Complex formation of Rhenium-186 with lipophilic ligands —Comparison with technetium-99m—

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Technetium-99m is the most used nuclide in diagnostic nuclear medical imaging because the energy of its gamma-ray emission (140 keV) is ideal for imaging using gamma cameras, and it can be produced on demand at medical facilities by using ^{99}Mo/^{99m}Tc generators. Various lesions can be visualized when ^{99m}Tc-labeled radiopharmaceuticals accumulate at the lesion site because of their unique mechanisms. In recent years, radiotheranostics have received considerable attention because radionuclide-targeted treatments are performed based on the imaging of the same target area.[1] Although ^{99m}Tc-radiopharmaceuticals are specialized for diagnostic imaging, their specific lesion accumulation properties are attractive for radiotheranostics. Rhenium, a group 7 congeneric element of technetium, is assumed to have chemical properties similar to those of Tc. ^{186}Re is an ideal radiotheranostic nuclide because it is a beta-emitting nuclide, and it emits gamma-ray associated with beta decay, whose energy is suitable for radionuclide therapy and imaging. Thus far, ^{186}Re has been produced by neutron irradiation in nuclear reactors, and it is difficult to obtain in Japan. At the RIKEN RI beam factory (RIBF), we succeeded in producing no-carrier-added, high-purity ^{186}Re using an accelerator-based ion beam irradiation. ^{99m}Tc-radiopharmaceuticals are complexes of ^{99m}Tc and a variety of ligands. Further rhenium is expected to form complexes as an analog of Tc. Therefore, it is important to evaluate the complex forming ability of Re. In this study, the complex formation of Re with lipophilic ligands was investigated using ^{186}Re produced at RIBF.

Rhenium-186 was produced in the ^{186}W$(d, 2n)^{186}$Re reaction. A 24-MeV deuteron beam delivered from the AVF cyclotron was irradiated onto a $^{186}WO_3$ pellet target (isotope enrichment of ^{186}W: 99.79%; thickness: 580 mg/cm^2). After irradiation, ^{186}Re was purified by chemical separation procedure.[2] The aqueous solution of ^{186}Re-perrhenate in 0.01 M HCl (radioactivity concentration: 83.0 MBq/mL) was supplied. MRP20 (N-(2(1H pyrolylmethyl)) N′-(4-pentene-3-one-2)) ethane-l, 2-diamine), ECD (ethyl cysteinate dimer), and BMEDA (n, n-bis(2-mercaptoethyl)-n′,n′-diethylethylene-diamine) were used as lipophilic chelating ligands. Stannous chloride was used as a reductant and GH (sodium glucoheptonate) was used as a stabilizer for ^{186}Re(V). The formation of ^{186}Re-ligand complexes was evaluated using octanol/water extraction and paper chromatography, and it was developed in methanol or physiological saline.

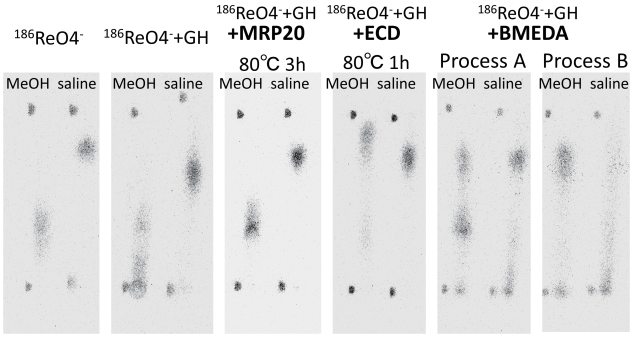

Fig. 1. Profiles of the paper chromatography of the reaction products of ^{186}Re with various lipophilic ligands. Development solution: methanol or physiological saline solution. Detection: Autoradiography using imaging plates.

We have been developing new radiopharmaceuticals by encapsulating various radionuclides in liposomes, which are capable DDS carriers.[3] We used remote loading methods, to achieve a high concentration of radionuclides in liposomes, that is, a ligand exchange reaction across the liposomal membrane using lipophilic and hydrophilic ligands. We successfully prepared ^{99m}Tc- liposomes using MRP20 as a lipophilic ligand. We first examined the reaction between ^{186}Re and MRP20; sit was found that ^{186}Re and MRP20 did not form chelate complexes under the same conditions as ^{99m}Tc. Therefore, the optimal conditions for the reaction of ^{186}Re with lipophilic ligands MRP20, ECD, and BMEDA were investigated. ^{99m}Tc could form stable complexes with each of these three ligands under mild conditions. The complex formation between ^{186}Re and these lipophilic ligands required 10 times more reducing agent, higher reaction temperatures, and longer reaction times than those of ^{99m}Tc. Representative paper chromatography profiles of these reaction products are shown in Fig. 1. ^{186}Re and ECD formed a lipophilic ligand complex that moved close to the solvent front in methanol. In the reaction of ^{186}Re with BMEDA, the products were different depending on the reaction process. The products of process A seemed to contain [$^{186}ReO_4^-$] and the lipophilic complex. ^{186}Re and MRP20 could not form a complex even with these severe conditions, and their chromatogram profiles were almost the same as those of [$^{186}ReO_4^-$]. Based on these results, we speculate that ^{186}Re was more difficult to reduce compared to ^{99m}Tc analogues; further, the reaction rate with ligands was slower than

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that of ^{99m}Tc. ^{186}Re seemed to be re-oxidizing with oxygen from the air back to [$^{186}ReO_4^-$], which may compete with the complex formation and inhibit the reaction.

It is believed that rhenium has similar chemical properties to technetium, and it can be handled in the same manner. However, the results of this study indicate that their chemical properties are very different at least in terms of the ligand-complex formation. Highly concentrated and stable ^{186}Re-labeling compounds are necessary to promote radiotheranostics. The present findings will help establish optimized labeling methods for ^{186}Re.

References

1) K. Herrmann *et al.*, Lancet Oncol. **21**, e146 (2020).
2) N. Shigeta *et al.*, J. Radioanal. Nucl. Chem. **205**, 85 (1996).
3) I. Ogihara-Umeda *et al.*, J. Nucl. Med. **37**, 326 (1996).