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REVIEW

Imaging pancreatic islet cells by positron emission tomography

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Abstract

It was estimated that every year more than 30000 persons in the United States - approximately 80 people per day - are diagnosed with type 1 diabetes (T1D). T1D is caused by autoimmune destruction of the pancreatic islet (β cells) cells. Islet transplantation has become a promising therapy option for T1D patients, while the lack of suitable tools is difficult to directly evaluate of the viability of the grafted islet over time. Positron emission tomography (PET) as an important non-invasive methodology providing high sensitivity and good resolution, is able to accurate detection of the disturbed biochemical processes and physiological abnormality in living organism. The successful PET imaging of islets would be able to localize the specific site where transplanted islets engraft in the liver, and to quantify the level of islets remain alive and functional over time. This information would be vital to establishing and evaluating the efficiency of pancreatic islet transplantation. Many novel imaging agents have been developed to improve the sensitivity and specificity of PET islet imaging. In this article, we summarize the latest developments in carbon-11, fluorine-18, copper-64, and gallium-68 labeled radioligands for the PET imaging of pancreatic islet cells.

Key words: Diabetes; Pancreatic islet cells; Positron emission tomography; Imaging tracers

Core tip: Positron emission tomography (PET) is an important non-invasive functional imaging modality that is being explored for the purpose of quantifying engrafted pancreatic islet. There are still several issues that must be overcome before PET can be adopted as the gold standard for the accurate, noninvasive, and non-toxic evaluation of native β cells or pancreatic islet mass *in vivo*, which remains a difficultly and highly challenging goal. To complement the previous review published in 2010 by our group, this review summarizes the latest developments in PET tracers (such as carbon-11, fluorine-18, copper-64 and gallium-68) for the imaging of pancreatic islet cells.

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Table 1 Representative beta-cell-specific biomarkers for positron emission tomography imaging of islets

Biomarkers	Probe name	Ref.
Vesicular monoamine transporter (VMAT2)	$[^{11}C]$ (+)-dihydrotetrabenazine $[(+)-^{11}C$-DTBZ]	[13,39-41]
	^{18}F-FP-(+)-DTBZ	[14,15,42,43]
	^{64}Cu-CB-TE2A-(+)-DTBZ	[44,45]
	^{64}Cu-CB-TE2A-(-)-DTBZ	[44,45]
Glucagon-like peptide-1	^{18}F-TTCO-Cys^{40}-Exendin-4	[23]
	^{18}F-FBEM-Cys^{x}-exendin-4	[26]
	^{68}Ga-DO3AVS-Cys^{40}-Exendin-4	[19,27,56,57]
	^{64}Cu-DO3A-VS-Cys^{40}-Exendin-4	[55]
	^{64}Cu-BaMalSar-Exendin-4	[22]
	^{64}Cu-Mal_2Sar-$(Exendin$-$4)_2$	[22]
	[Lys40(DOTA-^{64}Cu)-NH_2]-Exendin-4	[58]
Glucokinase	$[^{11}C]$AZ12504948	[20]
Somatostatin receptors	^{68}Ga-DOTA-octreotide	[63]

INTRODUCTION

Type 1 diabetes (T1D) remains the predominant form of diabetes in childhood. Although disease onset may occur at any time, the peak onset for diagnosis is in the mid-teens[1]. The prevalence of T1D in the United States population under 20 years of age has increased by 30% between 2001 and 2009[2].

Pancreatic islets are comprised of clusters of cells, of which there are five different types: Alpha, beta, delta, gamma, and epsilon cells, all of which produce hormones that are secreted directly into the blood-stream. However, the majority of the pancreatic islet mass is made up of beta cells (65%-80%), which help regulate blood glucose levels *via* their production of insulin. T1D is caused by the autoimmune destruction of the pancreatic beta cells[3], which limits or completely eliminates the production and secretion of insulin. As the result of long-term hyperglycemia, patients with T1D may develop serious micro- and macrovascular complications such as heart disease, stroke, kidney failure, blindness, leg amputations, and premature death[4-6].

Currently, there is no cure for T1D. Experimental treatments are based on strategies that aim to modify the autoimmune processes responsible for beta cell destruction, replace beta cell mass, or both, including stem cell and immunotherapy, as well as the transplantation of islets[7]. Compared to whole-pancreatic transplant, the current standard of care for diabetes, the transplantation of islets are much less invasive[8]. Islet transplantation using the Edmonton protocol can momentarily control blood sugar levels with insulin independence in T1D patients. Currently only one-tenth of patients have successfully upheld insulin independence for five years[9].

Due to the lack of suitable methods for tracking post-transplantation islet loss, detection of grafted islet fate and functionality are restricted to indirect measurement of patient's metabolism or exogenous insulin requirements, which is not always accurate due to vacillations in the metabolic state and insulin secretory capacity of beta cells under various pathophysiologic and physiologic condition[10,11].

A noninvasive methodology monitoring transplanted islets would localize its site in the liver and quantity the viability level of islets and estimate their functionality over time. This information would be crucial to creating and assessing the effectiveness of pancreatic islet transplantation, revealing why some islet transplants are more successful that others, and would lead to new methods for islet grafts to last longer periods of time on a more widespread basis for every T1D patients.

