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PET Agents in Dementia: An Overview

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This article presents an overview of imaging agents for PET that have been applied for research and diagnostic purposes in patients affected by dementia. Classified by the target which the agents visualize, seven groups of tracers can be distinguished, namely radiopharmaceuticals for: (1) Misfolded proteins (ß-amyloid, tau, α-synuclein), (2) Neuroinflammation (overexpression of translocator protein), (3) Elements of the cholinergic system, (4) Elements of monoamine neurotransmitter systems, (5) Synaptic density, (6) Cerebral energy metabolism (glucose transport/ hexokinase), and (7) Various other proteins. This last category contains proteins involved in mechanisms underlying neuroinflammation or cognitive impairment, which may also be potential therapeutic targets. Many receptors belong to this category: AMPA, cannabinoid, colony stimulating factor 1, metabotropic glutamate receptor 1 and 5 (mGluR1, mGluR5), opioid (kappa, mu), purinergic (P2X7, P2Y12), sigma-1, sigma-2, receptor for advanced glycation endproducts, and triggering receptor expressed on myeloid cells-1, besides several enzymes: cyclooxygenase-1 and 2 (COX-1, COX-2), phosphodiesterase-5 and 10 (PDE5, PDE10), and tropomyosin receptor kinase. Significant advances in neuroimaging have been made in the last 15 years. The use of 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) for quantification of regional cerebral glucose metabolism is well-established. Three tracers for ß-amyloid plaques have been approved by the Food and Drug Administration and European Medicines Agency. Several tracers for tau neurofibrillary tangles are already applied in clinical research. Since many novel agents are in the preclinical or experimental stage of development, further advances in nuclear medicine imaging can be expected in the near future. PET studies with established tracers and tracers for novel targets may result in early diagnosis and better classification of neurodegenerative disorders

Abbreviations: 6-OH-BTA-1, See PiB; Aß, Amyloid-ß; AChE, Acetylcholinesterase; AD, Alzheimer's disease; AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASEM, 3-(1,4-Diazabicyclo[3.2.2]nonan-4-yl)-6-^{18}F-fluorodibenzo[b,d] thiophene 5,5-dioxide; AUC, Appropriate use criteria; AV-45, See florbetapir; AZD2184, 5-(6-([Tert-butyl(dimethyl)silyl]oxy)-1,3-benzothiazol-2-yl) pyridin-2-amine; AZD4694, 2-(2-^{18}F-Fluoro-6-(methylamino)-3-pyridyl)benzofuran-5-ol; BAY 94-9172, See florbetaben; BF-227, 2-[2-(2-Dimethylaminothiazol-5-yl) ethenyl]-6-[2-(fluoro)ethoxy] benzoxazole; CFT, 2β-Carbomethoxy-3β-(4-fluorophenyl)tropane; CSF, Cerebrospinal fluid; DASB, 3-Amino-4-(2-dimethylaminomethyl-phenylsulfaryl)-benzonitrile; DED, Deuterium deprenyl; DLB, Dementia with Lewy bodies; DTBZ, Dihydrotetrabenazine; EMA, European Medicines Agency; FACT, Fluorinated Amyloid imaging Compound of Tohoku university, [^{18}F]2-[(2-((E)-2-[2-(dimethylamino)-1,3-thiazol-5-yl]vinyl)-1,3-benzoxazol-6-yl)oxy]-3-fluoropropan-1-ol; FC119S, 2-[2-(N-monomethyl)aminopyridine-6-yl]-6-[(S)-3-[^{18}F]fluoro-2-hydroxypropoxy]benzothiazole; FDA, Food and Drug Administration (United States); FDDNP, 2-(1-(6-[(2-[^{18}F]Fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene) malononitrile; FDG, 2-Fluoro-2-deoxy-D-glucose; FEOBV, (-)-5-[^{18}F]Fluoroethoxybenzovesamicol; FIBT, 2-(p-Methylaminophenyl)-7-(2-[^{18}F]fluoroethoxy)imidazo-[2,1-b] benzothiazole; FPYBF-2, 5-(5-(2-(2-(2-^{18}F-Fluoroethoxy)ethoxy) ethoxy)benzofuran-2-yl)-N-methylpyridin-2-amine; Florbetaben, 4-[(*E*)-2-[4-[2-[2-(2-(^{18}F)Fluoranylethoxy)ethoxy]ethoxy]phenyl]ethenyl] -*N*-methylaniline; Florbetapir, (E)-4-(2-(6-(2-(2-(2-^{18}F-Fluoroethoxy) ethoxy)ethoxy) pyridin-3-yl) vinyl)-N-methylbenzenamine; Flutemetamol, 2-[3-(^{18}F)Fluoranyl-4-(methylamino)phenyl]-1,3-benzothiazol-6-ol; FTD, Frontotemporal dementia; MAO, Monoamine oxidase; MCI, Mild cognitive impairment; MP4A, Methyl-4-piperidyl acetate; NAV4694, See AZD4694; NCFHEB, Norchloro-fluoro-homoepibatidine; NFTs, Neurofibrillary tangles; NMPB, N-methyl-4-piperidyl benzilate; PBB3, Pyridinyl-butadienyl-benzothiazole 3; PD, Parkinson's disease; PiB, Pittsburgh Compound-B, N-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole; PMP, Methyl-piperidin-4-yl propionate; RAGE, Receptor for advanced glycation endproducts; SB-13, 4-*N*-Methylamino-4′-hydroxystilbene; UCB-J, (*R*)-1-((3-(methyl-^{11}C)pyridin-4-yl)methyl)-4-(3,4,5-trifluorophenyl) pyrrolidin-2-one; vAChT, Vesicular acetylcholine transporter; VD, Vascular dementia; vMAT2, Vesicular monoamine transporter type 2

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and in accurate monitoring of therapy trials which involve these targets. PET data have prognostic value and may be used to assess the response of the human brain to interventions, or to select the appropriate treatment strategy for an individual patient.
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Introduction

This introductory review article on molecular imaging in dementia provides an overview of imaging agents for PET that have been used to study biochemical processes in the human brain that are associated with cognitive impairment. Such tracers can be classified in at least seven groups: (1) agents for visualization of misfolded proteins (ß-amyloid plaques and tau neurofibrillary tangles [NFTs]), (2) agents for visualization of neuroinflammation, (3) tracers for the cholinergic system (various targets), (4) tracers for monoamine neurotransmitter systems, including agents which target monoamine oxidase B and visualize astrogliosis, (5) agents for visualization of synaptic density which target the synaptic vesicle glycoprotein 2A, (6) metabolic tracers (particularly 2-[^{18}F]fluoro-deoxyglucose), and, finally, (7) experimental radioligands which target various processes. In the following pages, we will briefly discuss the most prominent compounds in each of these tracer groups. We will limit our overview to imaging agents that have been applied in human subjects since the number of those agents is already very large. For further information on the clinical value and implications of PET imaging in various dementia conditions, the reader may consult several book chapters that were recently published[1-7] and the other contributions to this issue of *Seminars in Nuclear Medicine*.

Imaging of Misfolded Proteins

PET Agents for Amyloid-ß

Alzheimer's disease (AD) is associated with the progressive deposition of amyloid-ß (Aß) peptides in the brain. These peptides accumulate in the extracellular space between neurons, resulting in the formation of senile plaques.[8-10] The accumulation of Aß is assumed to be the consequence of a dysregulation in the synthesis and secretion of an endogenous compound of the brain, the amyloid precursor protein (APP), of which the physiological function is unknown.[11] APP is normally cleaved by the enzyme α-secretase, which results in the formation of APP-α, a soluble and nontoxic metabolite. In the diseased brain, APP is cleaved by the sequential action of two enzymes, ß-secretase and γ-secretase, resulting in the formation of Aß peptides, mainly the isoforms Aß1-42 and Aß-1-40.[12-16] Oligomers of these peptides are toxic to neurons[17] and they have a tendency to aggregate and form plaques.[18] The deposition of Aß plaques in the brain is considered as a necessary, initiating event in the development of AD,[19-22] although subsequently occurring processes such as the deposition of phosphorylated tau proteins in NFTs and particularly the death of neurons finally lead to severe cognitive impairment.[22,23] Cognitive dysfunction is closely correlated with the amount of tau NFTs, but not, or much less closely, with the number of Aß plaques.[24-27] The deposition of Aß plaques in the human brain precedes the onset of clinical symptoms.[8,25,28] Imaging agents that selectively bind to Aß may therefore be valuable for the accurate diagnosis of AD and other neurodegenerative diseases associated with Aß deposition, the monitoring of disease progression and the evaluation of the response of patients to anti-amyloid therapies.

Positron-emitting imaging agents for amyloid-ß have been available for almost 15 years (see Table 1, Figs. 1 and 2). Initial studies employed either [^{18}F]FDDNP or [^{11}C]PiB. [^{18}F]FDDNP binds to both amyloid plaques and tau NFTs, thus, the tracer is not specific for a single type of misfolded protein[29-32] and its affinity to amyloid-ß appears to be lower than that of [^{11}C]PiB.[33] Another drawback of [^{18}F]FDDNP is the formation of radioactive metabolites that may enter the brain and may cause a uniformly distributed, high background signal.[34,35] In contrast to [^{18}F]FDDNP, [^{11}C]PiB proved to be a successful tracer of which the accumulation in the human brain is more closely correlated with the amyloid-ß load,[36-40] since the affinity of [^{11}C]PiB to amyloid plaques is considerably higher than its affinity to NFTs.[41] [^{11}C]PiB can better differentiate between patients with AD, patients with mild cognitive impairment (MCI) and healthy controls than [^{18}F]FDDNP.[42] Until now, most PET studies of Aß deposition in the human brain have employed [^{11}C]PiB. However, because of the short half-life of ^{11}C (20.4 minutes), [^{11}C]PiB cannot be distributed to remote imaging centers and thus, the tracer is only available in centers that dispose of an on-site cyclotron.

Several other PET tracers for amyloid-ß were later developed. These include the second-generation radiofluorinated agents [^{18}F]florbetaben,[75] [^{18}F]flutemetamol,[70] [^{18}F]BF-227[55], and [^{18}F]florbetapir,[66] besides the [^{11}C]-labeled probes [^{11}C]BF227[52] and [^{11}C]SB-13.[74] Radiofluorinated tracers have the advantages of a longer physical half-life of the positron emitter (109.8 minutes), which allows distribution to remote imaging centers. The brain uptake of [^{18}F]flutemetamol (Vizamyl),[71] [^{18}F]florbetapir (Amyvid),[67] and [^{18}F]florbetaben (Neuraceq)[64] was shown to correspond closely to histologically measured Aß deposition, and these three tracers have been approved by the US Food and Drug Administration and European Medicines Agency for clinical PET studies in patients.

Third-generation amyloid tracers include radiofluorinated [^{18}F]NAV4694 (= AZD4694),[49-51] [^{18}F]FPYBF-2,[72,73] [^{18}F]

Table 1 ß-Amyloid Tracers

Name	Radio-Nuclide	Synonym	Initial Keynote Studies	Advantages/Pitfalls
AZD2184	^{11}C		43-47	
AZD2995	^{11}C		46	
AZD4694	^{11}C	NAV4694	48	
AZD4694	^{18}F	NAV4694	49-51	
BF-227	^{11}C		52-54	Nonspecific binding in white matter and skull.
BF-227	^{18}F		55	Binds both to amyloid plaques and neurofibrillary tangles.
FACT	^{18}F		56,57	
FC119S	^{18}F		58,59	
FDDNP	^{18}F		30,31,33-35,42,60,61	Radiometabolite enters the brain. Binds both to amyloid plaques and neurofibrillary tangles.
FIBT	^{18}F		62,63	
Florbetaben	^{18}F	FBB, AV-1, BAY94-9172	63-65	Approved for clinical studies in patients.
Florbetapir	^{18}F	AV45, Amyvid	66-69	Approved for clinical studies in patients.
Flutemetamol	^{18}F	3'-F-PiB	70,71	Approved for clinical studies in patients.
FPYBF-2	^{18}F		72,73	
PiB	^{11}C	6-OH-BTA-1	36-41	Approved for clinical studies in patients.
SB-13	^{11}C		74	

FACT,[56] [^{18}F]FIBT,[62,63] and [^{18}F]FC119S,[58,59] besides the [^{11}C]labeled agents [^{11}C]AZD2184,[43–45] [^{11}C]AZD2995,[46] and [^{11}C]AZD4694.[48] [^{18}F]AZD4694 has been reported to provide data that are virtually identical to those of [^{11}C]PiB, but the tracer offers the advantage of a longer physical half-life.[51] [^{18}F]AZD4694 and [^{11}C]AZD2184 display less binding in white matter than [^{18}F]florbetaben, [^{18}F]flutemetamol and [^{18}F]florbetapir.[51,47] This suggests that tracers of the third-generation can detect smaller and more subtle ß-amyloid deposits than imaging agents of the second-generation.

