2-(1-{6-[(2-[^{18}F]Fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile

[^{18}F]FDDNP

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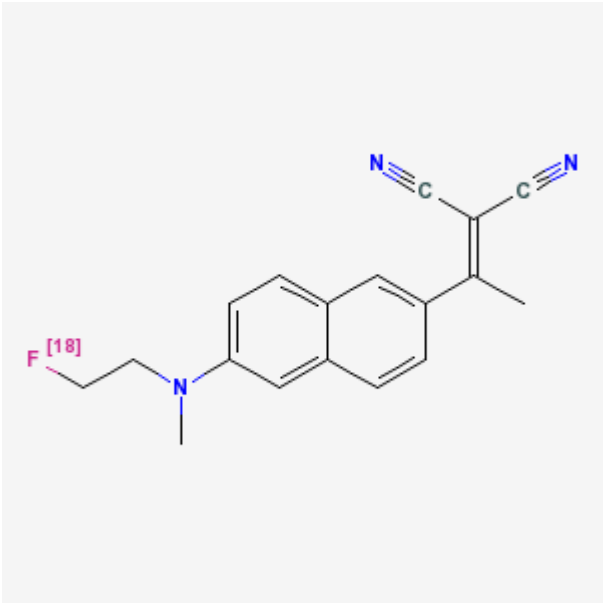
Chemical name:	2-(1-{6-[(2-[^{18}F]Fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile
Abbreviated name:	[^{18}F]FDDNP
Synonym:	
Agent Category:	Compound
Target:	Aggregates of amyloid-beta peptide and tangles tau protein
Target Category:	Acceptor
Method of detection:	PET
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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Background

[PubMed]

Alzheimer's disease (AD) is a form of dementia with a gradual memory loss and a progressive decline in mental functions overtime (1, 2). It is characterized pathologically by neuronal loss, extracellular senile plaques (SPs; aggregates of amyloid-beta peptides consisting of 40 to 42 amino acids) and intracellular neurofibrillary tangles (NFTs; filaments of microtubule-binding hyper-phosphorylated protein tau) in the brain, especially in the hippocampus and associative regions of the cortex (3, 4). Beta-amyloid peptides and tau protein are implicated as the main causes of neuronal degeneration and cell death (5, 6).

Early diagnosis of AD is important for treatment consideration and disease management. Various β-amyloid imaging agents have been developed for magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET) (7-12). The binding of different derivatives of Congo red, thioflavin, stibene, and aminonaphthalene has been studied in human post-mortem brain tissue and in transgenic mice. Out of these analogues, *N*-methyl-[^{11}C]-2-(4'-methylaminophenyl)-6-hydroxybenzothiasole, a amyloid-beta binding compound based on a series of neutral thioflavin-T derivatives (13), was radiolabeled with the positron-emitting radionuclide ^{11}C ([^{11}C]6-OH-BTA-1 or [^{11}C]PIB). [^{11}C]6-OH-BTA-1 was found to be a promising imaging agent for the senile plaques in the brain (9). On the other hand, 2-(1-(6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malono nitrile ([^{18}F]FDDNP) was studied in humans, showing more binding in the brains of patients with AD than in those of healthy people (14). Despite of its slow clearance kinetics for PET imaging, [^{18}F]FDDNP has been found to be a useful tool for detection of both neurofibrillary tangles (NFTs) and amyloid-beta senile plaques (APs) in AD patients.

