VII. 2. Radiosynthesis of \([^{124}\text{I}]\)Iomazenil and Imaging of Rat Brain by Means of Semiconductor High Resolution Animal PET Scanner

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Introduction

Iodine-124 (\(^{124}\text{I}\)) is one of the long-lived positron-emitting nuclides which have lately been interested. It has a long physical half-life (4.15 days) in comparison with the other positron-emitting nuclides (\(^{18}\text{F}\), \(^{11}\text{C}\), \(^{13}\text{N}\) and \(^{15}\text{O}\)) conventionally used for clinical PET studies. It is a potential substitute for \(^{125}\text{I}\)- or \(^{123}\text{I}\)-labeled biologically functional compounds. Moreover, \(^{124}\text{I}\) is suitable for labeling large molecules for functional imaging such as proteins, peptides, nucleic acids, and glycoproteins. Using \(^{124}\text{I}\), some researches in oncology have been carried out\(^1\), but there are few studies in neurology because of a disadvantage for PET imaging with \(^{124}\text{I}\). Its low positron abundance (only 22.9% of the disintegration), and prompt \(\gamma\)-rays were anticipated to degrade the image resolution and to increase the noise.

Recently, Ishii et al. developed an ultra high resolution semiconductor PET (Fine-PET)\(^2\). The trans-axial resolution (full width at half maximum:FWHM) of this PET scanner is less than 1 mm. To perform the rat brain receptor imaging with \(^{124}\text{I}\) using this scanner, we chose iomazenil (IMZ) as a \(^{124}\text{I}\) labeling compound, because it was used as a clinical tracer for central benzodiazepine receptor imaging.

In this study, we evaluated the feasibility of \(^{124}\text{I}\) as a potential nuclide for neurological PET studies by imaging rat brain using the ultra-high resolution semiconductor animal PET.
Materials and Method

$^{124}$I production

Production of $^{124}$I was carried out as described in our previous paper\(^3\). Briefly, it was produced by the $^{124}$Te(p,n)$^{124}$I reaction. The target was $^{124}$TeO$_2$/6 wt% Al$_2$O$_3$ solid solution and it was bombarded with 14 MeV proton beams.

Radiolabeling of IMZ with $^{125}$I

We selected iododestannylation reaction with the corresponding tributylstannyl precursor for radiolabeling iomazenil (Scheme 1). Aqueous hydrogen peroxide was added to a mixture of precursor in methanol (1 mg/ml, 0.3 ml), diluted HCl, and 0.1 M NaOH solution of $^{125}$I in a sealed vial. The reaction was allowed to proceed for 20 min at room temperature, after which it was terminated by the addition of sodium thiosulfite. After the reaction, radiochemical yield was determined by thin-layer chromatography (TLC). Normal phase TLC plate (Silica gel F$_{254}$) with an eluent of ethyl acetate/acetone/ammonia solution (90 vol%/10 vol%/1 vol%) was used. A 2 µL portion of reaction mixture was spotted 2 cm from the bottom of normal phase TLC plate. After developing 15cm from the spotting position, the TLC plate was contacted to the BAS-SR2025 imaging plate (Fuji Photo Film Co. Ltd.) and exposed for 10 minutes. The intensities on the imaging plate were calculated with the image analysis system (BAS-2000, Fuji Photo Film Co. Ltd., Tokyo, Japan).

$[^{124}]$IMZ radiolabeling

$[^{124}]$IMZ was radio-synthesized under the best conditions obtained from the results of $[^{125}]$IMZ radiosynthesis (Scheme 1). The radiochemical yield of $[^{124}]$IMZ was calculated from the Na$^{124}$I radioactivity added in the reaction vial and $[^{124}]$IMZ radioactivity.

PET imaging of $^{[124]}$I IMZ using ultra high resolution semiconductor PET scanner

$[^{124}]$IMZ (97 MBq) was administered from tail vein of male rat (250 g, 8-week old) under the ketamine and xylazine anesthesia. The scan was commenced from 1 hour after tracer injection with Fine-PET\(^2\).

All data were acquired using a Fine-PET in three-dimensional mode (pixel size,
0.6×0.6×0.6 mm) and reconstructed by the method of FORE + ML-EM (30 iterations). Data acquisition time was 1-2 hours.