Some important results of Aß imaging were the following:

i. *Time course:* Aß deposition in the human brain begins in the preclinical stage, increases during the stage of MCI, and peaks around the time that AD is diagnosed, but shows no further increase when dementia progresses.[76,77] However, according to a recent report a small increase of Aß deposition is detectable during the AD stage, if the PET data are corrected for the partial volume effect.[78]
ii. *Exceptions:* Some patients show AD-like cognitive and behavioral symptoms and AD-like patterns in FDG-PET or structural MRI, but their Aß PET scan results are negative.[68,79-83] On the other hand, subjects may show normal cognitive function at advanced age and yet have considerable Aß deposition in their brains.[68,84,85] These findings suggest that the pathological processes underlying dementia are more diverse and more complex than the Aß hypothesis suggests.
iii. *Other diseases:* Aß deposition occurs not only in AD, but also in other neurodegenerative disorders, such as Lewy body dementia (DLB).[86] These disorders often have a mixed pathology.
iv. *Secondary phenomenon:*Various studies have indicated that not Aß plaques, but misfolded Aß oligomers trigger the neurodegenerative process in AD.[17,22,87] Since the current PET tracers target Aß plaques, the existing imaging agents may visualize a secondary phenomenon rather than the primary process that is causing the disease.
v. *Prognosis:* Despite the caveats mentioned above, many studies have reported that PET scans of Aß deposition can predict whether subjects with MCI are likely to progress to AD.[60,61,65,88-93] PET scans of amyloid deposition may be combined with MRI scans of brain atrophy[94] or FDG-PET scans of cerebral glucose metabolism[95] to provide prognostic information. However, some authors judge that the sensitivity and specificity of second generation PET tracers like [^{18}F] florbetapir are insufficient to warrant the routine use of such tracers in clinical practice.[69] Clinical trials of drugs aimed at suppressing the formation of amyloid-ß in the human brain have led to disappointing results.[96-98] Thus, Aß imaging may be less useful for therapy monitoring than was expected when the first successful PET tracers for amyloid plaques were developed.

An extensive review on the imaging of Aß in aging, AD, and other neurodegenerative conditions has recently appeared.[2]

Aß Imaging in Clinical Practice

The advent of molecular and neuroimaging biomarkers in dementia research had an impact on the definition of the diagnostic criteria for AD. These have been revised and now recommend the inclusion of biomarkers for a final diagnosis[99-102] since biomarker values serve an important role in recognizing atypical AD manifestations (eg, memory impairments following biomarker evidence).

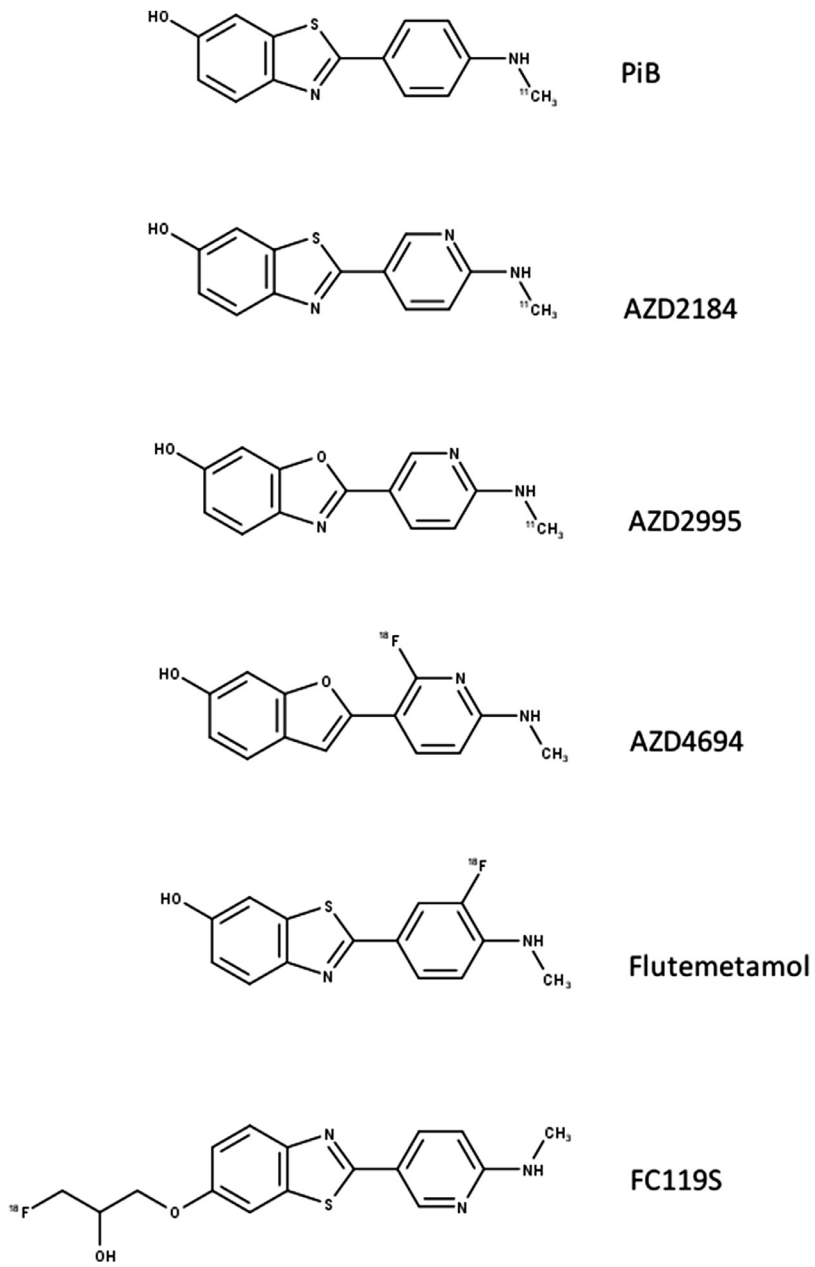

Figure 1 PET tracers for amyloid-ß structurally related to PiB (Pittsburgh compound B).

Whether PET imaging has clinical utility has been an object of discussion. Its impact is mostly measured in terms of diagnostic accuracy, diagnostic confidence, and therapeutic outcome. Cerebrospinal fluid (CSF) analysis seems to still be the molecular biomarker of choice for AD, probably due to its relatively low costs, although an increasing number of studies reports high concordance between CSF and PET measures concerning their diagnostic accuracy.[103,104]

Most findings examining the relevance of PET in daily clinical practice were focused on amyloid PET. According to the Amyloid Imaging Taskforce, use of amyloid PET is appropriate in three cases (appropriate use criteria – AUC): (1) persistent or progressive unexplained MCI, (2) dementia with unusual clinical progression or etiologically mixed manifestation, and (3) dementia with an early age of onset (<65).[105] A recent review reports amyloid PET to have added value to the standard diagnostic procedures in case of atypical patients and in a multidisciplinary setting.[106] Research investigating its clinical utility has been conducted with patients meeting the AUC. This research was clustered in two large studies, namely the "Imaging Dementia—Evidence for Amyloid Scanning" study in the USA and the Amyloid Imaging to Prevent AD study in Europe (which is still ongoing). Imaging Dementia—Evidence for Amyloid Scanning, a large multisite and practice-based study, reported PET results to contribute to a post-PET management plan, mostly concerning the use of AD drugs.[107,108] Amyloid Imaging to Prevent AD showed both amyloid-positive and amyloid-negative results to change the etiological diagnosis, diagnostic confidence, and ultimately patient treatment.[109]

A naturalistic study including 211 patients who met the AUC was aimed at assessing diagnostic confidence and treatment

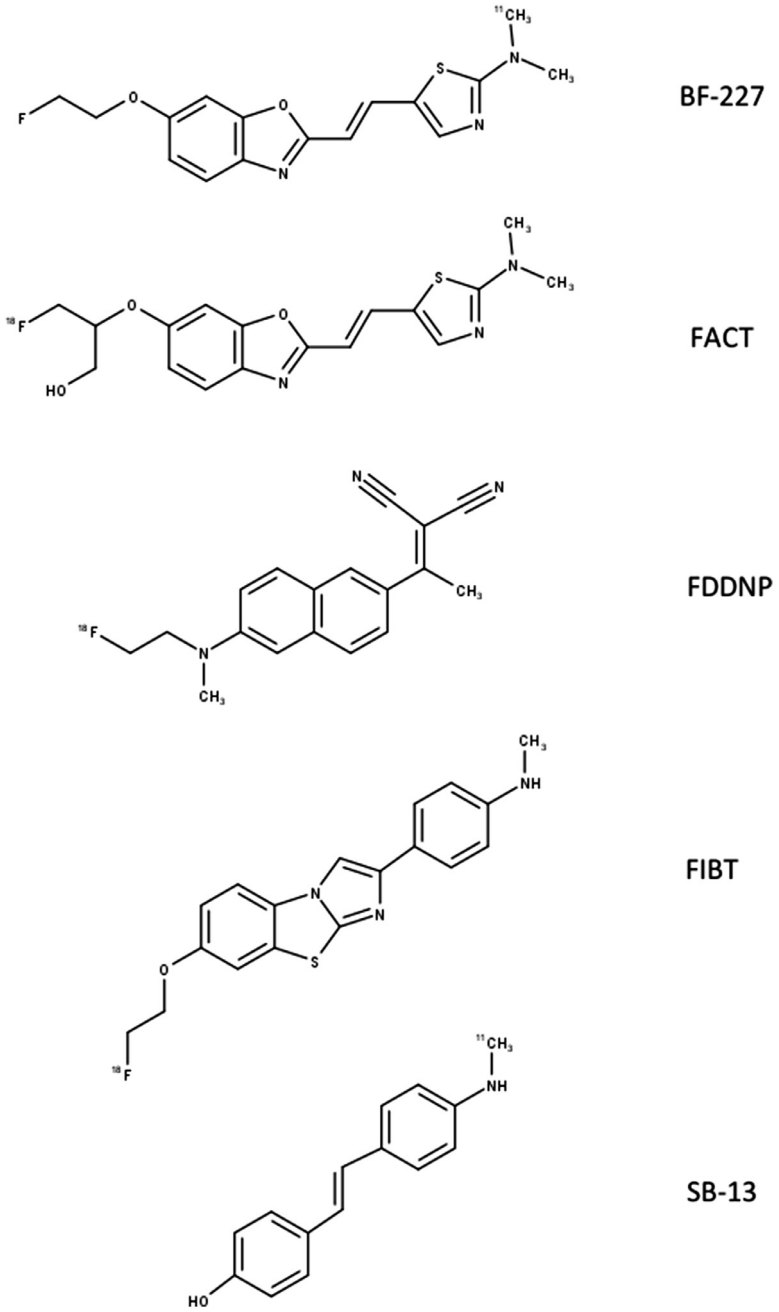

Figure 2 Additional PET tracers for amyloid-ß (structurally different from PiB).

plan, through the re-evaluation of possible diagnosis by a neurologist once amyloid-PET results were available. This study concludes that this technique is associated with an improvement in diagnostic confidence and therapeutic management.[110]

PET Tracers for Tau

The accumulation of tau protein in the form of NFTs is a second hallmark and possible causative factor of AD,[100,111] and is also considered as a potential target for treatment.[112-114] In the physiology of the healthy brain, tau is involved in the stabilization of microtubuli.[115,116] Such microtubuli are present in the axons of neurons, where they ensure axonal transport. The affinity of tau for microtubuli is regulated by phosphorylation. Since microtubuli need to be assembled and disassembled, tau phosphorylation may be an important regulatory mechanism. Excessive phosphorylation of tau occurs in AD, resulting in excessive detachment of the protein from microtubuli and aggregation of tau in the form of NFTs.[111,115] In contrast to amyloid plaques, such tangles are not deposited in the interneuronal space but intracellularly, within the neurons. Hyperphosphorylation of tau and the accumulation of NFTs is supposed to impair neuronal function and to ultimately result in neuronal death. This hypothesis is supported by the observation that cognitive dysfunction in Alzheimer patients is closely correlated with the amount of tau NFTs in their brains.[24-27,117-122] Regional tau

deposition is inversely correlated with regional cerebral glucose metabolism, high levels of tau being accompanied by reduced metabolism.[123]

