1-(2'-Deoxy-2'-[^{18}F]fluoro-β-D-arabinofuranosyl)-5-iodocytosine

^{18}F-FIAC

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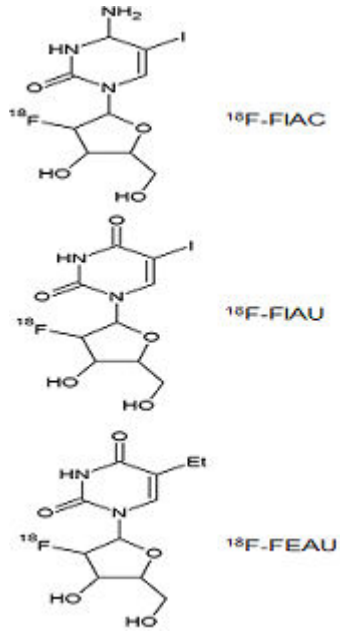
Chemical name:	1-(2'-Deoxy-2'-[^{18}F]fluoro-β-D-arabinofuranosyl)-5-iodocytosine
Abbreviated name:	^{18}F-FIAC
Synonym:	
Agent Category:	Compounds
Target:	Herpes simplex virus type 1 thymidine kinase (HSV1-tk)
Target Category:	Enzyme (reporter gene)
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Structures of ^{18}F-FIAC, ^{18}F-FIAU, and ^{18}F-FEAU (1, 2).

Background

[PubMed]

The ^{18}F-labeled 1-(2'-deoxy-2'-[^{18}F]fluoro-β-D-arabinofuranosyl)-5-iodocytosine, abbreviated as ^{18}F-FIAC, is a cytidine analog synthesized for positron emission

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tomography (PET) of herpes simplex virus (HSV) type 1 thymidine kinase (HSV1-tk) gene expression (1, 3).

The *HSV1-tk* reporter gene expression was first explored with radiolabeled nucleoside analogs by Tjuvajev et al. in 1995 to monitor the activity of *HSV1-tk* (4). This study opened a new field of imaging of *HSV1-tk* gene expression in gene therapy of cancer (2, 5). Since then, a large number of radiolabeled nucleoside analogs have been reported for PET imaging of *HSV1-tk* reporter gene expression (2, 3). These analogs have been developed on the basis of their antiviral properties against HSV for treatment of HSV encephalitis, which involves monophosphorylation of the nucleoside analogs by *HSV1-tk* to their monophosphates that are subsequently converted to their di- and tri-phosphates by host kinases (1). Basically, these analogs can be divided into two major classes: pyrimidine and purine nucleoside analogs (2). The pyrimidine analogs are 2'-^{18}F-fluoroarabinofuranisyluracil derivatives and a few other 5- and 6-substituted uracil derivatives. The purine analogs are fluorinated guanosine (acycloguanosine) derivatives. Pyrimidine analogs have two advantages over the guanosine analogs. First, pyrimidine nucleosides are more sensitive (by orders of magnitude) to *HSV1-tk* than guanosine nucleosides. Second, pyrimidine analogs are mainly cleared *via* the kidneys; therefore, the background activity is negligible, whereas most guanosine nucleosides are cleared through the hepatobiliary system, which leads to high radioactivity in the intestine. However, pyrimidine analogs are substrates of thymidine phosphorylase (TPase), and the glycosilic bond between the sugar and the base in the structure can be cleaved by TPase, whereas guanosine analogs are resistant to TPase; therefore, guanosine nucleosides often exhibit better tracer kinetics in this respect than the pyrimidine nucleosides. In addition, because guanosine nucleosides are not TPase substrates, they are more attractive for PET imaging of mutated *HSV1-tk* reporter gene expression (6).

FIAC is a potent inhibitor of HSV virus replication. In virus-infected cells, FIAC is transformed to mono-, di-, or tri-phosphate form and incorporated into the viral DNA sequence to cause anti-viral effects at concentrations as low as 10 nM (7, 8). At the same time, FIAC exhibits limited cytotoxicity (IC_{50} = 21.7 μM) to untransfected cells, indicating that FIAC might not be a proper substrate for the host thymidine kinase (8). These findings imply that FIAC might be an ideal probe for targeting HSV1-tk gene expression in living subjects. Chan et al. (1) tested the feasibility of ^{18}F-FIAC as a PET radiotracer for HSV1-tk gene imaging and compared it with two highly promising thymidine analogs, 2'-deoxy-2'-[^{18}F]fluoro-5-iodo-1-β-D-arabinofuranosyluracil (^{18}F-FIAU) and 2'-deoxy-2'-[^{18}F]fluoro-5-ethyl-1-β-D-arabinofuranosyluracil (^{18}F-FEAU) (9) in an NG4TL4-WT/STK sarcoma-bearing mouse model. This chapter summarizes the data obtained with ^{18}F-FIAC.

Related Resource Links:

Probers for gene reporter expression imaging in MICAD

HSV-related clinical trials

Nucleotide and protein sequences of HSV

HSV-related compounds and proteins in PubChem

Synthesis

[PubMed]

