6-Deoxy-6-[^{18}F]fluoro-D-fructose

6-[^{18}F]FDF

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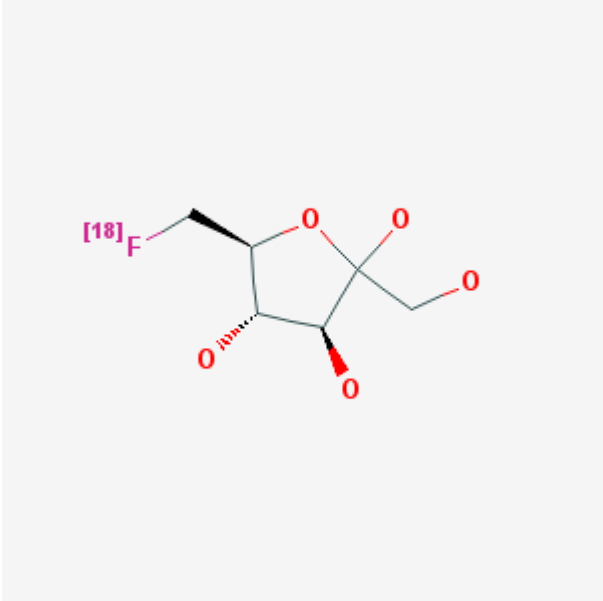
Chemical name:	6-Deoxy-6-[^{18}F]fluoro-D-fructose
Abbreviated name:	6-[^{18}F]FDF
Synonym:	
Agent Category:	Compound
Target:	Glucose transporters, ketohexokinase
Target Category:	Transporters, enzymes
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

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The phosphorylation of glucose, an initial and important step in cellular metabolism, is catalyzed by hexokinases (HKs) (1). There are four HKs in mammalian tissues. HKI, HKII, and HKIII have molecular weights of ~100,000 each. HKI is found mainly in the brain. HKII is insulin-sensitive and is found in adipose and muscle cells. HKIV, also known as glucokinase, has a molecular weight of 50,000 and is specific to the liver and pancreas. Most brain HK is bound to mitochondria, enabling coordination between glucose consumption and oxidation. Tumor cells are known to be highly glycolytic because of increased expression of glycolytic enzymes and HK activity (2), which is detected in tumors from patients with lung, gastrointestinal, and breast cancer. The HKs, by converting glucose to glucose-6-phosphate, help maintain the downhill gradient that results in the transport of glucose into cells through the facilitative glucose transporters (GLUT1-13) (3). GLUT4 and HKII are the major transporter and HK isoform in skeletal muscle, heart, and adipose tissue, wherein insulin promotes glucose utilization. HKIV is associated with GLUT2 in liver and pancreatic β cells.

2-Deoxy-D-glucose (2DG) was first developed to inhibit glucose utilization by cancer cells (4). HKs phosphorylate 2DG to 2-DG-6-phosphate, which inhibits phosphorylation of glucose. 2-[^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) was later developed for molecular imaging studies (5). FDG is moved into cells by glucose transporters (GLUT1 and GLUT3) and is then phosphorylated by HK to FDG-6-phosphate. FDG-6-phosphate cannot be metabolized further in the glycolytic pathway and remains within the cells. Tumor cells do not contain a sufficient amount of glucose-6-phosphatase to reverse the phosphorylation. The elevated rates of glycolysis and glucose transport in many types of tumor cells and activated cells enhance the uptake of FDG in these cells relative to other normal cells. Positron emission tomography (PET) with [^{18}F]FDG has been used to assess alterations in glucose metabolism in brain, cancer, cardiovascular diseases, Alzheimer's disease and other central nervous system disorders, and infectious, autoimmune, and inflammatory diseases (6-11).

Overall, [^{18}F]FDG PET showed 76%–89% sensitivity and 73%–80% specificity for the detection of primary breast cancer (12). Several clinical studies showed that 28%–47% of breast tumor samples were negative for GLUT1 (13, 14). The low or absent tumor expression of GLUT1 seems to account for the low sensitivity of [^{18}F]FDG PET in detecting these breast tumors. High-affinity fructose transporter GLUT5 was found to be overexpressed in 37% of breast tumor samples (13). 6-Deoxy-6-fluoro-D-fructose (6-FDF) is a substrate for GLUT5, whereas FDG is not (15). Wuest et al. (16) have evaluated 6-deoxy-6-[^{18}F]fluoro-D-fructose (6-[^{18}F]FDF) as a PET tracer for imaging GLUT5 expression.

