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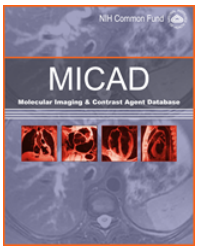

^{18}F-(*2S,4R*)4-fluoroglutamine

[^{18}F]4-FGln

Arvind Chopra, PhD[1]

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Chemical name:	^{18}F-(*2S,4R*)4-fluoroglutamine
Abbreviated name:	[^{18}F]4-FGln
Synonym:	[^{18}F]-(*2S,4R*)4-fluoroglutamine
Agent Category:	Compound
Target:	Amino acid transporter
Target Category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents

Click on above structure for information in PubChem.

Background

[PubMed]

Increased growth and proliferation are the typical characteristic features of cancer cells, and to maintain these processes the cells have an increased demand for energy. Adenosine triphosphate is the main source of energy in normal cells, and it is produced through the tricarboxylic acid (TCA) cycle in the mitochondria. However, in cells with a malignant phenotype, the TCA is redirected to synthesize metabolic intermediates that can be used to produce fatty acids and amino acids (aa) that are required for the growth and survival of the tumor cells (1). To meet the energy requirements of cancerous tumors, the aerobic glycolytic pathway, which uses glucose to produce energy, is upregulated and serves as the major source of energy in the tumor cells (2). Therefore, [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG), an analog of glucose that is transported into and metabolized similarly to glucose in the cell (after phosphorylation to [^{18}F]-FDG-6 phosphate it cannot be further metabolized by glycolysis and remains metabolically trapped within the cell), is often used to detect, stage, and monitor cancer

Author Affiliation: 1 National Center for Biotechnology Information, NLM, Bethesda, MD 20894; Email: micad@ncbi.nlm.nih.gov.

therapy with positron emission tomography (PET) [PubMed]. A major drawback of PET imaging with [^{18}F]-FDG is that, in addition to tumor cells, normal cells in the brain, heart, brown adipose tissue, etc., also have high metabolic rates and utilize above-average amounts of glucose, which often leads to the generation of false positive results (2). Moreover, it is known that [^{18}F]-FDG imaging cannot distinguish between infection, inflammation, and tumors (2).

There are indications that many tumors do not use the glycolytic pathway to produce energy and are consequently invisible to imaging with [^{18}F]-FDG (1). Such tumors are believed to produce sufficient energy for survival by metabolizing other nutrients such as glutamine (for details, see Koglin et al. (3)), which has the highest concentration in the blood (up to ~1 mM) among all of the aa circulating in the blood and is metabolized through the glutaminolysis pathway (1). It is believed that tumors that cannot be visualized with PET using [^{18}F]-FDG do not derive their energy through glycolysis and probably use the glutaminolysis pathway as an alternate source of energy. In a preliminary *in vitro* study with 9L (rat brain gliosarcoma cells) and SF188$_{Bcl\text{-}xL}$ (of human glioblastoma origin) tumor cells that are addicted to glutamine (for details, see Wise and Thompson (4)), it was shown that both cell types had a higher uptake of ^{18}F-labeled (*2S,4R*)4-fluoroglutamine ([^{18}F]4-FGln; an analog of glutamine) than of [^{3}H]-glutamine (5). It was also observed that the uptake of [^{18}F]4-FGln by the 9L cells was inhibited by L-glutamine, which indicated that both the aa were taken up by the cells through a common transporter. On the basis of these observations, Lieberman et al. studied the biodistribution of [^{18}F]4-FGln in normal mice and rats and in mice and rats bearing xenograft tumors (1). The ^{18}F-labeled compound was also evaluated for the PET detection of tumors in mice and rats bearing these lesions.

Related Resource Links

Amino acid transporter related chapters in MICAD

Amino acid transport across the plasma membrane [Reactome]

Glycolysis pathway

Synthesis

[PubMed]

The synthesis and ^{18}F labeling of 4-FGln have been described by Lieberman et al. (1). The final labeled product had a non-decay-corrected radiochemical yield of 8.4 ± 3.4%, a radiochemical purity (RCP) of 98 ± 1%, and an optical purity of 91 ± 8% (results were derived from ten separate experiments). The specific activity of [^{18}F]4-FGln was not reported.

