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REVIEW ARTICLE

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Development of radiopharmaceuticals for PET renography

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Abstract. Renography is a standard clinical diagnostic test frequently used to evaluate renal function in patients with suspected renal disorders. It is conducted by dynamic planar imaging using technetium-99m renal agents. Although renography in the current form provides adequate results for certain clinical applications, the planar imaging used in renography restricts its ability in providing accurate quantitative data and detailed pathophysiologic information. These drawbacks limit the possible use of renography in the early detection and monitoring of many renal diseases. The technical limitations of renography associated with the use of planar imaging can be eliminated by using positron emission tomography (PET). In this regard, several potential PET renal agents were developed, which are all listed in this review article. PET renography could provide the potential to diagnose renal diseases early and quickly implement appropriate preventive and/or treatment strategies to improve patient care and reduce the incidence of kidney failure.

Keywords. PET; renography; renal function; radiopharmaceuticals; tubular secretion agents; glomerular filtration agents.

Glomerular filtration rate (GFR) estimated using serum creatinine (SCr) concentration is considered the best indicator of overall kidney function, and its assessment is an important clinical tool in the care of renal patients.[1] It helps a clinician to assess the degree of renal dysfunction and progression of established renal disease and to determine proper drug dosages. However, the SCr concentration becomes abnormal only after the renal function is already significantly compromised.[2] In addition, it is greatly influenced by numerous non-renal factors, such as muscle metabolism and protein intake.[2] Significant renal disease can exist with minimal or no change in SCr concentration because of the renal reserve, enhanced tubular secretion of creatinine, and other factors.[3, 4] Most importantly, an intrinsic drawback of SCr or other serum biomarkers is that they provide only an overall renal functional status, and provide no information on the individual kidney function or renal pathophysiology.

Clinical imaging techniques such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear imaging play an important role in the evaluation of patients with renal diseases and overcomes the limitations of the serum markers.[5] Ultrasound and CT provide good anatomic images but limited functional information. CT utilizes iodinated radiocontrast agents that cause contrast-induced nephropathy in some patients.[6] MRI shows promise for evaluating patients with renal diseases because of the combined value of anatomical and functional information.[7–10] Although MRI was originally thought to be safe and without the nephrotoxic effects of iodinated contrast media, gadolinium-based media used in MRI have been reported to induce nephrogenic systemic fibrosis in some patients with renal dysfunction.[11] In this regard, nuclear imaging has great value in the diagnosis and management of patients with renal diseases.[12–14] Renography in particular has become an indispensable diagnostic tool for clinical evaluation of renal function.[15–18]

Renography is currently conducted by a dynamic planar gamma imaging technique using technetium-99m (half-life –6 h, E_γ = 141 KeV, 88%) labeled radiopharmaceuticals. Figure 1 shows the current clinically used radiopharmaceuticals for renography, namely, technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA), technetium-99m mercaptoacetyltriglycine (^{99}Tc-MAG3), and technetium-99m L,L-ethylenedicysteine (^{99m}Tc-L,L-EC).[19] ^{99m}Tc-DTPA is considered as a glomerular filtration agent

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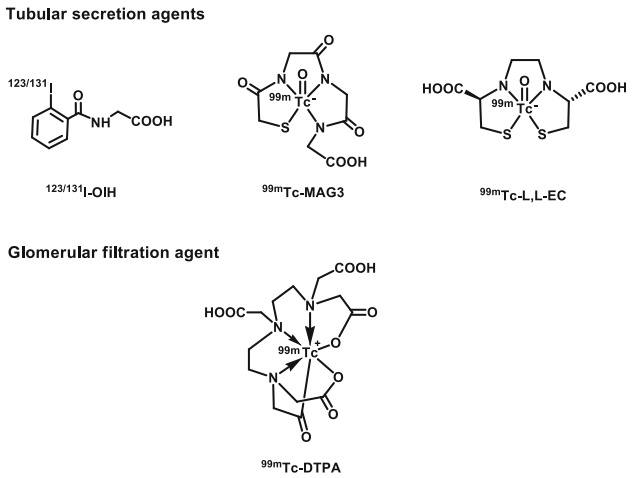

Figure 1. Chemical structures of the clinically used renal function imaging agents.

