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Short Report

Tau positron emission tomography imaging in tauopathies: The added hurdle of off-target binding

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Abstract Ligands targeting tau for use with positron emission tomography have rapidly been developed during the past several years, enabling the in vivo study of tau pathology in patients with Alzheimer's disease and related non-Alzheimer's disease tauopathies. Several candidate compounds have been developed, showing good in vitro characteristics with respect to their ability to bind tau deposits; off-target binding, however, has also been observed. In this short commentary, we briefly summarize the available in vivo and in vitro evidence pertaining to their off-target binding and discuss the different approaches that are needed for the future development of tau positron emission tomography tracers.

Keywords: Tau PET; Off-target; AV-1451; THK5351; THK5117; THK5317; T807; MAO-B; MAO-A; Flortaucipir

1. Background

Recent advances in positron emission tomography (PET) have made possible the in vivo imaging of pathological forms of aggregated tau in Alzheimer's disease (AD) and related non-AD, or primary, tauopathies. The recognition of a key role for tau pathology in these neurodegenerative diseases, including an established correlation between neurofibrillary tangles, neuronal dysfunction, and clinical features [1], has accelerated the development of several families of tau PET ligands. Although several of these have shown favorable pharmacokinetic characteristics in vitro toward tau deposits and have also been included in AD clinical trials, the in vivo characterization of the tracers' binding in AD and non-AD tauopathies has been especially hampered by ongoing questions pertaining to tracer specificity and off-target binding.

The first published report of "off-target" binding in the context of in vivo tau imaging was based on findings showing that hippocampal retention of [^{18}F]flortaucipir (formerly known as [^{18}F]AV-1451, [^{18}F]T807) in patients with mild cognitive impairment and AD did not increase with disease progression [2]. The authors speculated that this might be due to binding of the tracer to adjacent structures. Subsequent in vitro studies directed at this observation suggested that this putative binding of [^{18}F]flortaucipir in the choroid plexus might be more "on-target" binding due to the identification of structures resembling Biondi "ring" tangles [3], as well as epithelial cells containing tau tangle-like structures and β-pleated sheet proteins deposits [3]; in addition, electron microscopy evidence of paired helical filaments has been reported in this region [4]. Further postmortem studies, however, showed off-target binding of [^{18}F]flortaucipir in neuromelanin-containing cells from the substantia nigra of progressive supranuclear palsy cases [5,6]. In this short commentary, we thus aim to briefly summarize the ongoing research involving tau tracers in different tauopathies, with a focus on highlighting the challenges inherent to their shared limitation of off-target binding.

The authors have declared that no conflict of interest exists.

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2. In vivo tau PET and off-target binding

The three compound families that have thus far been most widely studied include [^{18}F]flortaucipir, [^{11}C]PBB3, and [^{18}F]THK5317 and [^{18}F]THK5351. Studies investigating their retention in vivo in clinically atypical parkinsonian syndromes associated with tau pathology (progressive supranuclear palsy and corticobasal degeneration) reported binding primarily in the basal ganglia and, secondarily, in distinct cortical areas, consistent with the neuropathological literature [7]. To date, however, studies investigating the potential discrimination in terms of retention between these syndromes and age-matched healthy volunteers have produced equivocal results [7,8]. The aforementioned inconsistency probably derives from the off-target signal of those tracers in the basal ganglia [7]; although basal ganglia structures are relatively spared of tau burden in syndromes not related to parkinsonism, the tracer signal of moderate-to-high intensity is detected in healthy volunteers and patients with AD (Fig. 1). Furthermore, the off-target signal in the basal ganglia is reported consistently, although with different intensity, across all tau tracers [7,9]; although binding to monoamine oxidase B (MAO-B) presumably explains most off-target binding in this region, the exact origins have yet to be firmly established. While preliminary evidence has shown similar off-target binding in head-to-head studies [9,10], multitracer antemortem/postmortem designs incorporating these comparisons, as well as blocking experiments, are crucial to fully characterize the binding properties of these ligands.

The only antemortem/postmortem tau PET study published so far showed binding of [^{18}F]THK5351 to MAO-B in AD, a finding consistent with the off-target signal of tau tracers in the MAO-B-rich basal ganglia [11]. In a related in vivo study, administration of an MAO-B inhibitor led to a global decrease in [^{18}F]THK5351 signal, quantified using standard uptake values. When using a standard reference region–based approach (standard uptake value ratios), however, the authors reported no statistically significant decreases in [^{18}F]THK5351 retention [12]. While the lack of significance when using standard uptake value ratios likely reflects a decline in MAO-B availability in the reference region used as a result of the pharmacological challenge, an alternative explanation may involve decreased brain perfusion, and thus delivery of the tracer, possibly via nitric oxide–mediated vasodilation [13]. In this way, a significant drop in brain perfusion could mask small differences in retention before and after the administration of the MAO-B inhibitor. While a recent retrospective study involving Parkinson's disease patients

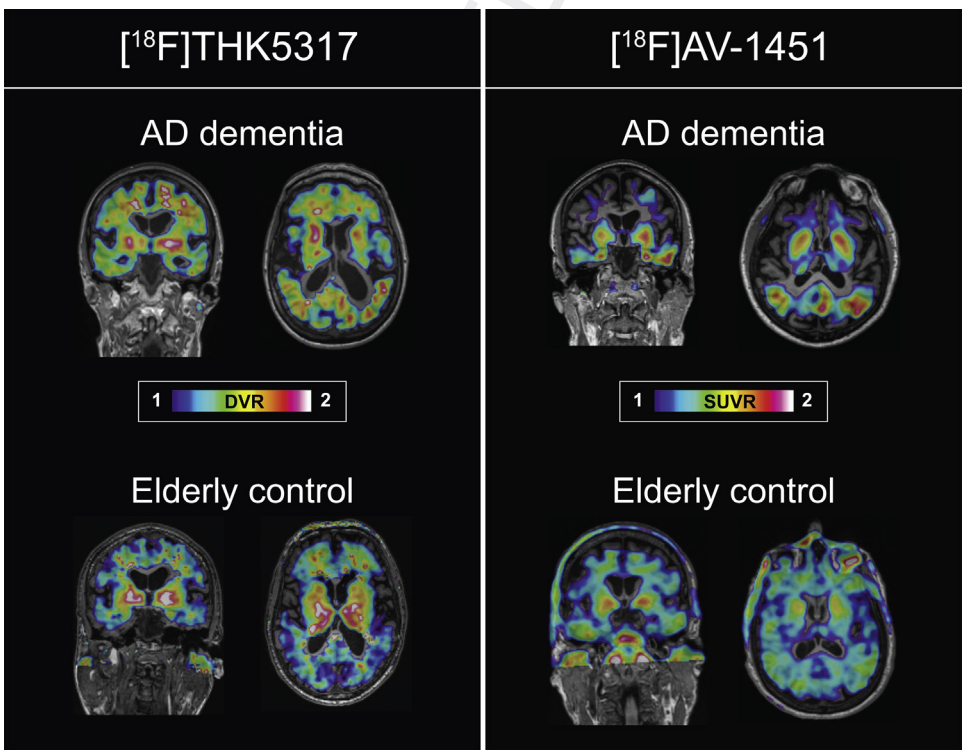

Fig. 1. Representative [^{18}F]THK5317 DVR (40–60 minutes) and [^{18}F]flortaucipir ([^{18}F]AV-1451) SUVR images (75–105 minutes) from AD dementia patients (top row) and elderly controls (bottom row). [^{18}F]flortaucipir images were obtained from the ADNI database (http://adni.loni.ucla.edu/). Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; SUVR, standard uptake value ratio.