Radiosynthesis, Photoisomerization, Biodistribution, and Metabolite Analysis of $^{11}$C-PBB3 as a Clinically Useful PET Probe for Imaging of Tau Pathology

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2-((1E,3E)-4-(6-(11C-methylamino)pyridin-3-yl)buta-1,3-dienyl)benzo[thiazol-6-ol (11C-PBB3) is a clinically useful PET probe that we developed for in vivo imaging of tau pathology in the human brain. To ensure the availability of this probe among multiple PET facilities, in the present study we established protocols for the radiosynthesis and quality control of 11C-PBB3 and for the characterization of its photoisomerization, biodistribution, and metabolism. 

Methods: 11C-PBB3 was synthesized by reaction of the tert-butylidemethylsilylethyl desmethyl precursor (I) with 11C-methyl iodide using potassium hydroxide as a base, followed by deprotection. Photoisomerization of 11C-PBB3 under fluorescent light was determined. The biodistribution and metabolite analysis of 11C-PBB3 was determined in mice using the dissection method.

Results: 11C-PBB3 was synthesized with 15.4% ± 2.8% radiochemical yield (decay-corrected, n = 50) based on the cyclotron-produced 11C-CO2 and showed an averaged synthesis time of 35 min from the end of bombardment. The radiochemical purity and specific activity of 11C-PBB3 were 98.0% ± 2.3% and 180.2 ± 44.3 GBq/μmol, respectively, at the end of synthesis (n = 50). 11C-PBB3 showed rapid photoisomerization, and its radiochemical purity decreased to approximately 50% at 10 min after exposure to fluorescent light. After the fluorescent light was switched off, 11C-PBB3 retained more than 95% radiochemical purity over 60 min. A suitable brain uptake (1.92% injected dose/g tissue) of radioactivity was observed at 1 min after the probe injection, which was followed by rapid washout from the brain tissue. More than 70% of total radioactivity in the mouse brain homogenate at 5 min after injection represented the unchanged 11C-PBB3, despite its rapid metabolism in the plasma.

Conclusion: 11C-PBB3 was produced with sufficient radioactivity and high quality, demonstrating its clinical utility. The present results of radiosynthesis, photoisomerization, biodistribution, and metabolite analysis could be helpful for the reliable production and application of 11C-PBB3 in diverse PET facilities.

Key Words: tau pathology; Alzheimer disease; PET; 11C-PBB3; photoisomerization

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Accumulation of intracellular tau fibrils is a neuropathologic hallmark of Alzheimer disease (AD) and related tau-positive neurodegenerative disorders, which are collectively referred to as tauopathies (1). Understanding of the mechanistic roles played by pathologic tau in AD and related tauopathies has stimulated increasing interest in the development of imaging probes that facilitate visualization of tau pathology in the brains of living humans and animal models of tauopathies (1). 18F-FDDNP (Fig. 1) was applied to PET imaging of intraneuronal neurofibrillary tangles for the first time (2). However, 18F-FDDNP showed a relatively low contrast and selectivity for tau lesions versus β amyloid in in vitro autoradiograms and PET images of AD brains (3). In addition to 18F-FDDNP, researchers have developed several promising PET probes for imaging tau protein in the brain (4–10). Among these radiotracers, 18F-T807, 18F-T808, 18F-THK523, and 18F-THK5105 (Fig. 1) have been used in clinical studies for AD patients (6,8–10), whereas its capability of capturing tau aggregates in non-AD tauopathies and transgenic animal models is yet to be determined.

Recently, we developed a new class of tau ligands, phenylpyridinyl butadienyl benzothiazoles/benzothiazoliums (PBBs). In vivo optical imaging of a transgenic mouse model demonstrated rapid and sensitive detection of intraneuronal tau inclusions by intravenous administration of these ligands, which are intrinsically fluorescent (11). Selected from these ligands, three 11C-labeled compounds were synthesized and evaluated for their potential as PET probes for imaging tau pathology in tau transgenic mouse models (11). After preclinical evaluation, 2-((1E,3E)-4-(6-(11C-methylamino)pyridin-3-yl)buta-1,3-dienyl)benzo[thiazol-6-ol (11C-PBB3, Fig. 1) was applied to clinical PET studies and was demonstrated to effectively display tau pathology in patients with AD and non-AD tauopathies. Notably, the high-level retention of 11C-PBB3 in the AD hippocampus wherein tau pathology is enriched sharply contrasted with that of a β-amyloid PET probe, 11C-Pittsburgh compound B (11C-PIB) (11,12).