Positron emission tomography (PET) is highly sensitive, noninvasive imaging methodology[12] in biomedical research, which uses the γ-rays associated with positron annihilation events to localize positron-emitting targeted tracers inside an organism. The low interaction of γ-rays in the human body allows physicians to accurately detect signals in patients even if they originate deep below the body surface. Given an appropriate tracer, PET can accurately detect the disturbed biochemical processes and physiological abnormality in living organism. Thus, the development of safe, effective and highly specific PET tracers of pancreatic islets (*i.e.*, primarily β cells) would help us the early diagnosis of β-cell-associated metabolic diseases, as well as the capability of monitoring the therapeutic efficacy of islet transplantation. This information will greatly assist us in developing new techniques for extending the survival of islet grafts on a more widespread basis for every T1D patients.

Many investigators are currently searching for and evaluating beta-cell-specific biomarkers for PET imaging of islets[13-20]. A number of potential candidates have been reported, such as glucagon-like peptide-1 receptor (GLP-1R)[19,21-28], vesicular monoamine transporter (VMAT2)[14,29-32], sulfonylurea receptor (SUR1)[33], glucose transporter 2, glucokinase (GK)[20], reporter gene[34], glycogen, zinc transporters, fluorodithizone[35], and monoclonal antibodies[34]. To complement the previous review published in 2010 by our group[36], this review summarizes the latest developments since 2011 in C-11, F-18, Cu-64, and Ga-68 labeled radioligands targeting these specific biomarkers for PET imaging pancreatic islet cells (Table 1).

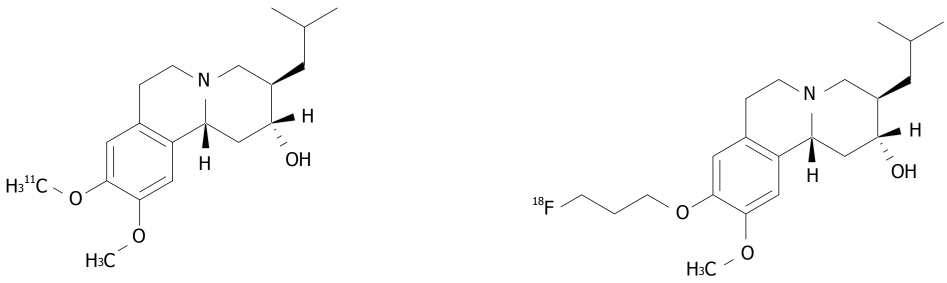


Figure 1 Structures of (+)-^{11}C-DTBZ and ^{18}F-FP-(+)-DTBZ.

^{11}C-, ^{18}F- AND ^{64}Cu-LABELED DTBZ ANALOGUES AS VMAT2 PROBES FOR IMAGING PANCREATIC ISLET CELLS

VMAT2 is mainly responsible for carrying monoamines, such as dopamine, from the neuron into the storage granules. It was demonstrated that VMAT2 mainly distributed in the central nervous system (CNS) and β-cells in the pancreatic islets by histology studies of gene expression[37]. VMAT2 expression is correlative with the insulin levels in monkey and human pancreatic tissue[38]. Therefore, VMAT2 could become a suitable target for trapping â-cell function. [^{11}C] (+)-dihydro-tetrabenazine [(+)-^{11}C-DTBZ, Figure 1] as VMAT2 ligand was first synthesized by DaSilva *et al*[39] in 1993, and has been applied for imaging VMAT2 in the pancreas of mice, non-human primate and humans[13,40]. However, recent findings of nonspecific binding of (+)-^{11}C-DTBZ in human pancreas overcasts its clinical applications[41].

Kung *et al*[42] developed a novel DTBZ fluorine-18 probe, ^{18}F-FP-(+)-DTBZ (Figure 1). It has been evaluated of VMAT2 pancreatic binding sites of animals and humans in PET imaging. In the *in vivo* rats biodistribution studies, the probe showed the highest pancreas uptake (5% ID/g at 30 min p.i.). In the blocking study, 78% blockade of pancreas uptake in rats was observed. PET imaging result indicated that F-18 tracer has avid pancreatic uptake in health rats[43].

In healthy and T1D subject studies[14], pancreatic uptake showed the significant difference uptake between control and T1D subjects (Figure 2): (1) pancreas uptake of T1D patients (10.7 ± 2.6) was lower than that of control subjects (17.2 ± 4.0); and (2) there is not different in the kidney cortex uptake (3.01 ± 0.34 *vs* 2.90 ± 0.48).

However, the initial result of ^{18}F-FP-(+) DTBZ-PET in T1D patient, similarly with (+) ^{11}C- DTBZ[41], indicated that it has more VMAT2 value than expected. For this reason, Harris *et al*[15] suggested that tracer non-displaceable binding in T1D and health pancreas are different. In the result indicted that it was distinctly increased approximately two-fold in tissues of diabetic individuals *vs* healthy individuals from fresh frozen cadaveric pancreas. This initial result supports their hypothesis and currently, they are ongoing to focus on directly measurement of V_{ND} in the healthy human and T1D patient pancreas by (R) and (S) enantiomers.

