(+)-2-Hydroxy-3-isobutyl-9-(3-[^{18}F]fluoropropoxy)-10-methoxy-1,2,3,4,6,7-hexahydro-11*bH*-benzo[*a*]quinolizine

[^{18}F]FP-(+)-DTBZ

Kam Leung, PhD[1]

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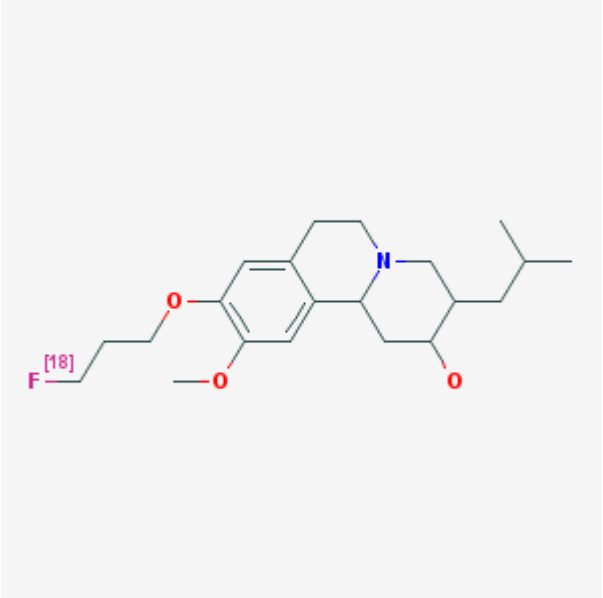
Chemical name:	(+)-2-Hydroxy-3-isobutyl-9-(3-[^{18}F]fluoropropoxy)-10-methoxy-1,2,3,4,6,7-hexahydro-11*bH*-benzo[*a*]quinolizine
Abbreviated name:	[^{18}F]FP-(+)-DTBZ, [^{18}F]AV-133
Synonym:	[^{18}F]FP-(+)-Dihydrotetrabenazine
Agent category:	Compound
Target:	Type 2 vesicular monoamine transporter (VMAT2)
Target category:	Transporter
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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	• Non-human primates • Humans	

Background

[PubMed]

Vesicular monoamine transporter (VMAT2) is present in brain monoaminergic neurons and is responsible for collecting neurotransmitters (dopamine, norepinephrine, and serotonin) from the cytoplasm and storing them in vesicles for synaptic release (1). VMAT2 is therefore an essential regulator of monoaminergic neuronal function. In the brain, VMAT2 is highly present in the striatum, hypothalamus, substantia nigra, and hippocampus, with low levels in the cerebellum and occipital cortex (2). In the striatum, >95% of VMAT2 is associated with dopaminergic neurons (3). Decreases in the VMAT2 level are implicated in movement disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD).

VMAT2 is highly expressed by β cells of the endocrine pancreas and not in exocrine pancreas. VMAT2 is expressed mainly on the β-cells in the islets of Langerhans and composed of 1-2% of the pancreatic mass. β-cell mass (BCM) is a useful indicator of the function of the pancreas. In type I diabetes, β-cells are destroyed leading to a dramatic decrease in BCM. In type II diabetes, there is a slow and insidious decrease in BCM because of peripheral insulin resistance and increase demand for insulin. Decreases in BCM in the human and monkey pancreases correlate to the decreases in insulin level in the blood. VMAT2 is a potential target for non-invasive assessment of BCM and pancreatic function.

VMAT2 has been studied *in vivo* by positron emission tomography (PET) using [^{11}C]dihydrotetrabenazine (2-hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7-hexahydro-11*bH*-benzo[*a*]quinolizine, also known as [^{11}C]DTBZ) with selective VMAT2 binding activity in neurons. Binding of DTBZ to the vesicular monoamine transporter is stereospecific (4). The (+)-enantiomer showed a high affinity for *in vitro* binding for to the VMAT2 in rat brain striatum (K_i = 0.97 ± 0.48 nM), whereas the (-)-enantiomer was inactive (K_i = 2.2 ± 0.3 μM). [^{11}C]DTBZ was developed as a PET agent for the non-invasive study of VMAT2 in the human brain and pancreas. To further improve the availability of PET imaging for VMAT2 neurons in the brain and pancreas,

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^{18}F-labeled analogs of DTBZ have been developed to provide a longer physical half-life of ^{18}F (110 min) *versus* ^{11}C (20 min) (5).

