

Radiopharmaceuticals for Positron Emission Tomography Imaging of Somatostatin Receptor Positive Tumors

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Abstract The targeting of somatostatin receptors in tumors has been a goal in cancer treatment and diagnosis since the 1980s. Over the past two decades, great strides have been made in the development of somatostatin analogs labeled with positron emitters for positron emission tomography (PET) imaging of somatostatin receptor positive tumors. In this review, the radionuclide production, radiochemistry, preclinical and clinical studies of somatostatin analogs labeled with several positron-emitting radionuclides are described. In the past 5 years, there have been clinical trials with ¹⁸F-, ⁶⁴Cu-, ⁶⁸Ga-, ⁸⁶Y- and ^{110m}In-labeled somatostatin analogs. In addition, radiochemistry and preclinical studies have been performed with ⁷⁶Br and ⁶⁶Ga. The advantages of these positron-emitting somatostatin analogs include increased image resolution with PET compared with γ scintigraphy, improved quantification capabilities with PET, and the ability to use the positron emitters as companion isotopes to therapeutic radionuclides such as the ⁸⁶Y (PET)/⁹⁰Y (therapy) pair.

Keywords Somatostatin · Positron-emitting radionuclide · Cancer therapy · Diagnosis · Positron emission tomography

Abbreviations

^{76}Br NHS	<i>N</i> -Succinimidyl 4- ^{76}Br bromobenzoate
CB-TE2A	4,11-Bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane
DFO	Desferrioxamine B
DOTA	1,4,7,10-Tetraazacyclododecane- <i>N,N',N'',N'''</i> -tetraacetic acid
DTPA	Diethylenetriaminepentaacetic acid
^{111}In -DTPA-OC	^{111}In -DTPA-D-Phe ¹ -octreotide
[^{18}F]FBA	4- ^{18}F fluorobenzoic acid
[^{18}F]FB-OC	4- ^{18}F fluorobenzoyl-OC
[^{18}F]FP-Gluc-TOCA	<i>N</i> $^{\alpha}$ -(1-deoxy-D-fructosyl)- <i>N</i> $^{\epsilon}$ -(2- ^{18}F fluoropropionyl)-Lys ⁰ -Tyr ³ -octreotate
OC	Octreotide
PET	Positron emission tomography
SPECT	Single-photon-emission computerized tomography
SSTr	Somatostatin receptor
SSTr2	Somatostatin receptor subtype 2
TATE	Octreotate
TETA	1,4,8,11-Tetraazacyclotetradecane-1,4,8,11-tetraacetic acid
TOC	Tyr ³ -OC
Y3	Tyr ³

1**Introduction**

Somatostatin is a 14-amino-acid peptide involved in the regulation and release of a number of hormones, including growth hormone, thyroid-stimulating hormone and prolactin. Somatostatin receptors (SSTr) are found on the cell surface and occur in a number of different normal organ systems, including the central nervous system, the gastrointestinal tract, and the exocrine and endocrine pancreas [1–3]. A large number of human tumors express SSTr [4], particularly SSTr subtype 2 (SSTr2). The targeting of SSTr in tumors has been a goal in cancer treatment and diagnosis since the 1980s. Somatostatin has a very short biological half-life, but analogs have been developed, such as octreotide (OC), that have much longer residence times [5].

OC has been labeled with ^{123}I and ^{111}In and used to image SSTr2-positive tumors in humans by conventional scintigraphy [6, 7]. ^{123}I -Tyr³-OC has a high hepatobiliary excretion that hinders visualization of tumors in the abdomen, whereas ^{111}In -diethylenetriaminepentaacetic acid-D-Phe¹-OC (^{111}In -DTPA-OC) clears primarily through the kidneys [7]. In the USA and Europe, ^{111}In -DTPA-OC is currently a clinically approved agent for imaging neuroendocrine tumors. Because of the limited sensitivity and resolution of single-photon-emission computerized tomography (SPECT), several research groups have worked towards the development of a positron-emitting agent for positron emission tomography (PET) imaging of SSTr-positive tumors. Using somatostatin analogs labeled with a positron-emitting radionuclide and PET, a quantitative assessment of tracer accumulation within tissues can be achieved,