The precise mechanisms causing pathological accumulation of tau are not completely understood, although hyperphosphorylation seems to play an important role. Tau aggregation is not limited to AD, but occurs also in other neurodegenerative diseases, such as progressive supranuclear palsy, corticobasal degeneration, Pick's disease, hereditary frontotemporal dementia (FTD), and parkinsonism linked to chromosome-17.[124] In AD, tau is accumulated together with Aß, but Aß accumulation is lacking in some other "tauopathies."[124] In FTD, tau deposition can be either present or absent.[125] Tau can be accumulated in a surprising variety of ways: as different isoforms (three or four microtubule-binding repeats, termed 3R or 4R), as different three-dimensional structures (straight and paired helical filaments, neurofibrils, pretangles, mature tangles, coiled bodies), in different cells (neurons or glia), and in different regions of the brain.[126-130]

Since the accumulation of NFTs is an important aspect of the pathophysiology of various neurodegenerative diseases, many research efforts have focused on the development of PET imaging agents for hyperphosphorylated tau. Successful agents may lead to improved understanding of disease mechanisms, could facilitate an accurate tauopathy diagnosis, might be used to assess disease severity and progression, and might offer the possibility of longitudinal monitoring of anti-tau therapies.[131] The development of such agents is even more challenging than the development of Aß probes, for various reasons:

i. Because of the intracellular location of NFTs, tau imaging agents must cross not only the blood-brain barrier, but also the neuronal or glial cell membrane.
ii. The target, hyperphosphorylated tau, is present at much lower densities in the diseased human brain than Aß. Thus, tau tracers must bind with high *affinity* to visualize their target.
iii. Since in many diseases Aß is present in great excess compared to hyperphosphorylated tau, tau probes should also have a great *selectivity* for their target in order to not cross-react with Aß.
iv. It is difficult to develop a probe that binds to the many different forms of tau with approximately equal affinities.[116,132-134]
v. Several promising ligands for aggregated tau show considerably affinity for other targets in the brain, particularly monoamine oxidase[135-137] and neuromelanin,[138-140] thus, they are not sufficiently tau-specific.

The first radiotracers for tau were already reported in 2005. [^{11}C]BF-158[141] and [^{18}F]THK523 were probes of the

Table 2 Tau Tracers

Name	Radio-Nuclide	Synonym	Initial Keynote Studies	Pitfalls/Advantages
BF-158	^{11}C		141	Only in vitro and mice data
Flortaucipir	^{18}F	AV-1451, T807, FTP	152-154	Binds to neuromelanin,[134,138-140] MAO-A,[135-137] hemorrhagic lesions.[134]
GTP-1	^{18}F	Genentech Tau Probe 1	155,156	Less defluorination than T808, off-target binding negligible.
JNJ-067	^{18}F		157	
JNJ-311	^{18}F	JNJ64349311	157,158	Low affinity for MAO[137] Binds to aggregated tau in slices from AD but not PSP or CBD brains.[158]
MK-6240	^{18}F		159-164	Low affinity for MAO [137]
N-Methyl-Lansoprazole	^{11}C		165	See the following agent.
N-Methyl-Lansoprazole	^{18}F		166	Insufficient uptake, no specific signal in human brain [167]
PBB-3	^{11}C		168-171	Radiometabolites enter brain.[170] Binds to other target than tau.[171] Low dynamic range.[172]
PM-PBB3	^{18}F	APN-1607	173-175	Improved dynamic range, negligible off-target binding.[173]
PI-2620	^{18}F		176-178	Reduced affinity for MAO compared to flortaucipir.[137]
Ro-643	^{11}C	Ro6931643	179,180	Lower target-to-nontarget ratio in human brain than Ro-948.
Ro-948	^{18}F	Ro6958948	179-183	Best in vivo results of the three Roche compounds.
Ro-963	^{11}C	Ro6924963	179,180	Lower target-to-nontarget ratio in human brain than Ro-948.
T808	^{18}F	AV-680	184-186	Rapid defluorination.
THK-523	^{18}F		38,142,144	High retention in white matter makes visual inspection difficult.[144]
THK-5105	^{18}F		143,145,146	As THK-5117.
THK-5117	^{18}F		143,147,148	High inter- and intra-case variability [187]
THK-5317	^{18}F	(*S*)-[18F]THK-5117		As THK-5117?
THK-5351	^{18}F	(*S*)-[^{18}F] THK-5151	149-151	Binds strongly to MAO-B[140,188-191]
TKF	^{11}C		192	Analog of THK523, only mouse data available.

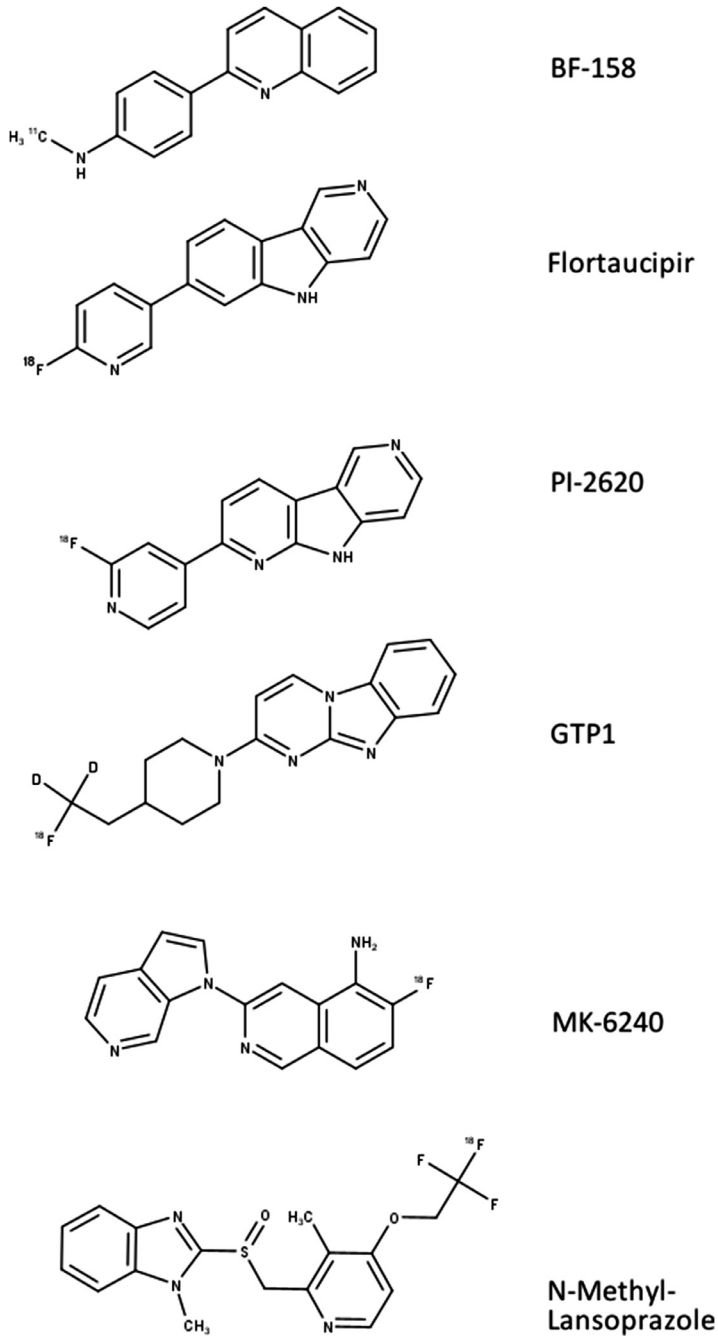

Figure 3 PET tracers for tau (neurofibrillary tangles). [^{18}F]GTP-1 is the deuterated equivalent of [^{18}F]T808.

early generation (see Table 2 and Figs. 3-5). [^{18}F]THK523 showed specificity for tau compared to Aß in brain autoradiography[38,142,143] and increased cerebral uptake in tau transgenic mice compared to wild-type mice.[142] The tracer demonstrated elevated uptake in several brain areas of AD patients compared to healthy controls,[144] but also a very high retention in white matter that prevented the analysis of PET images by visual inspection and hampered the use of [^{18}F]THK523 in a clinical setting.[144] Structurally modified analogs of THK523 were prepared with the aim of increasing the affinity of the derivatives for tau and to reduce their retention in white matter. These attempts resulted in the production of [^{18}F]THK5105,[143,145,146] [^{18}F]THK5117[143,147,148] and [^{18}F]THK5351,[149-151] which bind more avidly to tau than [^{18}F]THK523. The last of these three derivatives showed the best pharmacokinetics, the lowest white matter retention and the highest signal-to-noise ratio.

Agents structurally different from the first generation ones were [^{18}F]flortaucipir (also known as AV-1451, T807, and FTP,[152-154]) and lansoprazole analogs[166,165] that were either labeled with ^{11}C or with ^{18}F. Methylation of an NH-group in lansoprazole resulted in N-methyl-lansoprazole, a ligand with sub-nM affinity for tau.[193] In preclinical studies in mice, N-[^{11}C]methyl-lansoprazole showed a very low brain uptake due to active efflux of the tracer by P-glycoprotein (P-gp) at the blood-brain barrier. However, in nonhuman primates,

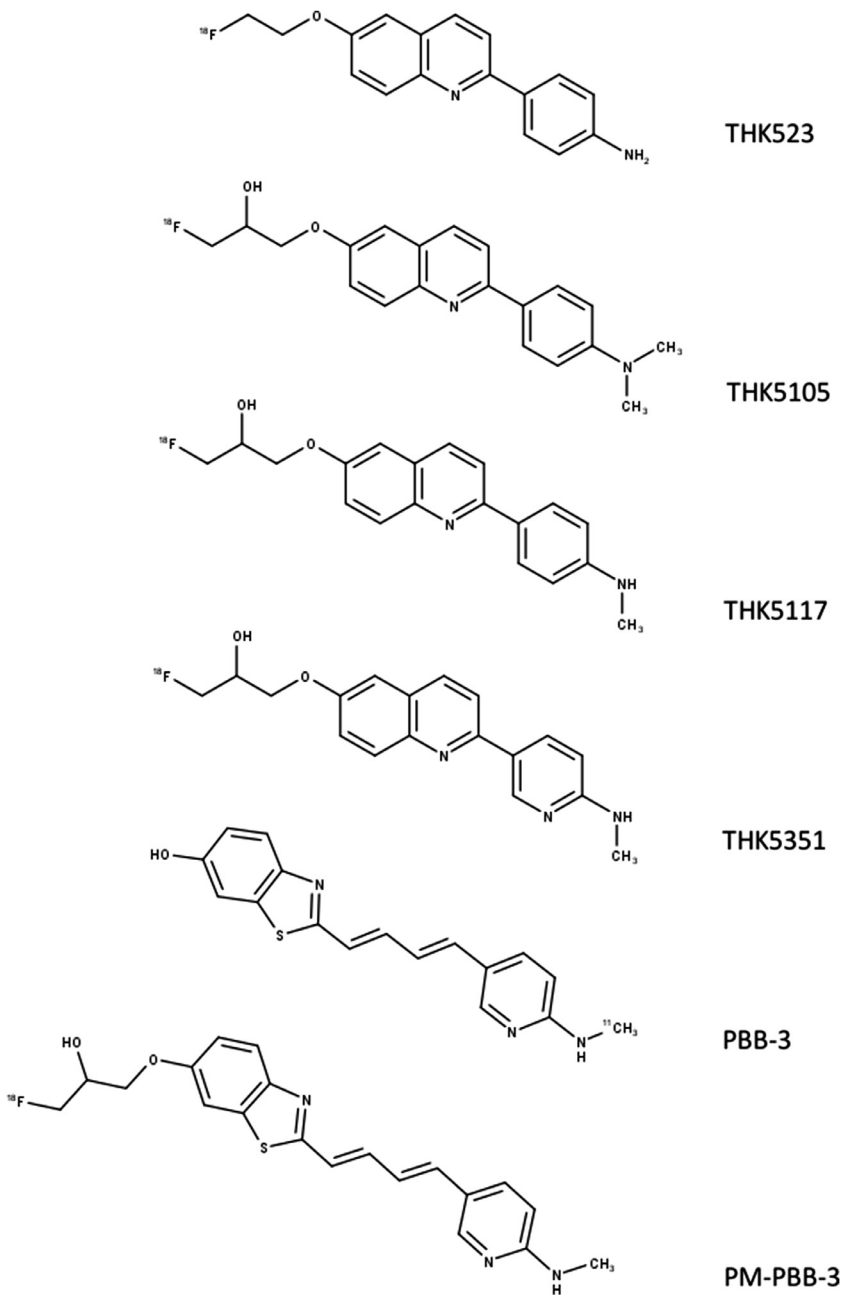

Figure 4 PET tracers for tau (neurofibrillary tangles) – continued. [^{18}F]THK5317 is the (*S*)-enantiomer of [^{18}F] THK5117.

the agent showed adequate brain uptake, which may be due to species differences between rodents and primates concerning the activity and substrate specificity of P-gp.[165,166] Unfortunately, a first-in-human study with N-[^{11}C]methyl-lansoprazole led to disappointing results. Tracer retention in patients' brains proved insufficient for accurate detection of NFTs.[167]

[^{18}F]Flortaucipir is the PET tracer that has been most widely used to study tau accumulation in the human brain. A disadvantage of this agent is its binding to substances in the basal ganglia that are not NFTs. Part of this off-target binding may occur to monoamine oxidase B,[135-137] but [^{18}F] flortaucipir may also bind to as yet unidentified cellular components and to neuromelanin in the substantia nigra.[138-140] [^{18}F]T808, a ligand structurally related to [^{18}F]flortaucipir, showed considerable in vitro selectivity for tau.[184,185] Initial [^{18}F]T808-PET images of the human brain were acquired,[186] but the ^{18}F-label of the ligand proved to be rapidly lost by defluorination.

