



Disclosing tau tangles using PET imaging: a pharmacological review of the radiotracers available in 2021

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Abstract

Neurological symptoms depend on the topography of the lesions in the nervous system, hence the importance of brain imaging for neurologists. Neurological treatment, however, depends on the biological nature of the lesions. The development of radiotracers specific for the proteinopathies observed in neurodegenerative disorders is, therefore, crucially important for better understanding the relationships between the pathology and the clinical symptoms, as well as the efficacy of therapeutical interventions. The tau protein is involved in several neurodegenerative disorders, that can be distinguished both biologically and clinically as the type of tau isoforms and filaments observed in brain aggregates, and the brain regions affected differ between tauopathies. Over the past few years, several tracers have been developed for imaging tauopathies with positron emission tomography. The present review aims to compare the binding properties of these tracers, with a specific focus on how these properties might be relevant for neurologists using these biomarkers to characterize the pathology of patients presenting with clinical symptoms suspect of a neurodegenerative disorder.

Keywords Tau PET · Neurofibrillary tangles · Radiotracers · PET imaging

Introduction

Tauopathies are neurodegenerative diseases characterized by the accumulation of tau protein aggregates in the brain. The most frequent tauopathy is Alzheimer's disease (AD), which involves both tau and amyloid- β (A β) aggregates. Currently, there is no disease-modifying treatment for any tauopathy. For long, neurology research has been hindered by the lack of biomarkers allowing to track disease progression and to evaluate drugs' efficacy rapidly. Without biomarkers accurately reflecting early brain damage: (1) patients with mild clinical symptoms (e.g., non-demented) could hardly

be included in clinical trials, as the pathology could not be ascertained; (2) target engagement could not be monitored in phase II clinical studies, and (3) only clinical outcomes could be used, which are highly variable and requires long follow-up before determining drugs' efficacy. This lack of biomarkers reflecting disease progression has resulted in a research involving unsustainable financial burden with limited benefits to patients.

The development of PET (positron emission tomography) radiotracers targeting A β plaques [1] has enabled the scientific community to disclose AD pathology early and to test target engagement in anti-A β clinical trials. However, A β PET imaging is positive (too) long before clinical decline, and does not correlate well with disease progression as it most often plateau in the clinical stage [2]. In contrast to A β plaques, neurofibrillary tangles (NFT), including aggregated hyperphosphorylated tau, have shown a better correlation with the severity of cognitive impairment in post-mortem studies [3], making tau PET imaging potentially a promising biomarker to track AD progression.

Besides, tau aggregates formed by different tau isoforms (3R/4R) are found in other tauopathies such as Pick's disease (PiD), progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD) (Fig. 1) [4] and the study of NFT

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Fig. 1 Differences in isoforms, filaments types and location for each of the four discussed tauopathies. *PHF* paired helical filaments, *SF* straight filaments. Both are constituents of neurofibrillary tangles in AD

<i>Tau</i>	AD	CBD	PiD	PSP
<i>Isoforms</i>	4R = 3R	4R > 3R	3R > 4R	4R > 3R
<i>Filaments</i>	PHF >> SF	SF >> Twisted	Twisted >> SF	SF
<i>Localisation</i>	Medial temporal lobe, temporal cortex, neocortex	Primary motor cortex, basal ganglia, white matter	Frontal lobe, Medial temporal lobe, basal ganglia	Basal ganglia, diencephalon

density in different brain sections successfully correlates with tauopathies severity [5] in these other diseases as well. Because tau-PET radiotracers could have different affinity for different tau aggregates, and because tau tends to aggregate in different brain regions depending on the tauopathy, tau-PET imaging could also potentially be used for the differential diagnosis between tauopathies (Fig. 1).

Over the past few years, many tau-PET radiotracers have been developed, for imaging both AD and non-AD tauopathies. Several have now proven to have high binding affinity to NFT. In the present article, we will review AV-1451, the first highly specific tau-PET tracer, then the THK family (focusing on the last THK-5351) and PBB3 [6], and finally, we will compare second-generation tracers such as PI-2620, MK-6240 and RO948 [7]. By reviewing the most sensitive and selective tau PET tracer for each type of tauopathies, it could be possible to accurately diagnose patients and include them in the most appropriate clinical trials. Moreover, tau PET tracers could be the best method to evaluate the efficacy of drug on each step of tauopathies, giving us a chance to find, the medication capable of slowing down these diseases.

