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Biodistribution, pharmacokinetics and PET Imaging of [^{18}F]FMISO, [^{18}F]FDG and [^{18}F]FAc in a sarcoma- and inflammation-bearing mouse model

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Abstract

2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG), [^{18}F]fluoroacetate ([^{18}F]FAc) and [^{18}F]fluoromisonidazole ([^{18}F]FMISO) were all considered to be positron emission tomography (PET) probes for tumor diagnosis, though based on different rationale of tissue uptake. This study compared the biodistribution, pharmacokinetics and imaging of these three tracers in a sarcoma- and inflammation-bearing mouse model.

Methods: C3H mice were inoculated with 2×10^5 KHT sarcoma cells in the right thigh on Day 0. Turpentine oil (0.1 ml) was injected in the left thigh on Day 11 to induce inflammatory lesion. Biodistribution, pharmacokinetics and microPET imaging of [^{18}F]FMISO, [^{18}F]FDG and [^{18}F]FAc were performed on Day 14 after tumor inoculation.

Results: The inflammatory lesions were clearly visualized by [^{18}F]FDG/microPET and autoradiography at 3 days after turpentine oil injection. The tumor-to-muscle and inflammatory lesion-to-muscle ratios derived from microPET imaging were 6.79 and 1.48 for [^{18}F]FMISO, 8.12 and 4.69 for [^{18}F]FDG and 3.72 and 3.19 for [^{18}F]FAc at 4 h post injection, respectively. Among these, the tumor-to-inflammation ratio was the highest (4.57) for [^{18}F]FMISO compared with that of [^{18}F]FDG (1.73) and [^{18}F]FAc (1.17), whereas [^{18}F]FAc has the highest bioavailability (area under concentration of radiotracer vs. time curve, 116.2 h×percentage of injected dose per gram of tissue).

Conclusions: MicroPET images and biodistribution studies showed that the accumulation of [^{18}F]FMISO in the tumor is significantly higher than that in inflammatory lesion at 4 h post injection. [^{18}F]FDG and [^{18}F]FAc delineated both tumor and inflammatory lesions. Our results demonstrated the potential of [^{18}F]FMISO/PET in distinguishing tumor from inflammatory lesion.

Keywords: [^{18}F]FDG; [^{18}F]FMISO; [^{18}F]FAc; Inflammation; KHT sarcoma; MicroPET; Turpentine oil

1. Introduction

Positron emission tomography (PET) offers a noninvasive means to assess neoplasms, in view of its sensitivity and accuracy in staging tumors and potential in monitoring therapeutic response [1]. Most malignant tumors have been shown to have increased energy utilization, poor blood perfusion and areas of low oxygenation (hypoxia) [2]. 2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) is currently the most widely used PET probe for many kinds of cancers due to the higher demand of glycolysis in tumors. The analogue of glucose, [^{18}F]FDG, enter cells through glucose transporters and is trapped after phosphorylation by hexokinase [3]. However, [^{18}F]FDG/PET for tumor imaging has drawbacks because the uptake of [^{18}F]FDG is not tumor specific. Various forms of infection, inflammation, granulomatous disease and many other physiological or pathological conditions also utilized [^{18}F]FDG and are the major cause of false-positive results [4].

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A variety of solid tumors demonstrate oxygen deficiency as a result of rapid growth and insufficient tumor angiogenesis. In the 1950s, Gray et al. first described that hypoxia in solid tumors limited the effectiveness of radiation therapy [5]. Hypoxia also appears to accelerate malignant progression and metastatic potential of primary tumors [6]. Fluoromisonidazole ([^{18}F]FMISO) is the most widely used PET radiotracer for imaging tissue hypoxia [7]. 2-Nitroimidazoles can undergo an oxygen-reversible, single-electron reduction in hypoxic environments, forming reactive oxygen radicals that subsequently bind covalently to macromolecular cellular components and trap in cells [8].

Radiolabeled acetate such as [^{11}C]acetate has been used for many years as a tracer for measuring oxidative metabolism [9] and also as tumor imaging agent, but the short half-life (20.4 min) limited its widespread applications. The fluorinated analogue [^{18}F]fluoroacetate, with a longer half-life than [^{11}C]acetate, have been developed as a useful alternative to [^{11}C]acetate for detecting tumor lesions in recent years. [^{18}F]Fluoroacetate ([^{18}F]FAc) has been reported to be a potential PET tracer with high sensitivity for the detection of prostate cancer and provided higher tumor-to-background ratio than [^{11}C]acetate [10]. Similar to acetate, fluoroacetate was also a substrate for acetyl coenzyme A synthase. It converts fluoroacetate to fluorocitric acid, which then inhibits aconitase, leading to the inhibition of the tricarboxylic acid cycle [11].

