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In vivo tau imaging: Obstacles and progress☆

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Abstract The military conflicts of the last decade have highlighted the growing problem of traumatic brain injury in combatants returning from the battlefield. The considerable evidence pointing at the accumulation of tau aggregates and its recognition as a risk factor in neurodegenerative conditions such as Alzheimer's disease have led to a major effort to develop selective tau ligands that would allow research into the physiopathologic underpinnings of traumatic brain injury and chronic traumatic encephalopathy in military personnel and the civilian population. These tracers will allow new insights into tau pathology in the human brain, facilitating research into causes, diagnosis, and treatment of traumatic encephalopathy and major neurodegenerative dementias, such as Alzheimer's disease and some variants of frontotemporal lobar degeneration, in which tau plays a role. The field of selective tau imaging has to overcome several obstacles, some of them associated with the idiosyncrasies of tau aggregation and others related to radiotracer design. A worldwide effort has focused on the development of imaging agents that will allow selective tau imaging in vivo. Recent progress in the development of these tracers is enabling the noninvasive assessment of the extent of tau pathology in the brain, eventually allowing the quantification of changes in tau pathology over time and its relation to cognitive performance, brain volumetrics, and other biomarkers, as well as assessment of efficacy and patient recruitment for antitau therapeutic trials.

Keywords: Alzheimer's disease; Chronic traumatic encephalopathy; Tau; Tauopathies; Molecular neuroimaging; Neurodegeneration; Radiotracer design

1. Introduction

Tauopathies is the term used to describe a group of neurodegenerative conditions characterized by the pathologic accumulation of tau aggregates in the brain. Along with Alzheimer's disease (AD) and some variants of frontotemporal lobe degeneration (FTLD), other tauopathies include Down's syndrome, Guam Parkinsonism-dementia complex, frontotemporal dementia with parkinsonism linked to chromosome-17 (FTDP-17), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and chronic traumatic encephalopathy (CTE) [1–5]. Although all these conditions share tau immunoreactivity in postmortem analysis, they can be composed of different tau isoforms and show distinct histopathologic and ultrastructural differences [2,6].

AD is the leading cause of dementia in the elderly, accounting for 50% to 70% of dementia cases [7], whereas FTLD is responsible for 10% to 20% of cases [8,9]. In AD, the typical macroscopic picture is gross cortical atrophy. Microscopically, there are widespread cellular degeneration and diffuse synaptic and neuronal loss, accompanied by reactive gliosis and the presence of the pathologic hallmarks of the disease: extracellular β-amyloid (Aβ) plaques and intraneuronal bundles of hyperphosphorylated tau aggregates [10–12]. In AD, these tau deposits can be

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recognized histologically as neurofibrillary tangles (NFTs) and neuropil threads, as well as dystrophic neurites in senile plaques, whereas ultrastructurally, they aggregate in paired helical filaments (PHFs) [2,5,13].

CTE is considered to be a slowly progressive tauopathy associated with repetitive (concussive and subconcussive) brain trauma, prevalent among contact sports athletes, physical abuse victims, and military personnel victim to blasts and other injuries in the battlefield [4,14,15]. CTE is clinically characterized by progressive cognitive decline affecting memory and executive function, as well as depression, higher impulsivity and aggressiveness, speech and gait abnormalities, suicidal ideation, parkinsonism, and dementia [16]. Neuropathologically, CTE is distinguished by cerebral atrophy, a fenestrated cavum septum pellucidum, atrophy of the hippocampus, brainstem, and mammillary bodies, and tau inclusions [4]. In CTE, in contrast with other tauopathies, NFTs are observed mainly in superficial cortical layers with a tendency to cluster around deep sulci and involvement of astrocytes [16]. In several cases, transactive response DNA-binding protein 43 (TDP-43) inclusions and Aβ plaques are also present [17].

Tau is found bound to tubulin to stabilize microtubules, which are critical for the axonal support of neurons. Based on the number of tubulin-binding repeats found on the tau protein, six isoforms have been identified [18]. Although the underlying mechanisms leading to tau hyperphosphorylation, misfolding, and aggregation remain unclear, tau aggregation and deposition follows a stereotyped spatiotemporal pathway both at the intraneuronal level [19,20] and in its topographic and neuroanatomic distribution in the brain [5,21–24]. Furthermore, mutations within the tau gene (*MAPT*) have been shown to lead to FTDP-17 [25], providing solid evidence that tau malfunction triggers neurodegeneration and dementia.

