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Selective Tau Imaging: *Der Stand der Dinge**

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Several neurodegenerative diseases are associated with aggregated protein(s), where a single aggregated protein can manifest as different phenotypes, or a particular phenotype can be caused by different aggregated proteins. The term tauopathies categorizes neurodegenerative conditions, such as Alzheimer's disease (AD), characterized by the pathological 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 while the mechanisms leading to tau hyperphosphorylation and aggregation have not been fully elucidated, tau deposition follows a stereotypical neuroanatomical pathway in the brain(*1*).

Since 2011(*2*), a steady stream of selective tau tracers for positron emission tomography (PET) have been developed and evaluated in clinical studies(*3-7*). Several groups have implemented and applied ^{18}F-AV1451 (a.k.a. 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 (*7-11*), (Figure 1) as well as in atypical AD presentations where ^{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 while mesial temporal tau is high irrespective of Aβ-amyloid levels, high tau in neocortical regions is associated with high Aβ-amyloid, suggesting *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 its close relationship with markers of neuronal injury such as ^{18}F-fluorodeoxyglucose or cortical grey matter atrophy(*14,15*).

It is also important to highlight that folded and aggregated tau is a challenging neuroimaging target, characterized by intracellular location, six different isoforms whose prevalence and combinations –linked to specific phenotypes- are subjected to multiple post-translation 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 (for in depth review see (*16*)).

Besides ^{18}F-AV1451(*3,8*), among first-generation of selective tau tracers for PET are the THK tracer series, namely ^{18}F-THK5317(*17*) and ^{18}F-THK5351(*7*), (Figure 1) and ^{11}C-PBB3(*4*). Most of these tau tracers bind to the 3R/4R tau isoform combination prevalent in AD. It should be noted that at this stage none of these tracers have been validated against pathology, although Avid Radiopharmaceuticals is near the completion of its ^{18}F-AV1451 Phase III trial.

Some issues arose when these tracers started to be used in clinical studies. While the vast majority of AD patients present with both high Aβ-amyloid and high tau(*8,9*), about 15-20% of subjects diagnosed as 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 ante-mortem/post-mortem inconsistencies (*20,21*). These inconsistencies do not apply to 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 post-mortem studies on some of these patients failed to show binding of the tracer to these structures despite 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, in other words, tracer retention in brain areas not known for having tau deposition, such as the basal ganglia or the choroid plexus(*19,21*). While some have proposed that these tracers bind to aggregated tau in the choroid plexus(*24*), others have proposed 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 ~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 suggests 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 marked “off-target” binding(*26*), while others such as ^{18}F-MK6240 (Figure 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, its relation to age, genotype and cognitive performance, helping elucidate the role tau plays 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 staging, prognosis and tracking progression, 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 Alzheimer’s disease and other neurodegenerative conditions.

REFERENCES

1. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging.* 1997;18:351-357.

2. Fodero-Tavoletti MT, Okamura N, Furumoto S, et al. 18F-THK523: a novel in vivo tau imaging ligand for Alzheimer's disease. *Brain.* 2011;134:1089-1100.

3. Chien DT, Bahri S, Szardenings AK, et al. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. *J Alzheimers Dis.* 2013;34:457-468.

4. Maruyama M, Shimada H, Suhara T, et al. Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls,. *Neuron.* 2013; 79:1094-1108.

5. Stephens A, Kroth H, Berndt M, et al. Characterization of novel PET tracers for the assessment of tau pathology In Alzheimer's disease and other tauopathies. Paper presented at: AD/PD; 31-Mar-2017, 2017; Vienna.

6. Walji AM, Hostetler ED, Selnick H, et al. Discovery of 6-(Fluoro-(18)F)-3-(1H-pyrrolo[2,3-c]pyridin-1-yl)isoquinolin-5-amine ([(18)F]-MK-6240): A Positron Emission Tomography (PET) Imaging Agent for Quantification of Neurofibrillary Tangles (NFTs). *J Med Chem.* 2016;59:4778-4789.

7. Okamura N, Furumoto S, Harada R, et al. Characterization of [18F]THK-5351, a novel PET tracer for imaging tau pathology in Alzheimer's disease. *Eur J Nucl Med Mol Imaging.* 2014;41:S260.

