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Preclinical and clinical evaluation of *O*-[^{11}C]methyl-L-tyrosine for tumor imaging by positron emission tomography

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Dedicated to Professor Dr. Willem Vaalburg on the occasion of his retirement (K.I.).

Abstract

We performed preclinical and clinical studies of *O*-[^{11}C]methyl-L-tyrosine, a potential tracer for imaging amino acid transport of tumors by positron emission tomography (PET). Examinations of the radiation-absorbed dose by *O*-[^{11}C]methyl-L-tyrosine and the acute toxicity and mutagenicity of *O*-methyl-L-tyrosine showed suitability of the tracer for clinical use. The whole-body imaging of monkeys and healthy humans by PET showed low uptake of *O*-[^{11}C]methyl-L-tyrosine in all normal organs except for the urinary track and bladder, suggesting that the *O*-[^{11}C]methyl-L-tyrosine PET has the potential for tumor imaging in the whole-body. Finally, the brain tumor imaging was preliminarily demonstrated.

Keywords: *O*-[^{11}C]methyl-L-tyrosine; Tumor imaging; Positron emission tomography

1. Introduction

For tumor diagnosis by positron emission tomography (PET), 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) is of first choice of radiopharmaceuticals worldwide. The whole-body imaging with the [^{18}F]FDG PET is routinely performed for tumor imaging; however, its limitations are well understood [1]. For example, high uptake of [^{18}F]FDG in the normal brain tissues hampers the tumor imaging in the brain. Uptake in the inflammatory tissues is sometimes troublesome for differential diagnosis [2]. Excretion of [^{18}F]FDG through the urinary track also sometimes makes tumor diagnosis difficult in a lower abdominal region. In contrast to [^{18}F]FDG, radiolabeled amino acids are taken in the normal brain tissue at much lower levels, which enables imaging of the majority of low- and high-grade brain tumors. Uptake of L-[*methyl*-^{11}C]methionine in the inflammatory tissues was low [3]. A variety of radiolabeled amino acids were prepared and evaluated, as reviewed by Vaalburg et al. [4] and Jager et al. [5]. So far, L-[*methyl*-^{11}C]methionine is widely used in most clinical studies because of its simple and efficient labeling procedure. The metabolism of L-[*methyl*-^{11}C]methionine was complicated for the kinetic modeling, whereas L-[1-^{11}C]tyrosine can be used for measuring the protein synthesis rate. On the other hand, the metabolically stable artificial amino acids are also available for evaluating the amino acid transport in the tumors.

In contrast to brain tumor imaging, the use of radiolabeled amino acids for the tumor diagnosis in the abdominal region was limited, because many amino acids including both natural and artificial ones are physiologically taken at high levels in abdominal organs such as the pancreas, liver, small intestine and kidney in experimental animals. By the whole-body imaging technique, high uptake of L-[*methyl*-^{11}C]methionine or L-[1-^{11}C]tyrosine in the liver and pancreas was

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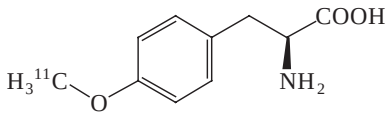

Fig. 1. Chemical structure of *O*-[^{11}C]methyl-L-tyrosine.

confirmed in humans [1,5]. However, Wester et al. [6] demonstrated very low uptake of the radioactivity in the pancreas and liver of humans after injection of *O*-[^{18}F]fluoroethyl-L-tyrosine, in spite of very high uptake of the tracer in the mouse pancreas. This artificial amino acid was originally developed as a tracer for imaging amino acid transport based on the concept that the longer half-life of ^{18}F (109.8 min compared to 20.4 min for ^{11}C) allows a single production to be sufficient for several patients, or alternatively, to be delivered to satellite PET centers. Other [^{18}F]fluorinated amino acids were also developed for the similar purpose: 4-[^{18}F]fluoro-L-phenylalanine [7], 4-[^{18}F]fluoro-L-proline [8], 1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid [9] and *O*-[^{18}F]fluoropropyl-L-tyrosine [10]. Recently, we also proposed *O*-[^{18}F]fluoromethyl-L-tyrosine, of which radiosynthesis is suitable for a large-scale routine production [11]. This amino acid and its ^{11}C-labeled counterpart, *O*-[^{11}C]methyl-L-tyrosine (Fig. 1), proved to be promising tracers for imaging amino acid transport in tumor tissues [12]. The short half-life of ^{11}C-labeled tracers has a potential disadvantage that the tracer is restrictedly used in a few subjects in PET centers with an on-site cyclotron; however, it in turn becomes a potential advantage that multiple tracers can be successively applied to the individual patients in the same day, that is, *O*-[^{11}C]methyl-L-tyrosine PET followed by [^{18}F]FDG PET, in addition to the low radiation-absorbed dose of the ^{11}C-labeled tracers compared with a longer half-lived ^{18}F tracers.

