Selective Tau Imaging: *Der Stand der Dinge**

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Several neurodegenerative diseases are associated with aggregated proteins. A single aggregated protein can manifest as different phenotypes, and a particular phenotype can be caused by different aggregated proteins. The term *tauopathies* categorizes neurodegenerative conditions, such as Alzheimer disease (AD), characterized by the pathologic accumulation of tau. Tau is a phosphoprotein whose major role is the stabilization of microtubules, critical for intracellular transport and cytoskeletal support. In AD, tau hyperphosphorylation leads to tau aggregation in the form of intracellular filamentous inclusions termed neurofibrillary tangles, and although the mechanisms leading to tau hyperphosphorylation and aggregation have not been fully elucidated, tau deposition follows a stereotypical neuroanatomic pathway in the brain (*1*).

Since 2011 (*2*), a steady stream of selective tau tracers for PET has been developed and evaluated in clinical studies (*3–7*). Several groups have implemented and applied ^{18}F-AV1451 (also known as flortaucipir or T807, the most widely used tau tracer to date), in the evaluation of AD and non-AD tauopathies (*8,9*), reporting a robust difference in tau tracer retention between cognitively normal elderly controls and AD patients (Fig. 1) (*7–11*), as well as in atypical AD presentations in which ^{18}F-AV1451 regional retention—not Aβ-amyloid as assessed by PiB—matched the clinical phenotype (*12*). Furthermore, ^{18}F-AV1451 also correlated with cerebrospinal fluid levels of total and phosphorylated tau (*13*). Interestingly, most studies are showing that although mesial temporal tau is high irrespective of Aβ-amyloid levels, high tau in neocortical regions is associated with high Aβ-amyloid, suggesting that detectable cortical Aβ-amyloid precedes detectable cortical tau. Tau imaging studies are showing not only that tau tracer retention follows the known distribution of aggregated tau in the brain (*1*) but also that it has a close relationship with markers of neuronal injury such as ^{18}F-FDG or cortical gray matter atrophy (*14,15*).

It is also important to highlight that folded and aggregated tau is a challenging neuroimaging target, characterized by intracellular location, 6 different isoforms whose prevalence and combinations—linked to specific phenotypes—are subjected to multiple posttranslation modifications, in turn leading to heterogeneous ultrastructural conformations of the aggregates that, in the particular case of AD, are in much lower concentrations than Aβ-amyloid aggregates in the same brain regions (*16*).

Besides ^{18}F-AV1415 (*3,8*), among the first generation of selective tau tracers for PET is ^{11}C-PBB3 (*4*), and the series developed by Tohoku (THK) University in Sendai, Japan, namely ^{18}F-THK5317 (*17*) and ^{18}F-THK5351 (Fig. 1) (*7*). Most of these tau tracers bind to the 3R/4R tau isoform combination prevalent in AD. At this stage, none of these tracers have been validated against pathologic findings, although Avid Radiopharmaceuticals is near the completion of its ^{18}F-AV1451 phase III trial.

Some issues arose when these tracers were first used in clinical studies. Although most AD patients present with both high Aβ-amyloid and high tau (*8,9*), about 15%–20% of subjects diagnosed with probable AD and with high Aβ-amyloid in the brain have low levels of cortical tau tracer retention. Moreover, there are discrepancies between the preclinical in vitro profile and the in vivo human PET studies (*18,19*), as well as some antemortem–postmortem inconsistencies (*20,21*). These inconsistencies do not apply to the 3R/4R tau found in AD but mainly to the straight 4R tau filaments found in progressive supranuclear palsy and corticobasal syndrome. For example, tau imaging studies in progressive supranuclear palsy patients show a distinct pattern of tracer retention in the pallidus, midbrain, and dentate nuclei of the cerebellum (*22,23*), but postmortem studies on some of these patients failed to show binding of the tracer to these structures despite their presenting the typical progressive supranuclear palsy tau lesions (*20,21*). Also, these tau tracers present with various degrees of what has been called "off-target" binding; that is, tracer retention in brain areas not known for having tau deposition, such as the basal ganglia or the choroid plexus (*19,21*). Although some have proposed that these tracers bind to aggregated tau in the choroid plexus (*24*), others have proposed that these tracers bind to other β-sheet aggregated proteins such as transthyretin, to pigments such as lipofuscin, or to the filaments constitutive of Biondi bodies (*18*). Recently, it has been reported that a single oral dose of selegiline blocked about 35% and 50% of the ^{18}F-THK5351 PET signal in the basal ganglia and cortex, indicating that a substantial percentage of the ^{18}F-THK5351 PET signal is due to binding to monoamine oxidase B (*25*), likely yielding ^{18}F-THK5351 not suitable for selective tau imaging studies.

On the other hand, preclinical and preliminary human studies conducted with second-generation tau tracers suggest they are less or not afflicted by off-target binding. Initial human studies of some second-generation tracers such as ^{18}F-RO69558948 have shown less severe off-target binding (*26*), whereas others such as ^{18}F-MK6240 (Fig. 1) or ^{18}F-PI2620 have shown no off-target binding so far (*5,6*).

Despite some still unresolved issues, tau imaging is allowing the assessment of the spatial and temporal pattern of tau deposition and its relation to age, genotype, and cognitive performance, helping

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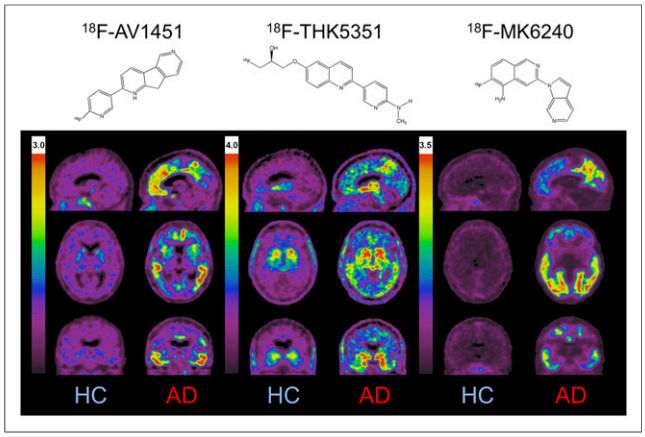

FIGURE 1. (Top) Chemical structures of first-generation (^{18}F-AV1451 and ^{18}F-THK5351) and second-generation (^{18}F-MK6420) tau tracers. (Bottom) Representative sagittal, transaxial, and coronal (top to bottom) PET images showing robust difference in tracer retention between healthy elderly controls (HC) and AD patients. Off-target binding in basal ganglia, midbrain (^{18}F-AV1451 and ^{18}F-THK5351), and choroid plexus (^{18}F-AV1451) is observed in PET images obtained with first-generation tracers, where a significant proportion of ^{18}F-THK5351 signal is due to binding to monoamine oxidase B. No off-target binding is observed in studies obtained with second-generation (^{18}F-MK6420) tracer.

elucidate how tau plays a role in sporadic and familial AD, as well as how it relates to Aβ and other imaging and fluid biomarkers. The accurate in vivo identification of tau deposits will allow disease to be staged, prognosis to be determined, and progression to be tracked, eventually leading—when available—to early disease-specific interventions, by optimizing patient selection, providing proof of target engagement, and eventually monitoring therapeutic effectiveness. Tau imaging has opened a unique window to expand our insight into the pathology of AD and other neurodegenerative conditions.

DISCLOSURE

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