A structurally different first generation tau tracer is [^{11}C] PBB3. This imaging agent showed favorable in vitro binding properties in brain tissue of patients with various neurodegenerative disorders, namely a higher selectivity for tau than [^{18}F]flortaucipir.[168,169] However, the in vivo results of [^{11}C] PBB3 were rather disappointing. They indicated entry of radiolabeled metabolites in the brain,[170] tracer binding to another target than tau in the basal ganglia,[171] and a rather poor dynamic range of [^{11}C]PBB3 PET scans.[172] The

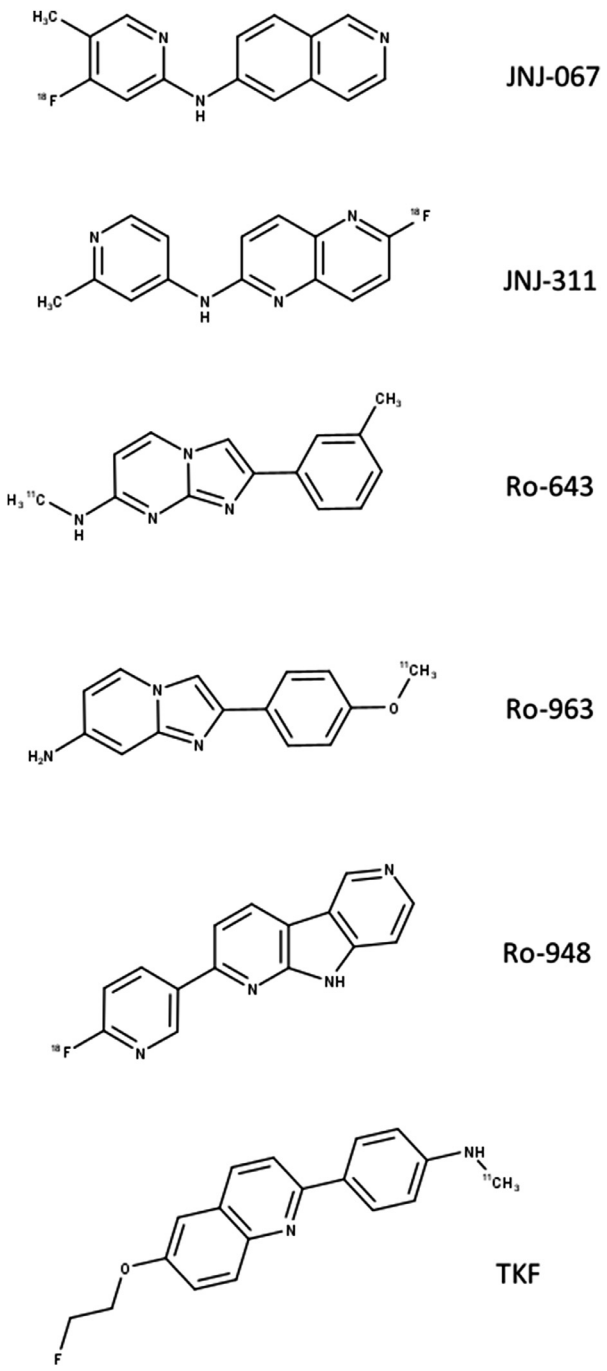

Figure 5 PET tracers for tau (neurofibrillary tangles) – continued.

structure of the lead compound PBB3 was therefore modified, resulting in the derivatives [^{18}F]AM-PBB3 and [^{18}F]PM-PBB3. These modified PET ligands showed a 1.5-fold to 2-fold higher dynamic range than [^{11}C]PBB3 and negligible off-target binding in the basal ganglia.[173] An in vivo study with [^{18}F]PM-PBB3 in Alzheimer patients indicated that the tracer can detect accumulation of hyperphosporylated tau and that the PET signal of [^{18}F]PM-PBB3 is closely correlated with impaired cerebral glucose metabolism and cognitive function.[174] An initial study with [^{18}F]PM-PBB3 in patients with FTD also reported promising results.[175]

Based on the initial findings with tau tracers, research efforts were focused on the development of agents with improved affinity and selectivity for tau and negligible off-targe binding. Some of the second-generation tau tracers were derivatives of first-generation agents, whereas others were completely novel compounds.

[^{18}F]GTP1, a product of Genentech, is a deuterated version of [^{18}F]T808 aimed at suppressing the susceptibility of [^{18}F]T808 to defluorination.[155] [^{18}F]GTP1 shows nanomolar affinity and selectivity for tau, negligible off-target binding, significantly increased uptake in the brain of Alzheimer patients compared to healthy control subjects, and levels of brain uptake that are negatively correlated with cognition.[155,156] [^{18}F]PI-2620 is a derivative of [^{18}F]flortaucipir aimed at reducing the affinity of that first-generation tau tracer to MAO-B. [^{18}F]PI-2620 shows a high affinity and selectivity for tau aggregates, a regionally increased brain uptake in Alzheimer patients compared to healthy controls, and levels of uptake that are inversely correlated with cognitive performance.[176,177] Moreover, in contrast to the lead compound [^{18}F]flortaucipir, [^{18}F]PI-2620 demonstrates no off-target binding in the basal ganglia.[178]

Three second-generation tau tracers were developed by Roche: [^{18}F]Ro-643, [^{18}F]Ro-948, and [^{18}F]Ro-963.[179-181] All of these agents share a high affinity and selectivity for tau aggregates in brain tissue of Alzheimer patients. [^{18}F]Ro-948 showed the best target-to-nontarget ratios in PET studies of the human brain.[179] In recent investigations, [^{18}F]Ro-948 was reported to have more favorable pharmacokinetics than [^{18}F]flortaucipir for clinical studies in patients[182] and to be specific for AD-type tau.[183] [^{18}F]MK-6240, a second generation tau tracer developed by Merck, is also considered as an imaging agent with high affinity and high selectivity for tau aggregates,[159-161] favorable pharmacokinetics for quantitative imaging,[162] negligible off-target binding in the human basal ganglia,[163] adequate test-retest repeatability[164] and suitability for longitudinal studies.[194,195] A recent review article judged that "of all in-human tau tracers, [^{18}F]MK-6240 is currently the most promising."[196]

Two other second-generation tau tracers, [^{18}F]JNJ-067 and [^{18}F]JNJ-311, have been developed by Johnson and Johnson.[157] Good preclinical data were reported for [^{18}F]JNJ-311, namely a high affinity for aggregated tau, a high in vitro selectivity for tau over Aß, and absence of radiolabeled metabolites in the brain.[158] Binding of [^{18}F]JNJ-311 to MAO-B was negligible[158] due to a low affinity of the agent for the enzyme.[137] In autoradiographic studies on postmortem samples of human brain, [^{18}F]JNJ-311 was observed to bind to tau aggregates in samples from patients with AD, but not progressive supranuclear palsy or corticobasal degeneration.[158]

PET imaging has indicated a different time course for the accumulation of tau than for Aß in AD. Whereas Aß accumulates before the symptoms of dementia appear and the PET signal of Aß tracers hardly increases after the clinical onset of AD, the signal of tau tracers like [^{18}F]flortaucipir and [^{11}C]PBB3 continues to rise during disease progression.[153,168] Although tau accumulation is strongly associated with cognitive impairment, SUV ratios of [^{18}F]flortaucipir in cognitive normal elderly persons and patients with MCI show

considerable overlap, which suggests that tau may not be a very accurate biomarker of MCI.[197]

Imaging of Neuroinflammation

Neurodegenerative diseases are not only accompanied by the accumulation of misfolded proteins, but also by neuroinflammation.[198-201] The significance of such inflammatory processes in the human brain is hotly debated: some researchers believe that they are pathogenic, that is, form part of the cause of the disease,[202,203] whereas others consider them as a secondary phenomenon that is required for the scavenging of neurons and neuronal processes, and the active removal of cellular debris. Neuroinflammation may be a "double-edged sword," in the sense that it can either counteract or promote neurodegenerative processes.[204,205] The significance of neuroinflammation may be age-, disease-, and disease stage-dependent, and may thus change during disease progression.[206] According to some researchers, chronic inflammation in neurodegenerative disease may ultimately exacerbate the pathogenic processes that initially triggered an inflammatory response.[199] Thus, anti-inflammatory agents have been proposed as therapeutic drugs that might slow the progression or delay the onset of AD.[207-213] Astrogliosis and microgliosis show a linear increase during AD progression, which time course does not correspond to the increase of amyloid plaques but rather to the burden of NFTs.[214]

Several targets in the brain are considered as indirect measures of neuroinflammation that could be employed for visualization of inflammatory processes with PET.[215] These include the 18 kD translocator protein (also known as TSPO or the peripheral benzodiazepine receptor), cyclooxygenase-1 and -2, histamine H4 receptors, alpha-7-nicotinic acetylcholine receptors, various purinergic receptors (P2X7 and P2Y12R), cannabinoid CB2 receptors (CB2R), colony-stimulating factor 1 receptor, and the triggering receptor expressed on myeloid cells — to mention just a few! [216,217] For most of these targets, tracer development is still at the experimental or preclinical stage. Most efforts to visualize neuroinflammation in neurodegenerative diseases have employed radioligands for TSPO (see Brooks[218] for an overview).

The interest of investigators in TSPO is due to the fact that TSPO is strongly overexpressed in activated compared to resting microglia,[219-222] and to a lesser extent also in activated astrocytes.[223] Because of this finding, several imaging agents for TSPO have been developed (see Table 3 and Figs. 6 and 7). The first successful PET ligand was [^{11}C]PK11195. Microglia activation is associated with an increase in the number of TSPO binding sites, but not with a change of their affinity to PK11195.[222] After initial studies with the racemic compound, (*R*)-[^{11}C]PK11195 was employed since this is the active enantiomer with reduced off-target binding compared to the racemate.[224] However, even (*R*)-[^{11}C]PK11195 has several disadvantages, such as a rather small uptake into the brain and a modest affinity for its target, resulting in poor target-to-nontarget (or signal-to-noise) ratios of [^{11}C]PK11195 PET images.

Many second-generation TSPO tracers were developed because of the limitations of (*R*)-[^{11}C]PK11195. These include: [^{11}C]DAA1106,[225-227] [^{11}C]DPA713,[228,229] [^{18}F]DPA-714,[230-233] [^{18}F]F-DPA,[234,235] [^{18}F]FEDAA1106,[236] [^{18}F]FEMPA,[237] [^{18}F]FEPPA,[238,239] [^{18}F]PBR06,[242] [^{11}C]PBR28,[243-252] and [^{11}C]vinpocetine[254] (Table 3, Fig. 6). All tracers have to some extent been applied in dementia research. They offer various advantages in comparison to [^{11}C]PK11195, such as: a longer physical half-life of the radionuclide (for radiofluorinated ligands), a higher brain uptake, higher affinity to the target, metabolites that do not cross the blood-brain barrier, reduced nonspecific binding and (in some subjects) a better signal-to-noise ratio. However, the binding of these imaging agents in the human brain is strongly affected by the rs6971 polymorphism of the TSPO gene. Depending on the TSPO genotype (*C*/*C*, *C*/*T*, or *T*/*T*), the target protein in a subject's brain may have a high, an intermediate or a low affinity for second-generation PET tracers.[255-257] In subjects with a low affinity genotype, activated microglia cannot be visualized.