Table 1 Positron-emitting radionuclides

Isotope	$T_{1/2}$ (h)	Methods of production	Decay mode	E_{β^+} (keV)	Reference
^{18}F	1.83	Cyclotron $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$	β^+ (97%), EC (3%)	635	[27]
^{60}Cu	0.4	Cyclotron, $^{60}\text{Ni}(\text{p},\text{n})^{60}\text{Cu}$	β^+ (93%), EC (7%)	3,920, 3,000, 2,000	[16]
^{61}Cu	3.3	Cyclotron, $^{61}\text{Ni}(\text{p},\text{n})^{61}\text{Cu}$	β^+ (62%), EC (38%)	1,220, 1,150, 940, 560	[16]
^{64}Cu	12.7	Cyclotron, $^{64}\text{Ni}(\text{p},\text{n})^{64}\text{Cu}$	β^+ (19%), EC (41%), β^- (40%)	656	[15]
^{66}Ga	9.5	$^{66}\text{Zn}(\text{p},\text{n})^{66}\text{Ga}$	β^+ (57%), EC (43%)	4.15 (max)	[10, 12]
^{68}Ga	1.1	$^{68}\text{Ge}/^{68}\text{Ga}$ generator	β^+ (90%), EC (10%)	1,880, 770	[8]
^{76}Br	16.2	$^{76}\text{Se}(\text{p},\text{n})^{76}\text{Br}$	β^+ (54.7%), EC (45.3%)	3,941 (max)	
^{86}Y	14.7	Cyclotron, $^{86}\text{Sr}(\text{p},\text{n})^{86}\text{Y}$	β^+ (33%), EC (66%)	2,335, 2,019, 1,603, 1,248, 1,043	[20]
$^{110\text{m}}\text{In}$	1.15	Cyclotron, $^{110}\text{Cd}(\text{p},\text{n})^{110\text{m}}\text{In}$ or $^{110}\text{Sn}/^{110\text{m}}\text{In}$ generator	β^+ (62%), EC (38%)	1,010, 2,260 (max)	[22, 24]
^{124}I	100.2	Cyclotron	β^+ (25%), EC (75%)	2,134, 1,533	[64]

potentially offering improvements over SPECT where quantitative results are needed, and where tumor size is small or the tumor is deep within the body. This review will provide an overview of the progress thus far towards the development of a PET SSTR imaging agent, using positron-emitting radionuclides that include ^{18}F , ^{76}Br , ^{68}Ga , ^{66}Ga , ^{64}Cu , $^{110\text{m}}\text{In}$ and ^{86}Y (Table 1).

2 Radionuclides for PET Imaging

There are two gallium radionuclides with decay characteristics that are suitable for PET imaging. ^{68}Ga ($T_{1/2}=68$ min; 90% β^+) is produced from the $^{68}\text{Ge}/^{68}\text{Ga}$ generator. The long half-life of the parent nuclide ^{68}Ge ($T_{1/2}=270.8$ days) allows the generator to be used for 1–2 years, making ^{68}Ga radiopharmaceuticals relatively economical. A commercially available generator was based on the design of Loc'h et al. [8], where the generator was eluted in 3 mL 1 N HCl. More recently, another $^{68}\text{Ge}/^{68}\text{Ga}$ generator has recently been reported, where the gen-

erator is eluted in 1 mL 0.1 N HCl, making it more convenient for radiopharmaceutical preparation [9]. ^{66}Ga is a cyclotron-produced positron-emitting radionuclide that has been used in a limited number of studies requiring a medium half-life positron-emitting nuclide where a half-life longer than 1 h is needed. This nuclide can be produced in small biomedical cyclotrons, utilizing the $^{66}\text{Zn}(p,n)^{66}\text{Ga}$ reaction [10–13].