Although the prevalent etiologic hypothesis for AD postulates that either misprocessing of the amyloid precursor protein or disruption of its clearance leads to the accumulation of Aβ in the brain in the form of plaques [26], human postmortem studies have shown that it is the density of NFTs and not of Aβ insoluble plaques that strongly correlates with neurodegeneration and cognitive deficits [27–32]. Concurring with the postmortem studies, Aβ burden as assessed by positron emission tomography (PET) does not strongly correlate with cognitive impairment in AD patients [33,34]. Moreover, although age-related limbic NFTs are frequently present in cognitively unimpaired individuals, neocortical NFTs are much less prevalent, in contrast with neocortical Aβ plaques, which appear abundantly in some nondemented individuals [33,35–39]. The lack of a strong association between Aβ deposition and measures of cognition, synaptic activity, and neurodegeneration in AD, in addition to the evidence of Aβ deposition in a high percentage of asymptomatic healthy controls, points to the involvement of other downstream mechanisms, such as tau aggregation and NFT formation, leading to synaptic failure and eventually neuronal loss, indicating that Aβ is an early and necessary, though not sufficient, cause for cognitive impairment in AD [40]. The fact that tau plays a key role in neurodegeneration [25,41–43] has led to the development of disease-specific therapeutic strategies aimed at either inhibiting tau hyperphosphorylation or aggregation or seeking direct stabilization of microtubules [44–52].

In this context, there is a need to develop reliable diagnostic and prognostic biomarkers that can identify incipient focal or diffuse pathology that will allow, when available, early therapeutic interventions. Definitive diagnosis of these neurodegenerative diseases can only be established by examination of the human brain at autopsy. Molecular imaging procedures are suited to overcome the need for a neuropathologic examination to identify the underlying pathology of these diseases. The last two decades have been focused on developing novel Aβ ligands for the noninvasive detection of Aβ deposition in the brain [33,53]. Among these tracers, 2-(1-{6-[(2-[18F]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (^{18}F-FDDNP) was the only one reported to bind to not only Aβ deposits but also NFTs [54]. Therefore, a selective and specific tau imaging agent will be necessary to achieve a more profound understanding of the pathophysiology of AD, CTE, FTLD, and other neurodegenerative conditions in which tau plays a role. The development of a selective tau imaging agent will also lead to improvements in differential diagnostic accuracy while accelerating treatment discovery and monitoring of therapeutics.

2. The idiosyncrasies of tau deposition

Tau is normally phosphorylated, and the degree of phosphorylation determines its binding to microtubules. The hyperphosphorylation of tau leads to weaker microtubule binding [55] and an increase of unbound phospho-tau concentration in the cytosol. Hyperphosphorylated tau migrates from the axonal compartment to the somatodendritic compartment [56] where its accumulation leads to the formation of the pathologic tau aggregates in the form of filamentous inclusions [57], found in neurons, astrocytes, and oligodendroglia [58].

There are several obstacles to be surmounted to be able to image tau deposits [59]. In contrast to Aβ, most tau aggregates are intracellular. Furthermore, there are six isoforms of tau, and different combinations of these isoforms are manifested as different clinical phenotypes [60,61]. To complicate matters, tau aggregates are subjected to a wide spectrum of posttranslation modifications such as phosphorylation, nitration, acetylation, glycosylation, truncation, prolyl-isomerization, glycation, ubiquitination, and so forth [62] that, in addition to the combination of different isoforms, lead to diverse ultrastructural conformations and typical pathologic lesions [2,6,63,64]. Another obstacle to be overcome by selective tau tracers is the coexistence of other misfolded

proteins sharing the same β sheet secondary structure, as is in the case of AD in which tau and Aβ are both colocalized in gray matter areas. This issue is further complicated by the much lower brain concentrations of tau than Aβ and aggregates in AD, where the concentrations of tau are, depending on the brain region, ~5 to 20 times lower than those of Aβ [65,66], requiring a radiotracer with high selectivity for tau over Aβ to be successful in AD.

These particular characteristics of tau deposition affect the design of selective tau tracers. For example, the intracellular location of tau aggregates means that a neuroimaging radiotracer has to be able to cross not only the blood-brain barrier (BBB) but also the cell membrane to reach its target, imposing certain constraints in tracer design in terms of lipophilicity and molecular size.

