18-[^{18}F]Fluoro-4-thia-oleate

[^{18}F]FTO

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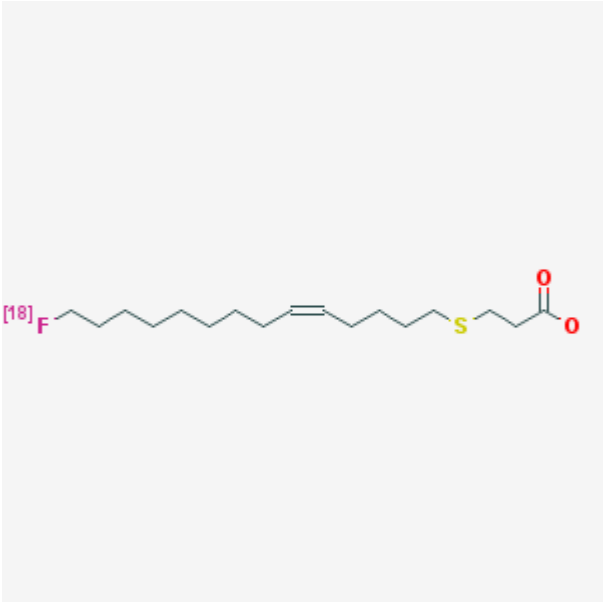
Chemical name:	18-[^{18}F]Fluoro-4-thia-oleate
Abbreviated name:	[^{18}F]FTO
Synonym:	
Agent category:	Compound
Target:	Fatty acid oxidation (FAO) enzymes
Target category:	Enzyme
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

β-Oxidation of long-chain fatty acids is the major (60%–80%) aerobic process for energy production in the heart, liver, and skeletal muscle. Abnormalities of fatty acid oxidation

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(FAO) are associated with several cardiovascular diseases, neurodegeneration, fatty liver, and diabetes (1-5). Myocardium has a high mitochondrial content because of high energy usage. Carnitine palmitoyltransferases (CPT1 and CPT2) mediate transfer of fatty acids into the mitochondrial matrix for β-oxidation (6, 7). Various radiolabeled, thia-substituted, fatty acid analogs have been found to be metabolically trapped in the myocardial mitochondria (8-10). 4-Thia fatty acids are oxidized in the mitochondria to 4-thia-enoyl-CoAs, which cannot be further metabolized and trapped (protein-bound) in the mitochondria. Oleate (18:1) is preferentially oxidized relative to palmitate (16:0) and stearate (18:0) by the mitochondrial FAO (11). DeGrado et al. (12) have synthesized 18-[^{18}F]fluoro-4-thia-oleate ([^{18}F]FTO) for evaluation as a positron emission tomography (PET) agent of FAO.

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (CPT1)
- Articles in OMIM
- Clinical trials (CPT1)

Synthesis

[PubMed]

[^{18}F]FTO was prepared as described by DeGrado et al. (12). [^{18}F]Fluoride/Kryptofix 2.2.2/K_2CO_3 and the bromoester precursor ((*Z*)-methyl-18-bromo-4-thia-octadec-9-enoate) were heated in acetonitrile for 15 min at 75°C, followed by hydrolysis with KOH for 4 min at 90°C. [^{18}F]FTO was purified with high-performance liquid chromatography with radiochemical yields of 20%–30% and a radiochemical purity of >99%. Specific activity of [^{18}F]FTO was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication is currently available.

Animal Studies

Rodents

[PubMed]

DeGrado et al. (12) performed *ex vivo* biodistribution studies of [^{18}F]FTO in rats. [^{18}F]FTO accumulated mainly in the liver and heart with 0.70 ± 0.30% injected dose/g (ID/g) and 1.19 ± 0.16% ID/g, respectively, at 30 min after injection. Retention of [^{18}F]FTO in the heart at 120 min was good with 0.82 ± 0.23% ID/g, whereas there was a slight washout in the liver (0.85 ± 0.22% ID/g). Pretreatment with the CPT1 inhibitor

