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NEUROIMAGING (DJ BROOKS, SECTION EDITOR)

Tau PET Imaging in Alzheimer's Disease

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Abstract In several neurodegenerative diseases that are collectively called tauopathies, progressive accumulation of tau in the brain is closely associated with neurodegeneration and cognitive impairment. Noninvasive detection of tau protein deposits in the brain would be useful to diagnose tauopathies as well as to track and predict disease progression. Recently, several tau PET tracers including T807, THK-5117, and PBB3 have been developed and succeeded in imaging neurofibrillary pathology in vivo. For use of tau PET as a biomarker of tau pathology in Alzheimer's disease, PET tracers should have high affinity to PHF-tau and high selectivity for tau over amyloid-β and other protein deposits. PET tau imaging enables the longitudinal assessment of the spatial pattern of tau deposition and its relation to amyloid-β pathology and neurodegeneration. This technology could also be applied to the pharmacological assessment of anti-tau therapy, thereby allowing preventive interventions.

Keywords Positron emission tomography · Amyloid · Tau · Neurofibrillary tangles · Dementia · Early diagnosis · Biomarker

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Introduction

Senile plaques (SPs) and neurofibrillary tangles (NFTs) are neuropathological hallmarks of Alzheimer's disease (AD). These protein deposits, SP and NFT, are composed of amyloid-β (Aβ) protein and hyperphosphorylated tau protein, respectively. A definitive diagnosis of AD can be established by the post mortem examination of the human brain. The amyloid cascade hypothesis, which proposes that abnormal production and accumulation of Aβ is the cause of AD, has been widely accepted as the concept of AD pathogenesis [1]. Preclinical amyloid pathology that has been observed in recent amyloid PET studies is considered as a high risk for future cognitive decline [2]. Many candidates for anti-amyloid drugs have been developed to reduce the amount of Aβ [3]. However, repeated failures of clinical trials for these drugs have increased, and shifted, our interest in using tau as another target for novel drug development [4, 5].

Hyperphosphorylation of the tau protein in AD forms insoluble fibers named paired helical filaments (PHFs) [6, 7]. PHFs accumulate in the neuronal cytoplasm and form NFTs [8, 9]. Initially, NFTs occur in the transentorhinal area, followed by the involvement of the entorhinal cortex and hippocampus, progressing to the temporal cortex and the other cortical areas [10, 11]. Postmortem studies have shown that the NFT, but not the SP, load correlates with the severity of dementia and neurodegeneration [12, 13], suggesting a more direct effect of tau aggregation on neurodegeneration than Aβ.

To facilitate the development of anti-tau drugs, it is important to measure the pathologic time course of NFT formation in the human brain. Recent developments allow us to visualize NFTs in the human brain using positron emission tomography (PET) by measuring the distribution of intravenously administered radiotracers that selectively bind to NFTs. Also, PET imaging is potentially useful for monitoring treatment outcomes and selecting patients for anti-dementia therapy [14].

Requirement for Tau PET Tracers

For using PET as a biomarker of tau pathology, the imaging measures should be quantitative, reproducible, and directly linked to the presence of tau deposits in the brain. Recently, several PET tracers have been developed for imaging tau pathology in the human brain [15–17]. Most of these tracers bind to the β-pleated sheet structure of tau protein fibrils in the same way as amyloid PET ligands. Therefore, these tracers are considered to be insensitive to tau oligomers. The ideal characteristics of tau-selective PET tracers are listed in Table 1. For successful imaging of NFTs in the AD brain, the tracer should have high binding affinity to PHF-tau. The binding affinity of tracers can be quantitatively evaluated by protein-ligand binding assay using synthetic tau fibrils or human brain homogenates. The assay using synthetic protein fibrils is widely used for the screening of protein-binding ligands. However, the measured value from synthetic fibrils should be interpreted cautiously because these fibrils do not completely imitate the conformation of native tau deposits.