Wu et al. described the synthesis of ^{18}F-FIAC in detail, which started from 2-*O*-(trifluoromethylsulfonyl)-1,3,5,-tri-*O*-ben-zoyl-a-D-ribofuranose (compound 1) (3). Fluorination of compound 1 with n-$Bu_4N^{18}F$ resulted in the production of 2-deoxy-2-[^{18}F]fluoro-1,3,5-tri-*O*-benzyl-a-D-arabinofuranose (compound 2). The radiochemical yield of compound 2 was >47%. ^{18}F-FIAC was then synthesized on the basis of compound 2. ^{18}F-FIAU and ^{18}F-FEAU were prepared according to the methods published previously. The radiochemical yields of the three tracers were 10%–20%, with radiochemical purities >98%. The total synthetic time for each tracer was ~3.5 h. The specific activities were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The *in vitro* accumulation studies of ^{18}F-FIAC, ^{18}F-FIAU, and ^{18}F-FEAU were conducted with HSV1-tk-positive NG4TL4-TK [tk(+)] cells and HSV1-tk-negative NG4TL4-TK [tk(–)] cells (1). Cellular uptake was expressed as cell/medium (C/M) ratio. In general, the accumulation of all three tracers in HSV1-tk-positive cells increased linearly with time. The tk(+) cells exhibited a more rapid and higher uptake of ^{18}F-FIAU and ^{18}F-FEAU than of ^{18}F-FIAC. The C/M ratios of ^{18}F-FIAC, ^{18}F-FIAU, and ^{18}F-FEAU in tk(+) cells after 120 min of incubation were 95.88 ± 32.21, 304.38 ± 47.78, and 281.78 ± 20.65, respectively. The tk(−) cells showed a moderate accumulation of ^{18}F-FIAU (3.99 ± 0.72) but only a limited uptake of ^{18}F-FIAC (1.44 ± 0.24) and ^{18}F-FEAU (1.14 ± 0.15) after incubation for 2 h. The tk(+)/tk(−) cellular uptake ratios of ^{18}F-FIAC, ^{18}F-FIAU, and ^{18}F-FEAU after 120 min incubation were 66.6 ± 25.1, 76.3 ± 18.2, and 247.2 ± 37.2, respectively. ^{18}F-FIAC exhibited similar *HSV1-tk* specificity compared with ^{18}F-FIAU. High correlations were observed between the cellular uptake of ^{18}F-FIAC, ^{18}F-FIAU (R^2 = 0.99; P <0.05), and ^{18}F-FEAU (R^2 = 0.99; P <0.005), which suggested that ^{18}F-FIAC behaved as an HSV1-tk gene expression probe, similar to ^{18}F-FIAU and ^{18}F-FEAU (1).

Animal Studies

Rodents

[PubMed]

The biodistribution of the three tracers was analyzed in FVB/N mice bearing both HSV1-tk-positive NG4TL4-TK [tk(+)] and HSV1-tk-negative NG4TL4-TK [tk(–)] tumors after

tail vein injection of 1.85 MBq (0.05 mCi) of each tracer (1). Mice were euthanized at different time points (n = 4 mice/time point per tracer). The accumulation in each tissue was expressed as the percentage of injection dose per gram of tissue (% ID/g) (Table 1).

The biodistribution results showed that the accumulations of the three tracers in tk(+) tumors were much higher than the accumulation in tk(−) tumors and in most normal organs except for kidneys (Table 1). The tk(+) tumor uptake of ^{18}F-FIAC and ^{18}F-FIAU increased with time after injection. The tk(+) tumor uptake of ^{18}F-FEAU was lower than that of ^{18}F-FIAC and ^{18}F-FIAU. However, the tk(+)/tk(−), tk(+)/muscle, and tk(+)/blood ratios for ^{18}F-FEAU were much higher than those for ^{18}F-FIAC and ^{18}F-FIAU, which may be due to the rapid blood clearance and fast urine excretion of ^{18}F-FEAU compared with ^{18}F-FIAC and ^{18}F-FIAU. The distribution profile of ^{18}F-FIAC was similar to that of ^{18}F-FIAU but was different from that of ^{18}F-FEAU. The high radioactivity in the kidney and urine indicated that all three tracers and their radioactive metabolites were mainly excreted *via* the urinary system.

Table 1: Accumulation of the tracers in selected organs 120 min after injection.

Tracer	Blood	Liver	Kidney	Bone	tk(+)	tk(−)	tk(+)/tk(−)	tk(+)/M	tk(+)/Blood
^{18}F-FIAC	2.71	3.47	4.54	1.18	51.59	4.11	12.6	21.9	19
^{18}F-FIAU	2.53	2.51	4.18	0.76	58.55	3.71	15.8	26.9	23.1
^{18}F-FEAU	0.34	0.27	0.52	0.68	14.56	0.30	48.0	42.8	42.8

tk(+), tk(−), and tk(+)/M represent HSV1-tk-positive, HSV1-tk-negative, and tk(+)/muscle ratio, respectively.

Analysis of the radioactive metabolites in urine at 30 min after injection of ^{18}F-FIAC in tumor-bearing mice showed that intact ^{18}F-FIAC only accounted for 4% of radioactivity in the urine, and the radioactivity of other metabolites including 1-(2'-deoxy-2'-[^{18}F]fluoroarabinofuranosyl)cytosine (^{18}F-FAC), ^{18}F-FIAU, and (1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)uracil (^{18}F-FAU) was 24%, 48%, and 2%, respectively. ^{18}F-FIAC may be regarded as the prodrug of ^{18}F-FIAU *in vivo* (1).

MicroPET scanning of the tk(+)/tk(−) tumor-bearing mice was conducted at 1 h after injection of 1.11 MBq (0.03 mCi) ^{18}F-FIAC, ^{18}F-FIAU, and ^{18}F-FEAU on three consecutive days (1). The tk(+) tumor was clearly delineated with high contrast in the PET images. The tk(+)/muscle ratio was 5.5 for ^{18}F-FIAC, 10.8 for ^{18}F-FIAU, and 7.0 for ^{18}F-FEAU. The tk(+)/tk(−) tumor uptake ratios were 4.8 for ^{18}F-FIAC, 6.7 for ^{18}F-FIAU, and 7.0 for ^{18}F-FEAU. These results were consistent with the results observed in the biodistribution studies.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

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