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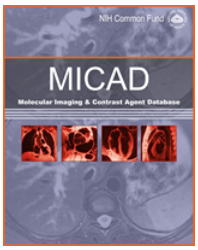

3'-Deoxy-3'-[^{18}F]fluorothymidine

[^{18}F]FLT

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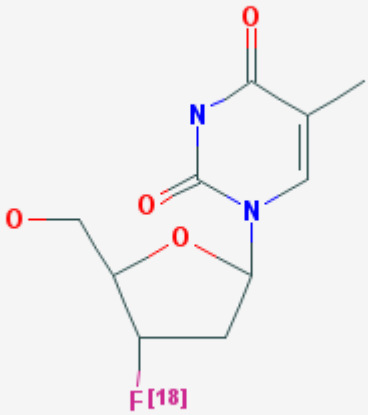
Chemical name:	3'-Deoxy-3'-[^{18}F]fluorothymidine
Abbreviated name:	[^{18}F]FLT, FLT
Synonym:	[^{18}F]Fluorothymidine
Agent category:	Compound
Target:	Thymidine kinase-1
Target category:	Transporters, enzymes
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Humans



Structure is currently not available in PubChem.

Background

[PubMed]

One of the characteristics of tumor cells is their unchecked proliferation. It is important to measure the proliferation rate of cancer lesions to help differentiate benign from malignant tumors and to characterize malignant tumors among normal tissues. 2-[^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) has been widely used in cancer imaging. However, enhanced uptakes of FDG also occur in inflammatory cells and lesions as well as in necrotic cells (1, 2). Thymidine (TdR) and TdR analogs are the standard markers for DNA synthesis, and [^{11}C]thymidine has been used in positron emission tomography (PET) imaging to measure tumor growth rate

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in situ. Because of the short half-life of ^{11}C and extensive metabolism of [^{11}C]TdR in the blood (3), 3'-deoxy-3'-[^{18}F]fluorothymidine (FLT) was developed for PET imaging.

FLT is an analog of TdR and is phosphorylated by thymidine kinase-1 (TK-1), an enzyme expressed during the DNA synthesis phase of the cell cycle (4). Most cancer cells have a much higher TK-1 activity than normal cells. FLT monophosphate is not incorporated into DNA and is impermeable to the cell membrane. Therefore, it is metabolically trapped inside the cells. The uptake and accumulation of FLT are used as an index of cellular proliferation. [^{18}F]FLT PET has been used to detect and monitor tumor proliferation, to evaluate the stages of tumor, and to detect metastases (5).

Related Resource Links:

- Chapters in MICAD (Thymidine kinase)
- Gene information in NCBI (Thymidine kinase)
- Articles in Online Mendelian Inheritance in Man (OMIM) (Thymidine kinase)
- Clinical trials ([^{18}F]FLT)

Synthesis

[PubMed]

A reliable radiosynthesis of [^{18}F]FLT has been developed based on [^{18}F]fluoride displacement of a protected nosylate precursor. A simple three-step synthesis was used to prepare 370 MBq (>10 mCi) of radiochemically pure [^{18}F]FLT, with a specific activity of 37 GBq/μmol (>1 Ci/μmol) at the end of synthesis within 100 min and with 13% radiochemical yield (end of bombardment; 7% end of synthesis) (6). Recently, Oh et al. (7) reported a new, fully automated method for the synthesis of [^{18}F]FLT with a yield of 50% radiochemical yield, by modifying a commercial FDG synthesizer and its disposable fluid pathway.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Expression of major pyrimidine metabolizing enzymes in pancreatic cancer cell lines, chronic pancreatitis tissue, and human pancreatic cancer and the *in vitro* uptake of [^{18}F]FLT were studied (8). TK-1 and thymidine synthetase mRNA were increased in six pancreatic cancer cell lines. High TK-1 activity was confirmed in all of these cancer cell lines as compared with normal pancreatic tissue and samples from patients with chronic pancreatitis. The cellular uptake of [^{18}F]FLT was 18.4% ± 3.6% and 5.2% ± 1.4% of the applied radioactivity after 240 min in SW-979 and BxPc-3 cells, respectively, whereas uptake of [^{18}F]FDG was only 0.6% ± 0.04% (SW-979) and 0.3% ± 0.13% (BxPc-3). In contrast, the cellular uptake of [^{18}F]FLT in isolated pancreas and growth-arrested HT1080 cells was lower as compared with the uptake of [^{18}F]FDG and with the malignant pancreatic cancer cell lines. The majority of [^{18}F]FLT was phosphorylated to the respective monophosphate in both cell lines. The incorporation of [^{18}F]FLT into the DNA was only 0.8% ± 0.12% (BxPc-3) and 1.3% ± 0.38% (SW-979) of the applied radioactivity. These results demonstrate the cellular uptake, intracellular trapping, and incorporation into the DNA of [^{18}F]FLT in pancreatic cancer cells *in vitro*. TK-1, as the rate-limiting enzyme of [^{18}F]FLT metabolism, is overexpressed in pancreatic cancer cell lines and in human pancreatic cancer.

It was recently reported that human lung adenocarcinoma A549 cells accumulated [^{18}F]FLT intracellularly as [^{18}F]FLT-nucleotides (49% monophosphate, 6% diphosphate, and 29% triphosphate) by high-performance liquid chromatography (HPLC) analyses (9). The rate-limiting step in the overall conversion of FLT to FLT-triphosphate was the phosphorylation of the monophosphate by thymidylate kinase. FLT-triphosphate was resistant to degradation and trapped in the cells, although it was not incorporated into DNA.

