2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-[^{18}F]fluoroethyl)nortropane

[^{18}F]FECNT

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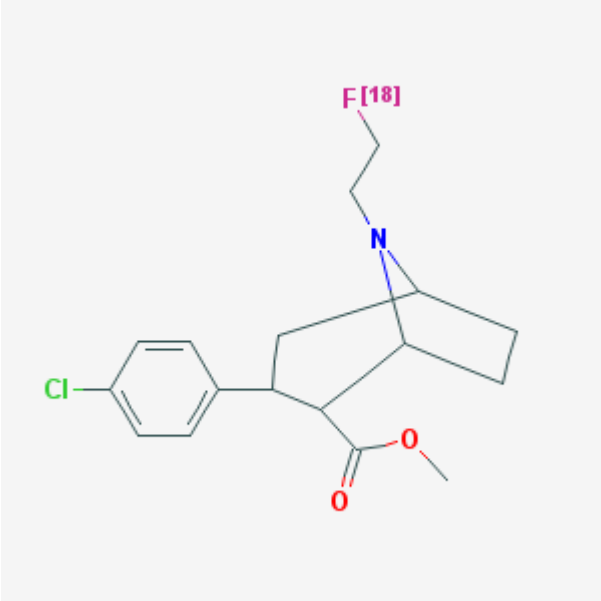
Created: October 27, 2005; Updated: January 15, 2008.

Chemical name:	2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-[^{18}F]fluoroethyl)nortropane
Abbreviated name:	[^{18}F]FECNT
Synonym:	
Agent Category:	Compound
Target:	Dopamine transporter
Target Category:	Binding to dopamine transporter
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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NLM Citation: Leung K. 2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-[^{18}F]fluoroethyl)nortropane . 2005 Oct 27 [Updated 2008 Jan 15]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

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 transporter (DAT) protein in the presynaptic nerve terminals (1, 2). DAT is important to the regulation of synaptic concentration of dopamine. However, reduction of DAT density is not necessarily a measure of the clinical severity of motor dysfunction in PD patients (3). Several cocaine analogs were developed for the evaluation of DAT density in striatal neurons of PD patients (4). 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 (5-8). [^{123}I]β-CIT was studied in humans in single photon emission computed tomography (SPECT), which showed slow tracer uptake kinetics (9, 10). ^{123}I tracer allows delayed scanning. [^{18}F]FP-CIT has been evaluated in humans (6). A switch was made to ^{18}F to gain better resolution and quantitation. However, the radiochemical yields were reported to be 1-4% (6, 8). This led to the development of 2β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-[^{18}F]fluoroethyl)nortropane ([^{18}F]FECNT) for positron emission tomography (PET) brain imaging in PD patients.

Synthesis

[PubMed]

[^{18}F]FECNT was synthesized by preparation of 1-[^{18}F]fluoro-2-tosyloxyethane using the standard potassium [^{18}F]fluoride Kryptofix complex, followed by alkylation of 2β-carbomethoxy-3β-(4-chlorophenyl)nortropane (11). This method provided a radiochemical yield of 21% (decay corrected to the end of bombardment) in 122 min, including high-performance liquid chromatography (HPLC) purification and a radiochemical purity of >99%, with a specific activity of 74 GBq/μmol (2 Ci/μmol).

In another synthesis, 2-[^{18}F]fluoro-1-(4-bromobenzenesulfonate)-ethanol was prepared by a nucleophilic fluorination of 1,2-ethanediol bis-(4-bromobenzenesulfonate) with potassium [^{18}F]fluoride Kryptofix complex (12). 2-[^{18}F]Fluoro-1-(4-bromobenzenesulfonate)-ethanol was used to alkylate 2β-carbomethoxy-3β-(4-chlorophenyl)nortropane to form [^{18}F]FECNT. The radiochemical yield of [^{18}F]FECNT was 16.5 ± 5.3%, and its radiochemical purity was 99.8%. The average specific activity was 38 ± 45 GBq/μmol (1.03 ± 1.22 Ci/μmol) at the end of bombardment. This method was later automated by Voll et al. (13) to reliably produce [^{18}F]FECNT in a 16% decay-corrected yield in a total time of 150 min. The specific activity of [^{18}F]FECNT was 74-92 GBq/μmol (2-2.5 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

FECNT was reported to bind selectively to human dopaminergic transporter (11). Binding affinities (K_i, nM) of FECNT for human DAT, serotonin transporter (SERT), and norepinephrine transporter (NET) were 1.53, 39.1, and 240, respectively. Selective binding to the DAT *versus* SERT and NET was also observed in rat brain homogenates with FECNT.

In vitro autoradiograms showed that the binding of [18F]FECNT was localized to the caudate nucleus and putamen of cortical sections of monkey brain. The DAT inhibitors GBR 12909 (100 nM) and CIT (100 nM) were able to block the [18F]FECNT binding in the caudate and putamen by 50% and 85%, respectively. On the other hand, the serotonin reuptake inhibitor paroxetine (100 nM) showed little inhibition of [18F]FECNT striatal binding.

Animal Studies

Rodents

[PubMed]

Blocking studies of [18F]FECNT binding to DAT by monoamine transporter inhibitors (5 mg/kg) were performed in rats (11). Brain uptake was the highest in the striatum (2.24% injected dose (ID)/g), followed by prefrontal cortex (1.17%), hypothalamus (1.00%), cortex (0.57%), and cerebellum (0.28%) at 60 min after injection of 2.2 MBq (0.06 mCI) of [18F]FECNT. The uptake of [18F]FECNT in the striatum was blocked only by the DAT inhibitor GBR 12909. The SERT inhibitor paroxetine and NET inhibitor reboxetine exhibited no effect on the striatal uptake of [18F]FECNT.