Although ^{11}C- and ^{18}F-labeled DTBZ as VMAT2 PET probes have been performed in the pancreas of animal and human subjects, they would be limited in clinical application due to non-specific issues. Currently, there have only been limited reports using other PET nuclides. Recently, Kumar *et al*[44] reported synthesis of the ^{64}Cu-specific bifunctional chelator scaffold DTBZ analogues: ^{64}Cu-CB-TE2A-(+)-DTBZ (IC_{50} = 16.8 ± 6.9 nmol/L) and ^{64}Cu-CB-TE2A-(-)-DTBZ (IC_{50} = 253.2 ± 107.8 nmol/L). As we knew that, the IC_{50} values of (+)-DTBZ and (-)-DTBZ were 0.97 ± 0.48 nmol/L and 2.2 ± 0.3 μmol/L, respectively[45]. The VMAT2 specific binding affinity of ^{64}Cu-CB-TE2A-(+)-DTBZ was not compromised by their chemical modifications, while that of its (-) counterpart remained low as in ^{11}C- or ^{18}F-labeled (±) DTBZ[44]. Currently, there are no further reports on PET imaging using ^{64}Cu-CB-TE2A-(+)-DTBZ in animal studies.

In conclusion, ^{11}C- and ^{18}F-labeled DTBZ analogues for β cell imaging/pancreatic islet cells imaging have been applied in primates and humans studies; however, nonspecific binding of (+)-^{11}C-DTBZ and ^{18}F-FP-(+)-DTBZ in human pancreas overcasts their clinical applications. The suitable imaging tracer should exhibit selective binding to β-cells along with low non-specific binding to adjacent tissues.

^{18}F-, ^{68}Ga-, AND ^{64}Cu-LABELING EXENDIN ANALOGUES AS GLP-1 PROBES FOR IMAGING PANCREATIC ISLET CELLS

Discovered in the early 1980s[46,47], GLP-1, an incretin peptide secreted by the intestine as a response to nutrient ingestion, plays a significant role in glucose homeostasis. GLP-1 is an endogenous incretin peptide released from the intestine in response to nutrient ingestion and plays a significant role in glucose homeostasis. Although GLP-1R is found in pancreas, brain, heart, kidney, and GI tract[48,49], a recent study revealed that

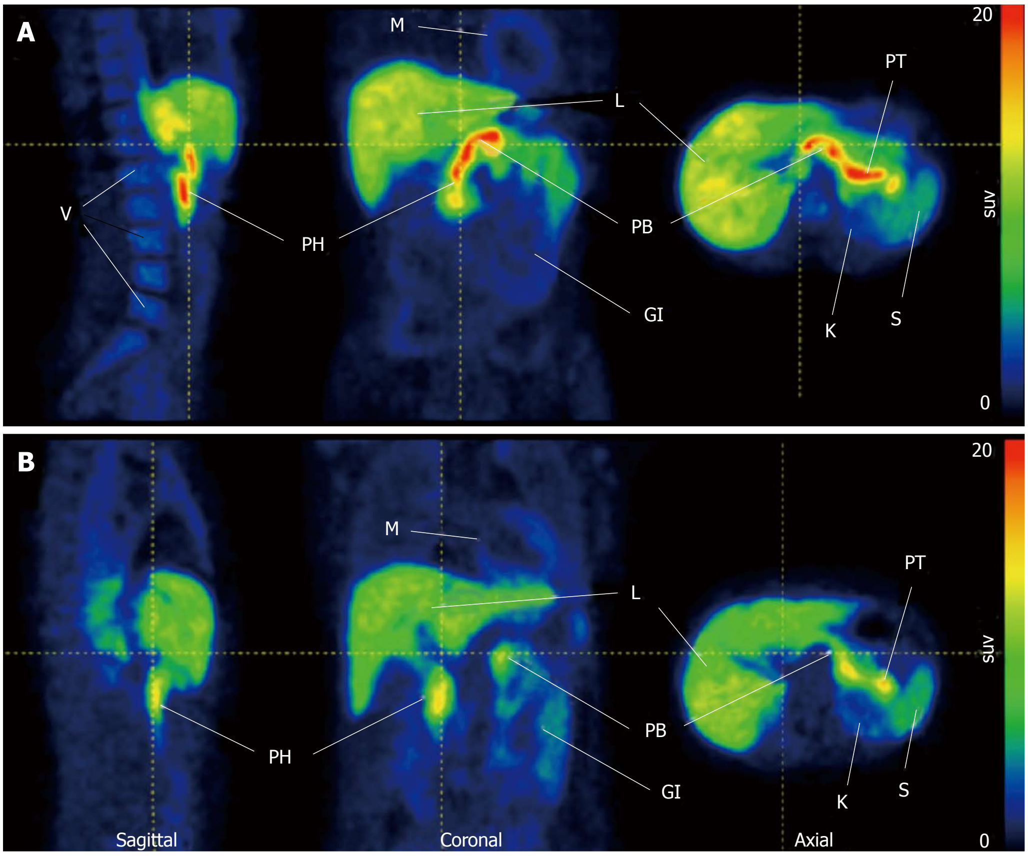


Figure 2 Representative ^{18}F-FP-(+)-DTBZ positron emission tomography images in healthy control subject and type 1 diabetes patient. A: High uptake in healthy pancreas; B: Compare with health control pancreas, lower uptake was observed in T1D patient. Both images PET data summed 0-90 min p.i. Reprinted with permission from Ref.[14]. GI: Gastrointestinal tract; K: Kidney; L: Liver; M: Myocardium; PB: Pancreas body; PH: Pancreas head; PT: Pancreas tail; S: Spleen; V: Vertebrae; T1D: Type 1 diabetes; PET: Positron emission tomography.

GLP-1R is highly expressed in β-cells in the pancreatic islet[50], suggesting that ligands of GLP-1R could be ideal tracers for imaging pancreatic islet. However, native GLP-1 is degraded rapidly (half-life < 2 min) by dipeptidyl peptidase-IV. Thus, dipeptidyl peptidase-IV-resistant agonist or antagonist targeted GLP-1R are suitable for PET imaging tracers[51,52].