because it is freely filtered by the glomerulus due to its low plasma protein binding of ~4% and it is neither secreted nor reabsorbed.[20] Thus, its renal excretion efficiency is considered to be about 20-25%, which is equal to the rate at which it is filtered. ^{99m}Tc-MAG3 and ^{99m}Tc-L,L-EC are considered tubular secretion agents because they are cleared almost exclusively by tubular secretion.[21, 22] The plasma protein binding of ^{99m}Tc-MAG3 is ~90% and it is not filtered by glomeruli or reabsorbed,[23] whereas the plasma protein-bound fraction of ^{99m}Tc-L,L-EC is ~30% and free ^{99m}Tc-L,L-EC is filtered by the glomerulus but is not reabsorbed.[22] The clearance of both ^{99m}Tc-MAG3 and ^{99m}Tc-L,L-EC is ~60% and ~75% of *ortho*-^{131}I-iodohippurate (^{131}I-OIH), respectively.[21, 22]

^{131}I-OIH introduced in the early 1960s is the first renal tubular agent clinically used for renography for decades.[24] It is considered as a gold standard for measuring effective renal plasma flow (ERPF).[25, 26] Because of the more favorable nuclear properties of ^{123}I (half-life = 13.2 hr, E_γ = 159 KeV, 84%) for imaging compared with those of ^{131}I (half-life = 8.04 d, E_γ = 364 KeV, 81%, E_β = 606 KeV, 89%), *ortho*-^{123}I-iodohippurate (^{123}I-OIH) was later developed and used for radionuclide renography.[27] Both ^{123}I-OIH and ^{131}I-OIH were approved for clinical use in the United States and discontinued after the introduction of ^{99m}Tc-MAG3 due to the high cost of iodine-123 and the suboptimal nuclear properties of iodine-131 for imaging.[28] However, ^{99m}Tc-MAG3 is not an ideal replacement for ^{131}I-OIH and ^{123}I-OIH. Its success was mainly due to the superior nuclear properties of technetium-99m for imaging, and not due to improvements in pharmacokinetic or biological properties. Since the clearance of the renal tubular secretion agents from the blood is faster than that of the filtration agents, they provide better quality images due to lower background radioactivity from various organs around the kidneys. These relatively higher quality images can be interpreted more accurately and reduce errors in the calculation of renal function. Thus, tubular secretion agents are preferred radiopharmaceuticals for renography.[19]

The tubular secretion agents are extracted from the plasma present in the peritubular capillaries into the tubular cells *via* the basolateral membrane governed by the organic anion transporter (OAT) system expressed in the proximal convoluted tubules, e.g., OAT1 and OAT3, with a larger contribution from OAT1.[29, 30] The carbonylglycine (-CO-NH-CH_2-COOH) moiety is generally believed to be essential for an efficacious fit with the receptor proteins of the OAT system, according to Despopoulos' theory.[31] Transport of the tubular secretion agents from the tubular cell into the urine via the luminal membrane is thought likely to be governed by the multidrug resistance-associated protein 2 (MRP2).[32]

Although renography provides important information about a renal function that aids in the diagnosis and management of patients with suspected renal and urinary tract problems, there are drawbacks associated with the use of the planar imaging technique.[33, 34] Planar (2D) imaging provides limited structural information and poor quantitative data.[35] Tomographic (3D) imaging methods, such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) overcomes the drawbacks of planar imaging. These tomographic imaging techniques provide substantially superior quantitative results compared to planar imaging, due to attenuation correction and lack of organ overlap.[36, 37] In addition, they provide pathophysiologic information from the two-dimensional slice images of radiotracer distribution.

While SPECT is superior to planar imaging, it still suffers from poor spatial and temporal resolutions and sensitivity compared to PET in the clinical setting.[37] For example, the comparative spatial resolution of PET camera is 4-6 mm versus 10-20 mm for the conventional SPECT camera, and the reported sensitivities differ by a factor of ~14 in favor of PET camera.[38, 39] It is important to note that the modern SPECT camera utilizing a solid-state cadmium-zinc-telluride (CZT) detector has superior sensitivity than a conventional SPECT camera utilizing a NaI(Tl) scintillation crystal detector.[40] All SPECT cameras use collimators to obtain spatial information about the gamma emissions from an imaging subject. The