Our previous study was focused on the development of PBBs and the application of 11C-PBB3 to PET imaging of a mouse model and human brains (11). Meanwhile, the growing interest in the clinical use of 11C-PBB3 in many PET facilities motivated us to establish protocols for its radiosynthesis and quality control and to characterize its chemical stability and its pharmacokinetic
and metabolic properties. Here, we determined the radiosynthetic conditions for \textsuperscript{11}C-PBB3 to obtain an appropriate amount of radioactivity with reliable quality for clinical application. Because of the chemical structure of pyridylbutadienylbenzothiazole in \textsuperscript{11}C-PBB3, which is considered to easily undergo photoisomerization by exposure to ultraviolet light (\textsuperscript{13}), we monitored the progress of photoisomerization of \textsuperscript{11}C-PBB3 under fluorescent light and investigated how to prevent it during radiosynthesis and quality control. To validate whether the radioactive signals in the mouse and human brains were derived from \textsuperscript{11}C-PBB3 itself, we performed metabolite analysis of \textsuperscript{11}C-PBB3 for the mouse plasma and brain homogenate.

MATERIALS AND METHODS

General

PBB3 and its precursor \((5-(((1E,3E)-4-(6-(\text{tert-butyldimethylsilyloxy})benzo[d]thiazol-2-yl)buta-1,3-dieryl)pyridin-2-amine (1, Fig. 2) for radiosynthesis were synthesized and supplied from the NARD Institute. Commercially available reagents and organic solvents (Sigma-Aldrich and Wako Pure Chemical Industries) were used without further purification. \textsuperscript{11}C was produced by \textsuperscript{14}N \((p, \alpha)\)\textsuperscript{11}C nuclear reaction using a CYPRIS HM18 cyclotron (Sumitomo Heavy Industries). Effluent radioactivity was monitored using a NaI (TI) scintillation detector system (Gabi Star PET; Raytest). If not otherwise stated, radioactivity was determined using an IGC-3R Curiemeter (Aloka).

Male ddY mice were purchased from Japan SLCL Inc. Animals were maintained and handled in accordance with the recommendations of the U.S. National Institutes of Health and the guidelines of the National Institute of Radiologic Sciences. Animal experiments were approved by the Animal Ethics Committee of the National Institute of Radiologic Sciences. Male ddY mice (35.2 ± 2.2 g) were fed ad libitum.

Radiosynthesis of \textsuperscript{11}C-PBB3

\textsuperscript{11}C-methyl iodide \((\textsuperscript{11}C-CH}_3\)I\) was synthesized from cyclotron-produced \textsuperscript{11}C-CO\textsubscript{2} using an automated synthesis system developed in-house (\textsuperscript{14}). The produced \textsuperscript{11}C-CH\textsubscript{3}I was trapped in a mixture of the \textsuperscript{11}C-PBB3 under fluorescent light and investigated how to prevent it during radiosynthesis and quality control. To validate whether the radioactive signals in the mouse and human brains were derived from \textsuperscript{11}C-PBB3 itself, we performed metabolite analysis of \textsuperscript{11}C-PBB3 for the mouse plasma and brain homogenate.

FIGURE 1. Chemical structures of PET probes for imaging of tau pathology in clinical use.
aqueous acetonitrile and 50 mM ammonium phosphate buffer (pH 9.3) (50/50 [0–1.2 min] and then 70/30 [1.2 min and onward], v/v) was used as the mobile phase. The tR of 11C-PBB3 was approximately 1.1 min at 1.0 mL/min. The identity was confirmed by coinjection with an authentic PBB3 sample. The specific activity was calculated by comparison of the assayed radioactivity to the carrier mass, which was measured on the basis of its ultraviolet peak at 379 nm. To determine the radiochemical stability of 11C-PBB3, the formulated product was maintained for 60 min at room temperature without fluorescent light. An analytic sample was taken from the formulated solution to measure the radiochemical purity again.