Table 3 TSPO Tracers

Name	Radionuclide	Application in PET Study Related to Dementia	Comments
DAA1106	^{11}C	225-227	
DPA-713	^{11}C	228,229	
DPA-714	^{18}F	230-233	
F-DPA	^{18}F	234,235	Only data in mouse model reported
FEDAA1106	^{18}F	236	
FEMPA	^{18}F	237	
FEPPA	^{18}F	238,239	
GE180	^{18}F	240,241	
PBR06	^{18}F	242	Only data in mouse model reported
PBR28	^{11}C	243-252	
(*R*)-PK11195	^{11}C	228,253	
Vinpocetine	^{11}C	254	

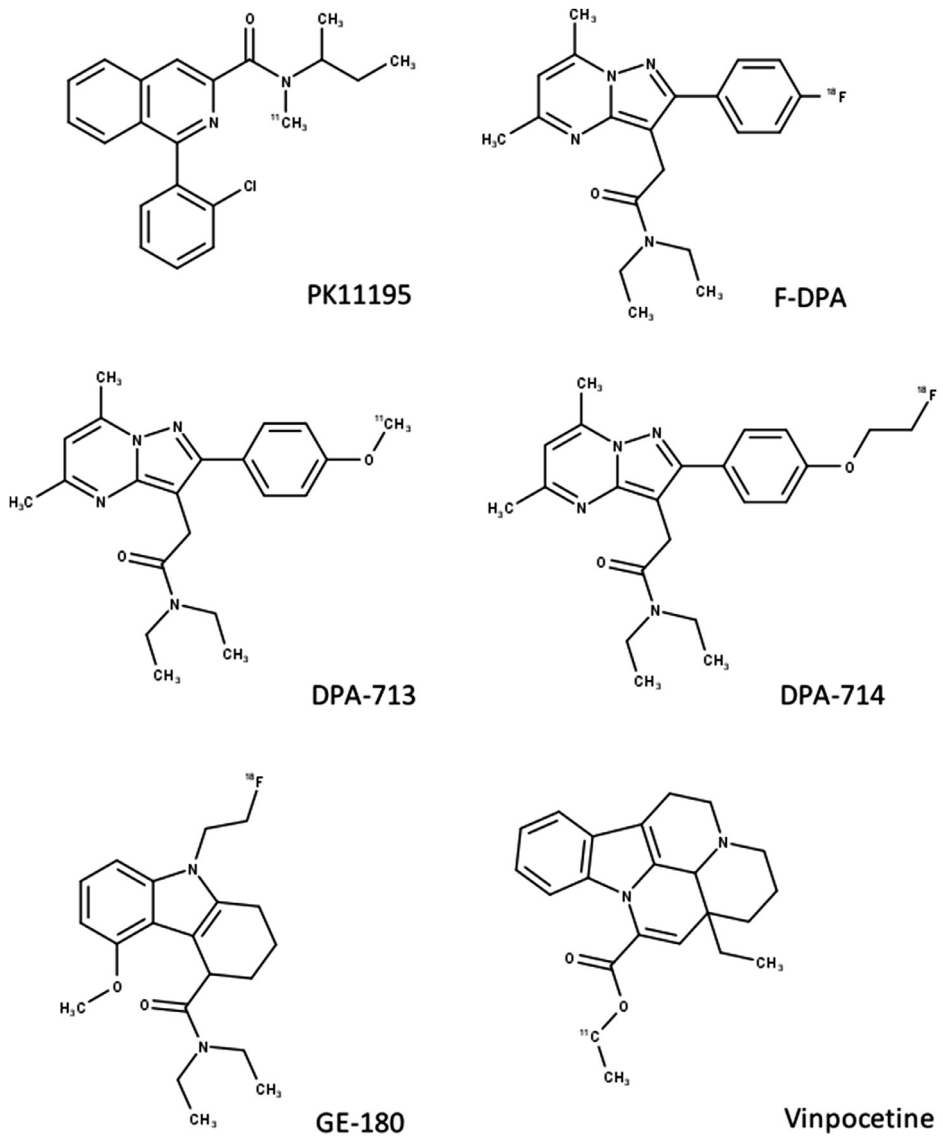

Figure 6 PK11195, the first TSPO ligand and agents for the same target that were later developed.

Third-generation TSPO tracers were developed in an attempt to reduce the sensitivity of probe binding to the rs6971 polymorphism. One of these novel imaging agents, [^{18}F]GE180 (also known as flutriciclamide), seems unsuccessful since in the human brain, its specific signal is much (20-fold) smaller than that of [^{11}C]PBR28.[240,241] The binding of another third-generation tracer, [^{11}C]ER176, has been reported to be sufficiently high for visualization of activated microglia, even in subjects with a low-affinity genotype.[258] Since [^{11}C]ER176 has also good imaging characteristics (better than [^{11}C]PBR28), it may be a promising agent for future research.[259,260] (R,S)-[^{18}F]GE387 is a third agent claimed to be insensitive to the rs6971 polymorphism, but for this compound, only preliminary data in rodents have been acquired.[261]

PET studies with TSPO ligands resulted in the following findings:

i. Higher binding potential values were noted in patients with AD,[226,228,229,233,237,239,243,244,246,250,252,253] in patients with frontotemporal lobar degeneration[251] and with some tracers also in subjects with MCI[227,245] compared to healthy controls, in many areas of the brain (if their TSPO genotype and binding status were taken into account). Higher binding potential values were also observed in patients with Parkinson's disease (PD) and MCI, particularly if they were amyloid-positive.[238] Increases in AD compared to age-matched healthy controls could not be detected with [^{18}F]FEDAA106 or [^{11}C]vinpocetine and in some cases also not with [^{11}C]PK11195, which may indicate that these tracers are not sufficiently sensitive to detect activated microglia in neurodegenerative disease.[228,236,254]
ii. The regional pattern of neuroinflammation in early AD is very similar to that of abnormal tau deposition.[229] Different subtypes of AD are associated with different patterns of neuroinflammation.[250]
iii. Levels of TSPO binding in the human brain are age-dependent, and show a more rapid rise in AD patients than in age-matched healthy controls.[248]

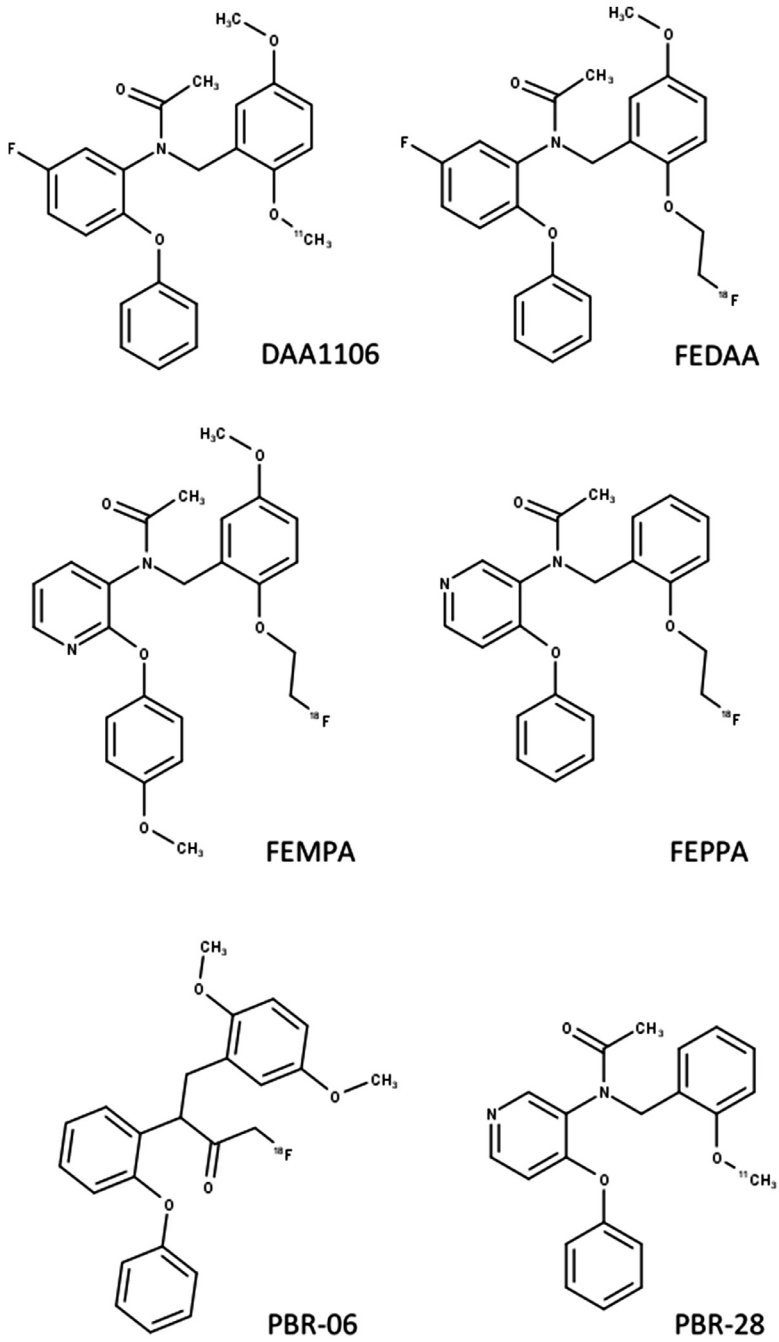

Figure 7 TSPO ligands structurally related to DAA1106.

iv. According to two studies, a high initial TSPO binding potential in the prodromal stage of AD is often followed by a subsequent slow increase (over a period of several years) and a relatively good clinical outcome. On the other hand, a low initial TSPO binding potential (only slightly elevated compared to healthy controls) is mostly followed by a subsequent rapid rise and a poor clinical outcome. The authors suggest that microglial activation appears at the prodromal and perhaps even the preclinical stage of AD and plays a protective role at these early stages. However, in later phases of the disease, neuroinflammation may no longer be neuroprotective but may exacerbate neuronal loss.[232,233]

As discussed above, many other targets in the brain than TSPO have been proposed as biomarkers of neuroinflammation. Although radioligands for these targets have been developed, most of these imaging agents have not yet passed the preclinical or first-in-human study stage (see eg,[262-264]). Pilot studies with the P2X7 ligand [^{11}C]JNJ-717 in patients with ALS and PD were disappointing, since tracer binding potential in the patient groups was not significantly different from the value in the healthy control group.[265,266] A pilot study with the cannabinoid receptor ligand [^{11}C]NE40 was also not successful, since a decrease rather than the expected increase of tracer binding was observed in AD.[267] This negative finding was attributed to the fact that the tracer is not sufficiently selective for the CB2 receptor but also binds to

the CB1 subtype. A pilot study with the cyclooxygenase-1 tracer [^{11}C]ketoprofen methyl ester in patients with AD or MCI also reported negative results.[268]

Imaging Cholinergic Targets

Cholinergic neurotransmission is an essential process underlying memory and cognitive function. If a cholinergic antagonist, such as the drug scopolamine, is administered to experimental animals or human volunteers, memory function is transiently and strikingly impaired, resulting in symptoms that resemble Alzheimer dementia.[269] On the other hand, drugs that inhibit the breakdown of acetylcholine can temporarily improve memory function in patients during early stages of AD.[270-272] Cholinergic deficits have been observed in several human disorders that are associated with cognitive decline.[273] Reduced acetylcholine synthesis or a loss of cholinergic neurons may either be the primary cause of the disease, or be triggered by the accumulation of misfolded proteins and be a secondary phenomenon in the disease process. Based on MRI studies of the brain, cholinergic neuron loss in the basal forebrain is considered as an early indicator of AD.[274,275] Although the cholinergic system plays an important role in cognition, cholinergic deficits can affect many other functions of the human brain depending on the brain regions where the deficits occur.[276,277]

Many PET tracers for the cholinergic system are available. These include: radioligands for muscarinic and nicotinic receptors, radiolabeled acetylcholinesterase (AChE) inhibitors and substrates, and ligands for the neuronal vesicular acetylcholine transport protein. Some of these tracers have been applied to study the mechanisms underlying human dementia (see Table 4 and Figs. 8 and 9). Unfortunately, acetylcholine synthesis in the human brain cannot be quantified with PET, since a successful tracer for the enzyme choline acetyltransferase has not yet been developed.