The assay using human brain samples is a more reliable method for the assessment of protein-ligand interaction than using synthetic fibrils. This method has been used for the assessment of amyloid-binding PET ligands [18, 19]. Most amyloid PET ligands exhibit high binding affinities to AD brain homogenates (Kd or Ki<20 nM) [20–23]. Tau PET ligands are also required to exhibit similar affinity to AD brain samples in region where NFTs are frequent (e.g. entorhinal cortex, hippocampus, and temporal cortex). In AD neocortex, the concentrations of tau are ~5–20 times lower than those of Aβ [16]. Therefore, tracers should be highly selective for tau over Aβ. Simulation studies estimate that a 20-50-fold selectivity for PHF-tau over Aβ will be required for selective imaging of PHF-tau in vivo [24]. The most reliable method for the assessment of radioligand binding selectivity is autoradiography of human brain sections, because the binding of ligands to tau fibrils can be directly assessed at a low nanomolar ligand concentration, which is achieved in the brain tissue during a PET scan. If the ligand has autofluorescence, ligand binding can also be evaluated microscopically. However, this method generally requires micromolar concentration of ligands, which is far higher than radiotracer concentrations in the brain. Lipophilic fluoro-amyloid β-sheet binding PET tracers tend to accumulate in the white matter as well as Alzheimer cortex, possibly because myelin contains β-sheet structures. Such non-specific white matter tracer binding needs to be kept minimal when developing PET ligands for tau.

In addition to these binding properties, radiotracers should have high blood–brain barrier (BBB) permeability. Most successful amyloid-PET tracers show an initial brain uptake above 4 % of the injected dose (%ID) at 2 min after intravenous injection in mice [23, 25, 26]. Lipophilicity is one of the most important determinants of BBB permeability. Ideally, a radiotracer should exhibit LogP values between 0.9 and 2.5 [27]. In addition, radiotracers should be cleared rapidly from background and non-target areas. Slower clearance of radiotracers prolongs the time for them to reach a secular equilibrium in a PET study. The brain 2-to-30 min ratio in normal mice is a good index of the clearance of radiotracer from non-target areas. The

Table 1 Ideal characteristics of tau PET tracers

Characteristics	Requirements
High binding affinity for PHF-tau	Kd or Ki<20 nM for tau-rich brain samples
High binding selectivity for PHF-tau	>20 fold selectivity for PHF-tau over Aβ
High blood–brain barrier permeability	>4 % ID/g at 2 min post injection in normal mice
Rapid clearance from normal brain tissue	2 min-to-30 min brain uptake ratio in mice>10
Moderate lipophilicity	LogP=1–3
Low non-specific binding	Low or no binding to subcortical white matter
Low metabolism	Metabolites should not enter into the brain

successful amyloid PET tracer [^{11}C]PiB shows high 2-to-30 min ratio (>10), reflecting a fast clearance from non-target regions [23]. An ideal radiotracer should readily enter the brain and selectively bind to its target in the absence of radiolabeled metabolites. Thus, the radiolabeled metabolites should not penetrate BBB. ^{18}F-labeled tracers are more clinically useful than ^{11}C-labeled tracers as the longer lived ^{18}F isotope allows time for tracer delivery to many PET centers [28]. Three ^{18}F-labeled amyloid PET tracers, including [^{18}F]florbetapir (Amyvid™), [^{18}F]flutemetamol (Vizamyl™), [^{18}F]florbetaben (Neuraceq™), have become commercially available in EU and US. However, in some ^{18}F-labeled ligands, defluorination can cause bone accumulation of ^{18}F, which might interfere with visual assessment of tracer distribution in the brain.

