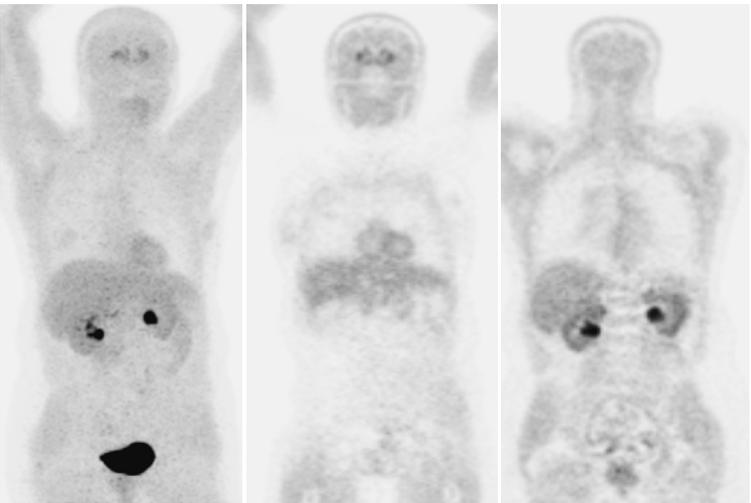
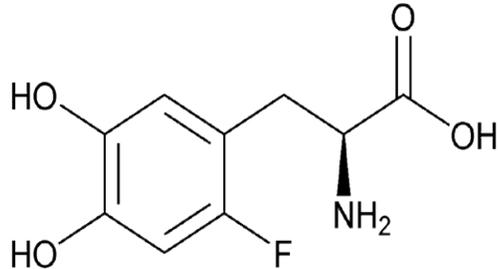


Fluorodopa F-18

[¹⁸F]FDOPA

Radiopharmaceutical Name	<p>L-3,4-Dihydroxy-6-[¹⁸F]fluorophenylalanine. Also known as: Fluorodopa F18, ¹⁸F-fluorodopa, [¹⁸F]Fluorodopa, ¹⁸F-6-L-fluorodopa, [¹⁸F]-fluoro-L-DOPA, L-6-[¹⁸F]fluoro-3, 4-dihydroxyphenylalanine, 6-[¹⁸F]Fluoro-L-DOPA.</p> <p>Abbreviations: FDOPA, ¹⁸-FDOPA.</p>	
Radiopharmaceutical Image  <p>Maximum intensity projection (left) and 2 coronal images of normal ¹⁸F-FDOPA biodistribution (uptake in basal ganglia, myocardium, mild uptake in skeletal muscle; excreted activity in urinary tract; uptake in pancreas was suppressed by premedication with carbidopa) <i>courtesy of Karel Pacak, MD, PhD (NICHD, NIH)</i></p>	Normal Biodistribution <p>The ¹⁸F-FDOPA biodistribution resembles the normal distribution of L-DOPA. It crosses the blood-brain barrier, where it is converted to ¹⁸F-Fluorodopamine by dopa decarboxylase. ¹⁸F-Fluorodopamine is stored intraneuronally in vesicles.</p>	Radiopharmaceutical Structure 
Radionuclide	¹⁸ F Half-life 109.7 minutes	
Emission	Emission positron: Emax 1.656 MeV	