Positron-emitting copper radionuclides have a wide range of half-lives (10 min–12.7 h) and are cyclotron- or generator-produced. ^{64}Cu was initially produced using a reactor by the $^{64}\text{Zn}(n,p)^{64}\text{Cu}$ nuclear reaction [14] but more recently is produced by the $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ nuclear reaction using a biomedical cyclotron [15]. A target has been specifically designed for the production of this nuclide [15], and by altering the enriched isotope of nickel used as the target, large quantities of ^{64}Cu , ^{60}Cu and ^{61}Cu have been produced [16]. ^{62}Cu is generator-produced from the decay of ^{62}Zn [17], and ^{60}Cu is produced with a biomedical cyclotron [16], but with 10- and 23-min half-lives, respectively, these radionuclides are not readily applicable to labeling somatostatin analogs or other peptide-based tumor imaging agents. ^{64}Cu is becoming widely-used for labeling peptide-based agents.

There are two radioisotopes of yttrium that are utilized in radiopharmaceuticals: ^{90}Y ($T_{1/2}=64.06$ h) and ^{86}Y ($T_{1/2}=14.7$ h). ^{90}Y is a pure β^- emitter produced following the decay of the parent nuclide ^{90}Sr ($T_{1/2}=27.8$ years) and has been widely used for targeted radiotherapy of cancer. ^{86}Y is produced by the $^{86}\text{Sr}(p,n)^{86}\text{Y}$ nuclear reaction and is a positron-emitting nuclide that has been used in PET imaging of patients that are undergoing therapy with ^{90}Y radiopharmaceuticals [18, 19]. No-carrier-added ^{86}Y can be produced with a biomedical cyclotron by the $^{86}\text{Sr}(p,n)^{86}\text{Y}$ reaction. As described by Rösch et al. [20], an enriched $^{86}\text{SrCO}_3$ target was irradiated yielding ^{86}Y , which was separated by a combined coprecipitation and ion-exchange purification process [20]. An improved procedure for separation and purification of ^{86}Y is an electrochemical separation that was recently reported [21], which produced ^{86}Y more rapidly and in high chemical purity, with the residual strontium content reduced to less than 0.1 ppm.

$^{111}\text{In-OC}$ has been used extensively in the imaging with SPECT for SSTR-positive tumors. $^{110\text{m}}\text{In}$ ($T_{1/2}=69$ min) is a short-lived positron-emitting isotope of indium and can be produced either from a $^{110}\text{Sn}/^{110\text{m}}\text{In}$ generator or by the nuclear reaction $^{110}\text{Cd}(p,n)^{110\text{m}}\text{In}$ with a low-energy cyclotron (11.8 MeV protons with beam currents up to 15 μA) [22–24]. Using a low-energy cyclotron, 1 h irradiation of ^{110}Cd produced more than 20 GBq (540 mCi) [25]. With its short half-life, $^{110\text{m}}\text{In}$ is suitable for the labeling of small peptides such as OC that have rapid kinetics.

The positron-emitting halogens with applications for labeling somatostatin analogs include ^{18}F , ^{76}Br and ^{124}I . From an imaging standpoint, ^{18}F ($T_{1/2}=110$ min) is an ideal isotope among all other halogen radionuclides for PET imaging, since it has 97% positron abundance with 0.64-MeV positron energy [26]. ^{18}F had historically been produced by a variety of cyclotron, linear-accel-

erator and reactor methods [27]. Currently, nearly all ^{18}F is produced using a single nuclear reaction, $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$, with the majority of the radionuclide isolated as the ^{18}F fluoride ion in aqueous solution [28]. More importantly, ^{18}F can be produced in relatively large quantities (gigabecquerels or curies) in standard commercial PET cyclotrons supplied by several manufacturers [29–31]. ^{76}Br ($T_{1/2}=16.2$ h) is practical for PET imaging applications and can be prepared by the direct reaction of $\text{Cu}_2^{76}\text{Se}$ alloy with protons at 16 MeV, producing ^{76}Br in high yield and low ^{77}Br contamination with a small medical cyclotron [32]. ^{124}I can be produced via the nuclear reaction $^{124}\text{Te}(\text{p},\text{n})^{124}\text{I}$ with a cyclotron [33]. Despite the disadvantage of ^{124}I , a lower positron abundance and subsequent emission of high-energy γ -rays, successful PET imaging with ^{124}I -labeled tracers is possible [34, 35].