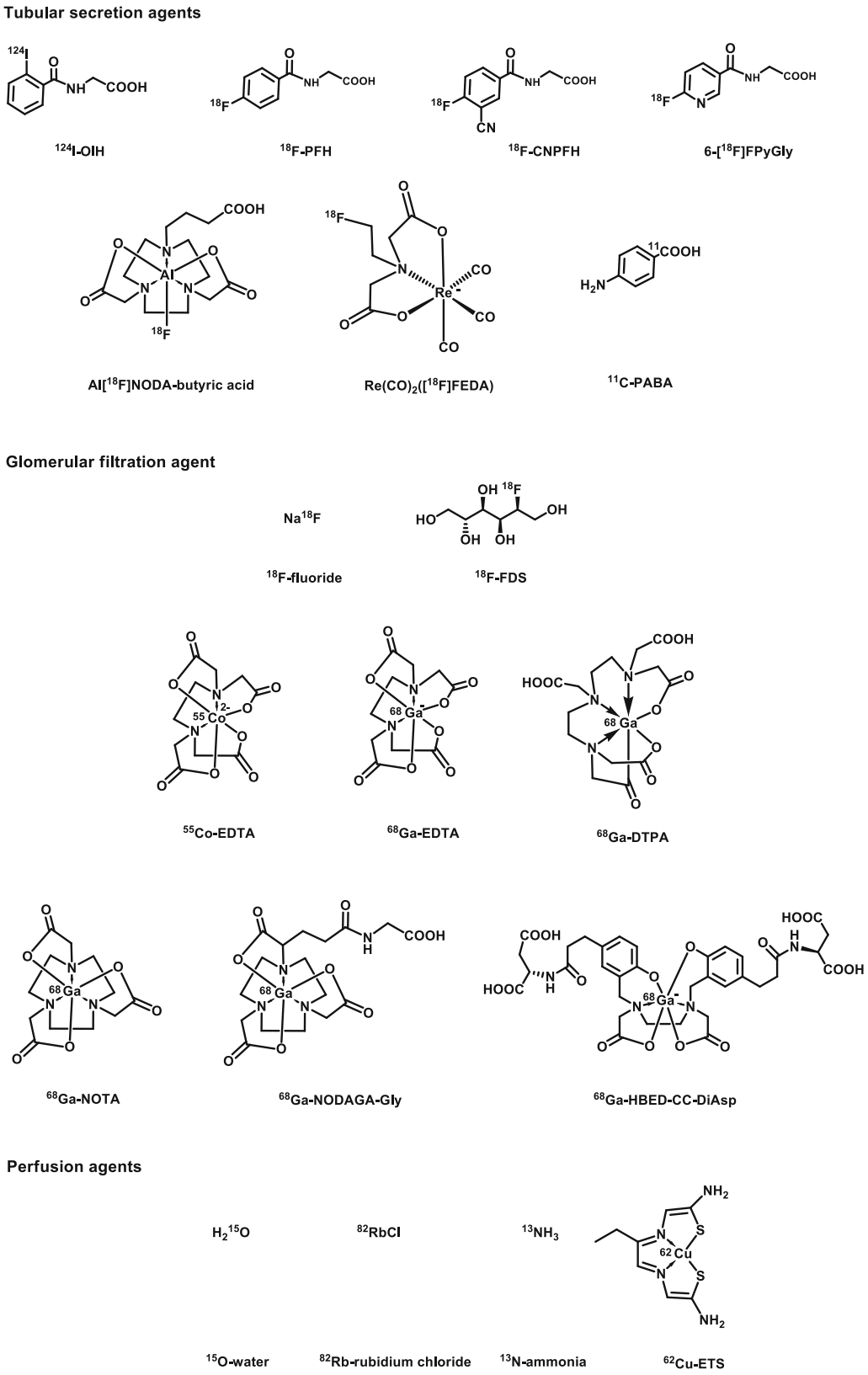

Figure 2. Chemical structures of all the PET renal function imaging agents reported to date.

collimator attenuates most incident gamma photons and thus greatly limits the sensitivity of the camera system. In contrast, a PET camera uses electronic collimation by detecting coincidence events. Electronic collimation not only improves the sensitivity but also enhances the spatial resolution. By allowing more