Initial and groundbreaking studies of the cholinergic system employed the PET tracer *(S)*(-)-[^{11}C]nicotine. Although this imaging agent showed poor target-to-nontarget ratios and suboptimal kinetics in the human brain, some interesting findings were reported. The density of nicotinic receptors appeared to be decreased in AD[279,317,325] and to be restored upon treatment of patients with cholinesterase inhibitors[279,318-320,325-327] or with nerve growth factor.[325] The decreases of nicotinic receptor density in AD patients seemed to occur mainly in the temporal cortex, frontal cortex and hippocampus.[321] In a group of 27 AD patients, levels of tracer binding in the cortex were significantly correlated with the cognitive function of attention.[322] In contrast to the binding of *(S)*(-)-[^{11}C]nicotine, the binding potential of the muscarinic receptor antagonist [^{11}C]benztropine in the temporal cortex was decreased after 3 months of treatment of patients with the AChE inhibitor tacrine.[279]

Later studies of muscarinic receptors in the human brain made use of the radiolabeled antagonist [^{11}C]NMPB. A significant decrease of tracer binding was noted in cortical brain regions of patients with mild to moderate AD, but the loss of muscarinic receptors was smaller than the decrease of regional glucose metabolism, as measured with the PET tracer [^{18}F]FDG.[315] A study from a different institution observed decreases of [^{11}C]NMPB binding in the human brain with normal aging, but could not detect any additional decrease in patients with AD.[316] Another PET tracer for cerebral muscarinic receptors, [^{11}C](+)3-MPB, has only been applied for studies in non-human primates.[313,314] Considerable levels of muscarinic receptor occupancy (>45%) by the muscarinic antagonist scopolamine were required to induce a significant impairment of working memory performance.[314]

Many PET studies have been aimed at measuring the expression or the activity of AChE in the human brain, using either radiolabeled AChE inhibitors or substrates (see Shinotoh[328] for a recent overview). The inhibitor [^{11}C]CP-126,998 binds to AChE and shows the expected regional differences in PET images.[280,281] Its uptake is suppressed when healthy subjects are pretreated with an excess of the drug donepezil.[280] To the best of our knowledge, no further PET studies with [^{11}C]CP-126,998 in patients with dementia were published, but such studies have been reported for another radiolabeled AChE inhibitor, [^{11}C]donepezil. Patients with mild AD demonstrated an 18-20% reduction of AChE

Table 4 Tracers for the Cholinergic System

Name	Radio-Nuclide	Target	PET Study Related to Dementia
ASEM	^{18}F	α7 nicotinic receptor	278
Benztropine	^{11}C	Muscarinic receptors	279
CP-126,998	^{11}C	Acetylcholinesterase	280,281
Donepezil	^{11}C	Acetylcholinesterase	282
F-A85380	^{18}F	α4ß2 nicotinic receptor	283-293
FEOBV	^{18}F	Vesicular acetylcholine transporter	294,295
(+)-Flubatine (aka NCFHEB)	^{18}F	α4ß2 nicotinic receptor	296-298
(R)-MeQAA	^{11}C	α7 nicotinic receptor	299
MP4A	^{11}C	Acetylcholinesterase	300-312
(+)3-MPB	^{11}C	Muscarinic receptors	313,314
NMPB	^{11}C	Muscarinic receptors	315,316
Nicotine	^{11}C	Nicotinic receptors	317-322
PMP	^{11}C	Acetylcholinesterase	320,323,324

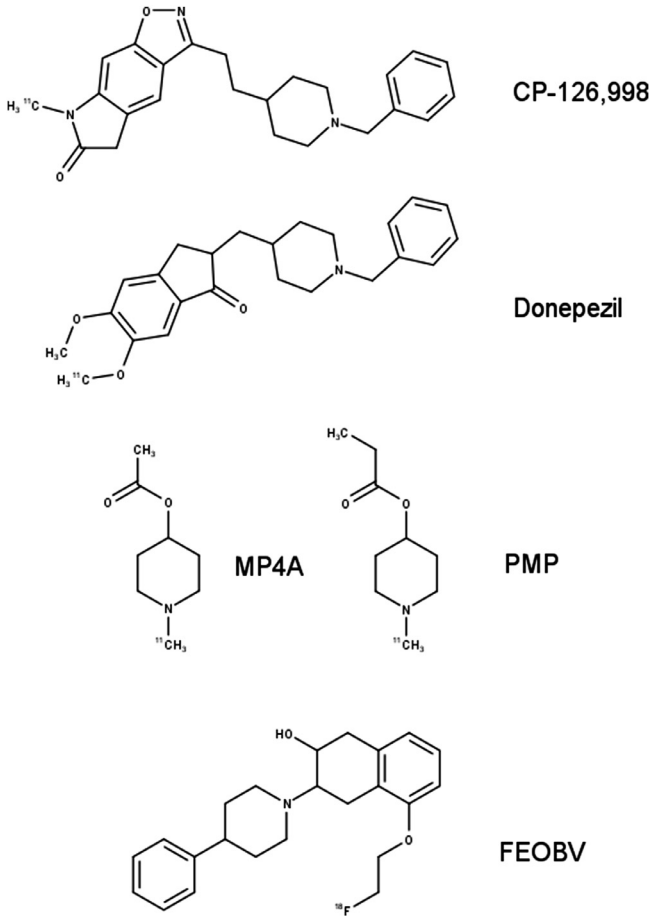

Figure 8 Chemical structures of the AchE inhibitors CP-126,998 and donepezil, the AChE substrates MP4A and PMP, and the vAChT ligand FEOBV.

expression in the neocortex and hippocampus, whereas moderate AD was associated with a 24%-30% reduction throughout the brain, in comparison to healthy age-matched controls.[282] [^{11}C]Donepezil has recently also been applied to study parasympathetic innervation of the gut in Parkinson patients.[329]

Most PET studies of cerebral AChE have used radiolabeled AChE substrates, particulary [^{11}C]MP4A and to a lesser extent [^{11}C]PMP (= MP4P). In an initial study with [^{11}C]MP4A, 31%-38% reductions of AChE activity were noted in the temporal and parietal cortex of AD patients, whereas smaller reductions were observed in other cortical areas.[300] This result was confirmed in later studies that reported a global decrease of cerebral AChE activity in dementia[301] with particular decreases in the lateral temporal lobes.[302] Reduced AChE activity was also noted in subjects with DLB, as compared to healthy controls.[303] In early AD and MCI, hippocampal AChE activity was shown to be only slightly reduced, which suggests that PET scans with [^{11}C]MP4A have limited value for early detection of Alzheimer dementia.[304] However, other investigators observed significant decreases of AChE activity in the amygdala and cerebral cortex (but not in the nucleus basalis of Meynert) both in early and moderate AD.[305] Their findings suggest that cholinergic deficits in the amygdala and neocortex are an early event in AD. That result was confirmed in a later study that involved a larger number of patients with MCI and applied advanced data analysis techniques.[306] A study from another group also reported widespread reductions of AChE activity in the MCI phase of AD, whereas a more variable amount of loss was present in early DLB.[307] Patients suffering from PD with dementia were found to have lower AChE activity in the parietal cortex than Parkinson patients without dementia.[308] In PD patients with dementia, AChE activities measured with [^{11}C]MP4A and PET were similar to those observed in patients with DLB.[309] PET studies with either [^{11}C]PMP[330,331] or [^{11}C]MP4A[310] can be used to discriminate AD from DLB since DLB is consistently associated with greated reductions in cortical AChE activity than AD. Cortical cholinergic dysfunction as measured with [^{11}C]MP4A-PET is more severe in patients with early-onset AD as compared to late-onset AD.[311] Regional patterns of AChE loss and reduced glucose metabolism at the MCI stage of AD are not identical, which may imply the presence of various, different underlying pathologies.[312]

An early PET study with the AChE substrate [^{11}C]PMP showed that the PET data for AChE activity that are acquired with this tracer correspond to the known regional distribution of the enzyme and with concomitant measurements of cholinergic terminal losses (using a ligand for the vesicular acetylcholine transporter), but not with decreases of glucose metabolism.[323] A 30%-40% reduction in cerebral AChE

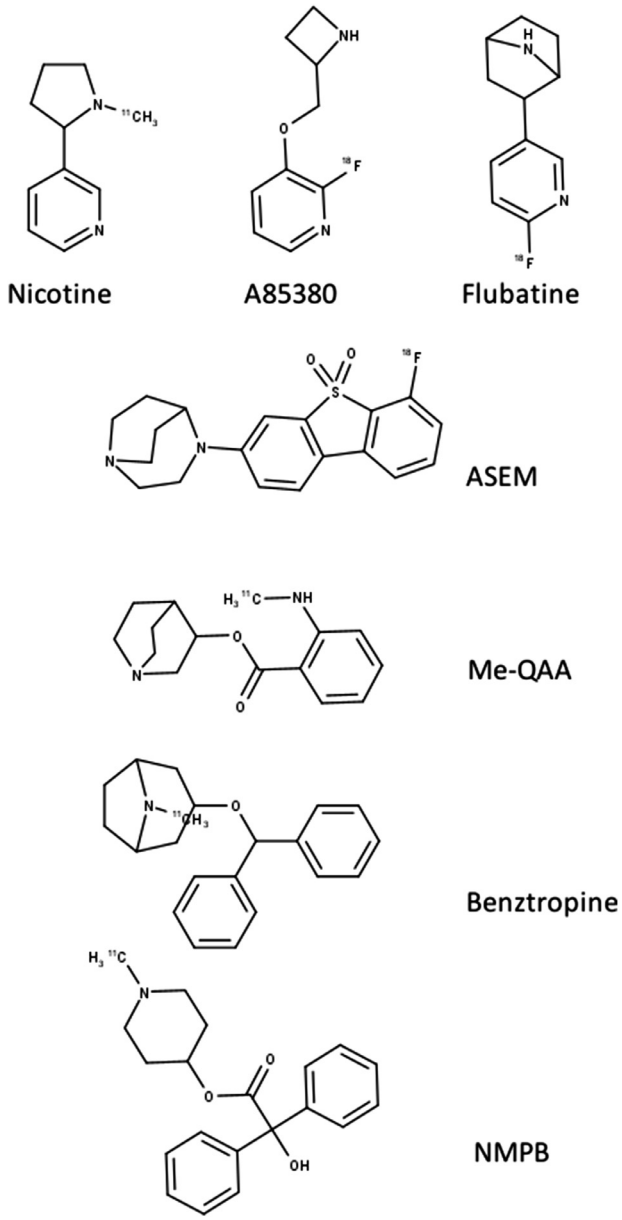

Figure 9 Nicotinic and muscarinic receptor ligands that have been employed for PET studies in subjects with dementia and MCI.

activity was measured in AD patients who were treated with galantamine (16-24 mg/day) for at least 3 weeks.[320] Levels of AChE activity in the CSF measured under these conditions closely matched those measured with PET in the brain.[324]

Nicotinic receptors in the living human brain have not only been studied with the agonist (*S*)(-)-[^{11}C]nicotine, but also with radiolabeled analogs of nicotine. Initial PET studies employed 2-[^{18}F]A-85380, a selective agonist at the $\alpha4\beta2$ subtype of nicotinic receptors. A disadvantage of such radioligands is their slow binding kinetics that result in long scanning times. In vitro autoradiography of sections of human brain indicated a strong (>60%) decrease of 2-[^{18}F]A-85380 binding in the occipital cortex and the thalamus of Alzheimer patients as compared to a healthy control group.[283] However, a later in vivo study using the same tracer could not detect any decrease of $\alpha4\beta2$ receptor density in patients with early AD, although these patients already demonstrated significant cognitive impairment. The authors suggested that 2-[^{18}F]A-85380 may be not sensitive enough to detect nicotinic receptor losses in early AD and that decreases in PET images become visible only at advanced stages of the disease.[284] A very different conclusion was reached in a German publication from the same year, that involved patients with MCI, early AD and advanced AD. In that publication, significant reductions of receptor binding were detected in patients with MCI and early AD, suggesting that a loss of $\alpha4\beta2$ nicotinic receptors occurs already in the early symptomatic stages of the disease.[285]