3. Radiotracer design

Useful neuroimaging probes are required to fulfill a number of key general properties: they should be nontoxic lipophilic molecules of low molecular weight (<450) that readily cross the BBB, with rapid clearance from blood and preferably not metabolized, and with low nonspecific binding while reversibly binding to its target in a selective and specific fashion [67–70]. It is also desirable that these novel tau tracers are labeled with isotopes with longer half-lives, such as fluorine 18 (^{18}F; half-life of ~2 hours), that allow centralized production and regional distribution, as is practiced worldwide in the fluorodeoxyglucose (^{18}FDG) supply. Among the aforementioned properties, binding affinity and lipophilicity are the most crucial for in vivo radioligands. Most successful neuroimaging radiotracers show an initial brain uptake above 5% of the injected dose at 2 to 5 minutes after intravenous injection [69]. This brain initial tracer uptake depends on several factors such as cerebral regional blood flow, plasma radiotracer concentration, BBB permeability, free fractions of the radiotracer in plasma and brain, and so forth [69]. Ideally, tracers with $LogP_{OCT}$ values between 0.9 and 3.0 are sufficiently lipophilic to adequately cross the BBB [71]. Within this ideal range, although more lipophilic radioligands will display faster accumulation of radioactivity in the brain than less lipophilic ones, they will also be bound by plasma proteins and usually undergo fast metabolism, leading to lower central nervous system uptake.

Exquisite selectivity is required for a tau radioligand. The selectivity required for a particular neuroimaging radiotracer depends on the concentration of available binding sites [68]. As mentioned before, in AD, there are higher cortical concentrations of Aβ than PHF tau. Although in vitro reports have already shown that based on affinity alone, a 3- to 30-fold selectivity for PHF tau is attainable [72–77], simulation studies estimate that a 20- to 50-fold selectivity for PHF tau over Aβ will be required to image PHF tau in vivo [78]. In addition to the initial assessment of safety, brain kinetics, and tracer metabolism, the evaluation of tau tracer selectivity in vivo poses some challenges. In the evaluation of novel neuroreceptor radiotracers, competition and/or displacement studies are used to ascertain selectivity and specificity of the binding. The relatively high density of aggregated tau in the brain requires micromolar concentrations of an unlabeled competitor to effectively compete or displace the tau radioligand, and untoward toxic effects are likely at those high doses. Therefore, validation of tau tracer selectivity relies on comparison of the regional distribution of the tracer in both controls and pathologic cases in parallel with other tracers that while sharing the property of binding to β sheet conformation have been shown to have selective binding to a different aggregated protein such as Aβ or α-synuclein, as well as comparison to the known regional brain distribution of tau aggregates amassed from neuropathologic studies of individuals with the same pathology. Further validation requires relating the binding of the tracer to clinical measures of cognitive impairment or to biomarkers such as gray matter atrophy, cerebrospinal fluid or plasma analytes, or cerebral glucose metabolism known to be directly affected by or correlated to tau deposition. The ultimate validation is attained by direct comparison of the regional distribution of tau as assessed antemortem by PET and the tau regional distribution assessed postmortem at autopsy.

4. Tau imaging tracers

The achievement of Aβ imaging with Pittsburgh compound B (PiB) [79] led to a renewed international effort to develop selective tau radiotracers. Given that the ultrastructural form that tau aggregates adopt in AD is PHF, most of the efforts for developing selective tau imaging radiotracers are focused on PHF tau. It is not clear at this stage if or how well these tracers recognize the other conformations of tau aggregates present in non-AD tauopathies. Although most of the proposed novel PHF tau imaging tracers in recent years originated from research groups working on therapeutic tau antiaggregation or defibrillization agents [72,80–82], the most successful attempts come from research groups concentrated on screening available or novel chemical libraries to identify potential high-affinity selective PHF tau compounds that might be amenable to radiolabeling [83–85].