Tau PET in Clinical Studies

FDDNP

The first successful PET tau imaging in humans was accomplished by using [^{18}F]FDDNP [29]. In the autoradiography of the AD brain sections raised [^{18}F]FDDNP binding was detected in the hippocampus where a high density of NFTs were observed by immunohistochemistry [30]. Patients with AD and 50 % of mild cognitive impairment (MCI) cases showed higher [^{18}F]FDDNP retention than healthy control subjects [31]. A direct comparison between FDDNP and PiB in the same AD patients found negligible PiB but strong FDDNP binding in the medial temporal cortex, compatible with FDDNP binding to NFTs [32]. However, FDDNP uptake was also increased in amyloid rich cortical association areas in AD. Intriguingly, recent [^{18}F]FDDNP PET study demonstrated an elevated FDDNP uptake in the subcortical brain areas and amygdala of football players suspected of chronic traumatic encephalopathy (CTE) [33], suggesting the potential utility of PET imaging for monitoring pathological tau deposits after traumatic brain injury [34]. Furthermore, [^{18}F]FDDNP is reported to be sensitive in imaging the regional localization of tau deposits in progressive supranuclear palsy (PSP) [35]. However, there are some limitations for use of this tracer as a biomarker of tau, because this tracer binds non-selectively to both SPs and NFTs and is less sensitive to tau deposits than more recently developed radiotracers shown below.

PBB3

[^{11}C]PBB3 is a PET tracer that is reported to allow in vivo detection of tau deposits in AD as well as in non-AD tauopathies, including PSP and corticobasal degeneration (CBD) [36•]. In clinical PET studies, this tracer can be produced with sufficient radioactivity and high quality [37] and it clearly differentiated AD brains from healthy control brains [36•]. [^{11}C]PBB3 retention in the hippocampus of AD patients confirms the binding ability of this tracer to NFTs. In addition, this study reported significant [^{11}C]PBB3 binding to tau deposits in the basal ganglia of a CBD case. Ongoing multicenter PET studies of [^{11}C]PBB3 will validate the clinical usefulness of this tracer in various types of tauopathies.

T807 and T808

[^{18}F]T807 and [^{18}F]T808 have been developed as tau-selective PET tracers [38•, 39, 40]. In vitro autoradiography studies showed that both radiotracers exhibit strong and selective binding to PHF-tau with nanomolar affinity on AD brain sections with little binding to amyloid plaques. The first-in-man PET study successfully demonstrated [^{18}F]T807 retention in the frequent areas of PHF-tau in the AD brain [38•]. In addition, [^{18}F]T807 retention was associated with increased disease severity. There was much more elevated and extensive [^{18}F]T807 retention in severe AD case than in MCI and mild AD cases. Unlike most ^{18}F-labeled amyloid PET tracers, [^{18}F]T807 shows very low non-specific binding of the tracer to the white matter, which may improve the grey-to-white matter contrast in the brain. The first-in-man PET studies of [^{18}F]T808 were performed in 11 subjects [39]. This tracer showed more rapid tracer distribution throughout the brain and more rapid clearance from normal brain tissue than [^{18}F]T807. Most AD cases showed elevated [^{18}F]T808 retention in the frequent areas of PHF-tau. However, substantial defluorination was observed in some cases.

THK-523, THK-5105 and THK-5117

Novel quinoline derivatives were initially identified as candidates for tau PET tracer by the screening of over 2,000 small molecules [41]. In vitro autoradiography studies using three ^{18}F-labeled derivatives ([^{18}F]THK-523, [^{18}F]THK-5105 and [^{18}F]THK-5117) demonstrated the high binding selectivity of these tracers to tau over Aβ on AD brain sections [42–44]. While [^{18}F]THK-523 PET failed to clearly visualize tau deposits in the human brain in vivo [45],. [^{18}F]THK-5105 PET successfully demonstrated radiotracer retention in sites susceptible to tau deposition in the AD brain [46••]. Recent [^{18}F]THK-5117 PET studies demonstrated higher signal-to-background ratio and better pharmacokinetics of this tracer than [^{18}F]THK-5105 [17]. [^{18}F]THK-5117 PET images in mild, moderate and severe AD patients are shown in Fig. 1. These tracer retentions were associated with clinical severity of dementia and brain atrophy [46••], which is consistent with the observation of postmortem brain analysis showing the association of tau pathology with dementia severity and neuronal loss.

