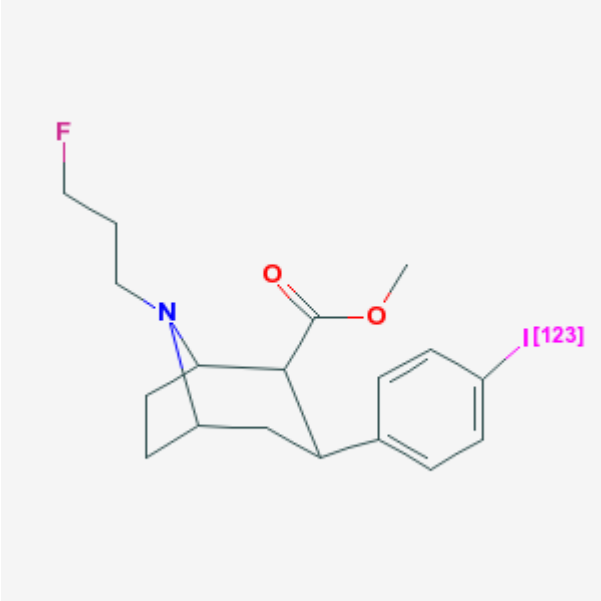
N-(3-Fluoropropyl)-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)nortropane

[^{123}I]FP-CIT

Kam Leung, PhD[1]

Created: December 16, 2004; Updated: February 1, 2011.

Chemical name:	*N*-(3-Fluoropropyl)-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)nortropane
Abbreviated name:	[^{123}I]FP-CIT, [^{123}I]β-CIT-FP
Synonym:	2-Carbomethoxy-8-(3-fluoropropyl)-3-(4-[^{123}I]iodophenyl)tropane, *N*-ω-Fluoropropyl-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)tropane, 123I-Ioflupane, DaTSCAN®
Agent category:	Compound
Target:	Dopamine transporter (DAT)
Target category:	Transporter
Method of detection:	Single photon emission computed tomography (SPECT)
Source of signal:	^{123}I
Activation:	No
Studies:	• *In vitro* • Rodents • 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 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]-analogues, 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), showing slow tracer uptake kinetics (7, 8). It took 20 to 30 h to reach a stable level in the striatum. Therefore, [^{123}I]FP-CIT was developed for SPECT brain imaging in PD patients (4). [^{123}I]FP-CIT was approved by the United States Food and Drug Administration (FDA) for detecting loss of functional nigrostriatal dopaminergic neurons by SPECT imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration in 2011.

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 ([^{123}I]FP-CIT)
- Drug information in FDA ([^{123}I]FP-CIT)

Synthesis

[PubMed]

[^{123}I]FP-CIT was synthesized by the chloramine-T method to iodinate the trimethylstannyl precursor using sodium [^{123}I]iodide. This method gave a radiochemical yield of 95% and a radiochemical purity of 98% (4). [^{123}I]FP-CIT is also commercially available (Amersham, Cygne, The Netherlands).

NLM Citation: Leung K. *N*-(3-Fluoropropyl)-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)nortropane. 2004 Dec 16 [Updated 2011 Feb 1]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

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 affinity (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 was more selective for serotonin over DAT. Therefore, [^{123}I]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]

Intravenous injection of [^{123}I]FP-CIT in rats resulted in high uptake of radioactivity in the striatum (10). Less pronounced uptake was seen in hypothalamus areas with high serotonin uptake sites. The striatal uptake of [^{123}I]FP-CIT was displaced significantly by GBR 12,909 (a specific DAT blocker) and not by fluvoxamine (a specific serotonin re-uptake blockers). On the other hand, fluvoxamine decreased [^{123}I]FP-CIT accumulation in the hypothalamus. The other organs with significant uptake were the liver, spleen, kidneys, and lung. Neither GBR 12,909 nor fluvoxamine blocked the uptake in these organs. In another study, Lavalaye *et al.* (11) showed that acute and sub-chronic administration of various dopaminergic drugs did not have any effect on [^{123}I]FP-CIT uptake in the striatum.

Other Non-Primate Mammal Studies

[PubMed]

No publication is currently available.

Non-Human Primate Studies

[PubMed]

SPECT studies were performed in baboons with [^{123}I]FP-CIT (12). The tracer entered the brain rapidly. There was a high uptake in the striatum and much lower uptake in the midbrain, occipital cortex, and cerebellum. The striatum/cerebellum ratio was about 3-4 at the time of peak uptake (30-60 min) and increased to 6-10 after 5 h. [^{123}I]FP-CIT kinetics were slow, with specific striatal washout rates of 5-7%/h, and showed major accumulation in the urinary bladder intestines, liver, kidneys and brain.

Monkeys were unilaterally treated with neurotoxic doses of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (10). There was a severe loss of striatal uptake of [^{123}I]FP-CIT at the treated side as compared with the untreated side. The striatum/cerebellum ratio was 3.9 at 3 h in the control monkeys. The ratio was 1 in the MPTP-lesioned monkeys.

Human Studies

[PubMed]

Human dosimetry of [^{123}I]FP-CIT was determined from blood samples and SPECT images in 12 human subjects after intravenous injection of 100 MBq (2.7 mCi) of [^{123}I]FP-CIT, which was cleared rapidly from the blood to 53% in 60 min (13). High uptake in the lungs and liver was observed after 10 min, with lower radioactivity in the brain and intestines. The images at 24 and 48 h showed persistent uptake in the liver, lungs, striatum, intestines, and urinary bladder. The effective dose equivalent was estimated to be 0.024 mSv/MBq (2.4 rem/mCi). The organ that received the highest dose was the striatum (0.23 mGy/MBq (0.85 rad/mCi)), followed by the urinary bladder (0.054 mGy/MBq (0.20 rad/mCi)), lungs (0.043 mGy/MBq (0.16 rad/mCi)), and liver (0.029 mGy/MBq (0.11 rad/mCi)).

It was reported that there is a significant correlation of PD severity and duration with [^{123}I]FP-CIT SPECT striatal uptake (14-16). In a recent study with 30 patents, [^{123}I]FP-CIT brain scans were compared with magnetic resonance imaging (MRI)/computed tomography (CT) scans (17). In 5 patients with normal [^{123}I]FP-CIT brain SPECT and MRI/CT scans, symptoms could be related to a benign disorder, such as essential tremor. Two patients had non-diagnostic FP-CIT brain SPECT, with MRI/CT scans compatible with subcortical cerebrovascular disease. In the remaining 23 patients, abnormal striatal [^{123}I]FP-CIT uptake correlated with neurological findings, significantly increasing the probability of PD. In these patients, MRI/CT scans were normal or showed mild brain atrophy or cerebral vascular disease. [^{123}I]FP-CIT scan is a useful tool in clinical practice to support the diagnosis of PD and to differentiate among other conditions [PubMed]. Moreover, [^{123}I]FP-CIT SPECT could significantly affect treatment selection and be used to noninvasively monitor the effectiveness of the therapies of these patients.

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