**Result & Discussion**

*Radio labeling condition of IMZ with \(^{125}\)I and Radiosynthesis of \(^{124}\)IIMZ*

To confirm whether the radiochemical yield of IMZ with radioiodine would be sensitive for HCl and hydrogen peroxide concentration, \(^{125}\)I was used for radio-synthesis of IMZ instead of \(^{124}\)I. The radiochemical yield of \([^{125}\text{I}]\text{IMZ}\) with iododestannylation reaction was strongly affected by the concentration of hydrochloric acid. HCl concentration ranging from 0.5 to 5 mol/L resulted in good radiochemical yield. The radiochemical yields were 2.5 ± 2.7, 9.2 ± 3.6, 49.8 ± 18.4, 75.7 ± 5.6, 46.8 ± 23.2 and 1.7 ± 1.6%, when we used HCl of 0.01, 0.1, 0.5, 1.0, 5.0 and 10.0 mol/L respectively (Fig. 1). Radiochemical yield of \([^{125}\text{I}]\text{IMZ}\) was also affected by the concentration of hydrogen peroxide. When we used 30% or 3% of hydrogen peroxide for reaction, radiochemical yield was higher than that of 0.3%. The radiochemical yields were 6.98 ± 2.5, 63.75 ± 10.1 and 75.7 ± 5.6%, when we used 0.3, 3 and 30% of hydrogen peroxide respectively (Fig. 2). The differences in yield may be affected by pH of the reaction solution. Therefore, it may be considered that hydrogen peroxide needs suitable pH as an oxidizing agent. However, high HCl concentration (over the 5.0 M) caused low yield. For this reason, it may be suggested that iodine was oxidized to I\(_2\) and became an inactive form. When a chrolamine-T was used as an oxidizing agent, a similar chemical tendency was observed (data is not shown). From these results, the conditions of 1 M HCl and 30% of hydrogen peroxide were used for radio-synthesis of \([^{124}\text{I}]\text{IMZ}\). The radiochemical yield of \([^{124}\text{I}]\text{IMZ}\) was 73% and radiochemical purity was over 98%. This yield of \([^{124}\text{I}]\text{IMZ}\) was almost the same as that of \([^{125}\text{I}]\text{IMZ}\). Consequently, it may be suggested that \(^{124}\)I labeled compounds were synthesized with the same methods of \(^{125}\)I labeled compound such as proteins, peptides, nucleic acids, and glycoproteins in similar radiochemical yield.

*PET imaging of \([^{124}\text{I}]\text{IMZ}\) using ultra high resolution semiconductor PET scanner*

The PET images with \(^{124}\)I are suitable for tumor detection but not for brain because low positron abundance (only 22.9% of the disintegration) and high positron energy (maximum energy was 2.135 MeV) of \(^{124}\)I could not visualize brain structures. Using Fine-PET, however, the \([^{124}\text{I}]\text{IMZ}\) radioactivity was observed in the cerebral cortices of the
rat brain and the [$^{124}\text{I}$]IMZ accumulations of the white matter, basal ganglia, and cerebellum were lower than those of cerebral cortices. The autoradiogram of [$^{124}\text{I}$]IMZ proved the PET image (Fig. 3). As a result, it could become clear that even when $^{124}\text{I}$ is used, the PET image of the brain was obtained using the ultra high resolution semiconductor PET (Fine-PET). This finding could facilitate the use of $^{124}\text{I}$-labeled compounds for in vivo brain PET imaging.

In conclusion, we synthesized [$^{124}\text{I}$]IMZ in good radiochemical yield with the same method of $^{125}\text{I}$, and [$^{124}\text{I}$]IMZ imaging of rat brain was obtained using the ultra high resolution semiconductor PET. It may be considered that this result expands the possibility to the use of $^{124}\text{I}$.

References

Scheme 1. Radiolabeling scheme of iomazenil.

Figure 1. The relationship of radiochemical yield of [$^{125}\text{I}$]iomazenil and hydrochloric acid concentration.
Figure 2. The relationship of radiochemical yield of $^{125}$Iiomazenil and hydrochloric acid concentration.

Figure 3. PET image (left) and ARG image (right) of rat brain with $^{124}$I-IMZ PET scanner: Ultra-High Resolution Semiconductor PET [CdTe detector: 1.1 mm×1.0 mm×5 mm, FOV: 64 mm in diameter, 26 mm in axis] Animal: Rat (wistar male, 8 weeks, 187 g), Injection dose: 97 MBq (i.v.). Data acquisition: 1 hours (1-2 hours after injection).