8. Johnson KA, Schultz A, Betensky RA, et al. Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Ann Neurol.* 2016;79:110-119.

9. Scholl M, Lockhart SN, Schonhaut DR, et al. PET Imaging of tau deposition in the aging human brain. *Neuron.* 2016;89:971-982.

10. Wang L, Benzinger TL, Su Y, et al. Evaluation of tau imaging in staging Alzheimer disease and revealing interactions between beta-amyloid and tauopathy. *JAMA Neurol.* 2016;73:1070-1077.

11. Cho H, Choi JY, Hwang MS, et al. Tau PET in Alzheimer disease and mild cognitive impairment. *Neurology.* 2016;87:375-383.

12. Ossenkoppele R, Cohn-Sheehy BI, La Joie R, et al. Atrophy patterns in early clinical stages across distinct phenotypes of Alzheimer's disease. *Hum Brain Mapp.* 2015;36:4421-4437.

13. Gordon BA, Friedrichsen K, Brier M, et al. The relationship between cerebrospinal fluid markers of Alzheimer pathology and positron emission tomography tau imaging. *Brain.* 2016;139:2249-2260.

14. Xia C, Makaretz SJ, Caso C, et al. Association of in vivo [18F]AV-1451 tau PET imaging results with cortical atrophy and symptoms in typical and atypical Alzheimer disease. *JAMA Neurol.* 2017;74:427-436.

15. Chiotis K, Saint-Aubert L, Rodriguez-Vieitez E, et al. Longitudinal changes of tau PET imaging in relation to hypometabolism in prodromal and Alzheimer's disease dementia. *Mol Psychiatry.* 2017;(In Press:doi:10.1038/mp.2017.1108).

16. Villemagne VL, Fodero-Tavoletti MT, Masters CL, Rowe CC. Tau imaging: early progress and future directions. *Lancet Neurol.* 2015;14:114-124.

17. Chiotis K, Saint-Aubert L, Savitcheva I, et al. Imaging in-vivo tau pathology in Alzheimer's disease with THK5317 PET in a multimodal paradigm. *Eur J Nucl Med Mol Imaging.* 2016;43:1686-1699.

18. Lowe VJ, Curran G, Fang P, et al. An autoradiographic evaluation of AV-1451 Tau PET in dementia. *Acta Neuropathol Commun.* 2016;4:58.

19. Marquie M, Normandin MD, Vanderburg CR, et al. Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. *Ann Neurol.* 2015;78:787-800.

20. Marquie M, Siao Tick Chong M, Anton-Fernandez A, et al. [F-18]-AV-1451 binding correlates with postmortem neurofibrillary tangle Braak staging. *Acta Neuropathol.* 2017;(In Press:doi: 10.1007/s00401-00017-01740-00408).

21. Marquie M, Normandin MD, Meltzer AC, et al. Pathological correlations of [F-18]-AV-1451 imaging in non-alzheimer tauopathies. *Ann Neurol.* 2017;81:117-128.

22. Ishiki A, Harada R, Okamura N, et al. Tau imaging with [18 F]THK-5351 in progressive supranuclear palsy. *Eur J Neurol.* 2017;24:130-136.

23. Perez-Soriano A, Stoessl AJ. Tau imaging in progressive supranuclear palsy. *Mov Disord.* 2017;32:91-93.

24. Ikonomovic MD, Abrahamson EE, Price JC, Mathis CA, Klunk WE. [F-18]AV-1451 positron emission tomography retention in choroid plexus: More than "off-target" binding. *Ann Neurol.* 2016;80:307-308.

25. Ng KP, Pascoal TA, Mathotaarachchi S, et al. Monoamine oxidase B inhibitor, selegiline, reduces 18F-THK5351 uptake in the human brain. *Alzheimers Res Ther.* 2017;9:25.

26. Gobbi LC, Knust H, Korner M, et al. Identification of three novel radiotracers for imaging aggregated tau in Alzheimer's disease with Positron Emission Tomography. *J Med Chem.* 2017.