In 1992, Eng *et al*[52-54] discovered exendin-4, which currently it is more attractive as a high-affinity probe. Exendin-4 has a 53% similar sequence identity to human GLP-1 and exhibits closely related properties[51]; on the other hand, it is much more stability than GLP-1. Thus exendin-4 has attracted significant attention on developing promising PET tracers for imaging pancreatic islet cells in rodent, primates and human studies since 2011, such as ^{18}F-TTCO-Cys^{40}-exendin-4[23], ^{18}F-FBEM-Cys^{x}-exendin-4 (x = 0 or 40)[26], ^{68}Ga-DO3AVS-Cys^{40}-exendin-4[19,27], and ^{64}Cu-DO3A-VS-Cys^{40}-exendin-4[55] (Figure 3).

We developed a novel fluorine-18 exendin-4 probe: ^{18}F-TTCO-Cys^{40}-exendin-4 (Figure 4)[23] with high radiosynthesis yield (80%) and high radiochemical purity (99%). An insulinoma INS-1 tumor model used in PET images of small animals, the result indicated that ^{18}F-TTCO-Cys^{40}-exendin-4 has high specific bind to GLP-1R (Figure 4A). Additionally, in contrast to the radiometal-labeled exendin-4 analogues, ^{18}F-tracer has a significantly lower uptake in kidney and quicker clearance rate[55].

We also tested the probe in the islet (1000 IEQ) graft in the liver in mice. The data indicated that the mice with transplanted islets (Figure 4D) had significantly higher (P < 0.01) uptake into the liver post injection as compared to the control mice (Figure 4E). To the blocking study, it also demonstrated that the tracer only specific GLP-1R in the liver. Currently, we are undertaking the evaluation of 18F-TTCO-Cys40-exendin-4 in non-human primates.

Recently, Selvaraju *et al*[27] developed a promising gallium-68 probe: ^{68}Ga-DO3AVS-Cys^{40}-exendin-4. Their imaging results in primates indicated the pancreas was easily visualized after injection ^{68}Ga-DO3A-exendin-4 by iv (injection dose, 0.05 μg/kg) (Figure 5). The probe was excreted in the urine and trapped in the kidney cortex (Figure 5, bottom row). No other organs displayed accumulation similarly with the pancreas and kidneys. The intestine, liver, spleen, heart, and lungs were displayed lower uptake.

In the specific study (Figure 5), co-injection of different doses of cold DO3A-exendin-4 (0.05-20 μg/kg)

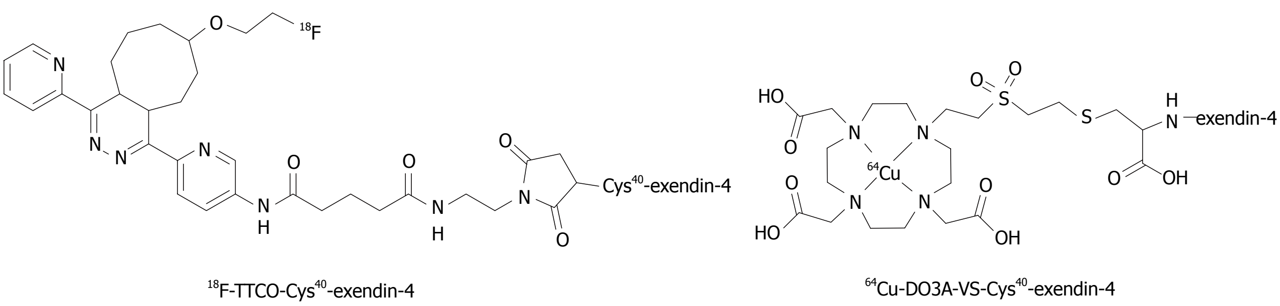


Figure 3 The structures of ^{18}F-TTCO-Cys^{40}-exendin-4 and ^{64}Cu-DO3A-VS-Cys^{40}-exendin-4 as glucagon-like peptide-1 receptor target probes.

