N-(3-[^{18}F]Fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane

[^{18}F]FP-CIT

Kam Leung, PhD[1]

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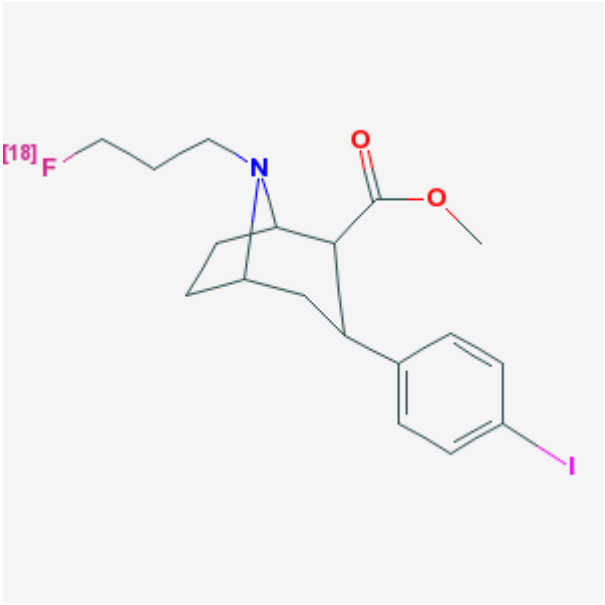
Chemical name:	*N*-(3-[^{18}F]Fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane
Abbreviated name:	[^{18}F]FP-CIT, [^{18}F]β-CIT-FP
Synonym:	2-Carbomethoxy-8-(3-[^{18}F]fluoropropyl)-3-(4-iodophenyl)tropane, *N*-ω-[^{18}F]Fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane
Agent category:	Compound
Target:	Dopamine transporter
Target category:	Transporter
Method of detection:	Positron emission tomography, PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Non-Human Primates • Humans



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[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

Background

[PubMed]

Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion. Parkinson's disease (PD) is associated with a loss of dopamine-containing neurons in the striatum, resulting in a loss of dopamine transporters (DAT) in the presynaptic nerve terminals (1, 2). Reduction of DAT density is inversely correlated with the severity of motor dysfunction in PD patients. Several cocaine analogs were developed for the evaluation of DAT density in neurons of PD patients. Radiolabeled 2β-carboxymethoxy-3β-(4-iodophenyl)tropane (β-CIT) and *N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (FP-CIT) have been used for brain imaging (3-6). Because of the short physical half-live of ^{11}C- of ^{11}C-labeled analogs, equilibrium conditions are difficult to achieve in positron emission tomography (PET) measurements. [^{123}I]β-CIT was studied in single photon emission computed tomography (SPECT), which showed slow tracer uptake kinetics (7, 8). This led to the development of *N*-(3-[^{18}F]fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{18}F]FP-CIT) for PET brain imaging in PD patients (4).

Related Resource Links:

- Chapters in MICAD (Dopamine transporter)
- Gene information in NCBI (Dopamine transporter)
- Articles in Online Mendelian Inheritance in Man (OMIM) (Dopamine transporter)
- Clinical trials (FP-CIT)
- Drug information in FDA (FP-CIT)

Synthesis

[PubMed]

[^{18}F]FP-CIT was synthesized by a nucleophilic fluorination of the mesylate precursor using the standard [^{18}F] potassium Kryptofix complex. This method was automated to give a radiochemical yield of 1-2% (not decay corrected) in 80 min and a radiochemical purity of 98% (4). In another synthesis, [^{18}F]fluoropropyl bromide was prepared by a nucleophilic fluorination of 1,3-dibromopropane with [^{18}F] potassium Kryptofix complex. [^{18}F]Fluoropropyl bromide was used to alkylate nor-CIT to form [^{18}F]FP-CIT with a radiochemical yield of 2-4% and a radiochemical purity of 99%. The total synthesis time was about 90 min (6).

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In Vitro Studies: Testing in Cells and Tissues

[PubMed]

FP-CIT was reported to bind to both dopaminergic and serotonergic transporters in rat forebrain membrane homogenates (9). The transporter-binding affinity of FP-CIT was evaluated by competitive radioaffinity assays for DAT, serotonin, and norepinephrine with [^{3}H]GBR 12935, [^{3}H]paroxetine, and [^{3}H]nisoxetine, respectively. Binding affinities (K_i, nM) of FP-CIT at DAT, serotonin, and norepinephrine were 3.50, 0.11, and 63.0, respectively. FP-CIT showed lower DAT affinity than β-CIT for DAT and more selective affinity for the serotonin over DAT. Therefore, FP-CIT is useful as a tracer for DA neurons in the striatum and for serotonin neurons in the other brain areas.

Animal Studies

Rodent Studies

[PubMed]

No publication is currently available.

Other Non-Primate Mammal Studies

[PubMed]

No publication is currently available.

Non-Human Primate Studies

[PubMed]

[^{18}F]FP-CIT PET studies were performed in cynomolgus monkeys (6). [^{18}F]FP-CIT entered the brain rapidly. There was a high uptake in the striatum and much lower in the thalamus, neo-cortex, and cerebellum. The striatum-to-cerebellum ratio was about 5 at time of transient equilibrium, which occurred after 60-100 min. After pretreatment with GBR 12909, radioactivity in the striatum was markedly reduced, thus indicating specific [^{18}F]FP-CIT binding to the dopamine transporters. The fraction of unchanged [^{18}F]FP-CIT in monkey plasma determined by high-performance liquid chromatography (HPLC) was 10-15% after 25-140 min.

Human Studies

[PubMed]

Human dosimetry of [^{18}F]FP-CIT was determined from blood samples and PET images in 12 human subjects after intravenous injection of [^{18}F]FP-CIT, which was cleared rapidly from the blood to <10% in 15 min (10). Uptake in the lungs, heart, spleen, kidneys and liver peaked in 15-30 min and fell rapidly. The effective dose equivalent was 0.012

mSv/MBq (44 mrem/mCi). The organ that received the highest dose was the urinary bladder (0.059 mGy/MBq or 218 mrad/mCi), followed by the lungs (0.019 mGy/MBq or 70 mrad/mCi) and the liver (0.019 mGy/MBq or 70 mrad/mCi).

[^{18}F]FP-CIT PET was first studied in one normal subject and one mildly affected PD patient (4). A higher uptake into striatal regions was observed in the normal brain than the PD brain. A reduction in putamenal uptake of 65% was observed in the PD patient. [^{18}F]FP-CIT PET images of striatal uptake were more superior than those of [^{123}I]FP-CIT SPECT. [^{18}F]FP-CIT was cleared from the blood in 30 min. HPLC plasma analysis using [^{18}F]FP-CIT indicated the presence of only one minor metabolite. A larger study was later performed using 15 early stage PD patients and 10 age-matched normal volunteers. Statistical parametric mapping was used to localize [^{18}F]FP-CIT binding reduction in PD patients as compared to the normal volunteers. A reduction of 70% in ipsilateral putamen was observed in PD patients (11).

[^{18}F]FP-CIT PET scan is a useful tool in clinical practice to support the diagnosis of PD and to differentiate between other pathological conditions. Moreover, [^{18}F]FP-CIT PET could significantly impact treatment selection and follow-up of these patients.

References

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