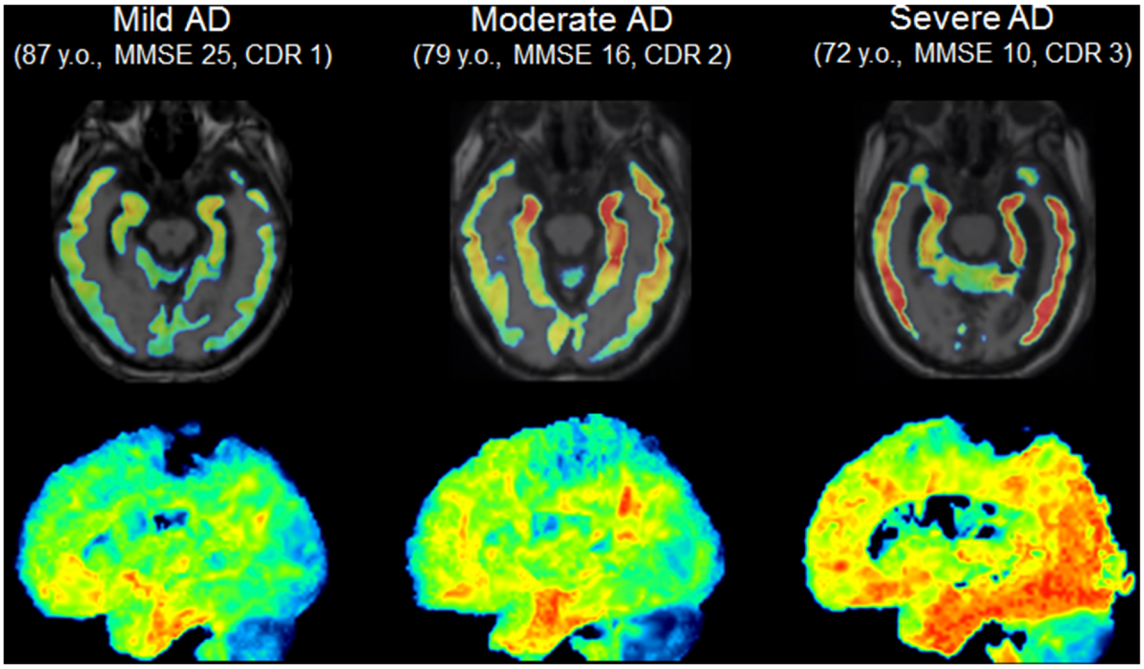

Fig. 1 [^{18}F]THK-5117 PET images in mild, moderate and severe AD patients. In mild AD case, specific [^{18}F]THK-5117 binding is confined to the medial, anterior and inferior temporal cortex. Moderate AD case shows additional [^{18}F]THK-5117 retention in association areas. Severe AD case shows more extensive and higher [^{18}F]THK-5117 retention in the neocortex

Potential role of Tau PET Imaging

PET enables us to study the interaction of Aβ and tau and their influences on neurodegenerative processes in the human brain. Tau PET has many target diseases including AD, frontotemporal dementia, PSP, CBD and CTE [15, 47] (Table 2). Recent PET studies described above have shown the potential utility of tau imaging for the diagnosis of non-AD tauopathies. One good example is CTE. CTE is known as a progressive tauopathy associated with repetitive traumatic brain injury [34, 48]. The pathology of CTE is characterized by the accumulation of phosphorylated tau protein in neurons and astrocytes. The morphological appearance of tau deposits in CTE is similar to that found in AD, however the spatial pattern of tau deposition is different from AD [49]. Therefore, tau imaging might distinguish the pathology related with CTE from AD by the pattern of tracer distribution. However, tau PET might not be able to visualize all kinds of tau deposits in vivo, because the conformation of protein fibrils is different in each disease and in each pathological deposit. Another