Fluorodopa F-18

[¹⁸F]FDOPA

MICAD	http://www.ncbi.nlm.nih.gov/books/NBK23043/
Molecular Formula and Weight	C ₉ H ₁₀ FNO ₄ 2145.18 g/mole
General Tracer Class	Investigational Diagnostic PET Radiopharmaceutical in the US; approved for clinical use in some European countries under the name IASODopa®
Target	<ol style="list-style-type: none"> 1. Neurology/Psychiatry: Dopamine receptors in the brain (<i>1-3</i>) 2. Oncology: a) Amino acid (AA) transporters (a feature of many benign and malignant tumors); b) overexpression of DOPA decarboxylase is a characteristic feature of neuroendocrine tumors (NET); this enzyme is usually co-expressed with other neuroendocrine markers such as chromogranin-A (<i>4</i>).
Molecular Process Imaged	<ol style="list-style-type: none"> 1. Regional distribution of neurotransmitter dopamine in the brain. 2. Amino acid uptake and metabolism in tumors
Mechanism for in vivo retention	<ol style="list-style-type: none"> 1. Neurology/Psychiatry: ¹⁸F-FDOPA crosses the blood-brain barrier where it is converted to ¹⁸F-Fluorodopamine by enzyme amino acid decarboxylase (AADC) in the striatum. ¹⁸F-Fluorodopamine is stored in presynaptic vesicles until the neuron activation triggers its release and subsequent binding to the dopamine receptors. (<i>1-3, 5</i>). 2. Oncology: [¹⁸F]-FDOPA is taken up into cancer cells by (predominantly L-type) AA transporters, which are overexpressed in cancer (<i>6</i>). In the cancer cell, AA may enter various pathways (e.g., peptide, protein, purine, pyrimidine or hormone synthesis; act as methyl group donors etc). FDOPA in particular undergoes decarboxylation; increased activity of L-DOPA decarboxylase is a hallmark of (benign and malignant) neuroendocrine tumors (<i>4</i>). In NET, F-DOPA uptake reaches a plateau within 20 min after intravenous injection, although later imaging time points may be preferred after premedication with carbidopa (see below) (<i>7, 8</i>).
Metabolism	<p>[¹⁸F]-FDOPA is converted to ¹⁸F-Fluorodopamine by dopa decarboxylase. ¹⁸F-FDOPA is also converted to 3-O-methyl-6-fluoro-L-DOPA (3-OMFD) by catechol-O-methyl transferase (COMT) (<i>1-3, 5</i>).</p> <p>Systemic metabolism can be inhibited by prior administration of the decarboxylase inhibitor carbidopa. When used for DA receptor imaging, premedication with carbidopa increases</p>

Fluorodopa F-18

[¹⁸F]FDOPA

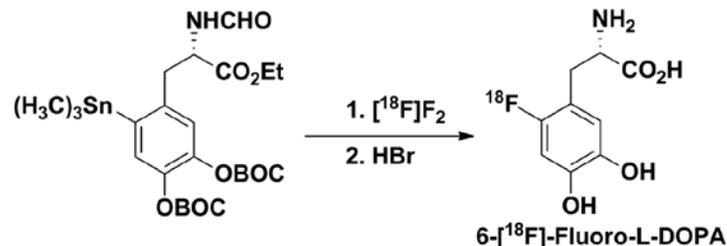
bioavailability and cerebral uptake of F-DOPA. When used for oncologic indications in the torso, carbidopa (e.g., 200 mg orally 1 hour before tracer injection) improves tumor uptake of F-DOPA (higher SUV), suppresses physiologic F-DOPA uptake in the pancreas, and decreases F-DOPA urinary excretion (8), thus potentially increasing the sensitivity for detecting NETs and their metastases.

Recent initial data suggest that pretreatment with COMT and MAO inhibitors, which decrease intracellular FDOPA breakdown, may improve visualization of pancreatic tumors on 18F-FDOPA PET (9).

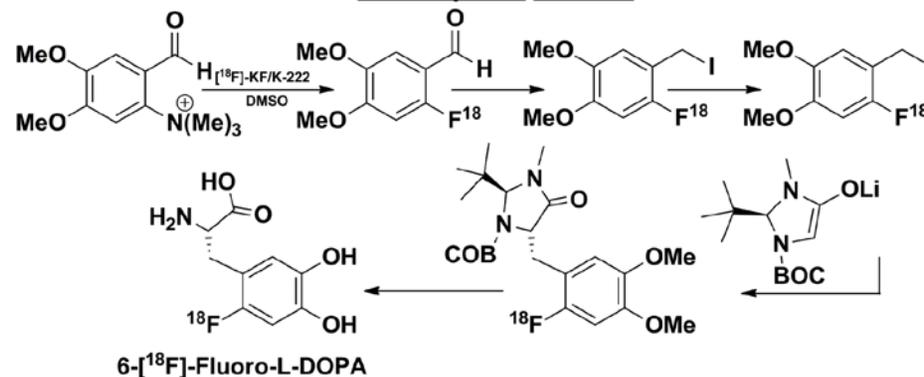
Radiosynthesis

¹⁸F-FDOPA can be synthesized either via electrophilic or nucleophilic substitution reaction methods. Additional information is available at Molecular Imaging and Contrast Agent Database (MICAD), Bethesda (MD): National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/books/NBK23043>).

