PET Radioligands for Imaging of Tau Pathology: Current Status

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Abstract The incidence of Alzheimer's disease (AD), a progressive neurodegenerative disorder, continues to soar with the rapid growth of the elderly population, thus creating an enormous social and economic burden. Although disease-modifying drugs to treat AD are not yet available, several candidate drugs are in clinical trials. Most of these drugs are expected to be effective at the early stages of the disease, and therefore the early and accurate diagnosis of AD will be a critical factor in efforts to improve the prognosis of patients with AD. This review focuses on lead radioligands developed to date and their preclinical data in order to facilitate the development of tau-specific positron emission tomography radioligands that are of great interest to the scientific community.

Keywords Alzheimer's disease · Tau · β -amyloid · Acetylcholinesterase · Radioligands · PET

Introduction

Our society is aging rapidly. This is leading to a substantial increase in the number of patients with dementia, a

progressive cognitive decline with gradual restriction of daily activities, resulting in serious personal as well as social and economic burden. Data released by the Ministry of Health and Welfare show that in 2012, approximately 9.2 % of the Korean population 65 years and older suffered from dementia [<http://www.mw.go.kr>]. The World Health Organization predicts that the number of people with dementia will almost double over the next 20 years, with an estimated 7.7 million new cases each year [<http://www.who.int>]. There is a real need, therefore, to find solutions to critical issues in dementia, including the establishment of better diagnostic and therapeutic approaches. Alzheimer's disease (AD), a progressive neurodegenerative disorder characterized by gradual deterioration of cognition and behavior, is estimated to account for about 71.3 % of all cases of dementia [<http://www.mw.go.kr>]. Today, approximately 40 million people worldwide are affected by AD. Moreover, the incidence of AD is surging as the aging population continues to increase.

Many global pharmaceutical companies are developing disease-modifying drugs to treat AD, and several candidate drugs are in clinical trials. Because most of these drugs are expected to be effective at the early stages of the disease, the early and accurate diagnosis of AD will be critical to provide a more favorable prognosis for AD patients. Currently, efforts to develop new positron emission tomography (PET) radioligands for diagnosis of AD are ongoing worldwide.

Imaging targets are based on a few hypotheses for AD pathogenesis, among which the *cholinergic hypothesis* is the oldest [1]. Here, AD is characterized by a deficiency of cholinergic activity in the brain. Histochemical studies of post-mortem brain tissues showed that activity of choline acetyltransferase and acetylcholinesterase (AChE) is significantly reduced in AD [2–5]. To increase brain acetylcholine (ACh) concentration, AChE inhibitors that inhibit ACh hydrolysis can be used. For this reason, AChE inhibitors are currently

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used to improve symptoms of AD patients, although they failed to show efficacy in clinical trials [6, 7]. Recent studies suggested that the ACh depletion alone may not be the cause of AD. McDonald et al. posited that cholinergic depletion may decrease the brain's ability to balance up for the accumulation of risk factors which develop AD with aging [8]. Numerous studies using radiolabeled AChE substrates or inhibitors were carried out to measure AChE activity or density for diagnosis of AD [9–15].

In the *amyloid cascade hypothesis* [16], the accumulation of the β -amyloid ($A\beta$) peptides in the brain is an important characteristic of AD pathology. $A\beta$ peptide is produced from amyloid precursor protein, and these fragments accumulate to form plaques in brains of patients with AD. This hypothesis has taken the major position in AD research and has been the basis of development of many AD-modifying drugs. Accordingly, in vivo monitoring of $A\beta$ plaques may be beneficial for the diagnosis of AD. Many specific imaging radioligands have been developed for imaging $A\beta$ plaques. Among these, the most well-characterized radioligand is ^{11}C -Pittsburgh compound B (^{11}C -PIB) (Fig. 1) [17]. However, routine clinical use of ^{11}C -PIB is limited due to its short half-life (20 min), despite its lower subcortical white matter uptake compared to ^{18}F -labeled radioligands [18]. Recently, three PET radiopharmaceuticals have been approved by the US Food and Drug Administration (FDA) for diagnosis of AD, including florbetapir (Amyvid™, Eli Lilly), florbetaben (Neuraceq™, Piramal Imaging), and flutemetamol (^{18}F) (Vizamyl™, GE Healthcare) [19–26].

