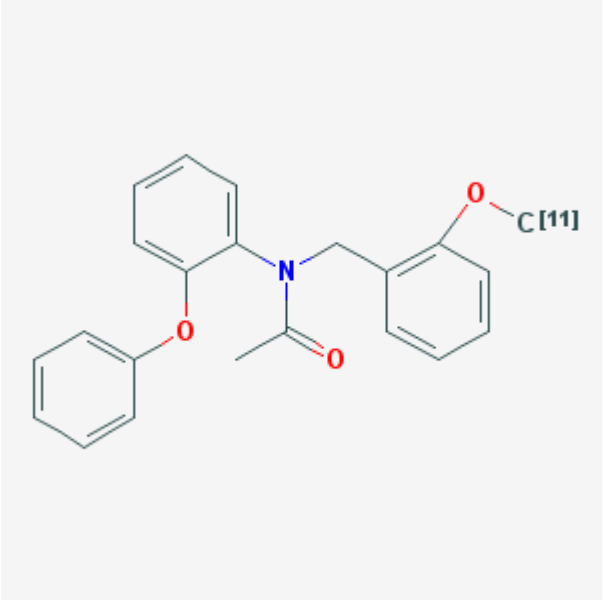
N-Acetyl-*N*-(2-[^{11}C]methoxybenzyl)-2-phenoxy-5-pyridinamine

[^{11}C]PBR28

Kam Leung, PhD[1]

Created: June 12, 2007; Updated: August 25, 2011.

Chemical name:	*N*-Acetyl-*N*-(2-[^{11}C]methoxybenzyl)-2-phenoxy-5-pyridinamine
Abbreviated name:	[^{11}C]PBR28
Synonym:	
Agent category:	Compound
Target:	Peripheral-type benzodiazepine receptor (PBR), also known as translocator protein (TSPO)
Target category:	Receptor
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.

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

Corresponding author.

NLM Citation: Leung K. *N*-Acetyl-*N*-(2-[^{11}C]methoxybenzyl)-2-phenoxy-5-pyridinamine. 2007 Jun 12 [Updated 2011 Aug 25]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[PubMed]

Benzodiazepines are potent psychoactive drugs used for their sedative and anxiolytic properties (1, 2). There are two types of benzodiazepine receptors, which have been designated as central benzodiazepine receptors (CBR) and peripheral benzodiazepine receptors (PBR, also known as translocator protein (TSPO)). The CBR is found exclusively in the central nervous system on the membranes of neurons and is coupled to the γ-aminobutyric acid receptor/chloride channel (3). In contrast, the PBR is a mitochondrial protein found in brain and peripheral tissues (adrenal gland, heart, lung, kidney, and testis) (4).The brain has lower levels of PBR than do the peripheral tissues. Both glial cells and macrophages contain high levels of PBR (5-7). Increased PBR expression after brain injury or neuroinflammation is associated with microglial activation, such as occurs with the neuronal damage that accompanies several neurodegenerative diseases, including Alzheimer's disease, Wernicke's encephalopathy, multiple sclerosis, and epilepsy.

PBRs have been studied *in vivo* by positron emission tomography (8) using 1-(2-chlorophenyl)-*N*-[^{11}C]methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide ([^{11}C]PK11195), an isoquinoline carboxamide with specific PBR antagonistic activity. [^{11}C]PK11195 has been developed as a PET agent for non-invasive studies of microglia and macrophage activation in the brain, lung, and heart. However, accumulation of this tracer in the brain is limited. *N*-(2,5-Dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide (DAA1106) was found to be a selective agonist for studying PBRs in the central nervous system (9, 10). DAA1106 was reported to have a higher affinity for PBRs in mitochondrial fractions of rat and monkey brains than PK11195 (9, 10). Therefore, both tracers are able to cross the normal cell membrane to reach the mitochondrial receptor sites. *N*-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-[^{18}F]fluoroethyl-5-methoxybenzyl)acetamide ([^{18}F]FEDAA1106) and [^{11}C]DAA1106 have been developed as potential PET ligands with highly selective and specific binding to PBR. *N*-Acetyl-*N*-(2-methoxybenzyl)-2-phenoxy-5-pyridinamine (PBR28), which has an aryloxyanilide structure, has been shown to have high affinity and selectivity for PBR (11). *N*-Acetyl-*N*-(2-[^{11}C]methoxybenzyl)-2-phenoxy-5-pyridinamine ([^{11}C]PBR28) has been developed for imaging PBR in the brain.