Methodology

Articles used in this review have been selected on PubMed, NCBI website (National Centre for Biotechnology Information) using the MeSH research engine. The first search was conducted in November 2019 and the last one in July 2021. The articles selection has first been based on broad terms such as “isoforms”, “tau protein” or “Neurodegenerative diseases” to become more and more specific, finally using some tracer names. Moreover, filters were directly added to refine the research (“reviews”, “clinical trial”, “human”, “over the last 5 years”). Because tau-PET tracers is an emergent field, priority was given to most recent reviews and articles, with a focus on those published in the last five to nine years (2012–2021). Afterwards, these different filters were broadened with the aim of leaving out as little as possible of the articles that are the basis of all these papers. After selecting fifty articles, the subsequent selection was based on their

bibliography to find basics chemistry articles about radio-synthesis research and, thus, deepen the research.

Some articles, including those who allowed to harvest epidemiological or more societal data, were found from extended research on different websites (WHO, Ligue Alzheimer ASBL, scientific reviews, etc.). The different figures were achieved with Biorender and the bibliography was created with EndNote X9 using the APA6th style.

Figure 2 presents the number of articles available on the NCBI website for each tracer between the publication of the first of them in 2012 and the closing of this article in July 2021.

Compliance with ethical standards

The authors disclose that they have used ^{18}F -MK6240 in an academic study (Ethical committee approval number: UCL-2016-121). Informed consents were obtained from the participants who provided MK6240-PET images for illustrating the review.

The authors disclose no other financial or non-financial conflict of interest.

Results

Tau protein, tauopathies, and tracer binding sites

Before detailing the characteristics of each tau-PET tracer and understanding the complexity of this field, it is important to describe of the characteristics of the tau protein. First of all, tauopathies are all characterized by hyperphosphorylated τ protein [8]. Then, each tauopathy has a unique signature formed by aggregates comprised of one–six isoforms of the hyperphosphorylated protein. Isoforms are mainly classified into two categories, named 3R and 4R, depending on exon 10 alternative splicing [9]. In physiological conditions, the ratio between these two isoforms is 1:1 but in neurodegenerative diseases, each tauopathy comes with a special ratio such as 3R predominance for PiD, 4R for CBD and PSP and variable 3R/4R ratio for AD in specific brain localization [5]. Furthermore, these ratios are associated

Fig. 2 Graphic representation of the number of publications by year for each analyzed tracer. Data include the different tracer names (e.g., T807 for AV-1451). THK compounds include THK5117, THK5351, etc. Source: www.ncbi.nlm.nih.gov

