2-Hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11b*H*-bezo[α]-quinolizine

[^{11}C]DTBZ

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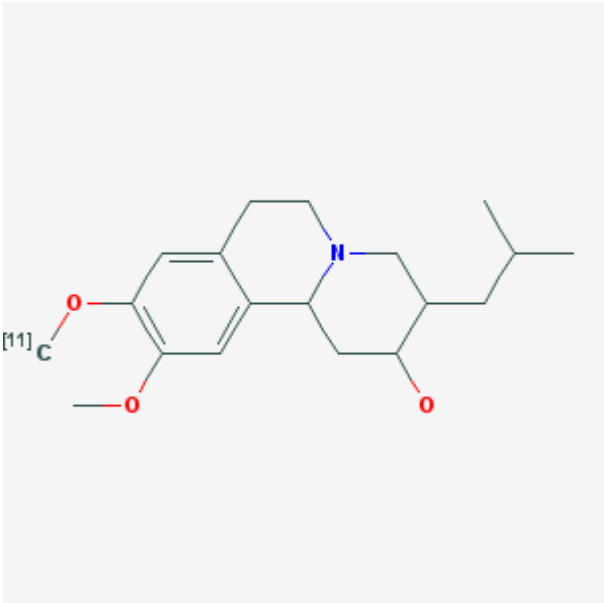
Chemical name:	2-Hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11bH-bezo[α]-quinolizine
Abbreviated name:	[^{11}C]DTBZ
Synonym:	[^{11}C]Dihydrotetrabenazine
Agent category:	Compound
Target:	Type 2 vesicular monoamine transporter (VMAT2)
Target category:	Transporter
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



Click on the above structure for additional information in PubChem.

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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 cerebellum and occipital cortex (2). In the striatum, greater 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 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-11b*H*-bezo[α]-quinolizine) ([^{11}C]DTBZ) with selective VMAT2 binding activity in neurons of the brain and pancreas . Binding of DTBZ to the vesicular monoamine transporter is stereospecific (4). The (+)-enantiomer showed a high affinity *in vitro* binding (K_i = 0.97 ± 0.48 nM) for the VMAT2 in rat brain striatum, whereas the (-)-enantiomer was inactive (K_i = 2.2 ± 0.3 μM). [^{11}C]DTBZ has been developed as a PET agent for the non-invasive study of VMAT2 in the human brain.

Related Resource Links:

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

NLM Citation: Leung K. 2-Hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11b*H*-bezo[α]-quinolizine. 2006 Mar 17 [Updated 2010 Oct 27]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

- Drug information in FDA (VMAT2)

Synthesis

[PubMed]

In the report by Jewett et al. (5), [^{11}C]dihydrotetrabenazine (2-hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,- hexahydro-11bH-bezo[α]-quinolizine) ([^{11}C]DTBZ) [^{11}C]DTBZ was synthesized by alkylation of the 9-hydroxy precursor 2-hydroxy-3-isobutyl-9-hydroxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11b*H*-bezo[α]-quinolizine) with [^{11}C]methyl iodide. Purification with column chromatography provided a radiochemical yield of 12% based on [^{11}C]CO_2, radiochemical purity >95%, and specific activity of 59-74 GBq/μmol (1.6-2.0 Ci/μmol) in 30 min.

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 striatum estimated a 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 of human postmortem brain with [^{3}H]DTBZ showed high binding in the caudate (766 fmol/mg protein), nucleus accumbens (751 fmol/mg protein), putamen (742 fmol/mg protein), substantia nigra (465 fmol/mg protein), hypothalamus (245 fmol/mg protein) pallidum (115-128 fmol/mg protein) hippocampus (83 fmol/mg protein) and frontal cortex (57 fmol/mg protein).

Animal Studies

Rodents

[PubMed]

Kilbourn et al. (4) reported *ex vivo* regional distribution studies in the brain of normal mice showing accumulation of radioactivity in the striatum, hypothalamus, hippocampus and cerebellum at 15 min after injection of (+)[^{11}C]DTBZ, [^{11}C]DTBZ or (-)[^{11}C]DTBZ. The highest brain accumulation and regional contrast was shown for the (+)-enantiomer, with a low and uniform uptake for the (-)-enantiomer. The racemic mixture showed intermediate accumulation. Pretreatment with 10 mg/kg (+)DTBZ 10 min before (+)[^{11}C]DTBZ injection in mice significantly reduced accumulation in the striatum and hypothalamus. Frey et al. (6) performed metabolic studies in rats after injection of [^{3}H]DTBZ. The fraction of unchanged [^{3}H]DTBZ in blood liver and brain, as determined by thin-layer chromatography, was 86%, 93%, and 99% at 15 min after injection, respectively. Collantes et al. (7) estimated a binding potential (BP) value of 1.10 ± 0.16 (n = 10) in the striatum in rats (+)[^{11}C]DTBZ PET imaging. In the rats treated with 6-OHDA, the striatal BP was reduced to 0.05.