3

Somatostatin Analogs Labeled with Positron-Emitting Metal Radionuclides

3.1

Somatostatin Analogs Labeled with Gallium Radionuclides

The first positron-emitting metal radionuclide-labeled somatostatin analog was ^{68}Ga -[DFO]-OC [36], where DFO is desferrioxamine B. OC was modified with DFO, which is a chelator that complexes Fe^{3+} and Ga^{3+} with high stability. The binding affinity of [Ga]-DFO-OC was tested against ^{125}I -Tyr³-OC in rat cortex membranes and gave a pIC_{50} of 8.2. The biodistribution of [^{67}Ga]-DFO-OC in normal and in pancreatic islet cell-tumor-bearing rats showed renal clearance and tumor uptake similar to that of ^{111}In -DTPA-OC. PET scans with ^{68}Ga -DFO-OC revealed rapid tumor uptake that peaked at 0.9% ID/mL at 30 min post injection [36]. Since the mid-1990s there have been no other publications on ^{68}Ga -DFO-OC, and it is unknown whether this agent was evaluated in a successful clinical trial.

A promising new somatostatin analog for PET imaging with the gallium isotopes is DOTA-Tyr³-OC (DOTATOC) (Fig. 1). OC was modified by replacing Phe in the 3-position of OC with tyrosine to increase the hydrophilicity for increased renal clearance and to allow dual labeling with ^{125}I for potential therapy applications [37]. Use of the bifunctional chelator 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid (DOTA) allowed labeling with a broad spectrum of 2⁺ and 3⁺ radiometals. In a biodistribution study comparing ^{67}Ga -DOTATOC (^{67}Ga , $T_{1/2}=78$ h) with ^{111}In -DTPA-OC (^{111}In , $T_{1/2}=2.8$ days) in rat pancreatic AR42 J tumor-bearing nude mice, the gallium compound had a significantly higher tumor uptake and a lower kidney uptake. Examination of the crystal structure of a model peptide chelate, Ga -DOTA-*D*-PheNH₂, revealed that one carboxylate group is free and deprotonated at physiological pH; this increased hydrophilicity may contribute to the improved tumor uptake and re-

