

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

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

Abbreviated name: [¹⁸F]FDDNP

Synonym:

Backbone: Compound

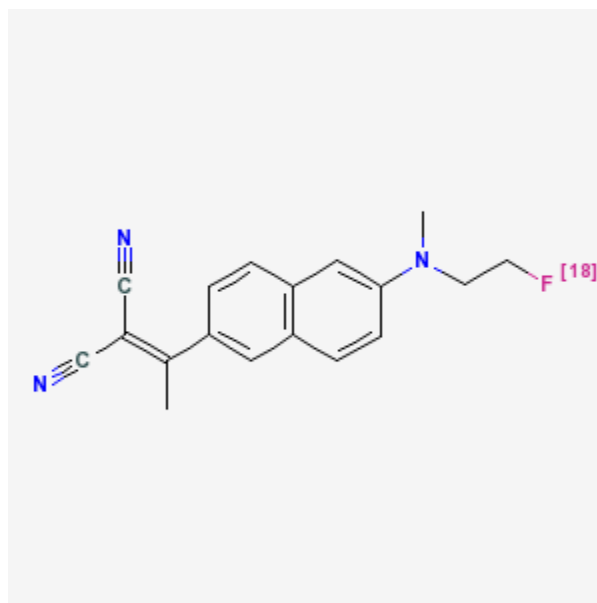
Target: Aggregates of Amyloid-beta peptide and tangles tau protein

Mechanism: Binding

Method of detection: PET

Source of signal: ¹⁸F

Activation: No



Studies: *In vitro*
 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 (7). Various amyloid imaging agents have been developed for MRI, SPECT, and PET (8-13). 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, 2-(1-(6-[(2-¹⁸F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malono nitrile (¹⁸F]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, ¹⁸F]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.

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 K¹⁸F]/Krytoxif 222 yielded ¹⁸F]FDDNP. After purification by high-performance liquid chromatography (HPLC), radiochemically and chemically pure ¹⁸F]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 K¹⁸F]/Krytoxif 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 ¹⁸F]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 ¹⁸F]FDDNP to homogenates of frontal cortex from age-matched control brain.

Confocal fluorescence microscopy and digital autoradiography revealed that ¹⁸F]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, ¹⁸F]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 [¹⁸F]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 [¹⁸F]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. NSAIDs 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, which were tested up to 1 μM.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

The first human study with [¹⁸F]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.

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