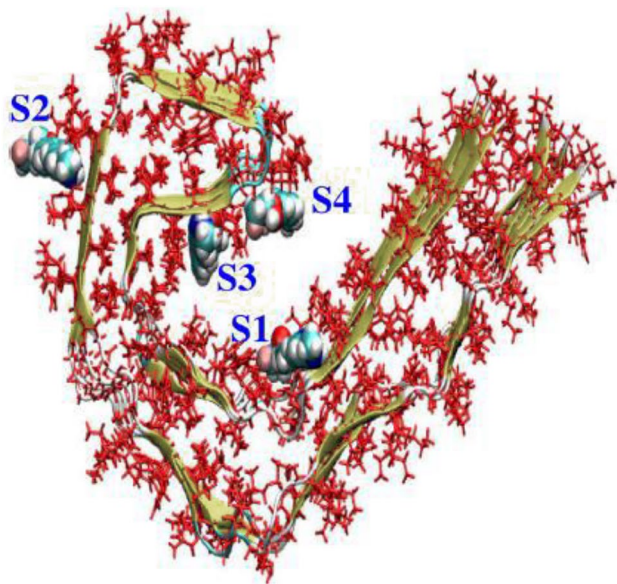
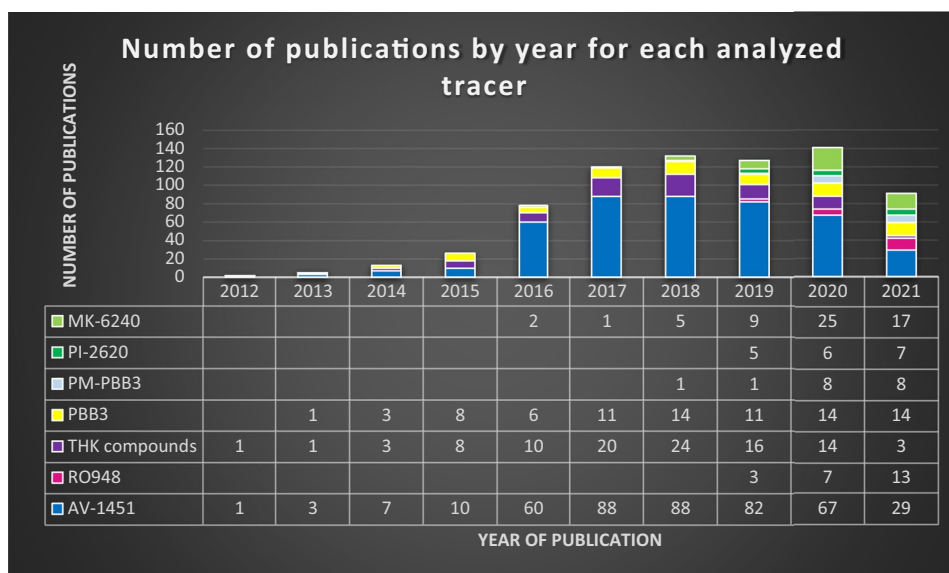


Fig. 3 Schematic three-dimensional representation of an AD tau protofibril, as determined via in silico modeling. S1–S4 indicate the four different binding sites on the AD tau fibril. Source: American Chemical Society Publications, Murugan et al. [11]

with various types of filaments: straight filaments for 4R and helical paired ones for 3R tau [10]. Last but not least, each tracer allows tau protein detection thanks to one of the four binding sites of the protein (S1–S4, Fig. 3) [11].

Different amino acids are involved in the different binding sites:

- Site 1: Pro59, Gly62, Asn63, Lys64.
- Site 2: Glu33, Val34, Lys35.
- Site 3: Gln46, Ser47, Lys48.

- Site4: Arg44, Val45, Gln46.

S2 is in surface, explaining that all the tracers bind to this site. S1, S3 and S4 are specific to one or a few tracers (Table 1).

AV-1451

Binding and physico-chemical properties

AV-1451, also known as T807 or Flortaucipir (FTP), is a pyridoindole derivative with the chemical formula $C_{16}H_{10}FN_3$ [5]. Originally developed for amyloid plaques, the tracer has shown more selective labeling for tau aggregates [12, 13]. In 2013, AV-1451 turned out to be the best tau PET tracer candidate among different pyridoindoles. However, as the molecule had none fluorescent properties and therefore, could not be observed, radioactive tag Fluorine-18 (^{18}F) has been added in order to obtain a PET tracer for medical in vivo imaging. Furthermore, ^{18}F -labeled tracers have a relatively comfortable half-life (109.8 min) for clinical use [14].

With a low molecular weight (262.1 g/mol) and a measured Log P (octanol/water partition coefficient) of 1.67, this tracer is able to cross the blood–brain barrier. In vivo PET imaging in mice also revealed fast wash-out for AV-1451: these studies revealed a nearly full wash-out 25 min after the injection, with an average peak percent injected dose per gram of $4.16 \pm 0.32\%$ ID/g at two minutes after the injection. Fluoride, which is one of the metabolites of T807, tends to accumulate in bones, but this does not seem to disrupt their development and activity [14].

Even if the radiotracer was the best candidate for labeling tau aggregates, it was necessary to prove its specificity.

