneously reported by two research groups, constitute representative ^{99m}Tc compounds based on the chemical design.[21, 22] Each compound possesses a ^{99m}Tc complex of N_2S_2 ligand at a different position in tropane moiety (Technephine: Figure 5B and TRODAT-1; Figure 5C). Despite the structural differences, both compounds crossed the intact BBB and bound to the dopamine pre-synaptic transporter. Specific uptake of TRODAT-1 in dopamine transporter located in the basal ganglia was demonstrated in human studies.[22, 23] These studies suggested that further studies on structure-distribution and structure-activity relationsip would provide ^{99m}Tc radiopharmaceuticals that target receptors or transporters in

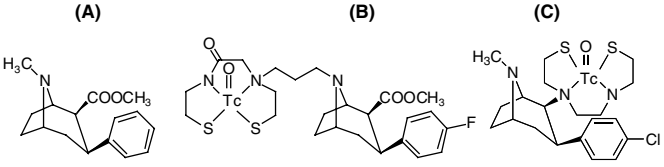

Figure 5. Chemical structures of (A) tropane, (B) technephine, and (C) TRODAT-I.

the brain or other tissues of interest. Recent development of organometallic technetium and rhenium complexes will also provide another design for ^{99m}Tc radiopharmaceuticals.

External imaging of energy production activity of living cells with ^{99m}Tc compounds constitutes another challenging task. Based on the studies of ^{11}C- and ^{123}I-labeled medium chain fatty acid analogs, our efforts were focused on developing medium chain fatty acid analogs that reflect β-oxidation activity in the liver. Monoamine-monoamide (MAMA) ligand was attached to the ω-position of hexanoic acid (HA), as shown in Figure 6A. In biodistribution studies, ^{99m}Tc-MAMA-HA showed high initial hepatic uptake, followed by rapid excretion of radioactivity into urine. Analyses of urine revealed ^{99m}Tc-MAMA-butylic acid (BA) as the major radiometabolite. ^{99m}Tc-MAMA-HA generated ^{99m}Tc-MAMA-BA when incubated in the presence of living liver slices. However, ^{99m}Tc-MAMA-HA remained intact when the experiments were performed in the presence of 2-bromooctanoate, an inhibitor for β-oxidation.[24] These findings indicated that ^{99m}Tc-MAMA-HA was recognized as a substrate for β-oxidation by the liver. On these bases, ^{99m}Tc-MAMA-derivatives of dodecanoic acid (DA) and hexadecanoic acid (HDA) were also synthesized to estimate whether similar chemical design is applicable to develop ^{99m}Tc-labeled fatty acid analogs recognized as substrates for β-oxidation in myocardium. In biodistribution studies, ^{99m}Tc-MAMA-HDA showed the maximum heat/blood ratio of 3.6 at 2 min post-injection. These kinetics were similar to those of [^{125}I]iodophenylpentadecanoic acid. Metabolic studies supported that ^{99m}Tc-MAMA-HDA was metabolized by β-oxidation in the body.[25] More recently, Lee et al. synthesized 8-[^{99m}Tc]cyclopentadienyltricarbonyltechnetium 8-oxooctanoic acid (^{99m}Tc-CpTTOA; Figure 6B). This organometallic technetium compound was also metabolized by the liver to generate 4-cyclopentadienyl counterpart.[26] Thus, although further studies are required, these studies suggest that ^{99m}Tc complexes may be recognized as substrates for energy production when appropriate structures are given.

Recently, tremendous efforts are being made to apply organometallic technetium and rhenium complexes to radiopharmaceutical. Alberto and co-workers published a new atomospheric synthesis for complexes $[MX_3(CO)_3]^+$ (M= Tc or Re; X= Cl or Br).[27] More recently, Dyszlewski et al. developed a freeze-dry formulation for the preparation of the $^{99m}Tc(CO)_3(OH)_3$ core in aqueous solution.[28] Further details of the organomtallic technetium complexes are found in recent review by Schibli.[29]

Cyclopentadienyl (Cp) ^{99m}Tc(I) and ^{186}Re(I) tricarbonyl complexes $[CpM(CO)_3]$ (M = Tc or Re) constitute another interesting precursors for ^{99m}Tc and $^{186/188}$Re radiopharmaceuticals. $CpTc(CO)_3$ is a kinetically inert, lipophilic core to which biomolecules can be appended through modification of the Cp ring. Spradau et al. reported a unique synthetic procedure for $CpRe(I)(CO)_3$ by means of a double ligand transfer reaction, which can be applicable to ^{99m}Tc(I).[30] The $CpTc(CO)_3$ was applied to labeling proteins, peptides[31] and an estradiol derivative.[32]