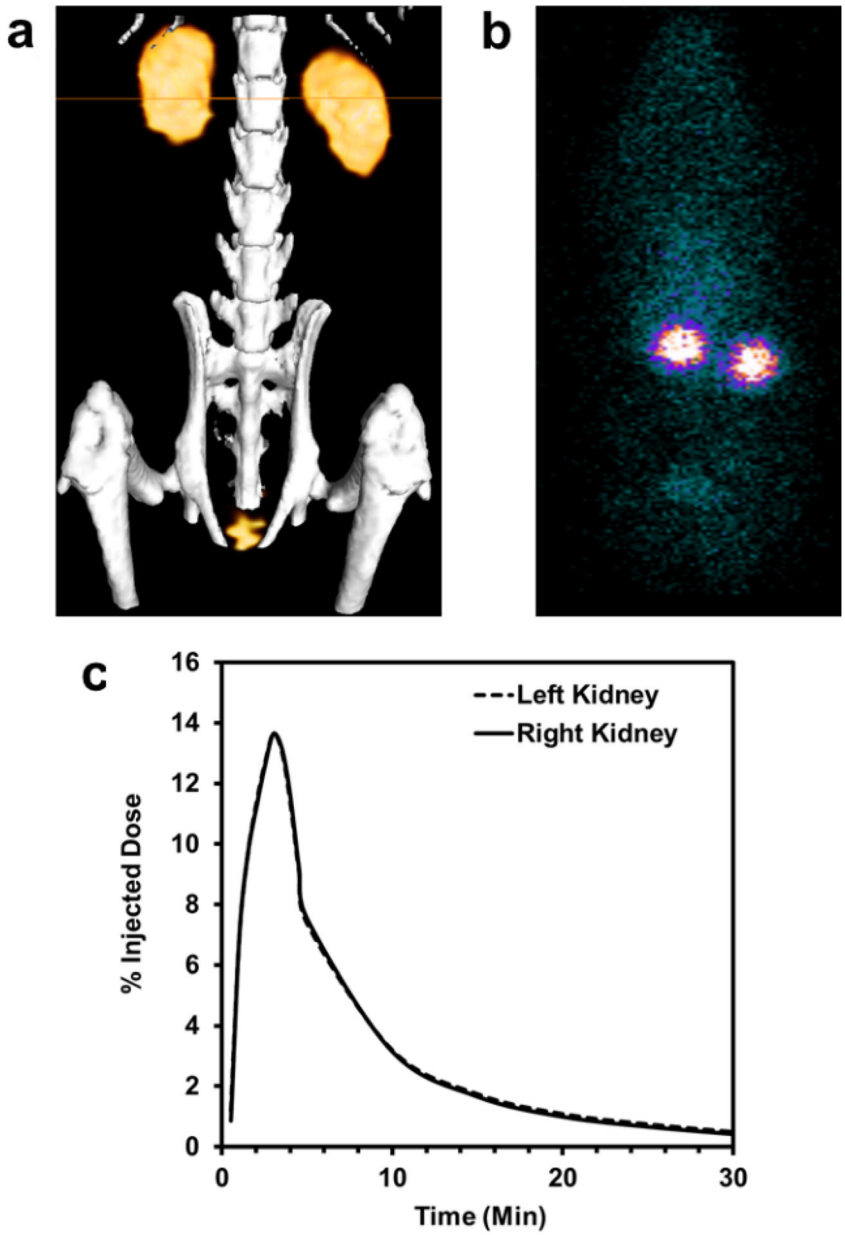

Figure 3. a) An abdomen PET/CT image, maximum intensity projection obtained at the renogram peak maximum, b) an abdomen ^{99m}Tc-MAG3 planar gamma image obtained at the renogram peak maximum, and c) a^{18}F-PFH PET renogram obtained in a healthy female Sprague Dawley rat.

valid counts (statistical improvement), PET is substantially more accurate in the quantitative assessment of the regional concentration of the radiotracers compared to SPECT. In addition, the tissue attenuation of 511 KeV emission from a PET radionuclide is much less than the 140 KeV emission of ^{99m}Tc used in renography. In PET, the annihilation photons must traverse the tissue without interaction; the attenuation is depth-independent and is a function of the total thickness of tissue, greatly simplifying the attenuation correction compared to SPECT.[41] In addition to the poor counting statistics, a SPECT camera using either a conventional NaI(Tl) scintillation crystal detector or a modern solid-state CZT detector is insufficient to acquire near real-time dynamic imaging data for fast-clearing renal tubular secretion agents.

To utilize the potential of PET in renal function imaging,[34, 42–45] several potential PET renal agents (Figure 2) labeled with iodine-124 (half-life: 4.2 d), cobalt-55 (half-life: 17.5 h), fluorine-18 (half-life: 110 min), gallium-68 (half-life: 68 min), carbon-11 (half-life: 20.4 min), nitrogen-13 (half-life: 10 min), copper-62 (half-life: 9.7 min), oxygen-15 (half-life: 2 min), and rubidium-82 (half-life:75 sec) were

developed.[46–69] The ideal properties required for a renal agent suitable for renography are: 1) exclusive clearance from the blood by kidneys into the urine with high extraction efficiency preferably through both glomerular filtration and tubular secretion, 2) no uptake by any organ other than the kidney, 3) no retention in any organ/tissue, and 4) no metabolic transformation. Most importantly, the renal kinetics of the agent should show significant differences between normal and pathologic kidneys.