Related Resource Links:

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

Synthesis

[PubMed]

Imaizumi et al. (11) reported the synthesis of [^{11}C]PBR28 by ^{11}C-methylation of the *O*-desmethyl precursor with [^{11}C]CH_3I. [^{11}C]PBR28 was purified by high-performance liquid chromatography (HPLC). The specific activity was 59.7 ± 2.7 GBq/μmol (1.61 ± 0.07 Ci/μmol) at the time of injection. Time of synthesis or radiochemical yield was not reported. Wang et al. (12) reported a fully automated synthesis of [^{11}C]PBR28 using [^{11}C]methyl triflate and the *O*-desmethyl precursor with radiochemical yields (decay-corrected) of 70-80% based on [^{11}C]CO_2 at the end of bombardment (EOB). The overall synthesis, HPLC purification and formulation time was 25-30 min from EOB. The specific radioactivity was in a range of 185-555 GBq/μmol (5-15 Ci/μmol) at EOB with >99% radiochemical purity.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro [^{3}H]PK11195 PBR-binding studies showed that PBR28 had an IC_{50} value of 0.6 nM. PBR28 has a lipophilicity value of 2.98 and little activity against various neurotransmitters and transporters (11). PBR28 showed inhibition constant (K_i) values >10 μM for several CBR subtypes.

Owen et al. (13) performed *in vitro* binding studies using human post-mortem brain tissues from normal subjects without any history of neurologic disease with [^{3}H]PBR28. PBR28 binds to PBR with high affinity (K_i = 3.4 ± 0.2 nM, n = 6 (40%), low affinity (K_i = 188 ± 7 nM, n = 5 (33%)), and mixed affinity (two sites: K_i = 4.0 ± 1.2 nM (high), K_i = 313 ± 38 nM (low), n = 4 (27%)). Differences in affinity between high affinity binders (HABs) and low affinity binders (LABs) are ~55-fold with PBR28, ~17-fold with PBR06, and ~4-fold with DA1106, DPA713 and PBR111. Mixed affinity binders (MABs) express one class of sites with an affinity, which approximately equal to the means of those for HABs and LABs. PBR28 is a more dominant mixed affinity ligand than PBR06. PK11195 binds equally well to all with one affinity (K_i = ~23 nM, n =15 (100%)). In an autoradiography study with brain tissues from 22 donors, Owen et al. (14) showed 23% of samples (LABs) with no detectable specific signal with [^{3}H]PBR28. The other samples showing signal were HABs (46%) and MABs (31%). On the other hand, all samples showed signal with [^{3}H]PK11195. There was no difference in binding affinity or binding site density for [^{3}H]PK11195 in samples showing no [^{3}H]PBR28 signal.

Animal Studies

Rodents

[PubMed]

Imaizumi et al. (11) reported PET studies of [^{11}C]PBR28 to localize PBRs in a permanent middle cerebral artery occlusion model of neuroinflammation in the rat. Regional volume of distribution (V'_T) was obtained by a two-compartment model with arterial input. In two bolus studies with scans up to 120 min, [^{11}C]PBR28 was injected intravenously over 6 min. [^{11}C]PBR28 showed high peak uptake of ~140, 170, and 200% standard uptake value in the contralateral side, the ischemic core, and the peri-ischemic core at 5–10 min after injection, respectively. Bolus to infusion (B/I) experiments were acquired with two different ratios (B/I = 2 and 5 h). There were 100–190% and 140–290% increases of V'_T in the ischemic core and the peri-ischemic core over the contralateral side, respectively. Injection of PK11195 (60 min after [^{11}C]PBR28) reduced radioactivity in the ischemic core and the peri-ischemic core region to that of the contralateral region. *In vitro* autoradiographic studies of [^{3}H]PK11195 showed significant correlation with the V'_T values of [^{11}C]PBR28 PET obtained in the contralateral side, the ischemic core, and the peri-ischemic core. The increase of [^{11}C]PBR28 binding in ischemic and peri-ischemic areas may represent a microglial activation because of cerebral artery occlusion.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