etomoxir (40 mg/kg, 120 min before [^{18}F]FTO injection) reduced the radioactivity level in the heart by 82% at 30 min after injection with only 28% reduction in the liver. Folch-type analysis of the excised hearts showed that 90% of [^{18}F]FTO radioactivity was protein-bound. Pretreatment with etomoxir reduced the protein-bound radioactivity to 24%. The heart/blood, heart/lung, heart/brain, and heart/muscle ratios were 44, 36, 37, and 48, respectively, at 120 min after injection. The uptake in the bone was 0.15% ID/g at 30 min and 0.46% ID/g at 120 min, indicating some defluorination of [^{18}F]FTO. Whole-body PET imaging showed that [^{18}F]FTO accumulated mainly in the heart and liver, with low accumulation in the lung. Good myocardial images were observed at 55–115 min after injection with little interference from the lung and liver. Some bone uptake was observed.

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.

NIH Support

R01 HL63371, R01 CA108620

References

1. Stanley W.C., Recchia F.A., Lopaschuk G.D. *Myocardial substrate metabolism in the normal and failing heart.* Physiol Rev. 2005;85(3):1093–129. PubMed PMID: 15987803.
2. Bergmann S.R., Herrero P., Sciacca R., Hartman J.J., Rubin P.J., Hickey K.T., Epstein S., Kelly D.P. *Characterization of altered myocardial fatty acid metabolism in patients with inherited cardiomyopathy.* J Inherit Metab Dis. 2001;24(6):657–74. PubMed PMID: 11768585.
3. Liu Y. *Fatty acid oxidation is a dominant bioenergetic pathway in prostate cancer.* Prostate Cancer Prostatic Dis. 2006;9(3):230–4. PubMed PMID: 16683009.
4. You M., Crabb D.W. *Recent advances in alcoholic liver disease II. Minireview: molecular mechanisms of alcoholic fatty liver.* Am J Physiol Gastrointest Liver Physiol. 2004;287(1):G1–6. PubMed PMID: 15194557.

5. Stanley W.C., Lopaschuk G.D., McCormack J.G. *Regulation of energy substrate metabolism in the diabetic heart.* Cardiovasc Res. 1997;34(1):25–33. PubMed PMID: 9217869.
6. Jogl G., Hsiao Y.S., Tong L. *Structure and function of carnitine acyltransferases.* Ann N Y Acad Sci. 2004;1033:17–29. PubMed PMID: 15591000.
7. Bonnefont J.P., Djouadi F., Prip-Buus C., Gobin S., Munnich A., Bastin J. *Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects.* Mol Aspects Med. 2004;25(5-6):495–520. PubMed PMID: 15363638.
8. Taylor M., Wallhaus T.R., Degrado T.R., Russell D.C., Stanko P., Nickles R.J., Stone C.K. *An evaluation of myocardial fatty acid and glucose uptake using PET with [18F]fluoro-6-thia-heptadecanoic acid and [18F]FDG in Patients with Congestive Heart Failure.* J Nucl Med. 2001;42(1):55–62. PubMed PMID: 11197981.
9. DeGrado T.R., Wang S., Rockey D.C. *Preliminary evaluation of 15-[18F]fluoro-3-oxa-pentadecanoate as a PET tracer of hepatic fatty acid oxidation.* J Nucl Med. 2000;41(10):1727–36. PubMed PMID: 11038005.
10. Stone C.K., Pooley R.A., DeGrado T.R., Renstrom B., Nickles R.J., Nellis S.H., Liedtke A.J., Holden J.E. *Myocardial uptake of the fatty acid analog 14-fluorine-18-fluoro-6-thia-heptadecanoic acid in comparison to beta-oxidation rates by tritiated palmitate.* J Nucl Med. 1998;39(10):1690–6. PubMed PMID: 9776270.
11. DeLany J.P., Windhauser M.M., Champagne C.M., Bray G.A. *Differential oxidation of individual dietary fatty acids in humans.* Am J Clin Nutr. 2000;72(4):905–11. PubMed PMID: 11010930.
12. DeGrado T.R., Bhattacharyya F., Pandey M.K., Belanger A.P., Wang S. *Synthesis and preliminary evaluation of 18-(18)F-fluoro-4-thia-oleate as a PET probe of fatty acid oxidation.* J Nucl Med. 2010;51(8):1310–7. PubMed PMID: 20660391.