Several strategies for developing tau imaging agents have been proposed. Based on the structure-activity relationship (SAR) of *N*′-benzylidene-benzohydrazides and their fluorescent staining profile and antiaggregating activity, it has been proposed that higher PHF tau selectivity can be attained by incorporating bulky hydrophilic groups, which prevent binding to Aβ fibrils, into these amphiphilic ligands [80]. Another group, also using SAR and tracer docking simulation studies as a way to address differences in protein composition and structural polymorphism, is proposing to achieve PHF tau selectivity of 2-aryl benzothiazole derivatives by altering the side chain composition of the compounds [72,86]. A group focused on PHF tau therapeutics [50,87] assessed different imidazothiazole, benzothiazole, and pyrimidazole derivatives in primuline displacement

studies and fluorescent studies in both human and tau transgenic mouse brains [81]. One of these derivatives, SKT04-137, was radiolabeled with ^{18}F for biodistribution studies in mice, in which it showed sufficient brain uptake but slow clearance from the brain (2 minute-to-60 minute ratio of 2.9) [81]. A series of thiohydantoin [88], oxindole [89], and styrylbenzimidazole [90] derivatives were designed and synthesized for the detection of tau pathology. Preclinical evaluation of these compounds showed that although all of them displayed somewhat high affinity for NFT in autoradiographic studies, only one of the styrylbenzimidazole derivatives presented with sufficient entry into the brain [90]. Several other scaffolds (e.g., bis(arylvinyl)pyrazines, -pyridazines, and -pyrimidines) have been proposed as potential tau and Aβ imaging agents [91].

4.1. ^{18}F-FDDNP

The first reported human amyloid imaging tracer with nanomolar affinity to Aβ fibrils [92] was ^{18}F-FDDNP (Fig. 1), a radiofluorinated 6-dialkylamino-2-naphthy ethylidene derivative developed, synthesized, and characterized by Barrio et al. at University of California, Los Angeles [93]. ^{18}F-FDDNP was reported to bind to both the extracellular Aβ plaques and the intracellular NFT in AD [94,95] ^{18}F-FDDNP was used to obtain the first human PET images of Aβ in an 82-year-old woman with AD, in whom it showed a differential tracer clearance in different areas of the brain, being slower in areas of Aβ and tau deposition, as pathologically confirmed later at autopsy [92,95]. In a follow-up study, AD patients again demonstrated higher accumulation and slower clearance of ^{18}F-FDDNP than controls in brain areas such as the hippocampus [94]. Retention time of ^{18}F-FDDNP in these brain regions was correlated with lower memory performance scores in patients with AD [96]. These findings were further confirmed in a larger series in which AD and mild cognitive impairment (MCI) participants were successfully differentiated from those with no cognitive impairment [97]. ^{18}F-FDDNP was also used in the assessment of adult Down syndrome patients [98] and football players suspected of CTE [99]. In a non-AD tauopathy such as PSP [99], the retention pattern of ^{18}F-FDDNP in subcortical and midbrain regions followed the known distribution of tau pathology in PSP [100]. It has been shown that ^{18}F-FDDNP also binds prion plaques in Creutzfeldt-Jakob disease [101] and Gerstmann-Straussler-Scheinker disease [102]. Independent direct comparison of ^{18}F-FDDNP with ^{11}C-PIB in monkeys [103] and human subjects highlighted the very limited dynamic range of ^{18}F-FDDNP [104,105]. ^{18}F-FDDNP still remains the only amyloid tracer showing retention in the medial temporal cortex of AD patients, suggesting higher binding affinity of FDDNP to NFT than to Aβ [105]. However, in vitro evaluation of FDDNP in concentrations similar to those achieved