As a part of works to develop ^{99m}Tc and $^{186/188}$Re-labeling reagent of low molecular weight polypeptides based on renal brush border strategy (Figure 9),[33] we investigated in vivo metabolism of [^{188}Re]cyclopentadienyltricarbonylrhenium ([^{188}Re]CpTR-COOH). This compound was quite stable in murine plasma. When injected to mice, [^{188}Re]CpTR-COOH was excreted from the body as its intact form and its glycine conjugate, suggesting that [^{188}Re]CpTR-COOH would be partially recognized as an aromatic acid and was metabolized as such by the body. On the other hand, [^{188}Re]CpTR-Gly was excreted in the urine as its intact structure. From these studies, CpTR-Gly would constitute potential alternative for meta-iodohippuric acid in preparing $^{186/188}$Re-labled reagents of low molecular weight polypeptides.[34]

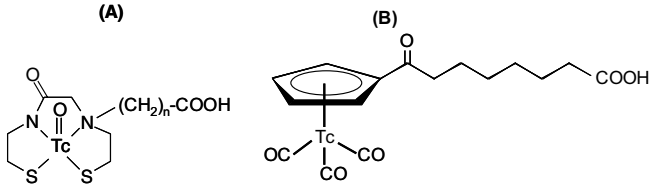

Figure 6. (A) ^{99m}Tc-MAMA-based medium (n = 6) and long chain (n = 10) fatty acids, and (B) cyclopentadienyltricarbonyl derivative of medium chain fatty acid analog, [^{99m}Tc]CpTTOA.

4. ^{99m}Tc Polynuclear Complexes of Bisphosphonates

Although developed in 1970's, ^{99m}Tc complexes of bisphosphonate (diphosphonate, abbreviated as BP) are still most widely used radiopharmaceuticals in clinical studies. They accumulate in bone, especially at sites of high calcium turnover in actively growing or cancerous bone with easily accessible unsaturated coordination sphere of Ca^{2+} in the basic bone structure hydroxyapatite, which render the radiopharmaceuticals useful for visualizing various skeletal cancers.[35] High and selective accumulation of ^{99m}Tc BP to cancerous bone promotes palliative treatment of bone metastases with $^{186/188}$Re complexes of BP.[36]

Despite widespread applications, both ^{99m}Tc complexes of MDP and HMDP are subject to a time lag of more than 2 h before bone scanning can be performed after administration, due to the slow elimination rates of radioactivity from systemic circulation and soft tissues. In addition, while a variety of non-radioactive BPs have found widespread application in clinical management of a variety of bone disorders such as bone metastases, osteoporosis, and Paget's disease, there are conflicting results as to whether previous non-radioactive BP treatment for metastatic bone disease would give rise to false-negative bone scintigraphies. To elucidate factors affecting the pharmacokinetics of ^{186}Re-labeled 1,1-hydroxyethylidenediphosphonate (^{186}Re-HEDP), chemical and biological properties of ^{186}Re-HEDP were compared with those of chemically stable tricarbonyl [^{186}Re](cyclopentadienylcarbonyl amino)-acetic acid] rhenium-conjugated 3-amino-1-hydroxypropylidene-1,1-bisphosphonate ([^{186}Re]CpTR-Gly-APD; Figure 7E). The effect of HEDP pre- or co-administration on the biodistribution of the two ^{186}Re-labeled compounds was also compared in mice. [^{186}Re]CpTR-Gly-APD exhibited higher plasma stability, lower plasma protein binding, and higher HA binding than did ^{186}Re-HEDP. In biodistribution studies, [^{186}Re]CpTR-Gly-APD registered significantly higher radioactivity levels in bone and faster clearance of radioactivity from blood than did ^{186}Re-HEDP. However, a significant decrease in bone accumulation was observed when [^{186}Re]CpTR-Gly-APD was co-injected with HEDP equivalent for that in ^{186}Re-HEDP. In contrast, no significant difference in bone accumulation was observed when [^{186}Re]CpTR-Gly-APD was injected in mice after 5 min injection of a higher amount of HEDP. Similar results were observed with ^{186}Re-HEDP in HEDP-pretreated mice. However,