Imaizumi et al. (15) performed brain (n = 6) and whole-body (n = 3) PET imaging in nonhuman primates after intravenous injection of [^{11}C]PBR28. Brain accumulation of radioactivity peaked at ~40 min with 300% standardized uptake value (SUV). The gray matter had higher radioactivity than the white matter with the highest radioactivity in the choroid plexus of the 4th ventricle. Co-injection of DAA1106 (3 mg/kg) reduced the SUV in the putamen to <100% at 80 min after injection. Whole-body PET scans showed that the BPR-positive organs such as lungs (56% injected dose (ID)), kidneys 7% ID), brain (6% ID) and heart (5% ID) exhibited moderate to high activity at 2-10 min after injection. Co-injection of PK 11195 (10 mg/kg) reduced the radioactivity in these organs by 50-70% at 60 min after injection.

Human Studies

[Pub Med]

Fujita et al. (16) performed [^{11}C]PBR28 PET brain scans in 12 healthy subjects for 120-180 min with one- and two-tissue compartmental analyses combined with serial radioactivity in arterial plasma. To obtain stable distribution volume (V_T) values 90 min of imaging and two-tissue model were required. The V_T values in humans were only ~5% of those in monkeys. Two subjects (14%) showed no significant binding in the brain, and

organs with the highest PBR densities such as the lungs and kidneys. Owen et al. (13) reported that the V_T values of three out of 35 (9%) healthy subjects could not be calculated because of low specific signal. It was concluded that these subjects are likely be to be LABs.

Brown et al. (17) performed dynamic whole-body scans after injection of 651 ± 111 MBq of [^{11}C]PBR28 in seven healthy subjects for radiation dosimetry measurement. For six subjects, the three organs with the highest radioactivity were the kidneys, spleen and lungs (organs with the highest PBR densities). The effective dose was 6.6 ± 1.7 μSv/MBq. One subject showed 60-90% less radioactivity in these three organs, resulting in 28% lower effective dose.

Supplemental Information

[Disclaimers]

Synthesis Protocol

Toxicology

Preclinical Pharmacology

Clinical Pharmacology

NIH Support

Intramural Research Program

References

1. Hunkeler W., Mohler H., Pieri L., Polc P., Bonetti E.P., Cumin R., Schaffner R., Haefely W. *Selective antagonists of benzodiazepines.* Nature. 1981;290(5806):514–6. PubMed PMID: 6261143.
2. Mohler H., Okada T. *Benzodiazepine receptor: demonstration in the central nervous system.* Science. 1977;198(4319):849–51. PubMed PMID: 918669.
3. Olsen R.W., Tobin A.J. *Molecular biology of GABAA receptors.* Faseb J. 1990;4(5): 1469–80. PubMed PMID: 2155149.
4. Anholt R.R., Pedersen P.L., De Souza E.B., Snyder S.H. *The peripheral-type benzodiazepine receptor. Localization to the mitochondrial outer membrane.* J Biol Chem. 1986;261(2):576–83. PubMed PMID: 3001071.
5. Jones H.A., Valind S.O., Clark I.C., Bolden G.E., Krausz T., Schofield J.B., Boobis A.R., Haslett C. *Kinetics of lung macrophages monitored in vivo following particulate challenge in rabbits.* Toxicol Appl Pharmacol. 2002;183(1):46–54. PubMed PMID: 12217641.
6. Kuhlmann A.C., Guilarte T.R. *Cellular and subcellular localization of peripheral benzodiazepine receptors after trimethyltin neurotoxicity.* J Neurochem. 2000;74(4): 1694–704. PubMed PMID: 10737628.