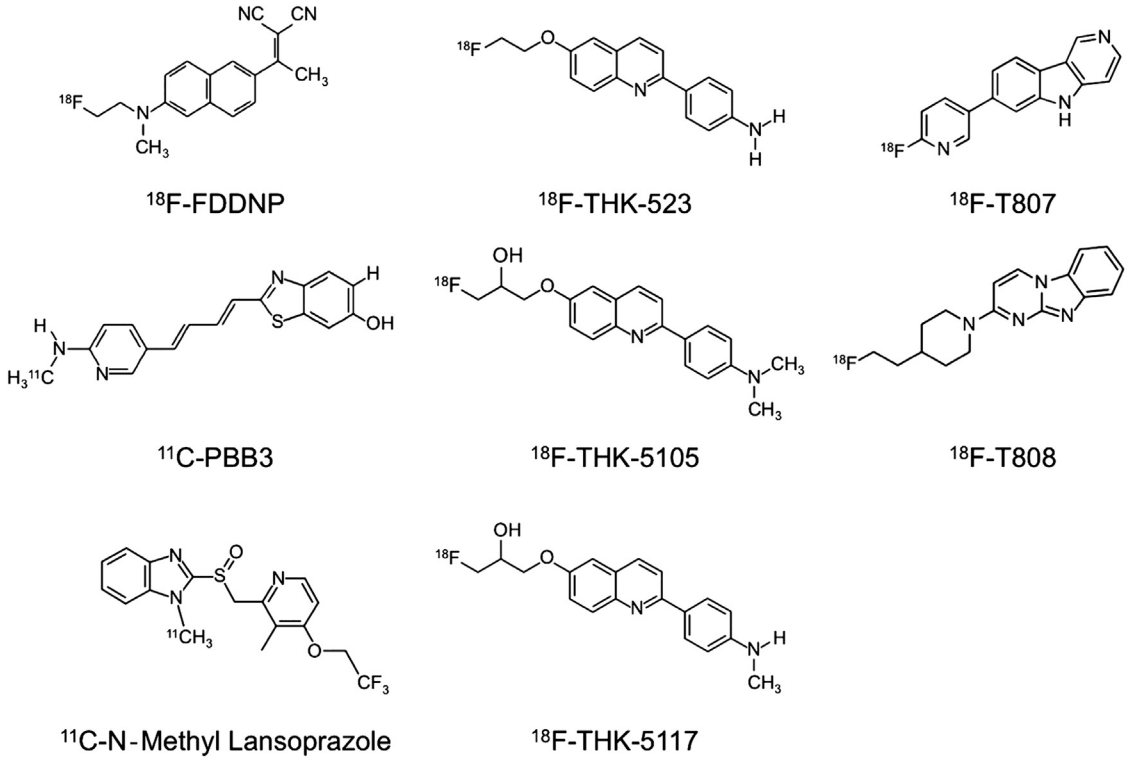

Fig. 1. Chemical structure of currently available tau radiotracers. Most of them have been evaluated in clinical studies.

during a PET scan showed limited binding to both NFT and Aβ plaques [106]. The lack of selectivity of FDDNP for tau might preclude its use in most cases requiring the identification of the misfolded protein responsible of a specific phenotype.

4.2. ^{11}C-lansoprazole

The benzimidazole derivatives lansoprazole and astemizole, based on their in vitro ability to bind Aβ and recombinant tau fibrils, as well as PHF tau isolated from AD brains, were also proposed as potential PHF tau imaging agents [107]. A derivative of lansoprazole, N-methyl-lansoprazole (Fig. 1), with a low nanomolar affinity for tau fibrils was radiolabeled with ^{11}C [108] and tested in mice and nonhuman primates [77]. The initial studies in mice showed no entry of the tracer into the brain, an effect that was reversed by inhibiting the permeability-glycoprotein 1 transporter with cyclosporine. [77] Although studies with rhesus monkeys showed unencumbered entry into the brain [77], no human studies have been reported to date.

4.3. ^{18}F-THK523, ^{18}F-THK5105, and ^{18}F-THK5117

Quinoline and benzimidazole derivatives were identified as candidates for tau imaging tracer by screening small molecules binding to β sheets [74,109,110]. A quinoline derivative, THK523 (Fig. 1), was radiolabeled with ^{18}F and preclinically tested [73]. In vitro saturation binding studies demonstrated that this tracer bound with higher affinity to tau (K_d = 1.67 nM) than to Aβ fibrils (K_d = 20.7 nM). Although autoradiography analysis indicated that ^{18}F-THK523 bound selectively to PHF tau deposits at tracer concentrations [111], fluorescent studies showed that THK523 selectively binds to PHF tau and not Aβ in AD brains, while failing to bind to tau lesions in non-AD tauopathies or to α-synuclein deposits in Parkinson's disease brains [112]. Furthermore, ^{18}F-THK523 can cross the BBB and successfully labeled tau protein deposits in the brain of a tau transgenic mouse model [73]. First-in-human PET studies of ^{18}F-THK523 were performed in AD patients and healthy elderly controls [113]. To assess radiotracer selectivity to tau over Aβ, all participants also underwent a ^{11}C-PiB PET scans. Significantly higher ^{18}F-THK523 retention was observed in the lateral temporal, parietal, orbitofrontal, and hippocampi of AD patients compared with age-matched healthy controls, and ^{18}F-THK523 retention was not associated with the retention of ^{11}C-PiB, suggesting that in vivo ^{18}F-THK523 binds selectively to tau and not to Aβ. Furthermore, ^{18}F-THK523 retention was correlated with cognitive parameters, which is in agreement with postmortem studies showing a strong association of neurofibrillary pathology with dementia severity. Interestingly, in those healthy controls with high Aβ burden as assessed by ^{11}C-PiB, although cortical ^{18}F-THK523 retention was low, ^{18}F-THK523 retention in hippocampus and insula was at the levels observed in AD [113,114]. However, ^{18}F-THK523 retention in gray matter is relatively lower than that in white matter, which does not allow clear visualization of the distribution of tau pathology by visual inspection of PET images [113].