Negative findings with 2-[^{18}F]A-85380 were again reported the following year: no significant decline of tracer binding in the human brain was observed with advancing age, although aging in the subject group was associated with cognitive decline.[286] Moreover, galantamine-induced improvements of cognitive function in patients with early AD

appeared to be not related to changes of $\alpha4\beta2$ nicotinic receptor availability, as measured with 2-[^{18}F]A-85380 and PET.[287] In contrast to these negative findings, a German publication detected decreased $\alpha4\beta2$ receptor binding in anterior cingulate cortex, putamen, midbrain, and occipital cortex of patients with PD that were significantly correlated to the severity of MCI and depression in the patient group.[288] Another publication from the same group reported significant decreases of 2-[^{18}F]A-85380 binding in the brain of patients with MCI and early AD that were also correlated with the severity of cognitive impairment.[289] A similar conclusion was reached in a later publication from Japan.[290] A subsequent Japanese publication reported that declines of 2-[^{18}F]A-85380 binding in the prefrontal cortex of AD patients were related to their working memory performance in cognitive tasks.[291] A French publication, in which PET data were corrected for partial volume effect, suggested that losses of $\alpha4\beta2$ nicotinic receptors during human aging occur mainly in the cortex, whereas additional losses in AD occur predominantly in the hippocampus.[292] A final, American publication detected reductions of 2-[^{18}F]A-85380 binding in specific brain regions in mild to moderate AD that were related to neuropsychiatric symptoms. The authors suggested that reduced $\alpha4\beta2$ receptor numbers in aged healthy subjects may be associated with a slower processing of cognitive and memory tasks.[293]

The variable outcome of studies with 2-[^{18}F]A-85380 may have been due to the fact that different methods of data analysis were used (eg, tracer distribution volume, distribution volume ratios, or binding potentials, data either uncorrected or corrected for partial volume effect) and that quantitative interpretation of 2-[^{18}F]A-85380 images is difficult because of the slow kinetics of the tracer. Because of this drawback of 2-[^{18}F]A-85380, second-generation imaging agents for $\alpha4\beta2$ receptors were developed.[285,296] (-)[^{18}F]Flubatine (also known as [^{18}F]norchloro-fluoro-homoepibatidine or NCFHEB) is one of these second-generation tracers. This radioligand has been reported to be more sensitive than the first-generation agents and to detect nicotinic receptor losses in more brain regions of AD patients than 2-[^{18}F]A-85380.[297] A negative correlation between (-)[^{18}F]flubatine binding and standardized uptake values of the ß-amyloid tracer [^{11}C]PiB was observed in several regions of the Alzheimer brain.[298]

Various radioligands for another subtype of nicotinic receptors, the $\alpha7$ receptor, have also been developed since this subtype is also known to be involved in the pathophysiological processes underlying AD. Using one of these tracers, [^{11}C]-(R)-MeQAA, decreases of $\alpha7$ receptor binding were noted in the nucleus basalis magnocellularis and medial prefrontal cortex of Alzheimer patients that were correlated to increases of the binding of [^{11}C]PiB and to decreased memory and frontal function scores in the patient group.[299] A surprising finding was reported using another $\alpha7$ receptor ligand, [^{18}F]ASEM. Binding of that ligand throughout the brain was higher in MCI patients than in healthy controls, and levels of tracer binding in MCI patients were not related to their verbal memory performance.[278]

Two comprehensive reviews on nicotinic acetylcholine receptor imaging in AD and MCI have recently been published and can be consulted for further information.[332,333]

Radioligands for the vesicular acetylcholine transporter (vAChT) may be used to visualize loss of cholinergic nerve terminals, since the vAChT is virtually only expressed by neurons. The regional binding of vAChT ligands is considered as a more direct and more pure biomarker of presynaptic cholinergic terminal density than the binding of other cholinergic PET tracers.[334,335] PET studies of cerebral vAChT have been performed using the tracer (-)-5-[^{18}F]fluoroethoxybenzovesamicol (FEOBV). This radioligand shows a regional distribution in the human brain that corresponds to the known distribution of cholinergic terminals.[294] In a comparative study using the PET tracers [^{18}F]FEOBV (for vAChT), [^{18}F]NAV4694 (for ß-amyloid) and [^{18}F]FDG (for glucose metabolism), [^{18}F]FEOBV showed the highest sensitivity for distinguishing AD patients and healthy controls.[295] Although these results of FEOBV seem promising, a disadvantage of this agent is its slow kinetics in the basal ganglia which may lead to long scan durations or to protocols in which subjects are scanned after a long delay. Moreover, it is very difficult to acquire proof for the in vivo selectivity of FEOBV (and vAChT ligands in general), since target blocking agents may have adverse pharmacological effects or may bind to additional targets, such as sigma receptors.[196]

Imaging of Monoamine Neurotransmitter Targets

The neurotransmitter dopamine is not only involved in motor control, motivation and addiction, but also in cognitive processes. [^{18}F]FDOPA can be used to quantify the functional integrity of the dopaminergic system.[336,337] This PET tracer is a radiolabeled analogue of L-DOPA, the metabolic precursor of dopamine. Another way to quantify dopaminergic neuron losses is PET imaging with a radioligand for the presynaptic dopamine transporter (DAT)[337,338] (see Table 5 and Figs. 10 and 11).

Imaging of the presynaptic dopaminergic function can be used to differentiate AD from DLB. Regional hypometabolism (similar to that observed in AD) combined with a decreased striatal DAT availability may indicate that DLB is a probable diagnosis. Decreased putaminal uptake of [^{18}F]FDOPA in DLB can be used to distinguish DLB from AD.[359] In patients with DLB, bilateral reductions of the binding of the DAT tracer [^{11}C]CFT were consistently observed, together with increased binding of the amyloid tracer [^{11}C]PiB in cerebral cortex and intact [^{18}F]FDG uptake in the posterior cingulate gyrus.[346]

In patients with FTD, losses of dopaminergic nigrostriatal neurons (quantified with PET and [^{11}C]CFT) were observed and shown to be correlated with the severity of extrapyramidal motor symptoms, particularly rigidity and akinesia.[347] However, in patients with AD the striatal uptake of [^{18}F]FDOPA was not significantly reduced, indicating that extrapyramidal symptoms in AD and PD (or FTD) may have a

Table 5 Tracers for Monoaminergic Neurotransmitter Targets (That Have Been Applied in Dementia Research)

Name	Radio-Nuclide	Target	PET Study Concerning Dementia
Altanserin	^{18}F	Serotonin 5-HT$_{2A}$ receptor	339-342
AV-133 (Florbenazine)	^{18}F	vMAT2	343-345
CFT	^{11}C	Dopamine transporter	346,347
DASB	^{11}C	Serotonin transporter	340,348
DED	^{11}C	MAO-B, astrocytosis	349-354
Deprenyl	^{11}C	MAO-B, astrocytosis	355
Deuteroaltanserin	^{18}F	Serotonin 5-HT$_{2A}$ receptor	356
Doxepin	^{11}C	Histamine H1 receptor	357
DTBZ	^{11}C	vMAT2	358
FDOPA	^{18}F	Dopamine synthesis	308,309,329,359-364
FMeNER-D2	^{18}F	Norepinephrine transporter	365
MPPF	^{18}F	Serotonin 5-HT$_{1A}$ receptor	366,367
SB207145	^{11}C	Serotonin 5-HT$_4$ receptor	368
Setoperone	^{18}F	Serotonin 5-HT$_{2A}$ receptor	369
WAY-100635	^{11}C	Serotonin 5-HT$_{1A}$ receptor	370

different neurochemical basis.[360,361] Although the average uptake of [^{18}F]FDOPA is similar in patients with AD and healthy control subjects, inter-individual variability in subjects with AD is greater and low influx values of FDOPA tend to be associated with wandering behavior of the patients.[362] PD is associated with a significant reduction of the striatal uptake of [^{18}F]FDOPA,[308,363,364] but the magnitude of this reduction in subjects with PD with or without dementia seems not significantly different.[308]

Monoamine oxidase enzymes in the brain are involved in the degradation and inactivation of monoamine neurotransmitters. The B-subtype of monoamine oxidase (MAO-B) is mainly present in astrocytes and is upregulated in neuroinflammatory processes. For this reason, radiolabeled MAO-B inhibitors have been tested as imaging biomarkers for neuroinflammation and astrogliosis in neurodegenerative diseases.[371] An initial study used the PET tracer [^{11}C]deprenyl in hemisphere autoradiography of postmortem brain samples of Alzheimer patients and age-matched healthy controls. Significantly increased binding of [^{11}C]deprenyl was observed in the temporal lobes and the white matter of the patients, and this increase was correlated with an increased number of reactive astrocytes.[355] For later PET studies in living subjects, [^{11}C]DED (deuterated deprenyl) was used since deuteration suppresses undesired tracer metabolism. For a first attempt, nine patients with moderate to severe AD and eleven age-matched healthy controls were scanned with the PET tracers [^{11}C]DED (MAO-B) and [^{11}C]PiB (ß-amyloid). Significant (22%-35%) increases of [^{11}C]DED binding were noted in the frontal, parietal, temporal and medial temporal lobes of the patients, and these increases were moderately correlated to increased regional retention of [^{11}C]PiB.[349] In a later multitracer study from the same group, [^{18}F]FDG was added to the multitracer imaging protocol and three subject groups were compared: patients with MCI (n = 8), patients with AD (n = 7), and age-matched healthy controls (n = 14). Increased [^{11}C]DED binding was detected in cortical and subcortical regions of the MCI patients, suggesting that astrogliosis occurs early in the development of AD. In this study, positive or negative correlations between the regional uptake of [^{11}C]DED and [^{11}C]PiB, or [^{11}C]DED and [^{18}F]FDG, were not observed.[350] In a mouse model of AD, increases of [^{11}C]DED were found to precede the deposition of amyloid plaques.[351] In a longitudinal PET study in subjects with autosomal dominant AD, the time course of astrocytosis (measured with [^{11}C]DED) was found to differ from the time course of deposition of amyloid plaques (measured with [^{11}C]PiB). Astrocytosis occurred early (already 17 years before the expected symptom onset) in the patient group and showed a subsequent decline, whereas plaque deposition showed a steady increase when AD progressed.[352] Presymptomatic autosomal dominant AD carriers had greater uptake of [^{11}C]DED and [^{11}C]PiB than noncarriers in almost all brain regions, except the hippocampus.[353] Early (1−4 minutes) frames of [^{11}C]DED scans can be used to estimate perfusion; thus, a single dynamic [^{11}C]DED scan can provide information both on perfusion and astrocytosis in the brain.[354]

Dementia is often associated with alterations of mood and anxiety. Such neuropsychiatric features suggest that the serotonergic system in the brain is disrupted.[372] Several PET studies have attempted to assess changes of serotonin receptors and serotonin transporters in patients with AD or other forms of dementia (see Table 5, Figs. 10 and 11, and Knudsen and Hasselbalch[373]).