Simpson et al. (8) performed *ex vivo* biodistribution studies in normal rats that demonstrated accumulation of radioactivity in the pancreas (5.43 ± 0.19% ID/g), liver (3.28 ± 0.41% ID/g), kidney (2.73 ± 0.06% ID/g), small intestine (1.63 ± 0.24% ID/g), stomach (1.38 ± 0.04% ID/g), heart (0.68 ± 0.05% ID/g), lung (0.51 ± 0.12% ID/g) and brain (0.44 ± 0.12% ID/g) at 30 min after injection of (+)[^{11}C]DTBZ. (+)[^{11}C]DTBZ PET dynamic imaging for 60 min in a rodent model of diabetes in rats (treated with streptozotocin (STZ) to induced BCM loss and diabetes). Imaging sessions were performed at 6 day after STZ treatment. Reduced radioactivity in the pancreata of STZ-treated rats (n = 5) was observed as compared to the pancreata of control rats (n = 5). Immunochemistry of pancreata of STZ-treated rats showed reduced islet areas and frequencies as compared to the pancreata of control rats. There was also loss of VMAT2 and proinsulin expression throughout the STZ-treated pancreata.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

Collantes et al. (7) performed (+)[^{11}C]DTBZ PET imaging in two monkeys and estimated BP values of 1.06 and 1.31 in the basal ganglia. MTPT treatment of one monkey exhibited a 39.7% reduction in the (+)[^{11}C]DTBZ accumulation. Murthy et al. (9) performed whole-body (+)[^{11}C]DTBZ PET imaging in five baboons with most of the injected radioactivity localized to the liver and lung, followed by the intestines, brain, and kidneys. Effective doses to adult female and male were estimated to be 0.0061 and 0.0070 mSv/MBq, respectively.

Human Studies

[PubMed]

Koeppe et al. (10-12) performed various human PET studies using Logan graphical analysis, nonlinear least-squares analysis, equilibrium analysis and two-tissue compartment model to be satisfactorily accounted for the cerebral kinetics of (+)[^{11}C]DTBZ. Distribution volume (DV), binding potential (BP) and transport constant (K_1) can be estimated from the accumulation of radioactivity in various brain regions as measurements of the integrity of the presynaptic neurons. Chan et al. (13) showed that [^{11}C]DTBZ PET studies in 10 normal volunteers to be reproducible using Logan analysis. Occipital cortex or cerebellum can be used as the reference region. The fraction of unchanged [^{11}C]DTBZ in plasma was 80, 64, and 47% at 10, 30, and 60 min, respectively.

Frey et al. (6) compared [^{11}C]DTBZ PET scans of 15 normal subjects (age, 22-70 years) with 7 PD patients (age, 57-79, receiving antiparkinsonian medication). There were

reductions of putamen DV with increasing age, corresponding to losses of 0.77% per year in VMAT2 binding. PD patients had significant reduction in DV in the putamen (-61%) and in the caudate nucleus (-43%). Later studies revealed there are significant correlations of [^{11}C]DTBZ binding reduction with PD severity of motor functions (14). Reduction of striatal VMAT2 binding was shown in patients with multiple system atrophy, but not in patients with essential tremor. Bohnen et al. (15) reported that there was a significant reduction of DV in the caudate (-33%) anterior putamen (-56%) and posterior putamen (-75%) in HD patients (n = 19) compared with normal controls (n = 64).

Gilman et al. (16) used PET with (+)[^{11}C]DTBZ to examine striatal VMAT2 density in 20 dementia patients with Lewy bodies (DLB), 25 with AD, and 19 normal elderly controls. Six DLB patients developed Parkinsonism at least 1 year before dementia (DLB/PD) and 14 developed dementia before Parkinsonism or at about the same time (DLB/AD). Striatal BP was decreased by 62 to 77% in the DLB/PD group and 45 to 67% in the DLB/AD compared to AD and control. BP was lower in the DLB/PD group than the DLB/AD. No differences were found between AD and control groups. Both DLB groups had an anterior to posterior binding deficit gradient relative to controls (posterior putamen > anterior putamen > caudate nucleus). The DLB/AD group showed significant binding asymmetry only in posterior putamen. Therefore, PET with (+)[^{11}C]DTBZ differentiates DLB from AD, and decreased binding in AD may indicate subclinical DLB pathology in addition to AD pathology.

Goland et al. (17) compared pancreatic [^{11}C]DTBZ PET scans of 9 normal subjects with 6 patients with long-standing type 1 diabetes. The pancreatic mean BP_{ND} values (estimated by the 2-parameter multilinear reference tissue model) decreased in patients (1.86 ± 0.05) to 86% of control values (2.14 ± 0.08) (P = 0.01). The functional binding capacity was decreased in patients (44 ± 11) to 40% of control values (109 ± 9) (P = 0.001). Thence, the changes in functional binding capacity and BP_{ND} were less than the near-complete loss of stimulated insulin secretion and BCM observed in the diabetic patients (P = 0.001) comparing to normal controls. The high nonspecific binding in the exocrine pancreas may appear to overestimate BCM with pancreatic [^{11}C]DTBZ PET scans.

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M01 RR00042, P01 NS15655, P50 AG08671, R01 MH47611, U42 RR016629-04, R01 DK63567-03, P30 DK063608-02, RO1 DK077493

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