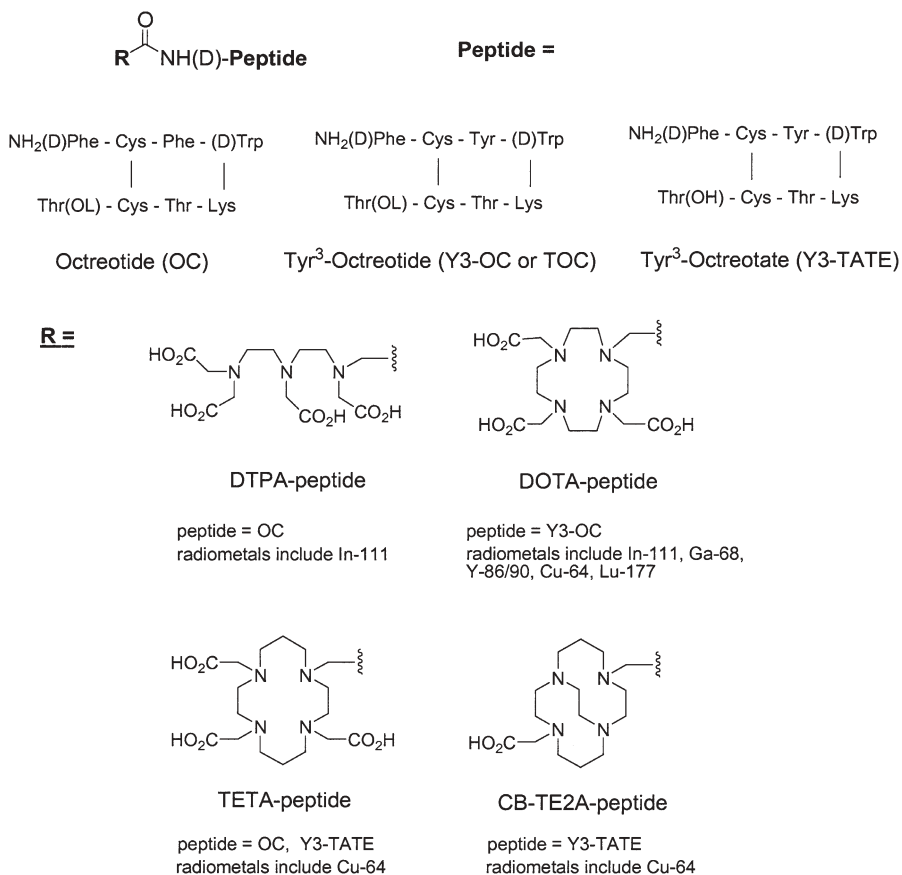


Fig. 1 Structures of somatostatin analogs and chelators for radiolabeling with metal positron-emitting radionuclides

nal clearance [37]. When affinities were compared in complete displacement experiments with ^{125}I -[Leu⁸, D-Trp²², Tyr²⁵]-somatostatin 28 using membranes from CCL39 cells stably transfected with human SSTR, Ga-DOTATOC was found to have a higher affinity ($\text{IC}_{50}=2.5$ nM) for SSTR2 than In-DTPA-OC (22 nM) [38].

Henze et al. [39] evaluated ^{68}Ga -DOTATOC as a potential agent for PET imaging of meningiomas. Dynamic PET scans were acquired over 120 min after intravenous injection of 175 MBq ^{68}Ga -DOTATOC in three patients with eight meningiomas. The radiolabeled compound showed rapid blood and renal clearance, with a half-life α of 3.5 min and a half-life β of 63 min. All meningiomas showed high uptake, with a mean standard uptake value of 10.6, and there was no tracer accumulation in the surrounding normal brain tissue. The ratio of uptake in tumor versus normal tissue reached 730 at 120 min post injection. The smallest lesions detected were 7–8 mm, which is a vast im-

provement over the lower imaging threshold with ^{111}In -DTPA-OC by SPECT (2.7 cm) [39].

^{68}Ga -labeled DOTATOC was evaluated as a potential imaging agent for carcinoid tumors by Hofmann et al. [40]. Dynamic PET scans were acquired over 180 min after intravenous injection of 80–250 MBq in eight patients with carcinoid tumors. The group predefined 40 lesions by CT and/or magnetic resonance imaging, and of these lesions, the PET imaging of ^{68}Ga -DOTATOC identified 100%, whereas SPECT imaging of ^{111}In -DTPA-OC identified only 85%. The PET imaging of ^{68}Ga -DOTATOC also identified additional lesions not previously defined. Blood clearance was rapid and renal accumulation was low enough to allow delineation of adrenal glands [40].

Recently, ^{68}Ga has been evaluated for use in receptor-targeted PET imaging [12, 41]. Ugur et al. [12] evaluated ^{68}Ga -DOTATOC in animal biodistribution and micro PET studies and compared this with ^{67}Ga - and ^{68}Ga -labeled DOTATOC in AR42 J tumor-bearing nude mice. Tumor uptake was rapid and the maximum values of the percentage infective dose per gram were comparable for all three isotopes. Blood clearance was rapider and kidney accumulation was lower in the case of ^{68}Ga -DOTATOC, with a maximum percentage infective dose per gram in the kidney of 4.5 versus 9.18 for ^{67}Ga and 11.4 for ^{68}Ga .

3.2

Somatostatin Analogs Labeled with Copper Radionuclides

OC has been conjugated to the chelator 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (TETA) for labeling with ^{64}Cu [42]. ^{64}Cu -TETA-OC showed high affinity for SSTR both in vitro and in vivo and cleared primarily through the kidneys, with relatively low liver accumulation. ^{64}Cu -TETA-OC was evaluated as a PET imaging agent for neuroendocrine tumors in eight patients [43]. Preliminary results showed that in two patients, ^{64}Cu -TETA-OC and PET detected more SSTR-positive lesions than the currently used agent, ^{111}In -DTPA-OC, and γ scintigraphy/SPECT. In one patient, ^{111}In -DTPA-OC and γ scintigraphy showed low uptake in a lung lesion that was not observed with ^{64}Cu -TETA-OC and PET.

