Development of 18F-Labeled Phosphonium Compounds for Imaging Mitochondria-rich Cells by Positron Emission Tomography

VI. 4. Development of ^{18}F-Labeled Phosphonium Compounds for Imaging Mitochondria-rich Cells by Positron Emission Tomography

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Introduction

Mitochondria, which is one of eukaryotic organelles, plays an important role in the production of ATP to supply energy required for various activities of cells. Cells of the heart and brown adipose tissue (BAT) contain many mitochondria and consume large amounts of energy. In vivo measurement of the mitochondrial activity could be valuable for diagnosis of diseases caused by mitochondrial dysfunction. ^{18}F-FBnTP is a fluorine-18 labeled triarylphosphonium (TAP) compound which accumulates in mitochondria depending on mitochondria membrane potential (MMP) (1). Although ^{18}F-FBnTP has been often used for imaging and assessing mitochondrial function of the heart and BAT in basic research, the complicated reaction procedures and sever reaction conditions for the radiosynthesis have hampered the clinical application of the tracer. To overcome this difficulty, we have been tried to develop new ^{18}F-labeled TAP derivatives (2). In this study, we have established a novel convenient method for synthesizing ^{18}F-labeled TAP compounds.

Methods

As the new radiosynthesis strategy different from conventional one, we devised a method to synthesize a ^{18}F-labeled phosphonium compound by synthesizing a ^{18}F-labeled triarylphosphine as an intermediate and then reacting it with an appropriate electrophile. Firstly, the reaction conditions of solvent and temperature for preparation of the phosphonium scaffold from ^{18}F-labeled phosphine intermediate and benzyl bromide (electrophile) were examined. Then, we tested several derivatives of benzyl bromide for synthesizing the ^{18}F-labeled phosphonium derivatives (^{18}F-TP-001~006) under the optimized reaction conditions.

Next, we biologically assessed the usefulness of ^{18}F-TP-001~006 as a mitochondrial

imaging tracer. Each tracer was injected into the mouse or rat tail vein and evaluated the tissue uptake rate of the tracer by biodistribution study and small animal PET imaging. Cellular uptake mechanism of the tracer was also examined by using a JC-10 probe for MMP measurement.

Results and Discussion

A ^{18}F-labeled triarylphosphine was prepared from the corresponding tosylate precursor by conventional radiofluorination method using ^{18}F-KF/K222, and then reacted with benzyl bromide. As the results of the examination of the second reaction conditions, the solvent, temperature, and time were optimized as acetonitrile, 100ºC, and 10 min, respectively. Under the conditions, ^{18}F-TP-001 was radiosynthesized in good radiochemical yields of 43±18% (Fig. 1). The other ^{18}F-TP derivatives were also prepared in moderate-to-good radiochemical yields under the same conditions. This method is a simple one-pot procedure and requires no corrosive reagents and sever reaction conditions, suggesting the feasibility of automated radiosynthesis of ^{18}F-TP.

Biodistribution study revealed that most of the derivatives showed high heart uptakes at 60 min post-injection. Especially, ^{18}F-TP-003 indicated higher accumulation in myocardium compared to other compounds with a large heart-to-liver uptake ratio (9.2). Cellular accumulation rate of ^{18}F-TP-003 was correlated well with a JC-10 uptake among three different cell lines, indicating that cellular accumulation of ^{18}F-TP-003 depends on MMP. Rat heart was clearly visualized by PET with ^{18}F-TP-003 (Fig. 2).

Conclusion

We developed a novel method for a synthesis of ^{18}F-labeled TP derivative by one-pot procedure. This method would increase the flexibility in drug design of ^{18}F-TP and be useful in the study on structure-activity relationship. ^{18}F-TP-003, one of the ^{18}F-TP derivatives, could be a potential candidate for a mitochondria imaging tracer.

References

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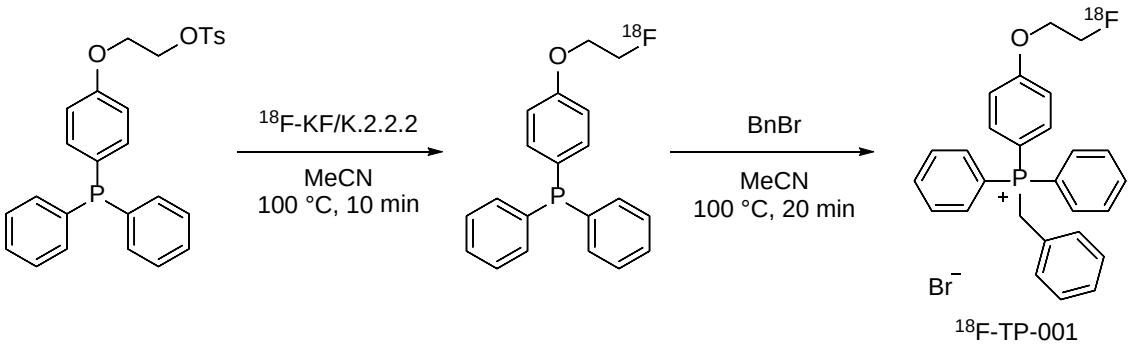

Figure 1. Radiosynthesis scheme of ^{18}F-TP-001.

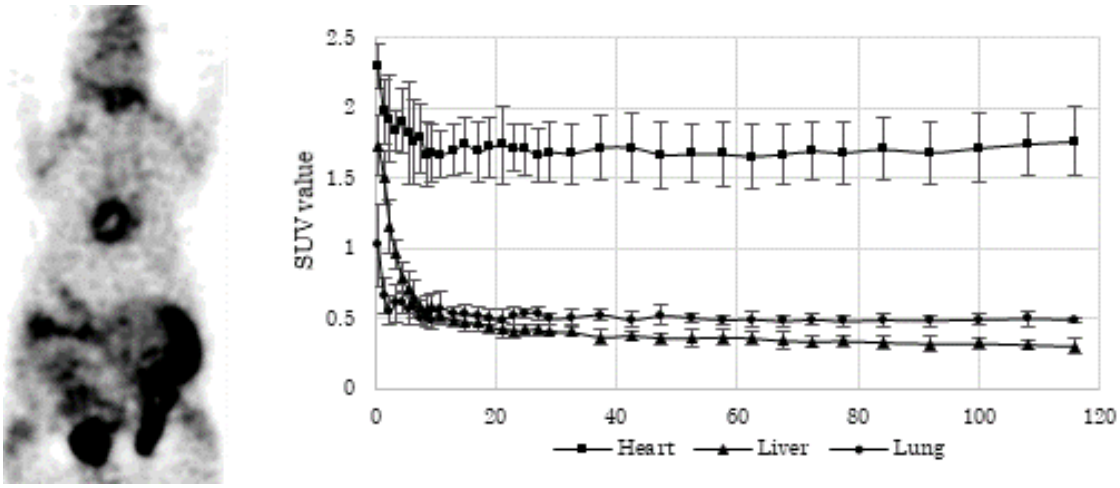

Figure 2. A rat PET image of ^{18}F-TP-003 (left) and time activity curves of the heart, liver, and lung (right).