Electrophilic Method



Nucleophilic Method



Fluorodopa F-18

[¹⁸F]FDOPA

Availability	As for any investigational PET radiopharmaceutical, an IND, NDA or ANDA filed with the Food and Drug Administration (FDA) is required for human use.
Status with USP / EuPh	The radiopharmaceutical is listed in the USP and the EuPh.
Recommended Activity and Allowable Mass	DOSAGE AND ADMINISTRATION IV administration, typically 6-12 mCi (222-444 MBq) with a specific activity of 20 to 40 MBq (740 to 1480 mCi) per micromole (2, 3, 10, 11).
Dosimetry	The effective dose equivalent (whole body) is estimated to be 0.026 mSv/MBq (100 mrem/mCi) for adults. The critical organs are the kidneys, the bladder, and the pancreas; they receive 0.089 mGy/MBq (389 mrad/mCi), 0.215 mGy/MBq (797 mrad/mCi) and 0.030 mGy/MBq (110 mrad/mCi) respectively (12).
Pharmacology and Toxicology	In vivo, ¹⁸ F-FDOPA exhibits pharmacodynamics and pharmacokinetics similar to Levodopa. Following intravenous administration, about 1% of the drug crosses the blood-brain barrier, but the vast majority remains in the periphery. In the periphery, ¹⁸ F-FDOPA can either be converted to 3-O-methyl-6-fluoro-L-DOPA (3-OMFD) by catechol-O-methyl transferase (COMT) or be converted to [¹⁸ F]-Fluorodopamine by aromatic amino acid decarboxylase (AAAD). The ¹⁸ F-Fluorodopamine can be further metabolized either via addition of the sulfate group to yield 6-[¹⁸ F]-fluorodopamine sulphate or via deamination by monoamine oxidase to yield 6-[¹⁸ F]-fluoro-dihydroxy-phenyl acetic acid (¹⁸ F-FDOPAC). ¹⁸ F-FDOPAC is methylated by COMT to give 6-[¹⁸ F]-fluoro-homovanillic acid (¹⁸ F-FHVA). ¹⁸ F-FDOPA metabolites are mainly renally excreted. In the striatum region of the brain, ¹⁸ F-FDOPA is converted to ¹⁸ F-Fluorodopamine by enzyme aromatic amino acid decarboxylase (AAAD), which is stored in pre-synaptic vesicles. In the non-dopaminergic regions of the brain, there is limited ¹⁸ F-FDOPA metabolic activity. The toxicology of ¹⁸ F-FDOPA is not fully investigated.
Current Clinical Trials	The NIH clinical trials registry (www.clinicaltrials.gov) should be consulted for a list of current trials using [¹⁸ F]-FDOPA. As of May 2013, thirteen clinical trials were listed, with six trials that were accruing patients.

Fluorodopa F-18

[¹⁸F]FDOPA

Reference Site / Person	The best reference site for ¹⁸ F-FDOPA trials is www.clinicaltrials.gov .
Imaging Protocol	<p>The imaging protocol for ¹⁸F-FDOPA can vary.</p> <p>Since ¹⁸F-FDOPA influx is inhibited by competition from other amino acids, patients should fast for at least 4 hours prior to tracer injection. Liberal water intake is allowed. If carbidopa is used for premedication (see above), 200 mg carbidopa is administered orally, followed by radiotracer injection at least 1 hour later.</p> <p>The injected activity may be in the range of 6-12 mCi (222-444 MBq).</p> <p>For research purpose, dynamic studies may be acquired for an extended period of time. If static imaging only is performed, data acquisition may start at ~ 10 min after ¹⁸F-FDOPA injection.</p>
Human Imaging Experience	<p>In the US ¹⁸F-FDOPA is classified as an investigational new drug (IND). An IND application is needed for clinical and research use. NDA is new drug application, aNDA is an abbreviated new drug application.</p> <p>Potential applications of proven clinical value include:</p> <ol style="list-style-type: none"> 1. Neurology/Psychiatry: ¹⁸F-FDOPA is used for the study of presynaptic striatal dopaminergic function in neurologic disorders (DDx of Parkinson's disease versus other neurodegenerative diseases with motor dysfunction). Decreased (initially often asymmetrical) tracer uptake in the putamen (in advanced stages also involving the caudate nucleus), in conjunction with normal ¹⁸F-FDG uptake, is a characteristic finding in patients with Parkinson's disease. Several psychiatric syndromes have been associated with abnormalities in Dopamine synthesis, storage, dopamine receptor expression, density and activation (reviewed in Patel et al. (13)). The dopamine hypothesis continues to be investigated in schizophrenia, and studies using ¹⁸F-FDOPA have shown increased tracer uptake in the presynaptic striatum, which may then lead to enhanced dopamine release into the synaptic cleft (14). 2. Oncology <ol style="list-style-type: none"> a) Neuroendocrine tumors: <p>¹⁸F-FDOPA is an excellent tracer for imaging NET, including pheochromocytoma, extraadrenal paraganglioma (PGL), medullary thyroid carcinoma, gastro-entero-pancreatic</p>