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (VMAT2)
- Articles in OMIM
- Clinical trials (VMAT2)
- Drug information in FDA (VMAT2)

Synthesis

[PubMed]

In the report by Goswami et al. (5), (±)-2-hydroxy-3-isobutyl-9-(3-[^{18}F]fluoropropoxy)-10-methoxy-1,2,3,4,6,7-hexahydro-11*bH*-benzo[*a*]quinolizine ([^{18}F]FP-(±)-DTBZ) was synthesized by a [^{18}F]fluoride nucleophilic displacement of the corresponding mesylate precursor in the presence of Kryptofix 2.2.2/K_2CO_3. [^{18}F]Fluoroethyl-DTBZ ([^{18}F]FE-(±)-DTBZ) was similarly prepared. Purification with high-performance liquid chromatography provided good radiochemical yields of 30–40% (decay-corrected), excellent radiochemical purity (>99%), and high specific activity of 74 GBq/μmol (2.0 Ci/μmol) in 50–55 min. Zhu et al. (6) reported synthesis of [^{18}F]FP-(+)-DTBZ via an automated module with radiochemical yield of 21-41% (decay-corrected, n = 10) and radiochemical purity of >95% in 40 min. The corresponding tosylate (+)-precursor was employed for the [^{18}F]-fluorination.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Henry et al. (2) reported that saturation binding experiments of [^{3}H]DTBZ in the synaptic vesicles from murine striata provided an estimated K_d value of 2.3 to 2.7 nM, with a B_{max} value of 1.35 pmol/mg protein. *In vitro* binding studies by Goswami et al. (5) of mouse striatal homogenates provided K_d values of 0.52 and 0.48 nM for [^{18}F]FE-(±)-DTBZ and [^{18}F]FP-(±)-DTBZ, respectively. Goswami et al. (5) also reported that *in vitro* autoradiography studies of mouse brain slices indicated a selective binding of [^{18}F]FP-(±)-DTBZ to the caudate putamen, olfactory tubercle, and nucleus accumbens, which is consistent with VMAT2 distribution. Tetrabenazine (TBZ), a VMAT2 inhibitor, abolished their binding for [^{18}F]FP-(±)-DTBZ. Kung et al. reported that K_i values were 0.19, 0.10, and >3,000 nM for FP-(±)-DTBZ, FP-(+)-DTBZ (AV-133), and FP-(-)-DTBZ using rat striatal homogenates and [^{3}H]TBZ, respectively.

Tsao et al. (7) reported that saturation binding experiments of [^{18}F]FP-(+)-DTBZ in the synaptic vesicles from rat β-cells provided two binding sites: site A: K_d value of 6.76 ± 1.08 nM with a B_{max} value of 60 ± 10 fmol/mg protein; site B: K_d value of 241.5 ± 7.8 nM with

a B_{max} value of 1,500 ± 20 fmol/mg protein. A single low affinity binding site (K_d value of 208.9 ± 22.5 nM with a B_{max} value of 74.4 ± 1.9 fmol/mg protein) was found using exocrine homogenates. In the rat striatal homogenates, a single high affinity binding site (K_d value of 0.19 nM with a B_{max} value of 45 fmol/mg protein) was found.

Animal Studies

Rodents

[PubMed]

Goswami et al. (5) performed *ex vivo* biodistribution studies in normal mice that demonstrated accumulation of radioactivity in the liver, kidney, spleen, lung, brain, and heart at 2 min after injection of [^{18}F]FE-(±)-DTBZ or [^{18}F]FP-(±)-DTBZ, with a gradual washout in all organs. Both tracers entered the brain readily with 4.66% and 7.08% injected dose/g (ID/g) for [^{18}F]FE-(±)-DTBZ and [^{18}F]FP-(±)-DTBZ at 2 min, respectively. [^{18}F]FP-(±)-DTBZ exhibited a faster brain washout than [^{18}F]FE-(±)-DTBZ (13% versus >50% remaining at 30 min, respectively). [^{18}F]FP-(±)-DTBZ exhibited a higher accumulation of radioactivity in the bone than [^{18}F]-FE-(±)-DTBZ, which indicates a faster defluorination for [^{18}F]FP-(±)-DTBZ. [^{18}F]FP-(±)-DTBZ accumulation was higher in the striatum (3.84% ID/g) and hippocampus (2.55% ID/g) and lower in the cortex (1.45% ID/g) and cerebellum (1.30% ID/g) at 30 min after injection, with a striatum/cerebellum ratio of 3.0 at 30 min. On the other hand, [^{18}F]FE-(±)-DTBZ exhibited a striatum/cerebellum ratio of 1.7 at 30 min. Coinjection of DTBZ (3 mg/kg) with [^{18}F]FP-(±)-DTBZ reduced binding to the striatum, hippocampus, and cortex to the background level of the cerebellum, whereas little inhibition was observed in the other organs studied. On the other hand, coinjection of 1.2 mg/kg raclopride (a dopamine $D_{2/3}$ antagonist) with [^{18}F]FP-(±)-DTBZ showed no effect on the striatum/cerebellum ratio. Further biodistribution studies in mice by Kung et al. (8) showed the active enantiomer [^{18}F]FP-(+)-DTBZ (AV-133) is a sensitive and selectively tracer for VMAT2 imaging with a higher striatum/cerebellum ratio (4.5) than the racemic tracer (3.0).