Table 2 Comparison of amyloid and tau PET imaging

	Amyloid PET	Tau PET
Radiotracer	[^{11}C]PiB [^{11}C]BF227 [^{18}F]Flutemetamol [^{18}F]Florbetapir [^{18}F]Florbetaben [^{18}F]NAV4694	[^{11}C]PBB3 [^{18}F]T807 [^{18}F]T808 [^{18}F]THK-5105 [^{18}F]THK-5117
Target diseases	Alzheimer's disease	Alzheimer's disease Frontotemporal dementia Progressive supranuclear palsy Corticobasal degeneration Chronic traumatic encephalopathy Senile dementia of the neurofibrillary tangle type Argyrophilic grain disease
Frequent areas of tracer uptake in Alzheimer's disease	Neocortex	Medial and lateral temporal cortex
Neocortical tracer retention in an asymptomatic state	Frequent	Rare
Association with clinical severity of dementia	No or little	High
Association with neurodegeneration	No or little	High

concern is whether the density of tau deposits in the brain is sufficient for in vivo detection or not.

Tau pathology is strongly associated with age and is frequently observed in late-onset dementias. Some of these cases are pathologically diagnosed as senile dementia of the neurofibrillary tangle type [50] or argyrophilic grain disease [51]. Tau PET might be useful for antemortem diagnosis of these diseases which differ from AD as amyloid PET gives negative results in these tauopathies [52]. Recent studies have shown that a population labelled suspected non-AD pathophysiology (SNAP) exists who have abnormal neurodegeneration biomarkers (atrophy, glucose hypometabolism) but absent brain amyloid pathology [53]. The pathological condition of these populations might be partially explained by the existence of tau pathology.

The distribution of amyloid PET tracers is diffuse and widespread in the neocortex. Even where widespread Aβ deposits exist in cognitively normal subjects, cortical tau pathology can be unremarkable [54] indicating that amyloid pathology is upstream of tau pathology in the neocortex [55, 56]. Presymptomatic Aβ pathology is recognized as a high risk factor for future progression to dementia [54]. However, amyloid PET studies have shown little association of brain amyloid load with clinical severity of dementia in AD patients, suggesting that the presence of Aβ plaques alone is not sufficient to produce cognitive impairment [57, 58]. In contrast, tau pathology in AD starts within a very limited area (medial temporal cortex) of the brain, and then gradually spreads to the neocortex as the clinical symptom of dementia progress. Pattern of tau pathology are strongly associated with neurodegeneration, reflected by brain atrophy [59]. In postmortem studies, NFTs in the hippocampal as well as temporal cortex were observed in MCI cases and in cases having very early symptomatic signs of dementia [11, 60]. Recent PET studies have successfully detected tau pathology in brain areas of mild AD cases [38•, 40, 45]. Therefore, the amount and extent of tau pathology could be a good marker of the severity and prognosis of preclinical AD and MCI. Tau deposits in the medial temporal cortex have been considered to be age-related, and are independent of AD disease process. However, the progression of tau pathology might be accelerated, inducing neurodegeneration and cognitive decline, once Aβ deposits start to accumulate in the neocortex [61–63]. The synergistic effect of these two protein deposits and their influences on neurodegenerative process should be clarified in the future by carrying out longitudinal analysis of tau and amyloid PET data.

Conclusions

Several PET tracers that have been developed for imaging PHF-tau have shown promising results in humans. These tracers are reported to be selective for PHF-tau in vitro. Additional studies are required to evaluate their reliability and quantitative performance, and to validate the in vivo binding selectivity of these tracers to tau pathology. PET tau imaging would be useful for early detection of disease-related pathology, for pharmacological evaluation of drug efficacy and for understanding the pathophysiology in AD and non-AD tauopathies. Longitudinal PET studies will clarify the interaction of tau and Aβ, and their influences on neurodegenerative process in the human brain.

Compliance with Ethics Guidelines

Conflict of Interest Ryuichi Harada, Hiroyuki Arai, and Kazuhiko Yanai declare that they have no conflict of interest.

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