Table 1 Summary of Tau-PET tracers results in vitro, in vivo (mice/human) and in post-mortem brain sections (human)

Tracers	In vitro results	In vivo results (mice)	In vivo results (human)	Post-mortem results (human)
AV-1451 (^{18}F)	- Bindings to AD τ protofibril: S1, S2 - Study of <i>MAPT</i> mutations: specific of AD type filaments	- Washout nearly full after 25 min - Fluoride (metabolite) accumulates in bones with no disruption of development/activity	- Higher signal for AD patients than for ones with homogeneous 4R tauopathy	- Autoradiography (frontal human brain section): 25.7 times higher signal for PHF-tau than Aβ plaques - Limited results for non-AD tauopathies (except for fronto-temporal lobar generation with aggregates similar to PHFs) - AD brain: bind to neurofibrillary tangles and not to Aβ
THK compounds (^{18}F)	- THK_5351: better signal-to-noise ratio - Bindings to AD τ protofibril: S1, S2, S3	- No really conclusive results in PiD, PSP or CBD	- Much more specific for AD than any other tauopathies	- AD brain: bind to neurofibrillary tangles and not to Aβ
PBB3 (^{11}C)	- Bindings to AD τ protofibril: S1, S4	- Good results for AD, PiD, PSP, CBD	- Good results for AD, PiD, PSP, CBD - Lot of off-target effects for AD	- Allows detection of AD and non-AD deposits - AD aggregates detection but lot of off-target effects
PM-PBB3 (^{18}F)	- Synthesized to overcome PBB3 limitations	- Immune-histochemistry study in rTg4519 Mouse Model: good results (correlated with AT8 presence)	- PSP: increasing binding in region specific to PSP + distinction between α-synucleinopathies and PSP - AD: good results (correlated with glucose metabolism and cognition)	
PI-2620 (^{18}F)	- Bindings to AD τ protofibril: S1, S2		- AD: good expected results $\rightarrow$ more effective to detect cortical τ deposits if Aβ plaques also present - PSP: allows detection (but less specific)	- Washout nearly full after 60 min
MK-6240 (^{18}F)	- Synthesized based on first-generation tracer - Bindings to AD τ protofibril: S1, S2	- No metabolites penetration into the brain	- Strong binding in NFT-rich regions - Negligible binding density in non-AD brain sections	

To do so, autoradiography studies have been carried out on frontal human brain sections. It turned out that the signal obtained from the PHF-tau-rich group was 25.7 times higher than the one from the A β plaques-rich group. This result was then confirmed with double immunostaining [15].

K_d value of AV-1451 was measured for tau aggregates and A β plaques. It turned out that the value for the first one was 14.6 nM, while it could not be measured for the second one, given that the signal could not be separated from the background. All these results confirm the specificity of AV-1451 for tau aggregates [14].

And last but not least, AV-1451 binds to τ , thanks to S1 and S2 [11].

Specificity of the tracer for tau isoforms

In the studies mentioned just before, the brain sections analyzed displaying Alzheimer's type tauopathies [12]. But to find the best tracer to diagnose a given tauopathy, it was necessary to try AV-1451 with other isoforms. As a reminder, Alzheimer's type tauopathies present PHF filaments composed of a mix of the six isoforms (3R/4R), PiD presents 3R filaments and PSP and CBD present 4R filaments [16]. Different studies have analyzed the selectivity of AV-1451 for these three types of aggregates and it turned out that the tracer seems to show best results for the diagnose of Alzheimer's type tauopathies. Indeed, during the study of *MAPT* mutations that alter the splicing of exon 10 generating 4R isoforms, it was shown that AV-1451 was actually specific of Alzheimer's type filaments and not for other ones [17].

An in vivo study shows that the signal is higher with AD patients than patients with a homogeneous 4R tauopathy [18] and in post-mortem studies on non-AD tauopathies, results were very limited excepting for tauopathies caused by mutations of tau causing fronto-temporal lobar degeneration characterized by tau aggregates similar to the PHFs of AD. Concerning PSP, the results are far from those obtained in AD, showing it could be necessary to synthesize tracers more specific to 4R isoforms [17].

Off-target effects

According to their structure, first-generation pyridoindoles derivatives have the property to bind with a high affinity ($pIC_{50}=7.7$) to monoamine oxidases (MAO) found in large quantities in the human brain, especially in the basal ganglia [19]. Please note that AV-1451 is a first-generation tracer. Other tracers from the same class have been modified to avoid these effects on MAO [20]. In addition, AV-1451 also has off-target effects on neuromelanin-containing cells [20] and on choroid plexus [10].