(GEP) NE tumors (reviewed in (15)).

In NET, ¹⁸F-DOPA may be particularly useful in patients with negative ⁶⁸Ga-somatostatin analogs and elevated serotonin levels (15b).

¹⁸F-FDOPA appears superior to MIBG for detecting extraadrenal and hereditary pheochromocytomas and paragangliomas (16).

¹⁸F-FDOPA may perform particularly well in patients with PGL who do not carry a SDHB mutation (17). (However, in pts with metastatic pheochromocytoma or PGL, ¹⁸F-FDG or ¹⁸F-Fluorodopamine may perform better than FDOPA (17, 18)).

In patients with MTC and elevated calcitonin levels, ¹⁸F-FDOPA PET/CT may serve as the first diagnostic test to define the extent of disease (19). However, combined imaging with ¹⁸F-FDOPA and ¹⁸F-FDG may be necessary in patients whose primary tumor marker is CEA (elevated CEA, but normal or only slightly elevated calcitonin) and for patients with dedifferentiated disease (20).

Some studies suggest that ¹⁸F-FDOPA provides better sensitivity than I-123 MIBG in neuroblastoma (21).

b) Brain tumors: ¹⁸F-FDOPA has been used for imaging of brain tumors. It accumulates in both high grade and low grade gliomas. In addition, based on limited data, ¹⁸F-FDOPA uptake in radionecrosis is lower than in recurrent brain tumors (22). Intensity of tumor uptake may correlate with tumor grade and cellularity (23). Changes in ¹⁸F-FDOPA uptake in brain tumors are potentially useful for early response assessment (24).

Bibliography

1. Firnau G, Garnett ES, Chirakal R, Sood S, Nahmias C, Schrobilgen G. [¹⁸F]fluoro-L-dopa for the in vivo study of intracerebral dopamine. *Int J Rad Appl Instrum A*. 1986;37:669-675.
2. Heiss WD, Wienhard K, Wagner R, et al. F-Dopa as an amino acid tracer to detect brain tumors. *J Nucl Med*. 1996;37:1180-1182.
3. Leenders KL, Palmer AJ, Quinn N, et al. Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. *J Neurol Neurosurg Psychiatry*. 1986;49:853-860.
4. Gazdar AF, Helman LJ, Israel MA, et al. Expression of neuroendocrine cell markers L-dopa