For comparison, a portion of the 11C-PBB3 injection sample was transferred to a colorless vial and maintained for 60 min at room temperature under fluorescent light. Analytic samples were taken from this vial to measure the radiochemical purity at 1, 10, and 60 min.

**Quality Control**

In addition to determination of radiochemical purity and specific activity, the physical appearance of the 11C-PBB3 injection was checked by visual inspection (15). pH was measured using a pH meter (F-71; Horiba) and a probe (9618-10D; Horiba). Sterility was tested using a soybean-casein digest broth (Merck) incubated with the injection sample at 20°C–25°C for 14 d and fluid thioglycollate medium (Merck) incubated with the sample at 30°C–35°C for 14 d. Absence of culture growth after 14 d indicates sterility (16). The endotoxin content in the injection sample was measured using a toximeter (ET-6000; Wako) (17). Residual organic solvents (acetonitrile and ethanol) were measured using a gas chromatography system (7890; Agilent Technologies) (18). A DB-WAX column (0.50 μm, 0.53-mm i.d. × 30 m; Agilent Technologies) was maintained at 40°C (0–8 min), raised to 120°C (8–28 min), and kept at 120°C (28–33 min). The makeup gas was nitrogen (99.9995%, 50 mL/min), and the carrier gas was helium (99.9995%, 4 mL/min). A flame ionization detector was used.

**Biodistribution Study**

11C-PBB3 (1.6 MBq in 0.1 mL; 49.6 GBq/μmol) was injected into the tail vein of mice (n = 4 for each time point) without fluorescent light. The blood, heart, lung, spleen, liver, small intestine, testis, kidney, muscle, and brain were dissected at 1, 5, 15, 30, and 60 min after injection. The radioactivity in each tissue was measured using a NaI(Tl) scintillation detector (S-2493A; OVEN); precolumn, XBridge Prep C18 Guard Cartridge (5 μm, 10 mm i.d. × 10 mm; Waters); main column, XBridge OSTM C18 (2.5 μm, 10 mm i.d. × 50 mm; Waters); mobile phase, 90% aqueous acetonitrile/0.02 M sodium phosphate buffer (pH 7.0) (30/70 [0–4 min], 40/60 to 70/30 [4–7 min], v/v); flow rate, 8.0 mL/min; tR, 11C-PBB3, 5 min. All the procedures in this section were conducted with the fluorescent light switched off.

**RESULTS**

Radiosynthesis of 11C-PBB3

11C-PBB3 was synthesized by N-methylation of the desmethyl precursor 1 with 11C-CH3I using KOH as a base (Fig. 2), followed by deprotection of the tert-butylidemethylsilyl group in the intermediate 11C-2 with water. After the reaction, HPLC separation (Fig. 3), and formulation, 11C-PBB3 was successfully obtained with a sufficient amount of radioactivity. At the end of synthesis, 11C-PBB3 of 1.6–3.1 GBq was obtained as an injectable solution of sterile normal saline after 30–35 min of proton bombardment at a beam current of 18 μA. The decay-corrected radiochemical yield of 11C-PBB3 based on 11C-CO2 was 15.4 ± 2.8% (n = 50) at the end of bombardment, and the specific activity was 180.2 ± 44.3 GBq/μmol (n = 50) at the end of synthesis. The averaged radiochemical purity of the 11C-PBB3 product in an amber vial was 98.0% ± 2.3% (Fig. 4A) and remained greater than 95% after 60 min (Fig. 4B) without fluorescent light. The total synthesis time was approximately 35 min from the end of bombardment.