The aim of the present study is to confirm suitability of *O*-[^{11}C]methyl-L-tyrosine in clinical use. For this end, we evaluated the radiation dosimetry of *O*-[^{11}C]methyl-L-tyrosine for humans from the distribution data in mice and the acute toxicity and mutagenicity of *O*-methyl-L-tyrosine. Uptake of *O*-[^{11}C]methyl-L-tyrosine in the inflammatory tissue was compared to that in tumor tissue in a rat model [12,13]. To investigate the applicability of *O*-[^{11}C]methyl-L-tyrosine PET for tumor diagnosis in the whole-body, dynamic whole-body imaging with the *O*-[^{11}C]methyl-L-tyrosine, PET was preclinically performed in monkeys in addition to brain imaging. Clinically pharmacokinetics of *O*-[^{11}C]methyl-L-tyrosine was evaluated in three healthy subjects. Finally, the *O*-[^{11}C]methyl-L-tyrosine PET was applied to a patient with brain tumor.

2. Materials and methods

2.1. General

L-Tyrosine disodium salt was purchased from Research Biochemicals International (Natick, MA). *O*-Methyl-L-tyrosine was purchased from Bachem (Bubendorf, Switzerland). Male ddY mice and male Donryu rats were obtained from Tokyo Laboratory Animals (Tokyo, Japan). Two male rhesus monkeys (*Macaca mulatta*) were purchased from Japan SLC (Shizuoka, Japan).

The animal studies with rodents were approved by the Animal Care and Use Committee of the Tokyo Metropolitan Institute of Gerontology. The PET study with monkeys was performed at the Central Research Laboratory of Hamamatsu Photonics K.K., Hamamatsu, Japan, in accordance with recommendations of the US National Institute of Health and the guidelines of the Central Research Laboratory, Hamamatsu Photonics K.K. The clinical study was performed at the Positron Medical Center of the Tokyo Metropolitan Institute of Gerontology after approval by the institutional Ethical Committee.

2.2. Preparation of *O*-[^{11}C]methyl-L-tyrosine

O-[^{11}C]methyl-L-tyrosine was prepared by the reaction of L-tyrosine disodium and [^{11}C]methyl triflate by a slight modification of the reported procedure [11,12]. [^{11}C]Methyl triflate was bubbled into a solution of L-tyrosine disodium salt (2 mg/ml) in dimethylsulfoxide (0.5 ml) at room temperature. Then, the reaction mixture was diluted with 1.0 ml of water and applied to high-performance liquid chromatography (HPLC): column, YMC-Pack ODS-A column (10-mm inner diameter×250-mm length; particle size, 5 μm; YMC, Kyoto, Japan); mobile phase, CH_3CN/50 mM CH_3CO_2H/50 mM $CH_3CO_2NH_4$ (8:46:46, v/v/v); and flow rate, 5 ml/min. The fraction of *O*-[^{11}C]methyl-L-tyrosine (retention time, 7.0 min) was evaporated to dryness. The residue was dissolved in physiological saline and sterilized by membrane filtration. The radiochemical purity of *O*-[^{11}C]methyl-L-tyrosine was >97%, which was determined by HPLC: column, TSKgel super-ODS (4.6-mm inner diameter×100-mm length; particle size, 2 μm; Toso, Tokyo, Japan); mobile phase, CH_3CN/50 mM CH_3CO_2H/50 mM $CH_3CO_2NH_4$ (5:47.5:47.5, v/v/v); flow rate, 1 ml/min; and retention time, 3.6 min. The specific activity of *O*-[^{11}C]methyl-L-tyrosine was 41–118 TBq/mmol. Finally, the sterility and apyrogenicity of the products were confirmed.

2.3. Radiation dosimetry

O-[^{11}C]methyl-L-tyrosine (10 MBq/220 pmol) was intravenously injected into mice (8 weeks old, 34.4±0.5 g). They were killed by cervical dislocation 1, 5, 15, 30, 60 and 90 min after injection (n=4). The blood was collected by heart puncture, and the tissues were harvested. The samples were measured for the ^{11}C radioactivity with an autogamma counter and weighed. The tissue uptake of ^{11}C was expressed as a percentage of the injected dose per organ (%ID/organ) or a percentage of the injected dose per gram of tissue (%ID/g). Radiation dosimetry for human adults was estimated by the MIRD method based on the tissue distribution data of *O*-[^{11}C]methyl-L-tyrosine in mice as described previously [14].