[^{18}F]Fluoro-2-deoxy-2-D-glucose

[^{18}F]FDG

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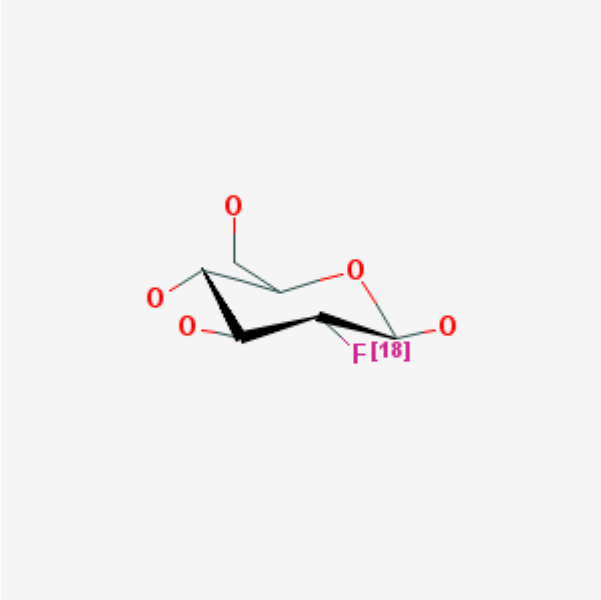
Chemical name:	[^{18}F]Fluoro-2-deoxy-2-D-glucose
Abbreviated name:	[^{18}F]FDG, FDG
Synonym:	[^{18}F]Fluorodeoxyglucose
Agent Category:	Compound
Target:	Glucose transporters and hexokinases
Target Category:	Transporters, enzymes
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



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Background

[PubMed]

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 approximately 100,000 each. HKI is found mainly in the brain. HKII is insulin sensitive and 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 was detected in tumors from patients with lung, gastrointestinal, and breast cancer. The HKs, by converting glucose to glucose-6-phosphate, help to 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 and is then phosphorylated by HK to FDG-6- phosphate. FDG-6- phosphate cannot be metabolized further in the glycolytic pathway and stays intracellularly in 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 alternations 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).

Related Resource Links:

- Chapters in MICAD (Hexokinase, glucose transporter)
- Gene information in NCBI (Hexokinase, Glut1).
- Articles in Online Mendelian Inheritance in Man (OMIM) (Hexokinase, Glut1)
- Clinical trials ([^{18}F]FDG)
- Drug information in FDA ([^{18}F]FDG)

Synthesis

[PubMed]

[^{18}F]FDG was synthesized by a direct electrophilic fluorination of 3,4,6-tri-*O*-acetyl-D-glucal with [^{18}F]F_2 gas with a radiochemical yield of 8% (12). [^{18}F]FDG was also prepared by reacting ^{18}F-labeled acetyl hypofluorite, prepared by reaction of ^{18}F-labeled molecular fluorine with sodium acetate in glacial acetic acid, and tri-acetyl-D-glucal at room temperature. Overall radiochemical yield was about 24% with a radiochemical purity of 98%. The specific activity of [^{18}F]FDG was about 25 GBq/mmol (685 mCi/mmol). The synthesis time was approximately 60 min (13). Subsequently, the radiochemical yields of [^{18}F]FDG were improved to 50-60% by using various methods involving nucleophilic fluorination using fluoride of high specific activity (14-17). An automated synthesis of [^{18}F]FDG using tetrabutylammonium [^{18}F]fluoride was reported to give a radiochemical yield of 12-17% with 96-99% radiochemical purity (18).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

FDG and other glucose analogs were investigated as anticancer agents by inhibiting glycolysis of tumor cells grown in cell cultures. *In vitro* uptake studies of [^{18}F]FDG by endothelial cells, monocytes, macrophages, neutrophils, granulocytes, lymphocytes, and tumor cells have been reported and shed some light on [^{18}F]FDG uptake mechanisms in these cells (19-23). On the other hand, in organs such as the liver, FDG is taken up and rapidly released because of dephosphorylation by FDG-6-phosphatase (24). Therefore, the overall FDG uptake into cells is dependent on the activity of glucose transporters, HKs, and phosphatases.

Uptake of [^{18}F]FDG in isolated human monocytes-macrophages (HMMs) *in vitro* was compared with that in human glioblastoma and pancreatic carcinoma cells (25). HMMs were cultured for 0, 7, and 14 days. [^{18}F]FDG uptake in HMMs significantly increased with culture duration as monocytes differentiated into mature macrophages. The uptake of day 14 macrophages was similar to the two cancer cell lines. Lipopolysaccharide stimulation further enhanced [^{18}F]FDG uptake in HMMs. [^{18}F]FDG uptake significantly decreased with increasing glucose concentration in the medium. Radio-thin layer chromatography of intracellular metabolites revealed that [^{18}F]FDG was trapped by HMMs mainly as [^{18}F]FDG-6-phosphate and [^{18}F]FDG-1,6-diphosphate. HMMs in tumors and inflamed tissues could result in high uptake of [^{18}F]FDG.