A series of ^{64}Cu -labeled somatostatin analogs was investigated to determine the optimal analog with respect to target tissue uptake and nontarget tissue clearance [44]. The chelator TETA was conjugated to OC, Tyr³-OC (Y3-OC, also referred to as TOC), octreotate (TATE), and Y3-TATE and labeled with ^{64}Cu . Binding affinity and biodistribution studies were performed in rat pancreatic CA20948 tumor-bearing rats. Of these agents, ^{64}Cu -TETA-Y3-TATE showed the best targeting and clearance properties.

In addition to optimizing for the somatostatin analog, it is also necessary to optimize the chelator. It was reported that ^{64}Cu dissociated from TETA-OC in rat liver in vivo [45], and this therefore suggested that a stabler chelator for complexing Cu(II) was required. Additional support for this argument is that although ^{64}Cu -TETA-OC was reasonably successful in imaging SSTR-positive tu-

mors in humans, there was a retention of activity in the blood and liver at longer times (from 4–24 h post injection) [43]. A new class of cross-bridged macrocyclic chelators for complexing copper radionuclides was reported by Sun et al. [46], and it was demonstrated in metabolism experiments in rats that ^{64}Cu -labeled 4,11-bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (CB-TE2A) was dramatically stabler in vivo than ^{64}Cu -TETA [47]. A preliminary report described the synthesis and biological evaluation of ^{64}Cu -CB-TE2A-Y3-TATE, showing improved target tissue uptake and blood and liver clearance compared with ^{64}Cu -TETA-OC [48].

3.3

Somatostatin Analogs Labeled with Yttrium and Indium Radionuclides

^{90}Y ($T_{1/2}=64.06$ h) labeled DOTATOC has been suggested to be a promising targeted radiotherapy agent for SSTR-positive cancers (for a review, see Ref. [49]). Although ^{90}Y is highly advantageous for cancer therapy since it has 100% abundance of β^- emission, ^{90}Y does not emit γ -photons for imaging applications. Dosimetry calculations for clinical trials with ^{90}Y -DOTATOC have been made using ^{111}In -DOTATOC and γ scintigraphy [50]. The disadvantages of using ^{111}In are that it might behave somewhat differently than ^{90}Y , and gamma scintigraphy is not as accurate for quantification as PET. A more accurate surrogate for ^{90}Y is ^{86}Y ($T_{1/2}=14.7$ h), although the shorter half-life does not allow biodistribution at very long times (more than 60 h). Förster et al. [51] compared ^{86}Y -DOTATOC with ^{111}In -DTPA-OC in three patients with metastatic carcinoid tumors, and their data suggested that ^{111}In -DTPA-OC underestimated tumor uptake, and therefore ^{86}Y -DOTATOC was closer to ideal. The pharmacokinetics and dosimetry of ^{86}Y -DOTATOC were evaluated in a phase I PET study of 24 patients with SSTR-positive neuroendocrine tumors, along with the effect of amino acid coinjection on renal and tumor uptake [52]. The use of ^{86}Y -DOTATOC allowed accurate dosimetry of tumor and kidneys, and was valuable in establishing the optimal amino acid regimen for decreasing renal absorbed dose.

$^{110\text{m}}\text{In}$, a positron-emitting radionuclide that is an alternative to ^{111}In , was used to label DTPA-OC in a clinical PET study with one patient [25]. $^{110\text{m}}\text{In}$ was prepared by irradiating an enriched ^{110}Cd target using the $^{110}\text{Cd}(p,n)^{110\text{m}}\text{In}$ nuclear reaction. In one patient, 175 MBq (4.7 mCi) ^{111}In -DTPA-OC was injected into a patient who had a small-intestine-carcinoma metastasis to the upper thorax, and the patient was imaged by SPECT. Into the same patient, 150 MBq (4.1 mCi) $^{110\text{m}}\text{In}$ -DTPA-OC was injected and the patient was imaged by PET. The 69-min half-life of $^{110\text{m}}\text{In}$ allowed the kinetics to be followed for 2 h. A comparison of the imaging studies clearly showed improvements in resolution and recovery with $^{110\text{m}}\text{In}$ PET versus ^{111}In SPECT.

thyroid and abdominal background activity [6, 55–57]. Radioiodinated carbohydrate N-terminal conjugates of SSTR analogs showed encouraging improvements in the biodistribution and tumor uptake kinetics [54]. With these improvements in developing iodinated SSTR analogs, it is anticipated that SSTR analogs labeled with ^{124}I will be reported in the near future.