Related Resource Links:

- Chapters in MICAD (Amyloid)
- Gene information in NCBI (Amyloid).
- Articles in Online Mendelian Inheritance in Man (OMIM) (Amyloid)
- Clinical trials (Amyloid, [^{18}F]FDDNP)
- Drug information in FDA (Amyloid inhibitors)

Synthesis

[PubMed]

The Bucherer reaction of 1-(6-hydroxy-2-naphthyl)-1-ethanone with 2-(methylamino)ethanol yielded 1-{6-[(2-hydroxyethyl)(methyl) amino]-2-naphthyl}-1-ethanone. The Knoevenagel reaction of the Bucherer product with malononitrile yielded 2-1-{6-[(2-hydroxyethyl)(methyl)amino]-2-naphthyl}ethylidene malononitrile, which upon reaction with 4-methylbenzenesulfonyl anhydride (14), resulted in the sulfonated

precursor. Reaction of the precursor with K[^{18}F]F/Kryptofix 222 yielded [^{18}F]FDDNP. After purification by high-performance liquid chromatography (HPLC), radiochemically and chemically pure [^{18}F]FDDNP was prepared in 10-20% radiochemical yield (end-of-synthesis) in a synthesis time of 90 min with specific activity of 222-999 GBq/μmol (6-27 Ci/μmol). Another method was to use p-toluenesulfonyl chloride (15) to form the tosylated precursor for K[^{18}F]F/Kryptofix 222 fluorination to give 11% radiochemical yield at the end-of-synthesis in a total synthesis time of 90 min. The specific activity was 74-222 GBq/μmol (2-6 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Agdeppa et al. (16) reported that unlabeled FDDNP binds to aggregated amyloid-beta(1-40) fibrils with two affinities with K_d values of 0.16 and 1.86 nM. The B_{max} values are 80.8 and 164 pmol/mg for the high affinity and low affinity binding sites, respectively. Saturation binding studies with [^{18}F]FDDNP to homogenates of frontal cortex from postmortem AD brain showed a K_d value of 0.74 nM and a B_{max} value of 144 nmol/g tissue. There was no specific binding of [^{18}F]FDDNP to homogenates of frontal cortex from age-matched control brain.

Confocal fluorescence microscopy and digital autoradiography revealed that [^{18}F]FDDNP is binding to both SPs and NFTs in the temporal and parietal cortices of AD patients (15). Their localizations were confirmed using antibodies to tau and amyloid-beta. Both white and gray matter of the same patient brain slices showed low background. FDDNP is able to cross the blood-brain barrier and the cellular membranes of neurons because it is highly lipophilic. Therefore, [^{18}F]FDDNP is able to detect both SPs and NFTs in AD brains.

Another interesting finding was that non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen and ibuprofen, inhibited [^{18}F]FDDNP binding to synthetic amyloid-beta(1-40) aggregates (17). The *K*i values were 2.6 nM for (*R*)-naproxen, 5.7 nM for (*S*)-naproxen, 44.4 μM for (*R*)-ibuprofen and 11.3 μM for (*S*)-ibuprofen. Naproxen and ibuprofen also blocked the [^{18}F]FDDNP binding sites on AD brain slices. Furthermore, FDDNP, naproxen and ibuprofen induced dissolution of aggregated amyloid-beta(1-40) fibrils. Diclofenac (another NSAID), Congo Red, and thioflavine did not show any inhibition of FDDNP specific binding in both the amyloid-beta(1-40) binding and anti-aggregation assays. An NSAID, such as naproxen is able to bind to SPs in AD and may act as anti-aggregation agent. NSIADs may be useful in therapeutic treatment of AD. The binding sites of FDDNP to amyloid-beta(1-40) aggregates were postulated to be different from those of Congo Red and thioflavine-S, which were tested up 1 μM.

Animal Studies

Rodents

[PubMed]