Through compound optimization process, novel ^{18}F-labeled 2-arylquinoline derivatives, ^{18}F-THK5105 and ^{18}F-THK5117 (Fig. 1), were further developed [110]. In vitro binding assays demonstrated higher binding affinity of ^{18}F-THK5105 to synthetic tau fibrils (K_d = 1.45 nM) than to $Aβ_{1-42}$ fibrils (K_d = 35.9 nM). In addition, both ^{18}F-THK5105 (K_d = 2.63 nM) and ^{18}F-THK5117 (K_d = 5.19 nM) showed higher binding affinity for tau-rich AD brain homogenates than ^{18}F-THK523. In an autoradiography analysis of AD brains, laminar distributions of ^{18}F-THK5105 and ^{18}F-THK5117 were observed in the deep layer of temporal gray matter and coincided with NFTs and neuropil threads [110]. Furthermore, the distribution of the binding of these tracers in AD brain sections was completely different from that of ^{11}C-PiB (Fig. 2). First-in-human PET studies of ^{18}F-THK5105 were performed in AD patients and healthy elderly controls [115]. PET images

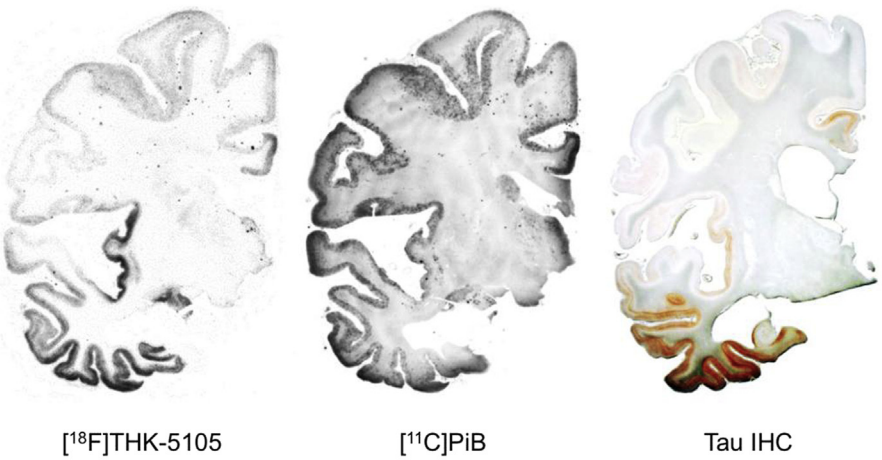

Fig. 2. Autoradiographic studies of contiguous AD hemibrain sections with ^{18}F-THK5105, ^{11}C-PiB, and tau immunostaining, showing the different binding pattern of ^{18}F-THK5105 and ^{11}C-PiB, where ^{18}F-THK5105 binding resembles tau immunostaining (modified from [110]).