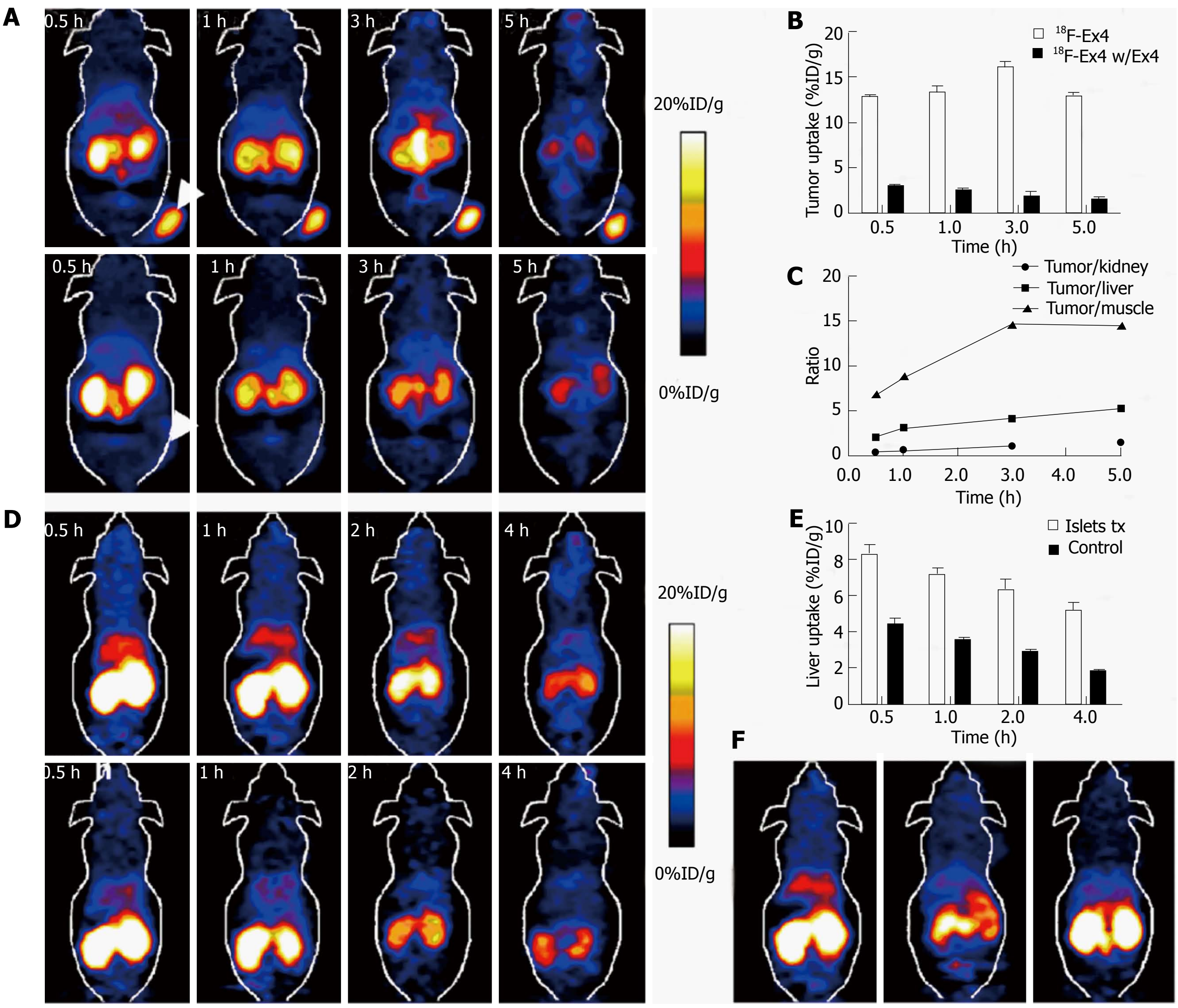


Figure 4 Representative ^{18}F-TTCO-Cys^{40}-exendin-4 positron emission tomography images in NOD/SCID mice. A: Representative microPET images of 18F-TTCOCys40-exendin-4 (top) and blocking (bottom) for NOD/SCID mice with INS-1; B: Tumor uptakes between control and blocking groups; C: Tumor to organs ratios of radiotracer at different time points p.i.; D: Representative microPET images of tracer in NOD/SCID mice transplanted with human islets into liver (top) and control mice (bottom) at different time points p.i.; E: Liver uptake between intraportal islet transplantation and sham control groups; F: MicroPET mages of mice transplanted with human islets (Left: Control; Middle: Blocking and sham control mice at 1 h p.i.). Reprinted with permission from Ref.[23]. PET: Positron emission tomography.

decreased the uptake in the pancreas from 9.2 to 0.8 in SUV curve (0.05-20 μg/kg) at 90 min p.i. The highest pharmacologic dose (20 μg/kg) was almost blocked more than 90% uptake. These imaging and kinetic results indicated that the tracer has specific binding to GLP-1R. The result of progressive competition with exendin-4 exhibited it was dose-dependently inhibited.