Teng et al. (18) performed [^{18}F]FDDNP PET imaging in a transgenic rat model of AD to measure [^{18}F]FDDNP binding profiles in relation to age-associated accumulation of amyloid-beta plaques. Cross-section [^{18}F]FDDNP images were obtained transgenic rats (n = 3/group) and wild-type rats (n = 2-4/group) ranging from 9 to 22 months of age. [^{18}F]FDDNP standard update value ratio (SUVR, cerebellium as reference) values increased with age in the hippocampus and frontal cortex of transgenic rats ($P < 0.001$). These values were significantly higher than those in age-matched wild-type rats ($P < 0.05$). The hippocampal and frontal SUVR values of transgenic rats were 1.09-1.12, 1.15, and 1.21 at 9, 14 and 20 months of age, whereas those (<1.08) of wild-type rats remained stable with age. Biochemical and Immunohistochemical analyses showed that the age-related changes in [^{18}F]FDDNP binding in the the hippocampus and frontal cortex of transgenic rats paralleled the age-related changes in amyloid-beta levels as measured with an antibody against synthetic peptide amyloid-beta$_{1-13}$ but not with thioflavine-S. Blocking studies (naproxen pretreatment) were performed with 17-month-old transgenic rats (n = 5) and 14-month-old wild-type rats (n = 2). Naproxen pretreatment decreased [^{18}F]FDDNP SUVR values in the hippocampus and frontal cortex from 1.18 to 1.11 ($P < 0.05$). The SUVR values returned to 1.17 after naproxen washout. Little changes in the SUVR values (1.08) were observed in the wild-type rats with naproxen blockade.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Noda et al. (19) compared [^{18}F]FDDNP and [^{11}C]PIB brain accumulation on five aged and five young adult male rhesus macaques using PET. Both tracers showed increased accumulation in the striatum, thalamus, cingulate and pons in the aged group. Compared to [^{11}C]PIB, [^{18}F]FDDNP showed higher accumulation in the cortical regions of aged and young monkeys. [^{18}F]FDDNP exhibited a higher non-specific binding than [^{11}C]PIB.

Human Studies

[PubMed]

The first human study with [^{18}F]FDDNP PET in 9 patients with early AD and 7 healthy people was reported by Shoghi-Jadid et al. (14). The subjects were given an intravenous

injection of 185-370 MBq (5-10 mCi) of [18F]FDDNP. The dynamic PET scans showed that [18F]FDDNP retention averaged 1.87 fold greater in brain regions (such as frontal, parietal, temporal, and occipital cortex, and hippocampus) that are known to contain APs and NFTs in AD patients than controls. The hippocampus had the highest relative residence time (RRT) of 8.13 min. There was low retention of [18F]FDDNP in the pons with little AP and NFT deposits in AD and controls. There is a direct correlation of RRT with mini-mental state exam scores (r_s = -0.87, p<0.0001; n = 16). There is an inverse correlation of [18F]FDDNP retention with low brain FDG metabolism and MRI atrophy in the cortical regions. Internal dosimetry data for [18F]FDDNP in humans is not available in the literature.

Tolboom et al. (20) performed paired [11C]PIB and [18F]FDDNP PET scans in 14 patients with AD, 11 patients with amnestic mild cognitive impairment (MCI), and 13 healty controls. Global cortical binding potential (BP_{ND}) of [11C]PIB showed higher binding in patients with AD than in controls and MCI patients. [18F]FDDNP uptake was higher in AD patients than in controls, but MCI could not be distinguished from AD or from controls. Global BP_{ND} values of both tracers were moderately correlated (r = 0.45; P = 0.005). In MCI, BP_{ND} of [11C]PIB showed a bimodal distribution, whereas BP_{ND} values for [18F]FDDNP were more widespread, with more MCI patients demonstrating increased accumulation. Regional [11C]PIB BP_{ND} showed different patterns across diagnostic groups, as AD patients showed an overall increase in binding, with the lowest binding in the medial temporal lobe. With [18F]FDDNP, patterns were similar across diagnostic groups. For all groups, highest BP_{ND} values were observed in the medial temporal lobe. Differences in BP_{ND} values between patients with AD, patients with MCI, and controls were more pronounced for [11C]PIB. The difference in regional binding, the moderate correlation, and the discrepant findings in MCI suggest that they measure related, but different, characteristics of the disease. In another study, Tolboom et al. (21) showed that increased [18F]FDDNP binding was associated with impairment of episodic memory, whereas [11C]PIB binding was associated with impairment in a broader range of cognitive functions.

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