- decarboxylase, chromogranin A, and dense core granules in human tumors of endocrine and nonendocrine origin. *Cancer Res.* 1988;48:4078-4082.
5. Garnett ES, Firnau G, Nahmias C. Dopamine visualized in the basal ganglia of living man. *Nature.* 1983;305:137-138.
 6. Youland RS, Kitange GJ, Peterson TE, et al. The role of LAT1 in (18)F-DOPA uptake in malignant gliomas. *J Neurooncol.* 2013;111:11-18.
 7. Neels OC, Koopmans KP, Jager PL, et al. Manipulation of [11C]-5-hydroxytryptophan and 6-[18F]fluoro-3,4-dihydroxy-L-phenylalanine accumulation in neuroendocrine tumor cells. *Cancer Res.* 2008;68:7183-7190.
 8. Timmers HJ, Hadi M, Carrasquillo JA, et al. The effects of carbidopa on uptake of 6-18F-Fluoro-L-DOPA in PET of pheochromocytoma and extraadrenal abdominal paraganglioma. *J Nucl Med.* 2007;48:1599-1606.
 9. Tuomela J, Forsback S, Haavisto L, et al. Enzyme inhibition of dopamine metabolism alters 6-[18F]FDOPA uptake in orthotopic pancreatic adenocarcinoma. *EJNMMI Res.* 2013;3:18.
 10. Ernst M, Zametkin AJ, Matochik JA, et al. Presynaptic dopaminergic deficits in Lesch-Nyhan disease. *N Engl J Med.* 1996;334:1568-1572.
 11. Holthoff-Detto VA, Kessler J, Herholz K, et al. Functional effects of striatal dysfunction in Parkinson disease. *Arch Neurol.* 1997;54:145-150.
 12. Mejia AA, Nakamura T, Itoh M, et al. Absorbed dose estimates in positron emission tomography studies based on the administration of 18F-labeled radiopharmaceuticals. *J Radiat Res.* 1991;32:243-261.
 13. Patel NH, Vyas NS, Puri BK, Nijran KS, Al-Nahhas A. Positron emission tomography in schizophrenia: a new perspective. *J Nucl Med.* 2010;51:511-520.
 14. McGowan S, Lawrence AD, Sales T, Quedsted D, Grasby P. Presynaptic dopaminergic dysfunction in schizophrenia: a positron emission tomographic [18F]fluorodopa study. *Arch Gen Psychiatry.* 2004;61:134-142.
 15. Balogova S, Talbot JN, Nataf V, et al. (18)F-Fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. *Eur J Nucl Med Mol Imaging.* 2013;40:943-966.
 - 15b. Haug A, Auernhammer CJ, Wängler B, Tiling R, Schmidt G, Göke B, Bartenstein P, Pöppel G. Intraindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2009 May;36(5):765-70.
 16. Fottner C, Helisch A, Anlauf M, et al. 6-18F-fluoro-L-dihydroxyphenylalanine positron emission tomography is superior to 123I-metaiodobenzyl-guanidine scintigraphy in the

- detection of extraadrenal and hereditary pheochromocytomas and paragangliomas: correlation with vesicular monoamine transporter expression. *J Clin Endocrinol Metab.* 2010;95:2800-2810.
17. Timmers HJ, Chen CC, Carrasquillo JA, et al. Comparison of 18F-fluoro-L-DOPA, 18F-fluorodeoxyglucose, and 18F-fluorodopamine PET and 123I-MIBG scintigraphy in the localization of pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab.* 2009;94:4757-4767.
 18. Timmers HJ, Chen CC, Carrasquillo JA, et al. Staging and functional characterization of pheochromocytoma and paraganglioma by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography. *J Natl Cancer Inst.* 2012;104:700-708.
 19. Beheshti M, Pocher S, Vali R, et al. The value of 18F-DOPA PET-CT in patients with medullary thyroid carcinoma: comparison with 18F-FDG PET-CT. *Eur Radiol.* 2009;19:1425-1434.
 20. Kauhanen S, Schalin-Jantti C, Seppanen M, et al. Complementary roles of 18F-DOPA PET/CT and 18F-FDG PET/CT in medullary thyroid cancer. *J Nucl Med.* 2011;52:1855-1863.
 21. Lu MY, Liu YL, Chang HH, et al. Characterization of neuroblastic tumors using 18F-FDOPA PET. *J Nucl Med.* 2013;54:42-49.
 22. Chen W, Silverman DH, Delaloye S, et al. 18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy. *J Nucl Med.* 2006;47:904-911.
 23. Pafundi DH, Laack NN, Youland RS, et al. Biopsy validation of 18F-DOPA PET and biodistribution in gliomas for neurosurgical planning and radiotherapy target delineation: results of a prospective pilot study. *Neuro Oncol.* 2013.
 24. Harris RJ, Cloughesy TF, Pope WB, et al. 18F-FDOPA and 18F-FLT positron emission tomography parametric response maps predict response in recurrent malignant gliomas treated with bevacizumab. *Neuro Oncol.* 2012;14:1079-1089.

SNMMI would like to acknowledge Heiko Schöder, MD; Kishore Pillarsetty, PhD; Serge Lyashchenko, PharmD; and Jorge Carrasquillo, MD for developing this content.