Eriksson *et al*[56] evaluated the first patient with pan-

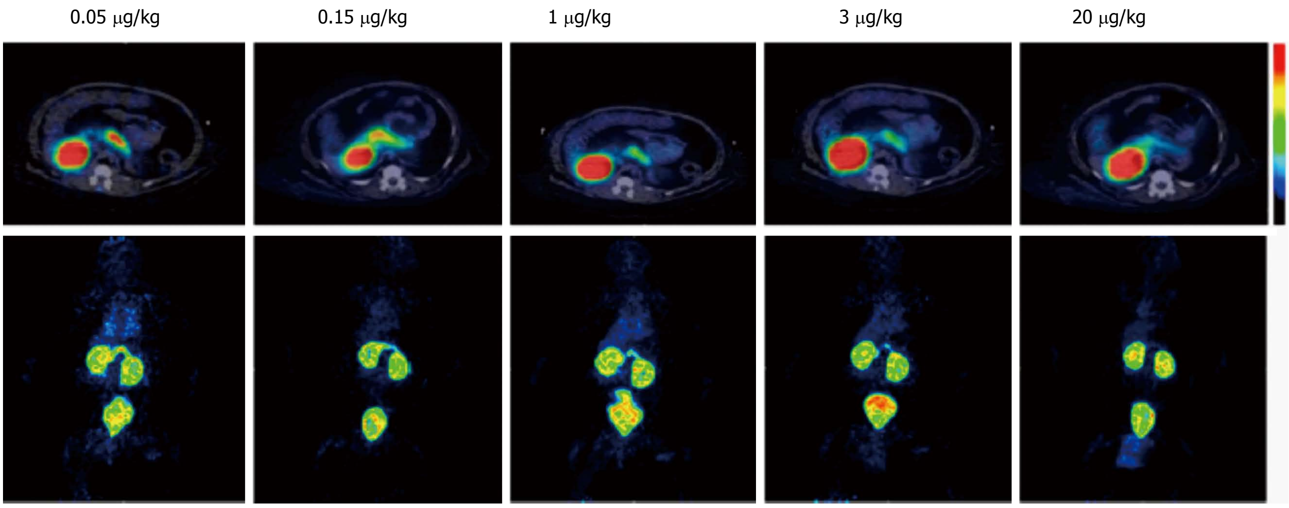


Figure 5 Positron emission tomography/computed tomography images of ^{68}Ga-DO3A-exendin-4 for cynomolgus monkeys. Increasing concentration of unlabeled peptide resulted in competition for glucagon-like peptide-1 receptor in pancreas only. Transaxial images (dynamic sequences 30-90 min, top row) and whole-body maximum-intensity projections (dynamic sequences 90-120 min, bottom row). Reprinted with permission from Ref. [27].

creatic insulinoma using ^{68}Ga-DO3AVS-Cys^{40}-exendin-4. PET/CT imaging of whole-body ^{68}Ga-DO3AVS-Cys^{40}-exendin-4 showed several small GLP-1R-positive lesions in the liver and a lymph node. Neither of the lesions had been conclusively detected by morphological imaging with CT and ultrasound or molecular imaging with [^{11}C]5-HTP or [^{18}F]FDG PET/CT. Native pancreas, containing a large number of cells positive for GLP-1R, exhibited marked uptake of ^{68}Ga-DO3AVS-Cys^{40}-exendin-4. The PET/CT imaging result indicated that ^{68}Ga-exendin-4 probe has more specific binding GLP-1R than other imaging techniques and provided the basis for continued systemic therapy.

Due to the renal excretion of [^{68}Ga]Ga-DO3A-VS-Cys^{40}-exendin-4 and the extensive intracellular retention of radioactivity in the kidney cortex, which remains a concern given the likelihood of repeated imaging studies in humans, Eriksson thus evaluated the dosimetry of [^{68}Ga]Ga-DO3A-VS-Cys^{40}-exendin-4 in rats, pigs, non-human primates and a human[57]: (1) human whole body effective dose: 0.014-0.017 mSv/MBq; (2) The absorbed dose in the kidneys: 0.28-0.65 mGy/MBq; and (3) The maximum yearly administered amounts: 536-455 MBq. More than 200 MBq of this probe can be serviced yearly in clinical, allowing for repeated (2-4 times) scanning.

In addition, several ^{64}Cu-labeled exendin-4 tracers also were reported: (1) [Lys40(DOTA-^{64}Cu)-NH_2]-exendin-4[58] showed high binding specificity to rodent β cells by *ex vivo* autoradiography; (2) ^{64}Cu-DO3A-VS-Cys^{40}-exendin-4 (Figure 3)[55], demonstrated the feasibility of *in vivo* PET imaging islets grafted in mouse liver by virtue of a high and specific uptake in INS-1 tumors despite high renal uptake; and (3) ^{64}Cu-BaMalSar-exendin-4 and ^{64}Cu-Mal$_2$Sar-(exendin-4)$_2$[22], indicated persistent and specific uptake in an INS-1 insulinoma model with high renal uptake.

Taken together, these results indicated that Exendin analogues hold great potential for non-invasive imaging of pancreatic islet cells/beta cells.

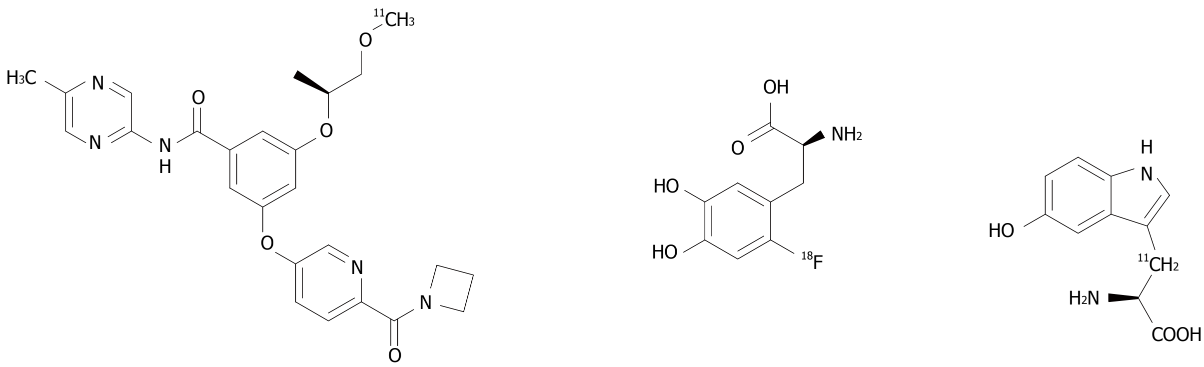
^{11}C-LABELED TRACER AS GK PROBE FOR IMAGING PANCREATIC ISLET CELL

GK as an enzyme predominantly presents in β cells in the pancreas[59] and in hepatocytes[60], which plays a key role on regulation of glucose homeostasis in blood[20]. GK could be a potentially biomarker for imaging pancreatic islet since it expressed in pancreatic β cells, not in exocrine cells.