In the past few years, tau and its role in AD have been the focus of immense interest. In the *tau hypothesis*, AD is caused by highly phosphorylated tau proteins that form neurofibrillary tangles (NFTs), one of the pathological hallmarks of the disease (Fig. 2). This hypothesis was based on neurobiological and clinical studies that revealed a high correlation between disease severity and increasing NFT accumulation in the brain [27]. Although the functions of tau are not fully established, it is widely accepted that tau binds to and stabilizes microtubules, which then regulates intracellular transport of organelles and substances [28, 29]. Upon hyperphosphorylation, tau is dissociated from microtubules and forms filaments [28]. More recently, the tau axis hypothesis has been proposed, in which tau mediates $A\beta$ toxicity in the dendrites of neurons [30]. There are six tau isoforms in the human brain, and they are hyperphosphorylated and aggregated as paired helical filaments (PHFs) in the brains of individuals with AD

Fig. 1 Chemical structures of ^{11}C -PIB and ^{18}F -DDNP

Fig. 2 Illustration of $A\beta$ plaques and neurofibrillary tangles in brain tissue with AD

[31, 32]. Different sets of the isoforms lead to different tau pathology, including AD, frontal temporal lobar degeneration, corticobasal degeneration, progressive supranuclear palsy (PSP), and Pick's disease [31–35]. In addition, both tau and $A\beta$ fibrils share the same β sheet structure [36–40]. Tau exists in much lower concentrations compared to $A\beta$ plaques in brains with AD, and depending on brain region, tau concentrations are 5 to 20 times lower [41, 42]. However, tau imaging may still be beneficial because the severity of tau deposits correlates well with cognitive impairment in AD patients. Furthermore, tau imaging may be useful for detecting tauopathies other than AD [43].

Tau Imaging Radioligands

Given the potential advantages of clinical tau imaging in AD, the development of radioligands for tau targeting is currently the focus of huge interest. In order to design ideal tau imaging radioligands, several criteria need to be met. This includes good penetration through neuronal cell membranes as well as the blood–brain barrier (BBB), not serving as a permeable glycoprotein 1 (Pgp) substrate, high binding affinity and selectivity for tau over $A\beta$ plaques, desirable pharmacokinetics in the brain, little or no lipophilic radioactive metabolite formation, and favorable dosimetry [43]. The first radioligand that labeled NFTs and $A\beta$ plaques in the brains of AD patients was 2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (^{18}F -DDNP) (Fig. 1). Barrio et al. modified a neutral and lipophilic fluorescent dye, DDNP, for ^{18}F -labeling [44, 45]. FDDNP exhibited K_d values of 36.7 ± 11.6 nM for K18 Δ K280-tau fibrils and 5.52 ± 1.97 nM for $A\beta_{42}$ fibrils [46] and was found to easily penetrate the BBB due to its high lipophilicity ($\log P = 3.71$) [40].

The most successful strategy for developing tau-specific radioligands to date is based on the screening of compounds from chemical libraries and further structure optimization to

increase binding affinity and selectivity for tau over A β fibrils. A research team from Tohoku University screened over 2000 compounds and found that quinoline and benzimidazole derivatives have selective binding for NFTs over A β plaques and show good penetration through the BBB [40, 47]. Based on the pharmacophore of the lead compounds, many tau-specific radioligands have been developed. 2-[(4-Methylamino)phenyl]quinoline (BF-158), one of the initially developed quinoline derivatives, exhibited relatively higher binding affinity for tau fibrils than for A β fibrils. Its ^{11}C -labeled form, ^{11}C -BF-158 displayed desirable pharmacokinetics in normal mouse brains, and autoradiography using the radioligand showed correlation of radioactivity uptake with tau immunostaining in AD brain sections. However, the radioligand was not entirely specific to tau pathology in AD brain tissues [47].

Maccioni et al. found that astemizole and lansoprazole bind to aggregated tau variants [48]. These benzimidazole derivatives are FDA-approved as antihistamine and gastrointestinal disorder drugs, respectively. Thereafter, a couple of research groups synthesized ^{11}C - and ^{18}F -labeled derivatives of astemizole and lansoprazole (Fig. 3) and reported that the ligands exhibited higher binding affinity for tau than A β fibrils (Table 1). They also found that the radioligands served as substrates for the rodent Pgp. Pre-treatment with cyclosporine A, a Pgp inhibitor, increased penetration of the radioligands through the BBB, possibly by inhibiting radioligand efflux. However, ^{18}F -labeled astemizole derivatives had poor brain uptake both in untreated rats and in cyclosporine A-pretreated