**Photoisomerization**

Figures 4C–4E show the photoisomerization of 11C-PBB3 in a colorless vial under fluorescent light. At 1 min after exposure to the fluorescent light, the radiochemical purity of 11C-PBB3 decreased to 77%. From 10 to 60 min, its radiochemical purity remained approximately 50%. The chemical structure of the 11C-impurity was not identified but was assumed to be the Z, Z or E, Z isomer of 11C-PBB3.
Quality Control

Table 1 summarizes the results of the quality control assessment for 3 different lots of $^{11}$C-PBB3 production. The physical appearance of the product was clear and without particles. The pH was $6.7 \pm 0.8$. In sterility testing, no viable bacteria or microorganisms were observed in soybean-casein digest broth or fluid thioglycollate medium. The endotoxin content was undetectable (<0.7 endotoxin units/maximum volume). The radiochemical purity of $^{11}$C-PBB3 was 98.2% ± 2.2% ($n = 3$) at the end of synthesis and was within the range of 97.0% ± 0.8% after 60 min. The residual amounts of ethanol and acetonitrile in the $^{11}$C-PBB3 injection sample were to be 6.7 ± 0.6 ppm and 1 ppm, respectively.

Table 2 shows the tissue distribution of radioactivity in the whole body of mice at 1, 5, 15, 30, and 60 min after injection of $^{11}$C-PBB3. Uptake in most tissues was the highest at 1 min among all sampling time points. The radioactivity levels in the blood, heart, lung, testis, muscle, and brain decreased rapidly after initial uptake, whereas the radioactivity in the liver, spleen, small intestine, and kidney reduced gradually after 5 min. The radioactivity in all tissues except the small intestine cleared to less than 1 %ID/g at 60 min. Brain uptake was 1.92 %ID/g at 1 min and then decreased rapidly to 0.03 %ID/g at 60 min.

Metabolite Analysis in Brain and Plasma

Figure 5 shows the HPLC chromatograms for the plasma and brain homogenate samples after injection of $^{11}$C-PBB3. In the plasma, the percentage of $^{11}$C-PBB3 rapidly decreased and a radiolabeled metabolite was observed as early as 1 min after injection (Fig. 5A). The fraction corresponding to unchanged $^{11}$C-PBB3 in the plasma was 1.9% ± 0.53% at 5 min (Fig. 5B) and was not detectable at 15 min (data not shown). The radiolabeled metabolite was more polar than $^{11}$C-PBB3, as estimated by its $t_R$ (2.0 min) on the HPLC charts. Despite the rapid metabolism in plasma, the percentage of unchanged $^{11}$C-PBB3 in the brain homogenate was 82% at 1 min (Fig. 5C) and 70% at 5 min (Fig. 5D). A radiolabeled metabolite was also detected in the HPLC charts of the brain samples, and its $t_R$ was similar to that of the metabolite in the plasma. Calculated from the total brain uptake (%ID/g), which was simultaneously measured for the same mice, radioactivity levels representing unchanged $^{11}$C-PBB3 and $^{11}$C-metabolite in the brain were found to be 1.58 ± 0.25 and 0.35 ± 0.06 %ID/g, respectively, at 1 min and 0.83 ± 0.06 and 0.35 ± 0.04 %ID/g, respectively, at 5 min. Recovery of radioactivity from HPLC analysis for all samples was greater than 95%. Because of the low...
radioactivity level, no further metabolite analysis was performed for the brain samples collected beyond 5 min.

**DISCUSSION**

In this study, $^{11}$C-PBB3, a PET probe clinically used for imaging tau pathology in the human brain, was reliably synthesized with sufficient radioactivity and high quality. The metabolite analysis demonstrated the presence of unchanged $^{11}$C-PBB3 as the major radiolabeled component in the mouse brain despite its rapid metabolism in the plasma.

For the radiosynthesis of $^{11}$C-PBB3, the tert-butyldimethylsilyl group-protected desmethyl compound 1 was designed as the precursor. $^{11}$C-methylation of 1 and subsequent deprotection of $^{11}$C-2 gave $^{11}$C-PBB3 in a 2-step, 1-pot process (Fig. 2). We initially attempted to perform $^{11}$C-methylation of 1 using $^{11}$C-CH$_3$OTf and no base, as is done for the synthesis of $^{11}$C-Pittsburgh compound B, which was easily labeled by direct $^{11}$C-methylation without requiring a base (20). However, this approach could not produce $^{11}$C-2, indicating that the $\alpha$-amino group in the pyridine ring of 1 did not have enough nucleophilicity to undergo $^{11}$C-methylation without a base. Use of organic bases gave only trace amounts of $^{11}$C-2. Because the low labeling efficiency with $^{11}$C-CH$_3$OTf without a base could not be improved even by heating the reaction mixture to 150°C for 5 min, this approach was not pursued further.