Recently, Jahan *et al*[20] reported the synthesis of [^{11}C]AZ12504948 (Figure 6) as a new probe for GK imaging in pancreas and liver. PET/CT imaging in pigs indicated that moderate pancreatic uptake was observed. The hepatic distribution was homogeneous and followed similar kinetics as the pancreas but with higher amplitude 30 min p.i. In the block study, co-injection of cold AZ12504948 with probe reduced radioactivity uptake by 24% in pancreas and by 15% in the liver after 30-60 min p.i. However, due to high uptake in the liver, it was not suitable to quantify the level of islet cells in liver for treatment of T1D by islet transplantation.

PANCREATIC SOMATOSTATIN RECEPTORS (SSTRS) -TARGETED PROBES FOR β-CELL IMAGING

Natural somatostatin as a peptide hormone, distributes in the hypothalamus, adrenals and pancreas, which it is a cyclic tetradecapeptide[61]. In the pancreas, somatostatin is considered an important regulator of insulin and other pancreatic endocrine hormones secretion[62]. In the rodent islets of Langerhans that consist of endocrine



[11C]AZ12504948 [18F]F-DOPA [11C]5-HTP

Figure 6 Chemical structures of [11C]AZ12504948, L-3,4-Dihydroxy-6-18F-fluoro-phenylalanine and 11C-5-hydroxy-Ltryptophan. [18F]F-DOPA: L-3,4-Dihydroxy-6-18F-fluoro-phenylalanine; [11C]5-HTP: 11C-5-hydroxy-Ltryptophan.

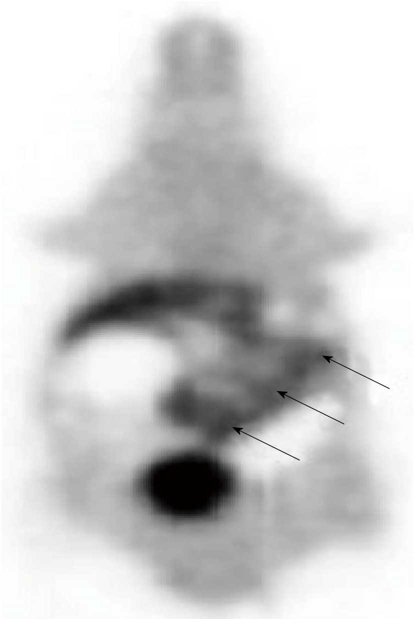


Figure 7 Positron emission tomography imaging of L-3,4-Dihydroxy-6-18F-fluoro-phenylalanine for detection of sites of viable islet cells transplanted in STZ-induced type 1 diabetes nu/nu mouse model. The images shown irregular distribution of radiotracer uptake at the site of the grafted islet cells in the abdominal wall (black arrows). Reprinted with permission from Ref. [16].

cells, the insulin-secreting beta cells are the majority of the cell population and abundantly express SSTRs. Therefore, the expression of SSTRs is considered a potential biomarker for the measurement of beta cells.

Sako *et al*[63] developed a novel gallium-68 analogue: ^{68}Ga-DOTA-octreotide. In normal and diabetic rats studies, high accumulation of ^{68}Ga-tracer was observed in the urinary bladder and kidney. Accumulation of ^{68}Ga-tracer was apparent in the normal pancreas, while weak radioactivity was detected in the liver. The ^{68}Ga-DOTA-octreotide radioactivity in the pancreas showed a rapid increase within 1 min p.i. and then gradually increased and reached 0.99% ± 0.24% ID at the end of the PET scans. In contrast, ^{68}Ga-tracer radioactivity in the liver quickly reached a peak at 15 s p.i. and decreased rapidly thereafter reaching 0.17% ± 0.08% ID at the end of the PET scans. The accumulation of ^{68}Ga-DOTA-octreotide was much higher in the kidney and urinary bladder. Blocking studies indicated that the pancreatic accumulation of ^{68}Ga-tracer was significantly decreased in the unlabeled octreotide-treated group. In the STZ-treated DM model rats, it exhibited lower accumulation in the pancreas than that in normal rats. Thus ^{68}Ga-tracer could be a potential PET tracer for quantifying islet cells.

OTHER PROBES FOR ISLET CELLS IMAGING

L-3,4-Dihydroxy-6-^{18}F-fluoro-phenylalanine

Sweet *et al*[35] discovered the scaffolds of L-Dihydroxyphenylalanine could become β-cell probes for PET imaging. [^{18}F]F-DOPA (Figure 7) was successfully radiosynthesized and its biochemical mechanism was researched. The mechanism of [^{18}F]F-DOPA was changed to ^{18}F-dopamine by decarboxylation in the aromatic amino decarboxylase has been confirmed by blocking study, which resulted in back diffusion of the PET probe from the neuroendocrine cells into extracellular spaces.

In 2014, Eriksson *et al*[16] attempted to use [^{18}F]F-DOPA as the probe for imaging transplanted islet cells. *In vivo* imaging revealed irregular distribution of the transplantation islet mass in the abdominal wall, since the probe was excreted in biliary excretion, which could be potentially effect of graft map (Figure 7).

^{11}C-5-hydroxy-Ltryptophan

5-hydroxy-L-^{11}C-tryptophan ([^{11}C]5-HTP, Figure 6) as biogenic precursor, was first applied for evaluation of rate of serotonin biosynthesis by dopa decarboxylase (DDC) in CNS[64]. High pancreas uptake of the probe in the health human has not previously been systematically investigated.