The [^{18}F]-FDG and L-[3,4-^{3}H(*N*)]-glutamine ([^{3}H]-Gln) for the *in vitro* cell uptake studies were purchased from commercial sources. The RCP and specific activity of [^{18}F]-FDG were not mentioned. The RCP and specific activity of [^{3}H]-Gln were >97% and1.11–2.22 TBq/mmol (~30–60 Ci/mmol), respectively.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The uptake of [^{18}F]4-FGln was studied in 9L and SF188 cells (these cells have an amplified c-*Myc* oncogene that leads to glutamine addiction and increases uptake of the aa) as described elsewhere (1). Both cell lines showed a high uptake of [^{18}F]4-FGln, and the 9L cells showed a linear increase in the incorporation of label up to a maximum of 15.7 ± 1.0% of the initial dose per 100 μg protein content (% ID/100 μg protein) at 120 min. The

SF188 cells had a different kinetics of [^{18}F]4-FGln uptake, and the maximum uptake of ~15% ID/100 μg protein was observed at 60 min, which decreased to ~10% ID/100 μg protein at 120 min.

In another study, the uptake of [^{18}F]4-FGln, [^{18}F]-FDG, and [^{3}H]-Gln was studied in SF188$_{Bcl\text{-}xl}$ cells (SF188$_{Bcl\text{-}xl}$ cells transfected with the B-cell lymphoma extra large outer mitochondrial transmembrane anti-apoptotic protein), and these cells showed a higher incorporation of [^{18}F]4-FGln from 30 min to 120 min than either [^{18}F]-FDG or [^{3}H]-Gln (1). From this study, the investigators concluded that the high uptake of [^{18}F]4-FGln compared to the other two tracers was most likely due to upregulation of the c-*Myc* gene in these cells.

The incorporation of [^{18}F]4-FGln into protein was measured at 30 min and 120 min in 9L and SF188 cells (1). For this study, [^{3}H]-Gln was used as a reference ligand. Both tracers showed a similar profile of incorporation into the proteins. The incorporation of [^{18}F]4-FGln and [^{3}H]-Gln in the 9L cells was 29% and 72% at 30 min and 120 min, respectively, and with the SF188 cells the incorporation was 12% and 62%, respectively, at the two time points.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{18}F]4-FGln was investigated in normal Imprinting Control Region mice as described by Lieberman et al. (1). The animals (under anesthesia; n = 5 mice/time point) were injected with 925 KBq (25 μCi) [^{18}F]4-FGln through the tail vein. The mice were euthanized at various time points ranging from 2 min to 240 min to remove the organs of interest and determine the amount of radioactivity accumulated in the different tissues. Data from this study were presented as percent of injected dose per gram tissue (% ID/g). From 2 min to 60 min postinjection (p.i.), the amount of label in the pancreas remained almost constant (~17.5% ID/g) before decreasing to 5.92 ± 0.87% ID/g at 240 min p.i. A similar trend was noted in the liver (6.92 ± 0.92% ID/g at 2 min p.i and 1.30 ± 0.18% ID/g at 240 min p.i.). The blood and lungs showed a gradual decrease in radioactivity from 6.19 ± 0.83% ID/g and 7.15 ± 0.76% ID/g, respectively, at 2 min p.i. to 0.48 ± 0.06% ID/g and 1.03 ± 0.15% ID/g, respectively, at 240 min p.i. A steady increase in radioactivity was observed in the bones (3.93 ± 0.37% ID/g at 2 min p.i and 19.4 ± 0.50% ID/g at 240 min p.i.), which the investigators suggested was probably due to the *in vivo* defluorination of [^{18}F]4-FGln.

The *in vivo* biodistribution of [^{18}F]4-FGln was also studied in Fischer 344 rats bearing 9L cell xenograft tumors (1). The animals (n = 6 animals/time point) were injected with 925 kBq (25 μCi) [^{18}F]4-FGln as described above. The rats were euthanized at 30 min and 60 min p.i. to determine the amount of label accumulated in the tumors and various tissues. In general, the biodistribution of the tracer in the various organs of the rats was the same as that observed in the normal mice (described above). The uptake of radioactivity by the tumor was 1.03 ± 0.14% ID/g at 30 min p.i. and decreased slightly to 0.76 ± 0.21% ID/g at 60 min p.i. The tumor/blood and tumor/muscle ratios in the rats were 2.39 and 2.78, respectively, at 30 min p.i. and 2.37 and 2.00, respectively, at 60 min p.i.

Dynamic small-animal PET images of rats bearing 9L xenograft tumors and transgenic mice bearing M/tomND tumors (these are spontaneous lesions in animals that have an upregulated *Myc* gene) were acquired for up to 2 h after intravenous injection of [^{18}F]4-FGln (1). From the images it was clear that the tumors could be visualized within 20 min after the injection, and the lesions remained visible for up to 2 h p.i. *Ex vivo* PET imaging of the organs and tumors obtained from the mice showed that the presence of radioactivity in the different tissues of the animals was consistent qualitatively with the biodistribution studies discussed above.

From these studies, the investigators concluded that [^{18}F]4-FGln can probably be used for the detection of tumors in rodents (1).

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.

Supplemental Information

[Disclaimers]

No information is currently available.

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