4.1

^{18}F -labeled Somatostatin Analogs

Over the past 20 years a wide variety of ^{18}F -labeled peptide-based radiopharmaceuticals have been prepared and evaluated for their potential as diagnostic imaging agents. They have been used primarily for tumor imaging and, to a lesser extent, for infection/inflammation imaging. ^{18}F -labeled somatostatin analogs are examples of tumor-imaging agents.

Unlike radioiodination of somatostatin analogs, where the labeling conditions are compatible with the presence of an active ester moiety in the labeling agents, radiofluorination of somatostatin analogs requires strong basic conditions for the specific introduction of [^{18}F]fluoride and can only be achieved via a suitable prosthetic group [58]. Guhlke et al. [59] successfully radiolabeled OC with ^{18}F via 2- [^{18}F]fluoropropionic acid 4-nitrophenylester as a prosthetic group and evaluated its binding affinity and biological activity as well as its in vivo distribution. This radiolabeling method involved two steps including the acylation of ϵ -Boc-Lys⁵-protected OC with the activated ester, and followed by an acidolytic deprotection leading to the desired product, 2- [^{18}F]fluoropropionyl-(D)Phe¹-OC. The use of the 2- [^{18}F]fluoropropionyl moiety provided certain advantages for the labeling of OC, such as high reactivity of the acylation agent, low steric impairment caused by the introduction of the fluoroacyl moiety and no side reactions. 2- [^{18}F]fluoropropionyl-(D)Phe¹-OC demonstrated high binding affinity to SSTR with slightly lower binding affinity than an iodinated somatostatin analog and a low nanomolar IC₅₀ value (around 3 nM). Unfortunately, the PET pharmacokinetics of 2- [^{18}F]fluoropropionyl-(D)Phe¹-OC in SSTR-positive tumor-bearing rats was unfavorable [60]. Although 2- [^{18}F]fluoropropionyl-(D)Phe¹-OC exhibited rapid blood clearance (0.1% ID/g for 1 h, 0.04% ID/g for 2 h) and high in vivo stability, the lipophilicity of this ^{18}F compound resulted in hepatobiliary excretion followed by increasing activity in the intestines over time (40% ID/g at 1 h). The low tumor uptake along with the short retention (0.52±0.24% ID/g for 1 h, 0.17±0.04% ID/g for 2 h) further limited its application for potential PET imaging.

Another approach to labeling OC with ^{18}F was reported by Hostetler et al. [61]. OC was labeled via an in situ peptide coupling of 4- [^{18}F]fluorobenzoic acid ([^{18}F]FBA) with the N-terminus of OC to provide 4- [^{18}F]fluorobenzoyl-OC ([^{18}F]FB-OC). The process of synthesizing [^{18}F]FB-OC involved a new efficient, one-pot synthesis of [^{18}F]FBA using a microwave cavity and the combination of reagents, 1,3-dicyclohexylcarbodiimide and 1-hydroxy-7-azabenzotriazole. Unfortunately, [^{18}F]FB-OC also showed high liver uptake and low uptake in so-

matostatin-rich organs such as CA20948 tumor, pancreas, and adrenal glands in tumor-bearing male Lewis rats.