We then used KOH powder as a base to form the salt of the amine group in situ for the $^{11}$C-methylation of 1 with $^{11}$C-CH$_3$I. The reaction conditions, including the amount of KOH, reaction solvent, time, and temperature, were optimized. It was found that the use of 10 mg of KOH, which was suspended in anhydrous dimethylsulfoxide for 20–30 s with an ultrasonic cleaner just before the synthesis, for reaction of 1 mg of 1 with $^{11}$C-CH$_3$I at 125°C for 5 min could give the highest yield of $^{11}$C-2.

To remove the protective tert-butyldimethylsilyl group in $^{11}$C-2, we initially used tetrabutylammonium fluoride. Although the deprotection was successful, perfect removal of tetrabutylammonium fluoride and its decomposing residues in the final formulated product remained challenging. In place of tetrabutylammonium fluoride, we then used water to remove the tert-butyldimethylsilyl group. As expected, deprotection

### TABLE 2

<table>
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<tr>
<th>Site</th>
<th>1 min</th>
<th>5 min</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
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<tr>
<td>Blood</td>
<td>4.34 ± 0.38</td>
<td>3.06 ± 0.65</td>
<td>1.27 ± 0.19</td>
<td>0.64 ± 0.12</td>
<td>0.12 ± 0.03</td>
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<tr>
<td>Heart</td>
<td>5.98 ± 0.72</td>
<td>2.10 ± 0.17</td>
<td>0.72 ± 0.07</td>
<td>0.32 ± 0.03</td>
<td>0.06 ± 0.02</td>
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<tr>
<td>Lung</td>
<td>12.51 ± 1.06</td>
<td>3.58 ± 2.46</td>
<td>2.12 ± 0.20</td>
<td>1.07 ± 0.28</td>
<td>0.21 ± 0.07</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.62 ± 0.40</td>
<td>3.49 ± 2.48</td>
<td>0.43 ± 0.03</td>
<td>0.23 ± 0.07</td>
<td>0.07 ± 0.01</td>
</tr>
<tr>
<td>Liver</td>
<td>8.01 ± 1.01</td>
<td>14.81 ± 1.29</td>
<td>9.01 ± 1.04</td>
<td>4.42 ± 0.76</td>
<td>0.88 ± 0.17</td>
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<tr>
<td>Small intestine</td>
<td>14.71 ± 3.97</td>
<td>45.58 ± 7.82</td>
<td>29.64 ± 8.02</td>
<td>16.72 ± 5.34</td>
<td>3.57 ± 1.44</td>
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<tr>
<td>Testis</td>
<td>0.56 ± 0.09</td>
<td>1.15 ± 0.54</td>
<td>0.68 ± 0.22</td>
<td>0.47 ± 0.10</td>
<td>0.09 ± 0.01</td>
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<tr>
<td>Kidney</td>
<td>12.49 ± 1.19</td>
<td>10.55 ± 0.81</td>
<td>4.36 ± 0.40</td>
<td>1.80 ± 0.26</td>
<td>0.30 ± 0.05</td>
</tr>
<tr>
<td>Muscle</td>
<td>2.59 ± 0.25</td>
<td>1.33 ± 0.23</td>
<td>0.55 ± 0.07</td>
<td>0.22 ± 0.02</td>
<td>0.04 ± 0.04</td>
</tr>
<tr>
<td>Brain</td>
<td>1.92 ± 0.13</td>
<td>0.97 ± 0.06</td>
<td>0.27 ± 0.02</td>
<td>0.11 ± 0.04</td>
<td>0.03 ± 0.01</td>
</tr>
</tbody>
</table>

Data are mean (± SD) %ID/g tissue (n = 4).
that 11C-PBB3 is rapidly metabolized to the same radiolabeled brain and prompt reduction of the parent probe in the plasma previous metabolite analysis for human plasma (1). The present data, taken together with the results of the 11C-PBB3 injection complied with our in-house quality control and quality assurance specifications (Table 1). These data have guaranteed a reliable supply of 11C-PBB3 with sufficient radioactivity and high quality for clinical application.