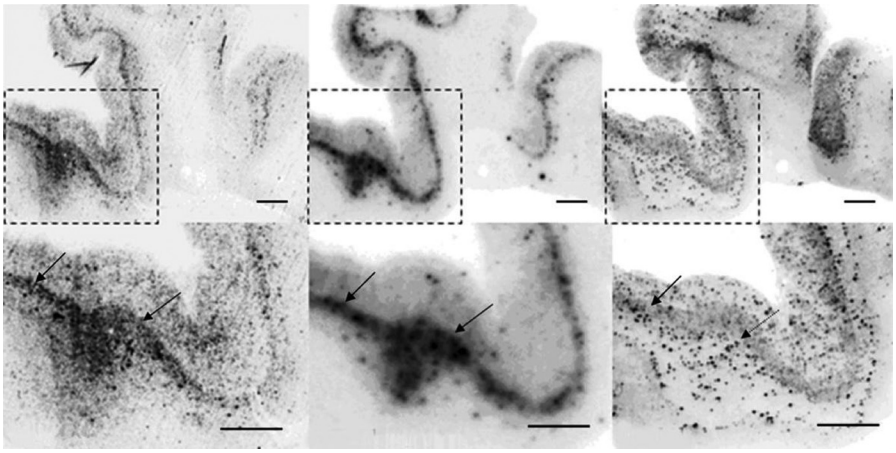

Fig. 3. ^{18}F-T807 autoradiography on brain sections from different groups and its comparison with paired helical filament (PHF) tau and amyloid-β (Aβ) double immunohistochemistry (IHC). ^{18}F-T807 colocalized with PHF tau but not with Aβ plaques. Low (top row) and high magnification from the framed areas (bottom row). Images of PHF tau (left) and Aβ (right) IHC double immunostaining and autoradiogram image (middle) from two adjacent sections (10 mm) from a PHF tau–rich brain (frontal lobe). Positive ^{18}F-T807 labeling colocalized with immunostaining of PHF tau but not with Aβ plaques, as indicated by arrows. Fluorescent and autoradiographic images were obtained using a Fujifilm FLA-7000 imaging instrument (Fuji Photo Film Co., Ltd. Tokyo, Japan). Scale bars, 5 2 mm (Reproduced with permission from *Alzheimer Dement* [116]).

clearly distinguished AD patients from healthy control subjects. In AD patients, ^{18}F-THK5105 retention was observed in those brain areas, such as the mesial and lateral temporal lobes, known to have high tau deposition. Similar to ^{18}F-THK523, ^{18}F-THK5105 retention in AD patients was not associated with ^{11}C-PiB retention but was correlated with dementia severity and brain atrophy [115]. First-in-human PET studies with ^{18}F-THK5117 are currently ongoing. Preliminary data indicate a better pharmacokinetics and better signal-to-noise ratios for ^{18}F-THK5117 than ^{18}F-THK5105.

4.4. ^{18}F-T807 and ^{18}F-T808

Using in vitro autoradiography to screen and characterize several novel benzimidazole pyrimidines derivatives [84], two novel tracers were identified, ^{18}F-T807 [116] and ^{18}F-T808 (Fig. 1), that bind with nanomolar affinity to PHF tau, displaying more than a 25-fold selectivity for PHF tau over Aβ. (Fig. 3) First-in-human ^{18}F-T807 PET studies in AD patients, MCI, and healthy participants have shown that cortical ^{18}F-T807 retention follows the known distribution of PHF tau in the brain [76] where higher ^{18}F-T807 cortical retention was significantly associated with increasing disease severity, consistent with postmortem studies showing the strong association of tau pathology with severity of dementia [117]. In contrast to ^{18}F-T807, human studies with ^{18}F-T808 in three healthy controls and eight AD patients showed better tracer kinetics than with ^{18}F-T807, but substantial deflurination was observed in some cases [118]. A PET-neuropathology correlation in one of the AD patients who died 5 months after undergoing a ^{18}F-T808 PET scan showed that the postmortem fluorescent PHF tau staining was largely in agreement with the observed in vivo ^{18}F-T808 cortical retention in several brain regions [119].

4.5. ^{11}C-PBB3

The latest entry in the roster of tau imaging agents is a ^{11}C tracer: ^{11}C-PBB3 (Fig. 1) [120] based on a phenyl/pyridinyl-butadienyl-benzothiazoles/benzothiazolium (PBB) scaffold. These compounds are characterized by a π-electron conjugated backbone with a specific extent ranging from 13 to 19 Å that apparently allows binding to a broad range of AD and non-AD tau aggregates [120]. Several PBB candidates underwent a thorough preclinical evaluation. Although in vitro autoradiographic studies in AD brain sections showed substantial nonselective binding to plaques and tangles, two-photon laser scanning fluorescence microscopy studies in a tau transgenic mouse model showed rapid clearance of the tracer with selective binding to tau tangles. Similar results were observed in micro-PET studies, showing higher PBB3 binding in the spinal cord of the same transgenic tau mouse model [120]. Preliminary clinical studies in three healthy control volunteers and three AD patients assessed with both ^{11}C-PBB3 and ^{11}C-PiB showed a different pattern of brain retention between the two tracers suggesting that at high specific activities, ^{11}C-PBB3 binds selectively to tau, although marked retention of ^{11}C-PBB3 in the venous sinuses was also observed [120]. A ^{11}C-PBB3 PET study in a patient diagnosed with CBD showed tracer retention in the basal ganglia region, suggesting ^{11}C-PBB3 might bind other non-AD tau conformations.