THK5351 and THK compounds

Binding and physico-chemical properties

THK compounds are arylquinolines derivatives detected, thanks to ^{18}F radioactive tag, giving them a decent half-life time (109.8 min) [6]. In the first research on arylquinolines, 2000 molecules were analyzed and a few of them were selected such as THK-523 and THK-5117. Despite their specificity for tau aggregates, they had the particularity to show a high retention in subcortical white matter which increased the PET scan background noise and thus, made the interpretation more complicated or hazardous [21]. To limit this effect, the benzene of the THK compounds was replaced by a purine, developing new arylquinolines derivatives [5].

THK-5351 is the most used THK compounds ($C_{18}H_{20}O_2N_3F$). In addition to its reduced off-target effects, this one has the ability to bind stronger and to dissociate faster to tau aggregates than its predecessors, allowing a better signal-to-noise ratio [21].

And last but not least, THK compounds binds to τ thanks to S1, S2 and S3 [11].

Specificity of the tracer for tau isoforms

Unlike some others, this type of tracers has been studied in different tauopathies. First of all, the studies began on post-mortem AD brain where it has been demonstrated that they actually bind to neurofibrillary tangles and not to A β [22]. Since they were showing good results on AD, THK compounds were then studied in 3 other tauopathies: PiD, PSP and CBD whose isoforms composition are far from AD's one. In fact, neither THK-523 nor THK-5351 have shown conclusive results in these tauopathies in vivo [22]. It is therefore clear that THK compounds, as well as AV-1451, are tracers much more specific to AD than any other tauopathies [19].

Off-target effects

THK compounds show off-target effects on MAO-B ($pIC_{50}=6.8$), present throughout the neocortex [20].

PBB3

Binding and physico-chemical properties

PBB3 is a tracer from the last class of first-generation radiotracer ($C_{16}H_{12}N_3S$) with two particularities in contrast to the others: the radioactive labeling is based on ^{11}C , giving it a shorter half-life time (20.4 min) [6] and it was developed with the aim to bind to most tauopathies [23].

Finally, PBB3 binds to τ , thanks to S1 and S4 [11].

Specificity of the tracer for tau isoforms

PBB3 seems to bind to its own site on tau aggregates which means that PET scan profiles are very different from the first tracers. Because of this difference, PBB3 is the first-generation tracer that can detect the widest range of tau aggregates [19]. This tracer allows indeed the detection of AD deposits as well as non-AD [21]. This detection capacity is actually due to the skeleton of the molecule: a π - σ - π conjugated system with a range from 13 to 19 Å allowing a high affinity for non-AD aggregates [11].

PBB3 has shown good results in AD in human brain sections using AT8 (phosphorylated anti-tau antibodies) as positive control in aggregates detection. However, other tracers already allow PHF deposits type detection with lower off-target effects [21]. The advantage for this tracer is actually its capacity to detect non-AD deposits. Although few studies comparing tracers have carried out, some of them have compared THK-5351 and PBB3 in PiD showing a well better detection of tau aggregates with the second one [23]. The same results have been obtained in PSP and CBD for PBB3 in contrast to other tracers in tauopathy mouse model even if the neuroanatomic location of tau aggregates in these two tauopathies is very specific [23].

What could be a problem for this tracer is the shorter half-life (20.4 min) compared to ^{18}F -labeled tracers (109.8 min). This specificity limits its use to centers with on-site cyclotron production while ^{18}F -labeled tracers can be transported to other centers and allow widespread clinical use.

Off-target effects

PBB3 shows off-target effects not only on α -synuclein but also on MAO and choroid plexus [10]. The α -synuclein binding could be annoying in PSP and CBD diagnose (Parkinsonian syndrome) since they are α -synucleinopathies [24].

A note on PM-PBB3: the second-generation tracer synthesized based on PBB3

^{18}F -PM-BB3 (also known as ^{18}F -APN-1607) is a second-generation tracer synthesized to overcome the limitations of ^{11}C -PBB3, such as the rapid in vivo metabolism and the short half-life [25]. This tracer has been first characterized with dynamic PET scans collected in the rTg4510 [26] Mouse Model of tauopathy between 2 and 11 months of age [25]. In this model, the nine-month-old group showed an increased tracer uptake in the brain cortex, the hippocampus and the striatum regions compared to the six-month-old group. This trend continued for the 11-month-old group

except in the brain cortex. These findings were well correlated with the presence of hyperphosphorylated tau (AT8) in immunohistochemistry study [25].