The results of the biodistribution study of 11C-PBB3 in mice suggest that the radioactivity might be cleared mainly via the hepatobiliary and intestinal reuptake pathways, with rapid washout from the body (Table 2). The present brain uptake indicates that 11C-PBB3 easily passed through the blood–brain barrier, out from the body (Table 2). The present brain uptake indicates that uptake of radioactivity into the mouse brain was attributable mainly to unchanged 11C-PBB3, which was more hydrophilic than 11C-PBB3, showed limited entry into the brain. This finding indicates that uptake of radioactivity into the mouse brain was attributable mainly to unchanged 11C-PBB3. The present data, taken together with the results of the previous metabolite analysis for human plasma (11), demonstrated that 11C-PBB3 is rapidly metabolized to the same radiolabeled metabolite in mouse and human plasma, as evidenced by the similar t1/2 in the HPLC charts for plasma samples from these 2 species. The percentage of unchanged 11C-PBB3 in human plasma at 3 min after injection was 7.8% ± 2.2%, and the metabolizing rate in human plasma was slightly slower than that in mouse plasma. These results indicate that the radioactive signals acquired by PET in the human brain may primarily reflect the kinetics of 11C-PBB3. However, the influence of the low-grade uptake of radioactive metabolites into the brain on pharmacokinetic measures of 11C-PBB3 should be clarified.

In both humans and mice, the rapid entry of 11C-PBB3 into the brain and prompt reduction of the parent probe in the plasma imply that the levels of 11C-PBB3 in the brain may be dependent largely on its first-pass extraction (11). This characteristic, along with its minimal nonspecific binding of 11C-PBB3 to the myelin-rich components (11), resulted in a rapid washout of this probe from the brain, thereby reducing the background signal in the brain. Moreover, the significant contribution of the first-pass extraction to the radioprobe kinetics in the brain indicates that regional cerebral blood flow may be a critical determinant of the amount of 11C-PBB3 entering the brain; accordingly, the specific binding of 11C-PBB3 to tau lesions may be underestimated in areas with profound hypoperfusion. In fact, PET imaging with 11C-PBB3 in the AD brain displayed high-contrast signals in the hippocampus and low nonspecific retention in the white matter and other myelin-rich regions (11). Although the brain uptake of 11C-PBB3 is lower than that of 18F-T807 and 11C-Pittsburgh compound B (5,11,23), a relatively low concentration of free 11C-PBB3 in the brain may be advantageous to its selective binding to high-affinity, low-capacity sites on tau fibrils, compared with the low-affinity, high-capacity binding sites on β amyloid (11).

A shortcoming of 11C-PBB3 may be the presence of the radiolabeled metabolite in the mouse brain, although brain uptake of this metabolite was lower than that of unchanged 11C-PBB3 in the brain. Determination of the metabolic pathway for 11C-PBB3 is currently ongoing and should provide clues for the design of new probes with improved biostability. Identification of the chemical structure of the major 11C-PBB3 metabolite should also be performed, and subsequent radiolabeling of this metabolite would facilitate evaluation of its plasma and brain kinetics and affinity for tau fibrils.

CONCLUSION

11C-PBB3, a clinically useful PET probe for tau pathology in the brains of humans and transgenic mouse models, was successfully synthesized by reaction of tert-butyldimethylsilyl desmethyl precursor I with 11C-CH3I in the presence of KOH, followed by deprotection with water. We have so far achieved more than 200 productions of 11C-PBB3 in our facility for various research purposes, including translational PET imaging of mouse models and clinical PET assessments of patients diagnosed as having AD and non-AD neurodegenerative disorders. The present results demonstrate the reliable production and widespread clinical potential of 11C-PBB3.

DISCLOSURE

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