Related Resource Links:

- Chapters in MICAD (Hexokinase, glucose transporter)
- Gene information in NCBI (Hexokinase, Glut1, Glut5).
- Articles in Online Mendelian Inheritance in Man (OMIM) (Hexokinase, Glut1, Glut5)

- Clinical trials ([18F]FDG)
- Drug information in FDA ([18F]FDG)

Synthesis

[PubMed]

6-[18F]FDF was readily synthesized with standard 18F-fluorination of the triflate derivative with ([18F]KF/Kryptofix 2.2.2, 8 min at 85°C) and subsequent acid hydrolysis with 2N HCl (8 min at 110°C) in an automated module (16). Overall radiochemical yields were 25%–35%, with a radiochemical purity of >95%. The synthesis time was ~120 min, including high-performance liquid chromatography purification. The specific activity of 6-[18F]FDF was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Wuest et al. (16) showed that 6-[18F]FDF entered murine EMT-6 and human MCF-7 breast tumor cells in culture with 30 ± 4% (n = 9) and 12 ± 1% (n = 7) incubation dose/mg protein after 60 min of incubation, respectively. In comparison, [18F]FDG accumulation in these two tumor cells was >10-fold higher. 6-FDF exhibited a 9-fold higher potency than D-fructose to inhibit 6-[18F]FDF accumulation in EMT-6 cells, whereas D-glucose showed no inhibition. 6-[18F]FDF was not retained in the tumor cells as >80% of radioactivity was found in the fresh medium after 60 min incubation. Approximately 65%–75% intact 6-[18F]FDF was found in the tumor cells. On the other hand, most of the radioactivity from [18F]FDG was trapped inside the cells. 6-[18F]FDF was rapidly phosphorylated by the human recombinant ketohexokinase but not by human recombinant HKII in cell-free enzyme assays.

Animal Studies

Rodents

[PubMed]

6-[18F]FDF accumulated rapidly in kidneys, heart, liver, spleen, gallbladder, lung, and intestines of normal mice (n = 3/group) at 5 min after injection, followed by rapid clearance (16). On the other hand, the moderate accumulation of the tracer in the brain remained relatively constant during the 2-h experiment. Radioactivity in the bone increased with time, indicating radiodefluorination of 6-[18F]FDF. *Ex vivo* biodistribution studies were also performed in mice (n = 3/group) bearing EMT-6 tumors. The organ with the highest accumulation was the kidney (12.3% injected dose/gram (ID/g)) at 5 min after injection. Tumor accumulation was 3.7% ID/g, 3.5% ID/g, and 1.8% ID/g at 5, 30, and 120 min after injection, respectively. Blood and muscle radioactivity levels were 1.5% ID/g and 0.9% ID/g at 120 min, respectively. Plasma contained 24% and 10% intact 6-

[^{18}F]FDF at 5 min and 60 min after injection with one more polar radiometabolite and one more lipophilic radiometabolite. No blocking study was performed.

PET imaging studies were performed in mice bearing EMT-6 tumors (n = 3/group) and nude mice bearing MCF-7 tumors (n = 3/group) with 6-[^{18}F]FDF and [^{18}F]FDG at 15 min and 120 min after injection (16). The EMT-6 tumors were visualized with both tracers at both time points. Both tracer accumulations in the MCF-7 tumors were less visible than in the EMT-6 tumors. 6-[^{18}F]FDF reached a maximum standard uptake value (SUV) of 1.23 ± 0.09 at 10–15 min and decreased to 0.54 ± 0.06 at 120 min. On the other hand, [^{18}F]FDG increased consistently over 120 min, reaching a maximum SUV of 1.80 ± 0.25 at 120 min. Maximum SUV values of both tracers (~0.75) in MCF-7 tumors were similar at 10–15 min after injection but were lower than those of EMT-6 tumors. No blocking studies were performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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