FIGURE LEGEND

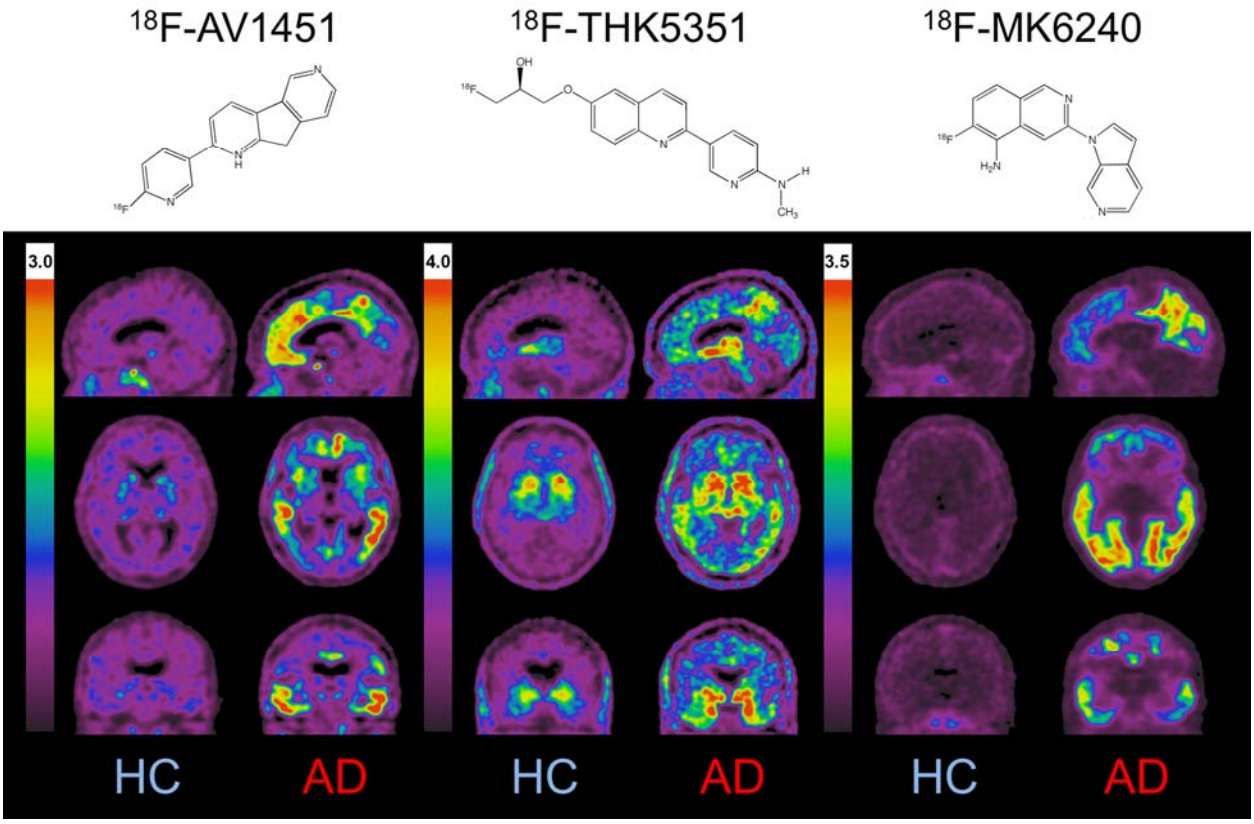

Figure 1. Tau imaging with first and second-generation tau tracers

Top. Chemical structures of first (^{18}F-AV1451 and ^{18}F-THK5351) and second generation (^{18}F-MK6420) tau tracers.

Bottom. Representative sagittal, transaxial and coronal PET images showing a robust difference in tracer retention between healthy elderly controls (HC) and Alzheimer's disease (AD) patients with first (^{18}F-AV1451 and ^{18}F-THK5351) and second generation (^{18}F-MK6420) tau tracers. "Off-target" binding in basal ganglia, midbrain (^{18}F-AV1451 and ^{18}F-THK5351) and choroid plexus (^{18}F-AV1451) is observed in the PET images obtained with first generation tau tracers, where a significant proportion the ^{18}F-THK5351 signal is due to binding to MAO-B. No "off-target" binding is observed in the studies obtained with a second generation (^{18}F-MK6420) tau tracer.