7. Zavala F., Lenfant M. *Benzodiazepines and PK 11195 exert immunomodulating activities by binding on a specific receptor on macrophages.* Ann N Y Acad Sci. 1987;496:240–9. PubMed PMID: 2886095.
8. Petit-Taboue M.C., Baron J.C., Barre L., Travere J.M., Speckel D., Camsonne R., MacKenzie E.T. *Brain kinetics and specific binding of [11C]PK 11195 to omega 3 sites in baboons: positron emission tomography study.* Eur J Pharmacol. 1991;200(2-3):347–51. PubMed PMID: 1782994.
9. Okuyama S., Chaki S., Yoshikawa R., Ogawa S., Suzuki Y., Okubo T., Nakazato A., Nagamine M., Tomisawa K. *Neuropharmacological profile of peripheral benzodiazepine receptor agonists, DAA1097 and DAA1106.* Life Sci. 1999;64(16): 1455–64. PubMed PMID: 10321725.
10. Chaki S., Funakoshi T., Yoshikawa R., Okuyama S., Okubo T., Nakazato A., Nagamine M., Tomisawa K. *Binding characteristics of [3H]DAA1106, a novel and selective ligand for peripheral benzodiazepine receptors.* Eur J Pharmacol. 1999;371(2-3):197–204. PubMed PMID: 10357257.
11. Imaizumi M., Kim H.J., Zoghbi S.S., Briard E., Hong J., Musachio J.L., Ruetzler C., Chuang D.M., Pike V.W., Innis R.B., Fujita M. *PET imaging with [11C]PBR28 can localize and quantify upregulated peripheral benzodiazepine receptors associated with cerebral ischemia in rat.* Neurosci Lett. 2007;411(3):200–5. PubMed PMID: 17127001.
12. Wang M., Yoder K.K., Gao M., Mock B.H., Xu X.M., Saykin A.J., Hutchins G.D., Zheng Q.H. *Fully automated synthesis and initial PET evaluation of [11C]PBR28.* Bioorg Med Chem Lett. 2009;19(19):5636–9. PubMed PMID: 19716298.
13. Owen D.R., Gunn R.N., Rabiner E.A., Bennacef I., Fujita M., Kreisl W.C., Innis R.B., Pike V.W., Reynolds R., Matthews P.M., Parker C.A. *Mixed-affinity binding in humans with 18-kDa translocator protein ligands.* J Nucl Med. 2011;52(1):24–32. PubMed PMID: 21149489.
14. Owen D.R., Howell O.W., Tang S.P., Wells L.A., Bennacef I., Bergstrom M., Gunn R.N., Rabiner E.A., Wilkins M.R., Reynolds R., Matthews P.M., Parker C.A. *Two binding sites for [3H]PBR28 in human brain: implications for TSPO PET imaging of neuroinflammation.* J Cereb Blood Flow Metab. 2010;30(9):1608–18. PubMed PMID: 20424634.
15. Imaizumi M., Briard E., Zoghbi S.S., Gourley J.P., Hong J., Fujimura Y., Pike V.W., Innis R.B., Fujita M. *Brain and whole-body imaging in nonhuman primates of [11C]PBR28, a promising PET radioligand for peripheral benzodiazepine receptors.* Neuroimage. 2008;39(3):1289–98. PubMed PMID: 18024084.
16. Fujita M., Imaizumi M., Zoghbi S.S., Fujimura Y., Farris A.G., Suhara T., Hong J., Pike V.W., Innis R.B. *Kinetic analysis in healthy humans of a novel positron emission tomography radioligand to image the peripheral benzodiazepine receptor, a potential biomarker for inflammation.* Neuroimage. 2008;40(1):43–52. PubMed PMID: 18093844.
17. Brown A.K., Fujita M., Fujimura Y., Liow J.S., Stabin M., Ryu Y.H., Imaizumi M., Hong J., Pike V.W., Innis R.B. *Radiation Dosimetry and Biodistribution in Monkey and Man of 11C-PBR28: A PET Radioligand to Image Inflammation.* J Nucl Med. 2007;48(12):2072–2079. PubMed PMID: 18006619.