To the best of our knowledge, a comparison of the selectivity of [^{18}F]FMISO, [^{18}F]FDG and [^{18}F]FAc for tumor and inflammatory lesion have not been reported yet. Therefore, we investigated the biodistribution, pharmacokinetics and PET imaging of these three ^{18}F-labeled radiotracers and evaluated their potential for differentiating tumor from inflammation in a tumor and inflammation lesion-bearing mouse model.

2. Materials and methods

2.1. Materials

(2′-Nitro-1′-imidazolyl)-2-*O*-acetyl-3-*O*-tosylpropanol was synthesized according to the method of Cherif et al. [12]. [^{18}F]FMISO was produced by nucleophilic fluorination reaction of the aforementioned precursor followed by deprotection. [^{18}F]FDG was synthesized with an automatic synthesis module (Coincidence, Tracer lab, USA). [^{18}F]FAc was produced by radiofluorination of ethyl bromoacetate followed by deprotection, according to the method of Sykes et al. [13].

2.2. Cell culture and animal model

KHT sarcoma cells were cultured in α-Minimum Essential Medium (MEM) (containing 10% fetal bovine serum, 100 U/ml penicillin and 100 μg/ml streptomycin) at 37°C in a humidified atmosphere with 5% CO_2. Eight-week-old male C3H mice were obtained from the National Animal Center of Taiwan (Taipei, Taiwan, ROC). The inflammation was induced by injecting turpentine oil, which is known to result in chronic inflammation with fibroblasts, vascular proliferation and macrophage infiltration [14]. Sixty-five mice were intramuscularly injected with 2×10^5 KHT cells in the right thigh on Day 0 and 100 μl turpentine oil (Wako Pure Chemical Industries, Tokyo, Japan) in the left thigh muscle on Day 11. The animal experiments were approved by the animal care and use committee of the institution.

2.3. MicroPET imaging and data analysis

MicroPET images were obtained using a Concorde R4 Microsystem (Knoxville, TN, USA), which produces 63 image slices over a 7.89-cm axial field of view, with a slice thickness of about 1.25 mm. To monitor the progression of inflammation, [^{18}F]FDG/microPET scanning was performed on the day before and 3 days after turpentine oil injection. MicroPET images were acquired at 30, 60, 120 and 240 min after intravenous (i.v.) administration of 5.5 MBq of [^{18}F]FDG, [^{18}F]FMISO and [^{18}F]FAc beginning from Day 14 after tumor implantation. All images were reconstructed with the OSEM method, with a 128×128-pixel image matrix, 16 subsets, four iterations and Gaussian filter. Transmission scanning was performed at 130 min post injection. Acquisition time was 600 s, and images were reconstructed using filtered back-projection. For data analysis, a region of interest (ROI) was placed on each tumor, inflammatory lesion and muscle along the spine in the transaxial images including the entire lesion volume. The average radioactivity within tumor or inflammatory lesion was obtained from the average pixel value within the multiple ROI volume. AsiPro software (Concorde Microsystems) was used for viewing microPET images and for data analysis. The counts in each ROI were converted to radioactivity per gram of tissue (nCi/g), assuming a tissue density of 1 g/ml and were then normalized to percentage of injected dose per gram of tissue (%ID/g) [15,16]. The %ID/g was defined as the average radioactivity concentration in several planes of the tumor or organs divided by the total injected dose.

2.4. Whole body autoradiography

At 3 days after turpentine oil injection, the whole body autoradiography (WBAR) was performed immediately after [^{18}F]FDG/microPET imaging. Two tumor- and inflammatory lesion-bearing mice were sacrificed by CO_2 euthanasia at 60 min post i.v. injection of 5.5 MBq of [^{18}F]FDG. Mice were immediately dipped in liquid nitrogen, and frozen carcasses were then embedded with 4% carboxylmethylcellulose. Coronal sections were obtained by a cryomicrotone (Bright Instrument Company Ltd., UK) with a slice thickness of 40 mm at −20°C. Whole body frozen sections were applied to the BAS-MP2040 imaging plate (Fuji Photo Film, Tokyo, Japan) and exposed overnight at −20°C. After completing the exposure, the imaging plate was analyzed with a BAS-1000 reader (Fuji Photo Film, Tokyo, Japan) and