Of all the PET renal function imaging agents reported to date, *para*-^{18}F-fluorohippurate (^{18}F-PFH), *ortho*-^{124}I-iodohippurate (^{124}I-OIH), Al^{18}F-NODA-butyric acid, Re(CO)$_3$([^{18}F]FEDA), *N*-(6-[^{18}F]Fluoropyridin-3-yl)glycine (6-[^{18}F]FPyGly), and [carboxy-^{11}C]4-aminobenzoic acid (^{11}C-PABA) are considered as tubular secretion agents suitable for renography.[46–48, 58–60, 70–73] In the case of ^{11}C-PABA, it is metabolized in the liver to form *para*-aminohippuric acid, which is clinically used to measure ERPF because of its high renal tubular secretion as well as active glomerular filtration once it enters the kidneys.[69] ^{124}I-OIH and ^{18}F-PFH are PET analogs of ^{131}I-OIH. A relatively long half-life of ^{124}I allows supplying clinical doses to the long distant clinical centers from a manufacturing site. Alternatively, ^{18}F is the most widely available pure PET radionuclide, and its low energy and high abundance positrons ($E_{\beta+\ max}$ = 0.635 MeV, 97% abundance) facilitate the acquisition of the highest resolution images among the clinically used PET radionuclides. ^{18}F-PFH was the first PET renal tubular secretion agent to be reported.[46] ^{18}F-PFH PET renography produced exceptionally better quality renograms and images than ^{99m}Tc-MAG3 renography (Figure 3).[70] In addition, it was able to predict future disease progression in Han:SPRD rats with slowly progressive autosomal dominant polycystic kidney disease (Figure 4).[72] ^{18}F-PFH combine the desirable biological properties of hippurate, the optimal nuclear properties of ^{18}F, and it can be easily produced for clinical use by a two-step procedure utilizing a spirocyclic iodonium(III) ylide precursor.[71] Both ^{18}F-PFH and ^{124}I-OIH are estimated to deliver a lower whole-body radiation dose when compared to ^{99m}Tc-MAG3, which is a significant benefit in terms of radiation safety, especially in pediatric patients and in adult patients with severe renal dysfunction.[65]

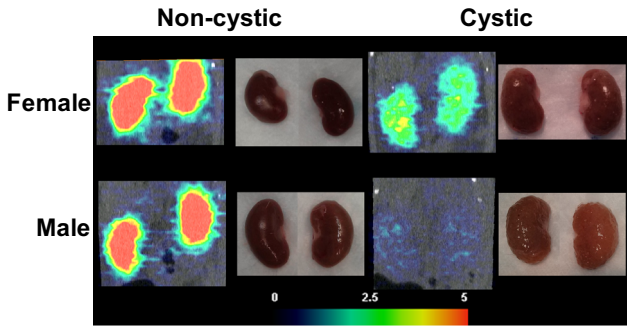

Figure 4. Kidney PET/CT images (coronal slice) obtained at 2 min p.i. of 26-wk old Han:SPRD rats injected with ^{18}F-PFH.

Most of the PET renal function imaging agents developed to date are glomerular filtration agents and are useful for GFR measurement.[50, 51, 53, 56, 61, 63, 68] PET agents such as ^{15}O-water, ^{82}RbCl, ^{13}N-ammonia, and ^{62}Cu-ETS are evaluated as renal perfusion agents.[52, 57, 66, 67] Feasibility of conducting a clinical study to determine renal function by PET/CT imaging was demonstrated in the recent years with ^{82}RbCl, ^{68}Ga-ethylene diamine tetraacetic acid (^{68}Ga-EDTA) and 2-deoxy-2-^{18}F-fluoro-D-sorbitol (^{18}F-FDS).[52, 62, 63, 69] In addition, dynamic 2-deoxy-2-18F-fluoro-D-glucose (^{18}F-FDG) PET/MRI was used to estimate GFR and ERPF in humans.[74] However, it is important to note that ^{18}F-FDG may not provide an accurate renal function information since it is involved in several physiological processes. Application of PET would significantly increase the clinical value of renography by providing both accurate quantitative data and higher resolution tomographic images. Although several PET renal agents have been developed and investigated in preclinical and clinical studies, further research is needed to identify the most beneficial clinical indications with PET renography. The current high cost associated with PET imaging makes it challenging to use PET renography as an advanced alternative to conventional renography. This problem would most likely be overcome in the future as further improvements in the camera technology and production/distribution of PET radionuclides/radiopharmaceuticals reduce the overall cost of PET imaging.

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