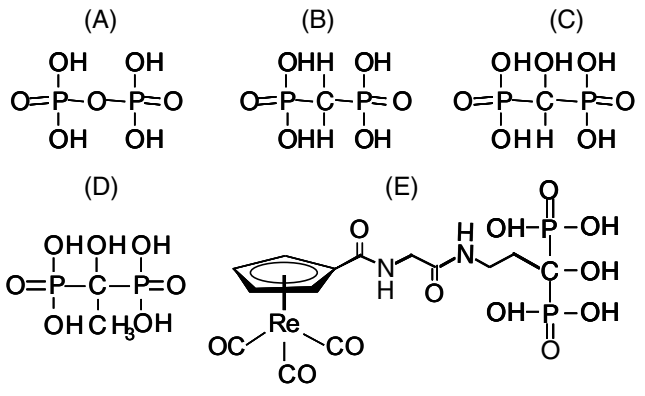

Figure 7. Chemical structures of polyphosphonate ligands (A) pyrophosphate, (B) methylenediphosphonate (MDP), (C) hydroxymethylenediphosphonate (HMDP), (D) 1-hydroxyethylidenediphosphonate (HEDP), and (E) [^{186}Re]CpTR-Gly-APD.

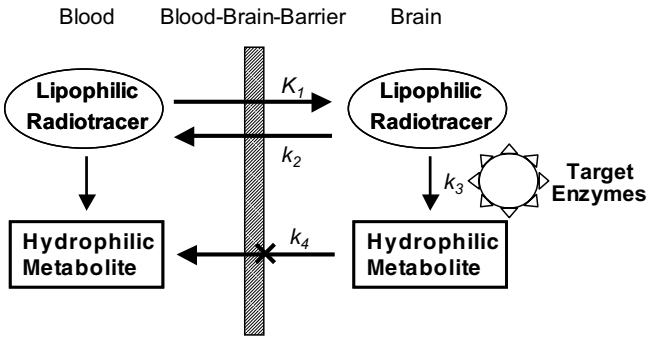

Figure 8. Chemical design of radiotracers based on metablic trapping principle. For measuring blood flow, k_3 should be much larger than k_2. However, an appropriate rate balance between k_2 and k_3 is required to determine k_3.

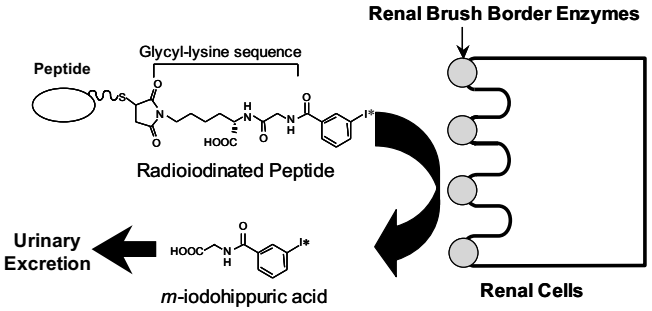

Figure 9. Chemical design of radiolabeled low molecular weight polypeptides for low renal radioactivity. The chemical linkage (glycyl-lysine) is cleaved by brush border enzymes present on the lumen of renal tubules before the polypeptide is internalized into renal cells. The resulting iodohippuric acid is rapidly excreted into urine.

a significant delay in blood clearance and high radioactivity levels in the kidney were observed especially with ^{186}Re-HEDP. These findings suggest that both specific activities and affinities to renal transport systems would play crucial roles in bone accumulation and blood clearance of ^{186}Re-labeled BPs. These findings would also provide a good basis for further design of ^{99m}Tc- and $^{186/188}$Re-labeled bisphosphonate that possess pharmacokinetics more suitable to diagnosis and radiotherapy.

5. Conclusion

Over the past 30 years, technetium chemistry has contributed to the development of a variety of ^{99m}Tc radiopharmaceuticals that are currently being used in clinical studies. During these times, significant knowledge has become available in the design of radiopharmaceuticals. The metabolic trapping strategy constitutes a representative approach to the design (Figure 8).[37] Chemical design of radiolabeled low molecular weight polypeptides utilizing renal brush border enzymes for low renal radioactivity levels constitutes another example of the design (Figure 9).[38] Future combination of the radiopharmaceutical design and technetium chemistry would pave the way to molecular imaging of a variety of disorders with ^{99m}Tc radiopharmaceuticals. The development of a new ^{99m}Tc radiopharmaceutical is a multidisciplinary effort and should need the collaboration of researchers in a variety of chemical and nuclear medicine fields.

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