As far as patients are concerned, two studies have shown the promising imaging capability of PM-PBB3. The first one investigates this tracer for patients with PSP enrolling 3 groups of patients (PSP, α -synucleinopathies and healthy controls). Results showed that not only does PM-PBB3 present increased binding in several subcortical regions specific to PSP but it also allows the distinction between α -synucleinopathies and PSP [27].

The second study investigates this tracer for Alzheimer's disease patients compared to healthy controls. The correlation of the tracer results with the cognition and glucose metabolism in brain suggest that it can sensitively detect tau deposition in AD [28].

While further investigation are still needed for other tauopathies, PM-PBB3 has shown promising results in detecting these pathologies.

PI-2620

Binding and physico-chemical properties

PI-2620 ($\text{C}_{16}\text{H}_9\text{FN}_4$) is a second-generation tracer from the same class of AV-1451 (pyridoindole). Like its predecessor, it is a ^{18}F -labeled tracer. [20].

Since this tracer is relatively recent, studies are still missing concerning some aspects (K_d , comparison to others, etc.). Nevertheless, this tracer's wash-out is as fast as for the others (0.3–60 min depending on the brain section analyzed) and its average peak percent injected dose per gram is about $4.16 \pm 0.32\%$ ID/g at two minutes after the injection [20].

And last but not least, PI-2620 binds to τ , thanks to S1 and S2 [11].

Specificity of the tracer for tau isoforms

Even if this tracer has been the base of a low number of studies, a comparison study between PI-2620 and AV-1451 has been made on AD and PSP patients [29]. Results in AD were expected to be good while the two tracers are from the same class. This study has actually led to two observations: first, the expected results have proven to be accurate with lower off-target effects for the second-generation tracer, giving it a higher specificity for tau aggregates [29]. Second, PI-2620 allowed detection of 4R isoforms in PSP which was a less expected result [30]. Even with weak clinical symptoms, high levels of the tracer were indeed detected in globus pallidus and in black matter. Nevertheless, if the results obtained in AD and PSP are compared, bindings are much less in the second tauopathy [29]. Furthermore, studies have been able

to confirm the binding properties of PI2620 in all the regions specific to AD in the patient's brain [31].

Finally, a recent study showed that PI-2620 is more effective to detect cortical tau deposits if the patient also presents A β plaques. This observation confirms that PI-2620 might be a sensitive tracer to detect A β + AD [32].

Off-target effects

Pyridindoles derivatives tend to bind to MAO-A. Chemical structure of the first-generation (AV-1451) has, thus, been modified to offset this effect [20]. The modification for PI-2620 was one nitrogen add and the modification of the arrangement of the fluorine and the nitrogen on the first aromatic cycle. MAO-A affinity then went from a pIC₅₀ of 7.7 to a non-measurable one [20].

Even with the modifications, PI-2620 still has off-target effects on neuromelanin containing cells including black matter [20].

MK-6240

Binding and physico-chemical properties

MK-6240 (C₁₆H₁₁FN₄) is a second-generation ¹⁸F-labeled radiotracer [7]. As its predecessor, it displays a rapid brain penetration and elimination kinetics, with no penetration of metabolites into the brain [33].

MK-6240 has been synthesized based on first-generation tracer to become an optimized PET imaging agent with

clean off-target profile. Its development required additions and modifications of aza-indole with the aim to optimize blood–brain barrier passage (non-P-gp substrate and good cell permeability), increase affinity for NFTs and reduce nonspecific binding [34].

In Belgium, specifically at both KULeuven and UCLouvain, MK-6240 is the most studied second-generation tracer for AD detection.