5. Conclusions

Imaging of tau pathology will allow a more profound insight into tau deposition in vivo, facilitating research into the causes, diagnosis, and treatment of major neurodegenerative conditions such as AD, CTE or some variants of FTLD, in which tau plays a role. Although the underlying mechanism remains unknown, CTE and traumatic brain

injury (TBI) have been postulated as risk factors for the development of AD [16,121]. Does TBI accelerate the development of Aβ pathology, of misfolded tau, or of both? [17,121,122] TBI is a growing problem in both military and civilian populations, and the availability of selective tau tracers to measure tau pathology in humans will help to provide insights concerning the pathophysiology of TBI and CTE. The development of selective tau tracers will allow not only the in vivo assessment of regional tau burden in the brain of AD patients but also a means to evaluate its relation to Aβ deposition [73,76,123–125]. By allowing assessment of the time course of tau accumulation to be correlated with current cognitive impairment and predict cognitive decline, it will assist in the evaluation of the neurobiology of AD and non-AD tauopathies. In conjunction with Aβ imaging, it will improve the specificity of diagnosis and allow for early detection of tau pathology in those individuals deemed at risk of developing AD or CTE.

The development of selective tau radiotracers is faced with several challenges [59]. From a tracer development perspective, a candidate radiotracer should be amenable for high specific activity labeling with ^{18}F or other long-lived radioisotopes to allow a more cost-effective and wider application of the technique. These tracers should be lipophilic, nontoxic, small molecules with a high selectivity for tau, preferably with no radiolabeled metabolites that enter the brain. The current research indicates that the design of tau radioligands with nanomolar or subnanomolar affinity for tau with an appropriate lipophilicity is feasible [73,74,77,116,120]. Although nanomolar or subnanomolar affinity for tau is desirable for selectivity and to provide an adequate signal-to-noise ratio, it might also delay reaching steady state, therefore requiring prolonged scanning times. By the same token, although lipophilicity is necessary for the tracer to penetrate the BBB, high lipophilicity might lead to high nonspecific binding and a reduction of the signal-to-noise ratio [68,69].

There are also challenges associated with the idiosyncrasies of tau deposition [59]. For example, in AD, a tau radiotracer needs to be highly selective to overcome higher Aβ concentrations. Even more relevant, different conformations of the tau aggregates, either due to specific tau isoforms or different posttranslational modifications, might prevent the development of a "universal" tau radiotracer that will recognize all types of tau pathologies. As with Aβ [126], the polymorphism of tau aggregates might affect tracer binding, where a radiotracer that is able to identify PHF tau might not be able to bind, or bind with the same affinity, to other known ultrastructural conformations of tau. This is evident in some Aβ imaging reports in which in some cases of familial autosomal dominant forms of AD [127,128] or early stages of Aβ deposition [129], lacking the typical fibrillar Aβ conformation seen in sporadic AD, there was little PiB retention. Moreover, although Aβ's amino acid sequence in human and nonhuman primates is identical, nonhuman primates do not develop the full AD phenotype, and most importantly, the Aβ plaques do not bind PiB [130]. This illustrates the critical role of fibril polymorphism in regards to tracer binding.

Therapies targeting irreversible neurodegenerative process have a better chance to succeed if applied early. Therefore, early detection of the underlying pathologic process is likely to be critical for therapeutic trials aimed at modulating PHF tau [87,131,132]. Tau imaging, by quantifying tau burden in living patients will allow improved selection of those individuals most likely to benefit from disease-modifying therapy, as well as longitudinal patient monitoring and assessment of efficacy, to properly evaluate whether the treatment response is related to a slowdown or reduction in tau deposition.

There is an increasing body of research focused on the development of tau radiotracers that is allowing to establish which radiotracer characteristics are relevant for selective and specific binding to tau deposits in the brain. There is still much to be done. Development of new leads and new and improved radiotracers will be decisive for further progress in the field. The inception of new tau imaging tracers will make possible a more precise characterization of the role of tau deposits in TBI and neurodegenerative conditions, potentially allowing development and assessment of disease-specific therapeutics that will delay or prevent the onset of cognitive impairment among the civilian population and injured military personnel returning from the battlefield.

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