Honer et al. (14) performed [18F]FECNT PET studies in mice showing a good visualization of the striatum from 1 to 30 min with low accumulation in the cerebellum. However, there was a fast washout from the striatum and the striatal radioactivity was similar to that of the cerebellum by 50 min. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (4X20 mg/kg) inhibited the striatal accumulation by 57% ($P = 0.008$) as compared with control mice.

Zoghbi et al. (15) showed that [18F]FECNT accumulated ~7-fold higher in the striatum than in the cortex and cerebellum at 60 min after the injection of 2 rats. The fraction of intact [18F]FECNT in striatum was 90 and 71% at 60 and 120 min, respectively, whereas 59 and 13% in the cerebellum and 13 and 10% in the plasma. A radiometabolite was distributed at equal concentrations in all brain regions. The LC-MS analyses identified *N*-dealkylated FECNT as a major metabolite in the rat brain. The radiometabolite likely was [18F]fluoroacetaldehyde, the product expected from the N-dealkylation of 18F-FECNT, or its oxidation product, [18F]fluoroacetic acid. [18F]FECNT was shown to be stable in both

rat whole blood and brain homogenates at 37°C up to 4 h. Zoghbi et al. (15) suggested that the radiometabolite was formed by P-450 oxidative metabolism in the liver and then accumulated uniformly in the brain.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

[^{18}F]FECNT PET studies were performed in rhesus monkeys (8). [^{18}F]FECNT entered the brain rapidly. There was a high uptake in the caudate and putamen, resulting in caudate- and putamen-to-cerebellum ratios of 10.5 at 60 min. After pretreatment with CIT (0.9 μmol/kg), radioactivity in the striatum was markedly reduced, thus indicating specific [^{18}F]FECNT binding to the DAT. The fraction of unchanged [^{18}F]FECNT in monkey plasma determined by HPLC was 91% at 2 min, 33% at 15 min, and 6% at 120 min.

Cocaine at doses that maintained maximum response rates was shown to decrease DAT occupancy by 53-87%, as determined by displacement of [^{18}F]FECNT in monkey brains (16). Similar results were observed with cocaine and cocaine analogs in other studies of monkeys (17, 18). Isoflurane, an anesthetic, was shown to decrease [^{18}F]FECNT binding potential in rhesus monkeys by 63% with no significant change in total DAT protein in the striatum (19). Control monkeys were administered 1% isoflurane, and experimental monkeys were administered 2% isoflurane.

Human Studies

[PubMed]

Human dosimetry of [^{18}F]FECNT was determined from biodistribution and PET imaging data from rats and monkeys after intravenous injection of [^{18}F]FECNT (20). The organ that received the highest dose was the basal ganglia (0.105 mGy/MBq or 387 mrad/mCi), followed by the heart (0.0417 mGy/MBq or 154 mrad/mCi) and the intestine (0.0175 mGy/MBq or 65 mrad/mCi). The effective dose equivalent was 0.018 mSv/MBq (67 mrem/mCi). In a later study, Tipre et al. (21) reported the effective dose equivalent to be 0.0273-0.0276 mSv/MBq (98-102 mrem/mCi) in rhesus monkeys after injection of 185 MBq (5 mCi) of [^{18}F]FECNT.

[^{18}F]FECNT PET was first studied in 6 normal subjects and 5 PD patients (12). A higher uptake into striatal regions was observed in the normal brain than the PD brain. The caudate and putamen reached maximum radioactivity at 90 min with healthy subjects, with average caudate- and putamen-to-cerebellum ratios of 9.0 ± 1.2 and 7.8 ± 0.7,

respectively. A reduction in basal ganglia uptake of >60% was observed in the PD patients. Only 40% of [^{18}F]FECNT remained in the plasma at 20 min after injection. HPLC plasma analysis indicated the presence of only one major polar metabolite. An [^{18}F]FECNT PET scan is a useful tool to reveal the state of dopamine occupancy of DAT in the brain.

Zoghbi et al. (15) performed comparative [^{18}F]FECNT PET studies in 3 monkeys and 2 humans. The plasma free fractions of [^{18}F]FECNT were 9.4% ± 2.7% (n = 6) in monkeys and 4.7% ± 1.3% (n = 4) in humans. At ~6 min after the administration of [^{18}F]FECNT, monkey plasma was composed of 50% radiometabolite and 50% parent [^{18}F]FECNT. The 50% radiometabolite/ 50% parent composition occurred at 18 and 27 min after injection in humans. The distribution volume in the cerebellum increased up to 1.7-fold in humans between 60 and 300 min after injection and 2.0-fold in monkeys between 60 and 240 min after injection. Plasma [^{18}F]FECNT was used as the input function for compartmental nonlinear least squares analysis. The increases suggest an entry of radiometabolite into the cerebellum. On the other hand, the distribution volume in the striatum did not increase during the same time points. Zoghbi et al. (15) suggested that analysis using the cerebellum as the reference region would produce more variations than a measured arterial input function.

Supplemental Information

[Disclaimers]

Toxicology

Animal Dosimetry

Human Dosimetry

NIH Support

Intramural research program, R01 GM63824, RR-00165,

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