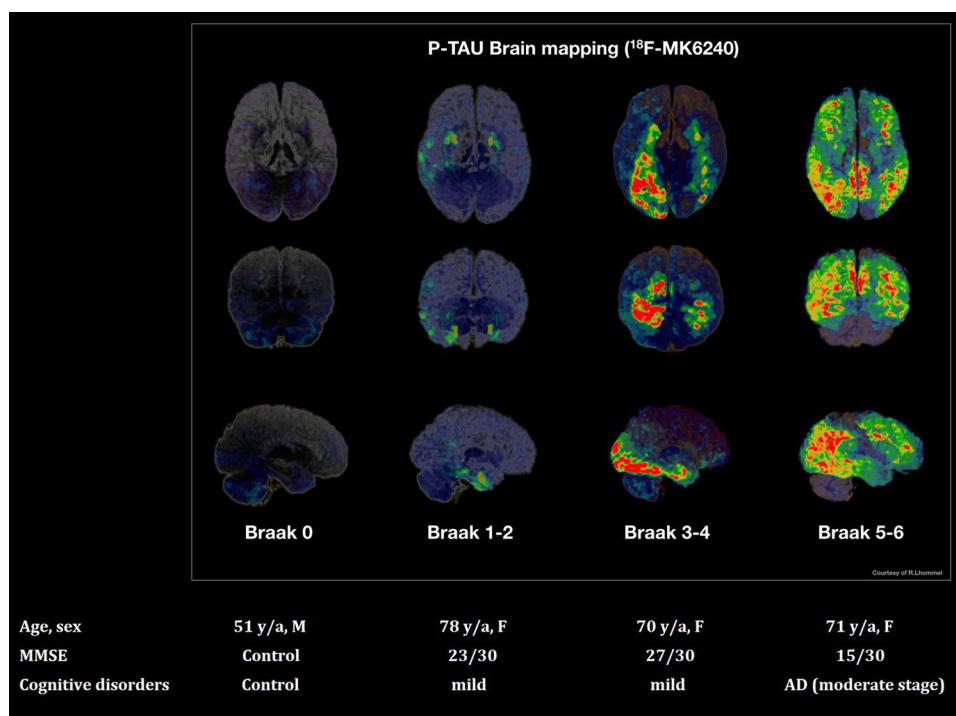
Specificity of the tracer for tau isoforms

Since MK-6240 has been developed to bind to NFT, it is expected to be a very specific diagnostic tool in AD type tauopathies [35]. As expected, its preclinical anatomopathological characterization showed strong binding in NFT-rich regions such as hippocampus and none in neighboring NFT-poor subcortical regions in AD brain sections (Fig. 4) but displayed negligible displaceable binding density in non-AD brain sections [34].

As soon as it was discovered, studies have been conducted to compare MK-6240 and AV-1451. Research reveals that MK-6240 binds to the same tau binding site as AV-1451, S1 and S2 but the second-generation tracer does it with a subnanomolar K_d for NFT (0.26 ± 0.08 nM). Furthermore, all comparative studies between these two have shown that MK-6240 has less off-target effects [34].

Finally, recent study comparing AV-1451, MK-6240 and RO948 showed that target the temporal regions of interest can be used as a differential diagnosis of dementia with high accuracy [36].

Fig. 4 In vivo P-Tau Brain mapping using ¹⁸F-MK6240. Individuals are organized by image-based Braak stages



Off-target effects

Even with all the modifications completed on MK-6240, there are still some off-target effects, such as neuromelanin [10].

Discussion

Tracers can be compared in three aspects: (1) Types of tau aggregates to which the tracer is binding (resulting in detection of different tauopathies), (2) off-target bindings, and (3) half-life time (Table 2).

Tracers' comparisons have limitations. Most importantly, because very few direct comparative studies have been carried out, and the ones that have been published only included two tracers in the same patients [37]. Moreover, these studies mostly used the first-generation tracers [19]. However, with a technique such as PET scan, it is essential to normalize between them obtained results to draw conclusions [19].

Three studies can be highlighted among those that have compared tracers: ^{18}F -THK-5351/ ^{11}C -PBB3/ ^{18}F -AV-1451, ^{11}C -THK-5351/ ^{11}C -PBB3/ ^{11}C -AZD2184, ^{11}C -PBB3/ ^{18}F -AV-1451.

^{18}F -THK-5351/ ^{11}C -PBB3/ ^{18}F -AV-1451

The first study compared the three first-generation tracers on post-mortem AD brains [19]. Different conclusions can be drawn based on this study: on the one hand, they observed competition between THK-5351 and AV-1451 for at least one binding site with the THK compounds having four times more affinity for this site than AV-1451. This common binding site explains bindings of these two tracers on AD brains. On the other hand, PBB3 seemed to bind to a completely different binding site, giving a first clue for differences between tracers [19].