Recently, Eriksson *et al*[65] reported that *in vitro* binding assay for [^{11}C]5-HTP in endocrine cells, and

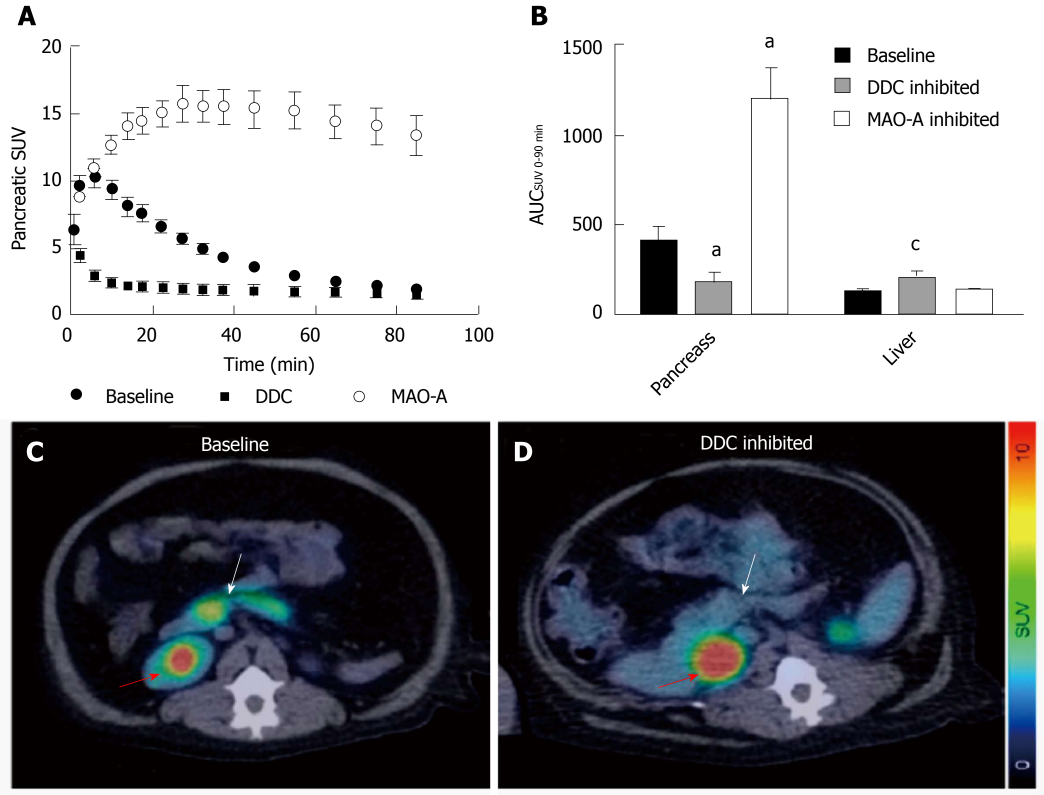


Figure 8 Positron emission tomography/computed tomography imaging of 5-hydroxy-L-^{11}C-tryptophan in non-human primates. A: SUV of [^{11}C]5-HTP uptake in pancreas of nonhuman primate after 0-100 min p.i.; B: Pancreas uptake was significantly decreased by pretreated inhibitors (^{a}P < 0.05; ^{c}P < 0.001); C and D: Abdominal HTP and PET/CT fusion images. Pancreas: White arrow; Kidney pelvis: Red arrow. Reprinted with permission from Ref.[65]. [^{11}C]5-HTTP: 5-hydroxy-L-^{11}C-tryptophan; PET/CT: Positron emission tomography/computed tomography. DDC:Dopa decarboxylase.

exocrine cells. The result showed that only specific binding in insulinoma cell line and human islets, namely endocrine cells. The further studied indicated that the probe targeted serotonin, which was produced by intracellular. In the non-human primate studies, they were pretreated by inhibition of DDC enzyme, which the probe was converted to ^{11}C-serotonin, and inhibition of monoamine oxidase-A (MAO-A), which was responsible for serotonin degradation (Figure 8). In the result indicated that it was distinctly decreased in DDC and increased in MAO-A in primates pancreas. It displayed the similarly result in the rat by inhibition of MAO-A, and uptake was decreased in rodent with induced diabetes. Therefore, [^{11}C]5-HTP as PET probe could be suitable to quantitative the level of the serotonergic system in pancreas.

CONCLUSION

Ideal islet and β cell imaging probes would have a suitable washout and residence time in the subjects, be able to provided high specific binding for PET images with lowest non-specific binding in surrounding tissues without toxic to islets, and without pretreatment of islets before transplanted islet.

Currently, many research investigators are developing and evaluating biomarkers specific for pancreatic islet cells, particularly beta cells. A number of potential candidates for islet cell imaging have been reported, such as VMAT2, GLP-1R, SUR1, and GK. Carbon-11, fluorine-18, gallium-68 and copper-64 labeled PET tracers targeting these biomarkers have been evaluated in rodents, non-human primates, and humans. Among them, some tracers displayed great potential for non-invasive imaging of pancreatic islet cells. For example, ^{18}F-TTCO-Cys^{40}-exendin-4 demonstrated specific binding to GLP-1R and was suitable to quantity the level of islet cells in the rodent; [^{68}Ga]Ga-DO3AVS-Cys^{40}-exendin-4 displayed promising data of PET imaging in human studies and evaluated the dosimetry in rats, pigs, monkey and one patient for transfer into clinic study.

However, the accurate, noninvasive, and safe detection of β-cell mass or grafted islet mass *in vivo* remains a highly and difficultly challenging goal. Developing PET tracers with nontoxic, high specific binding to β-cell in the pancreatic islet is an important objective for future studies.

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