Cells derived from human esophageal carcinoma were grown for 2 days and incubated with cisplatin, 5-fluorouracil (5-FU), methotrexate, or gemcitabine. The cytotoxic drugs methotrexate, 5-FU, and gemcitabine caused an increase in [18F]FLT accumulation with similar [18F]FDG uptake as compared with untreated cells. There was a rebound effect of the cancer cells to increase the uptake of FLT. The cytostatic drug, cisplatin, showed a decrease in [18F]FLT uptake and little change in [18F]FDG uptake (10). Not all of the anticancer drugs have the same effect on FLT uptake, depending on their mechanisms of action.

Animal Studies

Rodents

[PubMed]

The use of [18F]FLT to monitor the response of tumors to antiproliferative treatment in mice was studied (11). The accumulation of [18F]FLT was significantly higher in blood, plasma, liver, kidneys, and small intestine and significantly lower in brain, spinal cord, heart, and muscle than [18F]FDG in C3H/Hej mice bearing the radiation-induced fibrosarcoma-1 tumor. The tumor-bearing mice were treated with 5-FU (165 mg/kg i.p.). Changes in tumor volume and biodistribution of [18F]FLT and [18F]FDG were measured in three groups of mice (n = 8-12/group): group a, untreated controls; group b, 24 h after 5-FU; and group c, 48 h after 5-FU. In addition, dynamic [18F]FLT PET imaging was performed on a small animal scanner for 60 min. Tumor [18F]FLT uptake decreased after 5-FU treatment. The drug-induced reduction in tumor [18F]FLT uptake was significantly greater than that of [18F]FDG. The PET image data confirmed smaller tumor [18F]FLT retention in group c compared with group a, despite a trend toward higher tracer delivery for group c. Other than phosphorylation in tumors, [18F]FLT was found to be metabolically stable *in vivo*. The decrease in tumor [18F]FLT uptake correlated with tumor proliferation and tumor volume changes after 5-FU treatment. Compared with group a, TK-1 levels were lower in group b (78.2%) but higher in group c (141.3%; $P < 0.001$). In contrast, a stepwise decrease in ATP levels was observed from group a to group b to group c ($P < 0.001$). In this murine model system, the radiotracer uptake was correlated with tumor proliferation. The decrease in [18F]FLT uptake after 5-FU treatment was more drastic than that of [18F]FDG. [18F]FLT is a marker for monitoring antiproliferative drug activity in oncology.

Other Non-Primate Mammals

[PubMed]

[18F]FLT was infused into normal dogs, as well as one dog with spontaneous lymphoma, and one with sarcoma before treatment (5). Dynamic PET imaging was performed for 60 min over the upper abdomen in normal dogs or over the tumors. For comparison, dynamic imaging with [11C]thymidine was also performed in two dogs. Images from normal dogs demonstrated a selective uptake in the marrow. There was also a high retention of FLT in the nose of the dog and the submandibular lymph node. The kidneys and the bladder showed a high uptake activity. The brain had a low uptake of FLT. The mean standardized uptake value (SUV) for FLT in dog marrow was 4.6 (4.1-5.5; n = 3), compared with 2.5 for [11C]thymidine (2.4-2.6; n = 2) There was a progressive FLT uptake in the bone marrow during the 60 min of imaging. On the other hand, [11C]thymidine, which is largely degraded within minutes of injection, did not accumulate in tissues after its initial uptake and retention in DNA. HPLC analysis of the dog urine after [18F]FLT administration showed that over 95% of the activity was present as unchanged [18F]FLT. Similarly, analysis of late blood samples (50 min) demonstrated that 90–97% of the activity remained as the parent compound. FLT was retained in cells as the phosphorylated form, and most FLT was intact when it was cleared by the kidneys. In a dog with spontaneous non-Hodgkin's lymphoma, there was a greater uptake in the tumor (SUV, 7.1) than was seen for the marrow (SUV, 5.5). Also, in a dog with a large soft tissue sarcoma (11 cm in diameter), a rim of increased FLT accumulation (SUV, 3.1) was observed. The central region of the tumor showed little FLT uptake because it was necrotic.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Dosimetry of [^{18}F]FLT was calculated from the biodistribution data of 18 patients (12). The effective dose equivalent was estimated to be 0.031 mSv/MBq (114 mrem/mCi). The major radioactivity was in the bladder, liver, kidneys, and bone marrow. In 11 patients with non-small cell lung cancer, there was a strong correlation of [^{18}F]FLT PET with cytochemical staining of nuclei with MIB-1 monoclonal antibody (13). In another study (14), 26 patients with pulmonary nodules on chest CT were examined with the uptake of [^{18}F]FDG and [^{18}F]FLT. Of 18 malignant tumors, 17 showed increased [^{18}F]FDG PET uptake. [^{18}F]FLT PET was falsely negative in the carcinoma, in another non-small cell lung cancer with a low proliferation index, and in a patient with lung metastases from colorectal cancer. Increased [^{18}F]FLT uptake was related exclusively to malignant tumors. By contrast, [^{18}F]FDG PET was falsely positive in 4 of 8 patients with benign lesions. Comparative studies of FLT and FDG were performed in patients with B-cell lymphoma (15), metastatic melanoma (16), breast cancer (17), and thoracic sarcoma (18).

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