^{11}C -THK-5351/ ^{11}C -PBB3/ ^{11}C -AZD2184 (A β tracer)

A second study compared THK-5351, PBB3 and AZD2184 on AD patients [37]. This research has the great advantage of having been carried out on living patients, making it possible to compare PET and cognitive (MMSE) results and to inject different tracers on the same day in the same patient using the short half-life time of ^{11}C -PBB3. In this study, THK-5351 was shown more specific to AD tau aggregates than PBB3. Moreover, the regional distribution of the THK compounds seems to correlate more with the tau aggregates distribution in AD. On the contrary, PBB3 and the amyloid tracer have some correlations. This observation can lead to a postulate: PBB3 seems to bind preferentially on tau aggregates near amyloid plaques in AD. As a result, it confirmed that PBB3 could be preferably used in non-AD tauopathies allowing a better distribution of the tracer [37].

^{11}C -PBB3/ ^{18}F -AV-1451

A last study compared PBB3 and AV-1451 on post-mortem brain sections from different tauopathies. This one has confirmed that AV-1451 is only specific for AD aggregates and that PBB3 has a greater specificity for all non-AD tauopathies [38].

Comparison of all the tracers studied

The PBB3 specificity to bind to non-AD tau aggregates can be explained by its π - σ - π conjugated system that was synthesized to bind to a maximum of tauopathies [23]. This system is totally absent in the other tracers that were not synthesized to bind to tau aggregates. AV-1451 was indeed first synthesized for amyloid plaques even if it has more affinity for tau aggregates in AD [13]. PI-2620 has also more specificity for tau aggregates as it was synthesized based on its predecessor [20]. Finally, THK compounds and MK-6240 were synthesized with the aim of detecting NFT, aka as AD tau aggregates [39].

Table 2 Tau-PET tracers comparison

	Aggregates binding	Detected tauopathies	Properties	$T_{1/2}$ (min)
			Off-target binding	
^{18}F -AV-1451	4R = 3R	AD	MAO Neuromelanin Choroid plexus	109.8 min
THK compounds	4R = 3R	AD	MAO-B	109.8 min
^{11}C -PBB3	4R = 3R	AD	MAO	20.4 min
	4R > 3R	PiD	α -synuclein	
	4R < 3R	CBD PSP	choroid plexus	
^{18}F -PI-2620	4R = 3R 4R > 3R	AD PSP	Neuromelanin (Black matter)	109.8 min
^{18}F -MK-6240	4R = 3R	AD	Neuromelanin	109.8 min

Another aspect of the comparison between all the tracers is the binding sites on AD tau protein. As a reminder, AD tau protein shows four binding sites (S1–S4) [11]. The study having highlighted these sites also studied the binding affinities of radiotracers at these sites. All tracers bind to S2 and it turned out that AV-1451, PI-2620 and MK-6240 all bind to S1. THK-5351 binds to S1 as well as S3. The S1 binding of THK-5351 was actually analyzed in the first comparative study mentioned previously. The additional link to the S3 site explains the greater affinity of THK-5351 to AV-1451. Finally, PBB3 binds to S1 and S4. Contrary to S3 which binds many tracers, S4 only allows a high affinity binding to PBB3 which reinforces the difference between this tracer and the others [11].

Conclusions

Using a unique tracer to diagnose all tauopathies is obviously impossible. Different tracers were indeed analyzed in this paper and none of them is able to do it even if each one of them is promising in its own field. Nevertheless, we must not neglect the clinical symptoms specific to each tauopathy despite their common physiological basis. The most promising way to confirm the diagnostic of these diseases could, therefore, be to take clinical symptoms as the basis for a hypothetic diagnose that could be confirmed using the most appropriate tracer for the considered tauopathy.

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Availability of data and material All the data used can be traced, thanks to the sources except for the figure on MK6240 for which PET imaging was obtained from patients at Cliniques Universitaires Saint-Luc.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The authors disclose that they have used 18F-MK6240 in an academic study (Ethical committee approval number: UCL-2016-121).

Informed consent Informed consents were obtained from the participants who provided MK6240-PET images for illustrating the review.

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