Animal Studies

Rodents

[PubMed]

[^{18}F]FDG was accumulated rapidly into kidneys, liver, lung, and small intestine of normal mice, followed by a rapid clearance (26). On the other hand, the accumulation of the tracer in the brain and heart remained relatively constant during the 2 h of the experiment. [^{18}F]FDG was tested as a tumor diagnostic agent in a transplantable rat

tumor (27). Tissue distribution studies in rats showed high uptakes of [^{18}F]FDG in the tumor, heart, intestine, and brain. Tumor uptake reached 2.65% dose [^{18}F]FDG/g at 60 min and remained relatively constant until 120 min. Blood clearance [^{18}F]FDG was very rapid, and tumor/blood ratios reached 22.1 at 60 min. Tumor/tissue ratios were very high in most organs, especially in the liver, kidneys, and pancreas.

Increased glucose metabolism of inflammatory tissues is the main source of false-positive [^{18}F]FDG PET findings in oncology. The biodistribution of 3'-deoxy-3'-[^{18}F]fluorothymidine [^{18}F]FLT and [^{18}F]FDG was studied in Wistar rats that bore tumors (C6 rat glioma in the right shoulder) and also had sterile inflammation in the left calf muscle (induced by injection of 0.1 ml of turpentine). Tumor/muscle ratios of [^{18}F]FDG at 2 h after injection (13.2 ± 3.0) were higher than those of [^{18}F]FLT (3.8 ± 1.3). [^{18}F]FDG showed high uptake in brain and heart, whereas [^{18}F]FLT showed high uptake in bone marrow. [^{18}F]FDG was also accumulated in the inflamed muscle, with 4.8 ± 1.2 times higher uptake in the affected thigh than in the healthy thigh. In contrast to [^{18}F]FLT, [^{18}F]FDG uptake was not significantly different between the two thighs. In [^{18}F]FDG PET images, both tumor and inflammation were visible, but [^{18}F]FLT PET showed only the tumor (28).

Other Non-Primate Mammals

[PubMed]

There was an early and high uptake of [^{18}F]FDG in a variety of transplantable tumors in mice, rats, hamsters, and rabbits (29). Tumor/blood and tumor/normal tissue ratios ranged from 2.6 to 17.8 and 2.1 to 9.2, respectively. Various [^{18}F]FDG uptake studies were performed using dogs [PubMed], pigs [PubMed], sheep [PubMed], and rabbits [PubMed].

Non-Human Primates

[PubMed]

Regional cerebral blood flow (rCBF) and regional cerebral metabolic rate of glucose (rCMRglc) were measured in old and young monkeys by PET. Studies were performed on six old and six young-adult male rhesus monkeys. rCBF and the rCMRglc were serially measured using PET with [^{15}O]H_2O and [^{18}F]FDG, respectively. All PET emission scans were performed in the conscious state for the cerebellum, hippocampus, striatum, occipital cortex, temporal cortex, frontal cortex, and cingulate. Old monkeys had significantly lower rCBF in the cerebellum, hippocampus, striatum, occipital cortex, temporal cortex, and frontal cortex and significantly lower rCMRglc in the cerebellum, hippocampus, striatum, occipital cortex, temporal cortex, frontal cortex, and cingulate, compared with young monkeys (30).

Pathogenesis of simian immunodeficiency virus (SIV) infection in rhesus macaques begins with acute viremia and then progresses to a distributed infection in the solid lymphoid tissues. PET imaging with [^{18}F]FDG from SIV-infected animals was

distinguishable from uninfected controls and revealed a pattern consistent with widespread lymphoid tissue activation. Significant [18F]FDG accumulation in colon, along with mesenteric and ileocecal lymph nodes, was found in SIV infection, especially during terminal disease stages. Areas of elevated [18F]FDG uptake in the PET images were correlated with productive SIV infection. [18F]FDG PET images of SIV-infected animals correlated sites of virus replication with high FDG accumulation. Therefore, [18F]FDG can be used to evaluate the distribution and activity of infected tissues in a living animal without biopsy (31).

Human Studies

[PubMed]

In 1976, the first images of [18F]FDG metabolism in humans were obtained and showed the high uptake in the bladder, heart, and brain (5, 32). Regional kinetic constants and rCMRglc in normal human subjects were determined by [18F]FDG PET (33-36). Human dosimetry [PubMed] was estimated from absorbed dose in organs after intravenous administration of [18F]FDG using whole-body PET scans in six normal volunteers (37). The bladder received the highest dose of radioactivity, followed by the spleen, heart, and brain. Mejia et al (38) estimated the effective dose equivalent to be 0.024 mSv/MBq (81 mrem/mCi).

[18F]FDG PET imaging techniques are widely used in clinical applications. In central nervous system disorders [PubMed], the clinical applications are in Alzheimer's disease, dementia, epilepsy, brain trauma, Huntington disease, cerebrovascular disorders, brain tumors, Schizophrenia, and mood disorders (39, 40). In oncology [PubMed], the clinical applications are in diagnosis, treatment monitoring, and tumor staging have been used in non-small cell lung cancer, colorectal carcinoma, malignant melanoma, Hodgkin and non-Hodgkin lymphoma, esophageal carcinoma, head and neck cancer, breast cancer, and thyroid carcinoma (9, 41). In cardiovascular disorders [PubMed], the clinical applications are in myocardial viability and atherosclerosis (42). In infectious and inflammatory diseases [PubMed], the clinical applications are in orthopedic infections, osteomyelitis, ileitis, sarcoidosis, rheumatologic disease, and vasculitis (42).

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