Kung et al. (9) performed *ex vivo* biodistribution studies in normal rats that demonstrated accumulation of radioactivity in the pancreas (5.50 ± 0.97% ID/g), liver (2.82 ± 0.24% ID/g), striatum (2.25 ± 0.48% ID/g), kidney (1.06 ± 0.06% ID/g), spleen (1.03 ± 0.18% ID/g), lung (0.69 ± 0.03% ID/g), and heart (0.41 ± 0.03% ID/g) at 30 min after injection of [^{18}F]FP-(+)-DTBZ. A gradual washout was observed in all organs except the pancreas. The radioactivity level in the blood was low (0.23 ± 0.06% ID/g). The accumulation of the inactive enantiomer [^{18}F]FP-(-)-DTBZ in the pancreas (1.23% ID/g) and striatum (0.16% ID/g) was low at 30 min after injection. Pretreatment with FP-(+)-DTBZ (3.5 mg/kg, 5 min) reduced the radioactivity by 73% and 85% in the pancreas and striatum at 30 min after injection, respectively. PET imaging in rats showed that the pancreas was clearly visualized as the organ with the highest radioactivity at 30-40 min after injection of [^{18}F]FP-(+)-DTBZ.

Singhal et al. (10) evaluated [^{18}F]FP-(+)-DTBZ PET imaging in a rodent model of diabetes in rats (treated with streptozotocin (STZ) to induced BCM loss and diabetes). Imaging sessions were performed at 13 – 96 h after STZ treatment. Pancreatic standard uptake value (SUV) was observed to decrease with the progressive loss of pancreatic insulin content (R^2 = 0.366, p = 0.002) as well as BCM loss (R^2 = 0.470, p = 0.0002). Displacement studies were performed with ~5,500-fold excess FP-(+)-DTBZ (2.5 mg/kg) in control rats (n = 9) and STZ diabetic rats (n = 6) at 90 min after [^{18}F]FP-(+)-DTBZ injection. The SUV values were ~7.3 for the control pancreases and ~5.3 for the STZ pancreases. These SUV values were reduced to 2.7 for the control pancreases and 2.5 for the STZ pancreases after displacement.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Kilbourn et al. (11) performed PET imaging in one rhesus monkey to obtain calculated striatal distribution volume ratios (DVR) relative to cerebellum. The striatal DVR values for [^{11}C]-(+)-DTBZ, [^{18}F]FP-(±)-DTBZ and [^{18}F]FP-(+)-DTBZ were 4.54, 3.32, and 6.20, respectively. Administration of TBZ at 40 min after injection of [^{18}F]FP-(+)-DTBZ exhibited a rapid loss of radioactivity in the striatum, thalamus and raphe but no change in the cerebellum and cortex.

Human Studies

[PubMed]

Lin et al. (12) performed radiation dosimetry in nine healthy human subjects after injection of 391 MBq (10.6 mCi) of [^{18}F]FP-(+)-DTBZ. The radioactivity uptake in the brain was the highest at 7.5% ± 0.6% injected dose at 10 min after injection. High absorbed doses were found in the pancreas, brain, liver and upper large intestine wall. The organ with the highest radiation dose was the pancreas, which received 153.3 ± 23.8 μGy/MBq. The effective dose equivalent and effective dose for [^{18}F]FP-(+)-DTBZ were 36.5 ± 2.8 and 27.8 ± 2.5 μSv/MBq, respectively.

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