rats, despite its high binding affinity for tau fibrils and high lipophilicity of astemizole ($\log P=5.57$) [48, 49]. While ^{11}C -*N*-methyl lansoprazole and ^{18}F -*N*-methyl lansoprazole are not substrates for non-human primate Pgp, ^{18}F -lansoprazole did not show uptake even in non-human primate brains [50, 51]. ^{18}F -*N*-methyl lansoprazole is found to be favorable in terms of high selectivity for tau over amyloid, low white matter binding, and good in vivo kinetics. In addition, ^{11}C -*N*-methyl lansoprazole and ^{18}F -*N*-methyl lansoprazole showed potential for tau imaging in PSP as well as in AD patients [51].

Arylquinoline derivatives are found to be selective for tau over A β fibrils (Table 2) [47]. The initially designed derivative, 6-(2-[^{18}F]fluoroethoxy)-2-(4-aminophenyl)quinoline (^{18}F -THK523) showed unfavorable kinetics in normal mouse brains (Fig. 4; Table 2). It also demonstrated high uptake in the white matter and had no tau-specific uptake in non-AD tauopathies [28]. Therefore, ^{18}F -THK523 was chemically optimized to produce a series of other THK derivatives. ^{18}F -THK5105 and ^{18}F -THK5117 were found to bind to tau-rich regions, which was confirmed by co-localization with Gallyas-positive and immunoreactive tau protein deposits. ^3H -THK5117 was shown to bind to NFTs in postmortem brain tissues, in a manner that was clearly distinguished from ^3H -PIB retention [52]. Furthermore, PET studies demonstrated that both ^{18}F -THK5105 and ^{18}F -THK5117 retention in the inferior temporal cortex, a tau-rich region in brains of AD patients were greater than that of age-matched healthy controls based on regional standardized uptake value (SUV)-to-cerebellar cortex SUV ratio time activity curves [52, 53].

Fig. 3 Chemical structures of ^{11}C - and ^{18}F -labeled lansoprazole and astemizole derivatives

Table 1 ^{11}C - and ^{18}F -labeled astemizole and lansoprazole derivatives

Radioligand	K_d (nM)		Log P
	Tau ^a	A β ^b	
^{18}F -Labeled astemizole derivative [48]	$K_i=1.67$	–	5.57 (Astemizole)
^{18}F -Lansoprazole [48, 51]	$K_d=3.3$	$K_d=11.0$	1.47
^{11}C - <i>N</i> -Methyl and ^{18}F - <i>N</i> -Methyl lansoprazole [51]	$K_d=0.7$	$K_d=8.2$	2.18

^a Human tau 441^b Mouse A β_{1-42}

However, the pharmacokinetics of ^{18}F -THK5105 was slower than that of ^{18}F -THK5117 in normal mice and humans, which makes ^{18}F -THK5117 a more favorable imaging agent [40, 52, 53]. ^{18}F -THK5117 brain PET image of an AD patient was named “Image of the Year” at the 2014 annual meeting of the Society of Nuclear Medicine and Molecular Imaging (<http://www.snm.org>). The recently developed ^{18}F -THK5351 exhibited high binding affinity for AD hippocampal homogenates ($K_d=2.9$ nM) and had faster kinetics in normal mice compared to ^{18}F -THK5117. Furthermore, ^{18}F -THK-5351 showed selective binding to tau and had a higher signal-to-background ratio on autoradiography of AD brain sections compared to other THK derivatives [29, 54]. PET images of patients with mild cognitive impairment showed ^{18}F -THK-5351 retention in the same brain regions as detected in AD patients [55]. This radioligand is shown to be more specific and less non-specific than ^{18}F -THK5117.

Murayama et al. designed tau-specific radioligands by screening fluorescent chemicals that bind to β -sheet conformations in brains of AD and non-AD tauopathy patients as

well as PS19 mice [56]. They developed a series of phenyl/pyridinyl butadienyl benzothiazoles/benzothiazoliums (PBBs) based on their finding that the lipophilicity and core length (15–18 Å) of ligands binding to β -sheets are major factors to determine their selectivity for tau over A β fibrils [43, 56]. Among these derivatives, ^{11}C -PBB3 (Fig. 4) exhibited high and selective binding for tau over A β fibrils (A β /tau ratio=40~50), and favorable kinetics in mouse brains (Table 2) [28, 43, 56]. PET studies showed that the radioligand was taken up by the tau-rich hippocampus of AD brains, whereas this region did not take up the A β imaging radioligand, ^{11}C -PIB [39]. Although ^{11}C -PBB3 undergoes photoisomerization in the presence of fluorescent light, its isomer is much less active. In addition, photoisomerization of the radioligand is readily preventable by removing fluorescent light [57].