Improved and more efficient ^{18}F labeling methods for SSTR ligands via prosthetic groups have been developed in recent years, and successes in decreasing the lipophilicity of the ^{18}F -labeled SSTR analogs have also occurred, thereby improving target tissue uptake with decreased hepatobiliary clearance. Carbohydrated ^{18}F labeled octreotate, N^α -(1-deoxy-D-fructosyl)- N^ϵ -(2-[^{18}F]fluoropropionyl)-Lys⁰-Tyr³-octreotate ([^{18}F]FP-Gluc-TOCA) showed promising biokinetics as a potential PET imaging agent of SSTR [62]. The synthesis of [^{18}F]FP-Gluc-TOCA applied a trifunctional linker concept and it was completed in around 3 h with a specific activity of more than 37 GBq/ μmol . [^{18}F]FP-Gluc-TOCA demonstrated higher selective binding affinity to human SSTR2 (IC_{50} = 2.8 ± 0.4 nM) over other SSTR subtypes such as human SSTR4 (IC_{50} = 437 ± 84 nM) and SSTR5 (IC_{50} = 123 ± 8.8 nM), and this agent had no affinity at all for human SSTR1 and SSTR3 (IC_{50} >1,000 nM). The decreased lipophilicity of [^{18}F]FP-Gluc-TOCA with a $\log P$ of -1.70 ± 0.02 led to rapid renal excretion ($8.69\pm 1.09\%$ ID/g at 1 h) with lower liver ($0.72\pm 0.14\%$ ID/g at 1 h) and intestinal uptake ($1.88\pm 0.52\%$ ID/g at 1 h). Even more encouraging is that [^{18}F]FP-Gluc-TOCA showed impressive tumor uptake ($13.54\pm 1.47\%$ ID/g at 1 h) in AR42 J tumor-bearing mice. Human PET imaging of [^{18}F]FP-Gluc-TOCA in a patient with a history of a histologically proven metastatic carcinoid in the liver revealed rapid clearance of the radioactivity from the blood pool within the first hour of injection by renal excretion [62]. Multiple liver metastases were clearly delineated with standard uptake values in the regions of interest, ranging from 21.4 to 38.0, which were only visible as regions of large, pronounced liver uptake by SPECT.

It is important to keep in mind that hydrophilic prosthetic groups are important for renal rather than hepatobiliary clearance. Wester et al. [62] have demonstrated this with their carbohydrate analogs. Since ^{18}F possesses inherent imaging advantages, the development of a simple and rapid synthesis which will enable ^{18}F -SSTR ligands to be clinically practical is also important.

4.2

^{76}Br -labeled Octreotide

^{76}Br is an alternative to ^{18}F for labeling the SSTR2 ligand for PET imaging of SSTR-positive tumors. To the best of our knowledge, there is only one approach to ^{76}Br -labeling of OC using prosthetic groups to decrease the lipophilicity of the labeled peptide [63]. The OC was conjugated to N -succinimidyl 4-[^{76}Br]bromobenzoate ($^{76}\text{BrNHS}$) and N -succinimidyl 5-[^{76}Br]bromo-3-pyridinecarboxylate using microwave heating. The SSTR binding affinity of these two ^{76}Br conjugates was disappointing. The ^{76}Br -conjugate via $^{76}\text{BrNHS}$, 4-[^{76}Br]bromobenzoyl-OC, showed lower binding to meningioma than the other ^{76}Br conjugate (5-[^{76}Br]bromo-3-pyridinecarboxy-OC). High nonspecific binding (more than 20%) to meningioma in heart tissue was observed for both ^{76}Br -

conjugates. Improved brominated analogs and radiochemistry methods will be needed for this area of research to grow.

5 Summary and Conclusions

Over the past 2 decades, great strides have been made in the development of somatostatin analogs labeled with positron emitters for PET imaging of SSTR-positive tumors. In this review, we described clinical trials with ^{18}F -, ^{64}Cu -, ^{68}Ga -, ^{86}Y - and $^{110\text{m}}\text{In}$ -labeled somatostatin analogs, all of which have been performed in the past 5 years, as well as discussed some radiochemistry and preclinical studies with ^{76}Br and ^{66}Ga . The advantages of these positron-emitting somatostatin analogs include increased image resolution with PET compared with SPECT, improved quantification capabilities with PET, and the ability to use the positron emitters as companion isotopes to therapeutic radionuclides such as the $^{86}\text{Y}/^{90}\text{Y}$ pair. The availability of a clinically approved PET somatostatin analog for diagnosis and/or as a companion to therapeutic studies with ^{90}Y will be a major benefit for cancer imaging and therapy.

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