Kolb et al. screened more than 900 compounds of different classes using a competitive autoradiography assay for binding to native tau and A β aggregates in AD brain tissue sections [58]. 5*H*-Pyrido[4,3-*b*]indole and benzo[4, 5]imidazo[1,2-*a*]pyrimidine derivatives, ^{18}F -T807 and ^{18}F -T808, (Fig. 4) were

Table 2 Tau-specific radioligands that have been evaluated in clinical PET studies of AD patients

Radioligand	K_d (nM)		Mouse brain uptake at 2 min (% ID/g)	Mouse brain uptake ratio (2/30 min)	Log P
	Tau	A β (A β /tau)			
^{18}F -DDNP [40, 46]	$K_{d1}=36.7^a$	$K_{d1}=5.52^a$ (0.15)	6.23	2.02	3.71
^{18}F -THK523 [40, 46]	$K_{d1}=1.99^a$ $K_{d2}=50.7^a$	$K_{d1}=30.3^a$ (15)	2.72	1.85	2.40
^{18}F -THK5105 [40]	$K_{d1}=1.45^a$ $K_{d2}=7.40^a$ $K_d=2.63^b$	$K_{d1}=35.9^a$ (25)	9.2	2.55	3.03
^{18}F -THK5117 [40]	$K_i=10.5^a$ $K_d=5.19^b$	–	6.06	10.27	2.32
^{18}F -THK5351 [54]	$K_d=2.9^b$	–	–	–	–
^{11}C -PBB3 [28, 56, 57]	$K_{d1}=2.5^b$ $K_{d2}=100^b$	(40~50)	1.92 (1 min) 0.97 (5 min)	17.45 (1/30) 8.82 (5/30)	3.30 (Calc.)
^{18}F -T807 [62]	$K_d=14.6^b$	(>27)	4.43 (5 min)	7.15 (5/30)	1.67
^{18}F -T808 [58, 61]	$K_d=22.0^b$	(27)	6.7 (2.5 min)	2.9 (2.5/20)	–

^a K18 Δ K280-tau fibrils^b Human brain sections

Fig. 4 Chemical structures of tau-specific radioligands

designed and synthesized [59–61]. The radioligands exhibited high binding affinity and selectivity for tau fibrils over A β fibrils (Table 2) and showed favorable kinetics in mice [58, 62]. The two radioligands had good pharmacokinetics in human studies with low radioactivity uptake in the white matter [58, 59, 61]. Furthermore, these radioligands were shown to bind to PHFs of tau in AD brains and their retention was associated with disease severity [59, 61]. Although ¹⁸F-T808 has better pharmacokinetics in rodents than ¹⁸F-T807 [58, 61, 62], it appeared to undergo slow metabolic defluorination in rodents and humans. This was also shown when ¹⁸F-T808 was incubated with mouse or human microsomes and nicotinamide adenine dinucleotide phosphate (NADPH), which displayed metabolic instability that was more severe by mouse microsomes [58].

Challenges and Perspectives

It is more challenging to develop tau-specific imaging radioligands than A β plaque imaging radioligands, partly because of the intracellular location of tau proteins (Fig. 2). Furthermore, both tau protein and A β plaques have β -sheet conformations and co-exist in many regions in AD brains, which make it difficult to develop radioligands that bind exclusively to tau and not A β . In addition, tau proteins exist in much lower concentrations than A β plaques in brains with AD. However, clinical tau imaging has several advantages,

including correlation of radioligand uptake with AD progression and the ability to also detect non-AD tauopathies. Current development of tau imaging radioligands is based on several lead compounds, each of which has strong and weak points. Further research will thus be important to design more optimal radiopharmaceuticals that allow early and accurate diagnosis of AD and non-AD tauopathies, as well as facilitate new drug development for AD treatment.

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Conflict of Interest Yeom Seong Choe and Kyung-Han Lee declare that they have no conflict of interest.

Ethical Statement The study was approved by an institutional review board or equivalent and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This article does not contain any studies with humans or animals performed by any of the authors.

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