An early PET study with the radioligand [^{18}F]setoperone reported significant reductions of serotonin 5-HT$_{2A}$ receptor availability in various cortical regions of patients with AD, particularly the frontal and temporal cortex.[369] In later PET studies using a different 5-HT$_{2A}$ receptor ligand, [^{18}F]altanserin, similar changes were observed in the Alzheimer brain but not in the brain of patients with late-life depression.[339,340] A smaller, but still significant, global reduction of cortical 5-HT$_{2A}$ receptor availability was noted in patients with MCI of the amnestic type, even after correction of the PET data for atrophy.[341] Using deuterated [^{18}F]altanserin and a constant infusion protocol for radioligand administration, significant reductions of tracer binding potential and

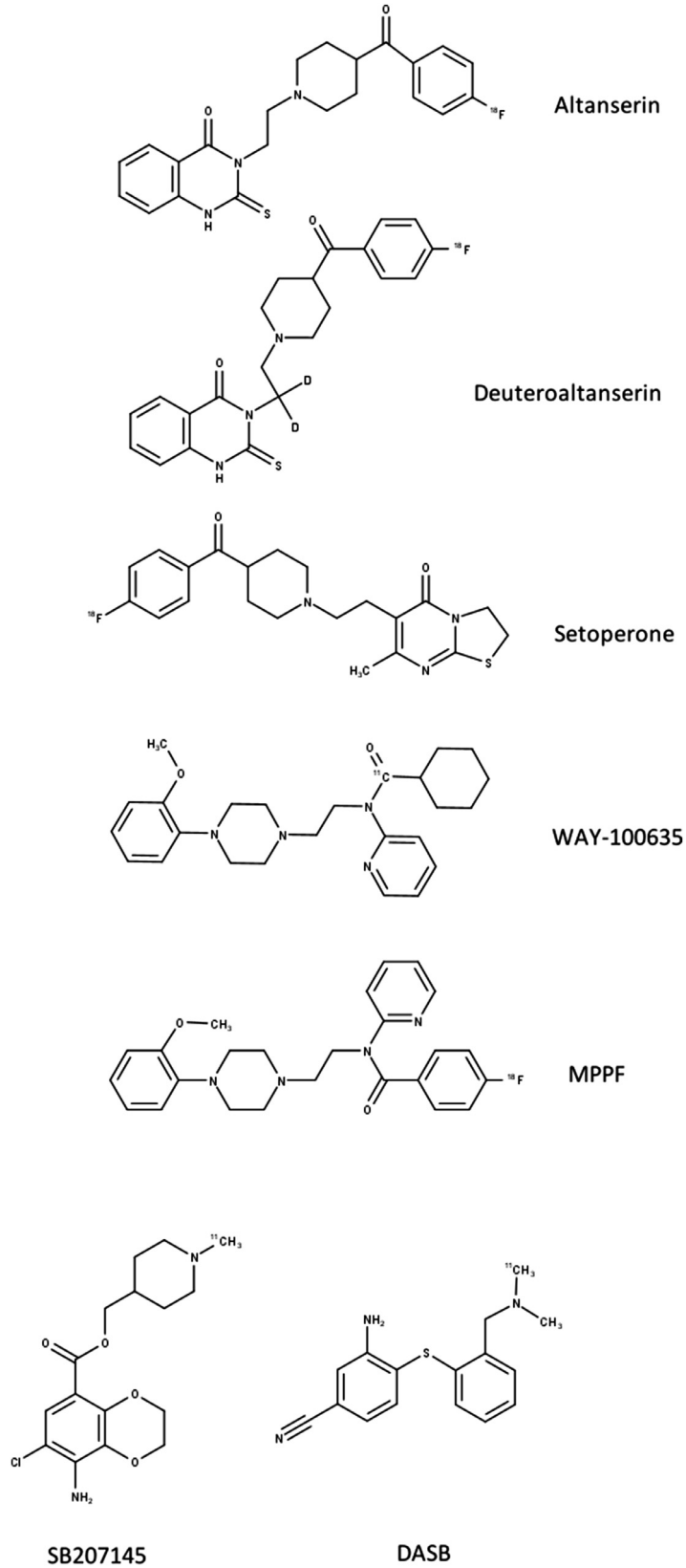

Figure 10 Serotonergic PET tracers that have been applied in dementia research.

tissue/plasma ratios of radioactivity were noted in the anterior cingulate cortex of Alzheimer patients, but these reductions were not correlated with behavioral symptoms.[356] Data from a longitudinal study with [^{19}F]altanserin in MCI patients that used a bolus-infusion protocol suggested that reductions of cortical 5-HT_{2A} binding are an early feature in MCI, whereas the progression of MCI to AD is associated with only minor additional reductions.[342]

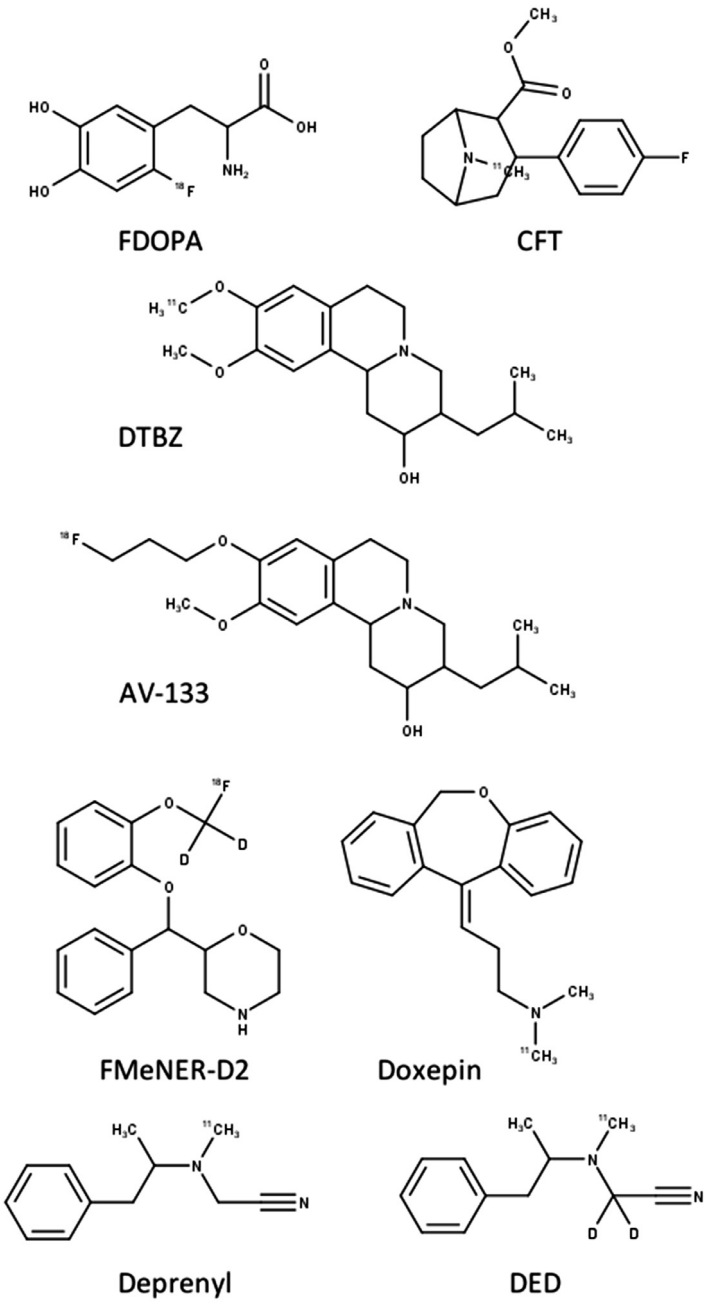

Figure 11 Other monoaminergic PET tracers that have been applied in dementia research.

Using the radioligand [^{18}F]MPPF, decreases of serotonin 5-HT$_{1A}$ receptor availability were detected in the hippocampus and raphe nuclei of patients with AD, and losses in the hippocampus were correlated with Mini Mental State Exam scores.[366] A PET study with another ligand, [^{11}C}WAY-100635, reported decreases of 5-HT$_{1A}$ receptor availability in the right medial temporal cortex of patients with AD.[370] Amnestic MCI patients were found to differ from subjects with AD in the sense that they showed increased rather than decreased binding of the 5-HT$_{1A}$ ligand [^{18}F]MPPF.[367]

Binding of the serotonin 5-HT$_4$ ligand [^{11}C]SB207145 was found to be increased in subjects who were amyloid-positive in an [^{11}C]PiB scan. Thus, 5-HT$_4$ receptors may be upregulated in response to Aß deposition in the preclinical stages of AD.[368]

In contrast to the frequently reported major loss of serotonin 5-HT$_{2A}$ receptors, losses of the serotonin transporter in Alzheimer patients as measured with the PET tracer [^{11}C]DASB were reported to be less prominent and often insignificant in one study.[340] However, another PET study with [^{11}C]DASB reported widespread reductions of serotonin transporter availability in cortical areas of patients with MCI.[348]

The norepinephrine transporter, another protein involved in monoamine neurotransmitter reuptake, demonstrated significant decreases in the locus coeruleus and thalamus of AD patients compared to healthy controls in a postmortem autoradiographic study with the PET tracer (S,S)-[^{18}F]FMeNER-D2.[365,374]

In a PET study using [^{11}C]DTBZ, a tracer for the vesicular monoamine transporter type 2, regional decreases of tracer K_1 (reflecting blood flow) were detected in the brain of patients with MCI and early AD that strongly resembled the regional decreases of cerebral glucose metabolism.[358] Subsequent PET studies concerning vMAT2 used a radiofluorinated ligand, [^{18}F]Florbenazine (AV-133). In the first of these studies, significant decreases of vMAT2 binding were reported in the putamen and caudate nucleus of patients with DLB and PD, but not in the brain of subjects with AD.[343] According to the investigators[344] and the authors of a later study,[345] PET imaging with the tracers [^{18}F]AV-133 and [^{11}C]PiB (or [^{18}F]florbetaben) can be useful for the differential diagnosis of DLB and AD. An overview of the available tracers for PET imaging of vesicular monoamine transporters has recently been published.[375]

Besides acetylcholine and dopamine, the neurotransmitter histamine is known to modulate cognitive processes (learning, memory, and attention)[376-380] and to be involved in neuroprotection.[381,382] Histaminergic deficits in patients with AD have been observed in postmortem studies of the human brain.[383] A PET study with the ligand [^{11}C]doxepine indicated reduced histamine H1 receptor availability in the temporal and frontal lobes of AD patients compared to healthy controls. The reductions in [^{11}C]doxepine binding were correlated with the severity of clinical symptoms and Mini-Mental State Examination scores.[357]

Imaging of Synaptic Density

Synaptic vesicle glycoprotein 2A (SV2A) is expressed throughout the brain and is involved in the transmission of neuronal impulses. The precise mechanism of action of the protein is unknown, but SV2A is supposed to be required for the fusion of synaptic vesicles with the presynaptic plasma membrane, so that these vesicles can release their neurotransmitters in the synaptic cleft. SV2A is the target of the antiepileptic drugs levetiracetam and brivaracetam.[384-386]

Several neurodegenerative and neuropsychiatric disorders are known to be associated with a progressive reduction of synaptic density in some areas of the brain. A significant loss of synapses has been reported in AD,[387-391] PD,[392] epilepsy,[384,393,394] major depressive disorder,[395,396] and schizophrenia.[397-400] The magnitude of these losses is correlated to the severity of cognitive impairment in AD[388,389,391] and to depression severity in major depressive disorder.[396] Until recently, synaptic density in the human brain could only be quantified post mortem. However, positron-emitting derivatives of levetiracetam have been developed that allow the measurement of SV2A availability in living subjects with PET[385] (Fig. 12). Reduced SV2A availability is supposed to reflect synaptic loss, although altered tracer binding can (in theory) also reflect an altered affinity of the protein for the radioligand or altered competition of endogenous substances with the tracer for a limited number of binding sites. PET imaging of synaptic density may allow quantification of reduced neuronal connectivity in human disease and assessment of the impact of therapies on the progression of such losses.

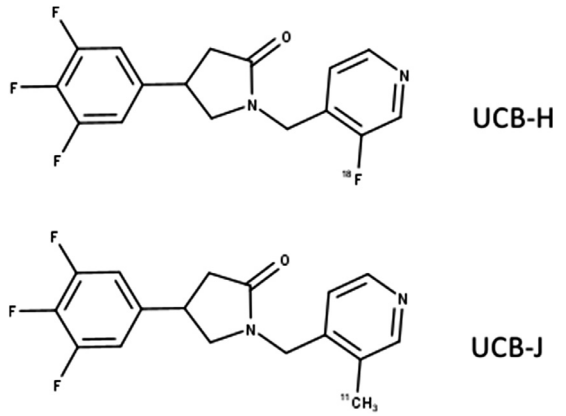

Figure 12 Chemical structures of the SV2A tracers [^{18}F]UCB-H and [^{11}C]UCB-J.

A PET study with the SV2A tracer [^{11}C]UCB-J reported a 41% lower binding potential in the hippocampus of patients with AD as compared to age-matched, cognitively normal subjects. This reduction remained significant after partial volume correction and the magnitude of the reduction was correlated with memory performance in the patient group.[401] Widespread reductions of [^{11}C]UCB-J binding in mediotemporal and neocortical brain regions of AD patients as compared to healthy controls were later reported.[402] Using another SV2A tracer, [^{18}F]UCB-H, significant decreases of tracer distribution volume were noted in various cortical areas (11%-18%) and in the thalamus (16%) of Alzheimer patients, whereas the largest decrease (31%) was observed in the hippocampus.[403] This study also showed that the loss of synapses in the hippocampus is related to cognitive decline in AD, significant loss resulting in unawareness of the patients of their own memory problems.[403] In a very recent study with [^{11}C]UCV-J in patients with amnestic MCI, decreases of SV2A binding and increases of tau deposition were observed in the medial temporal lobe that were both related to cognitive performance.[404] Another recent study demonstrated good repeatability of quantitative [^{11}C]UCB-J PET scans, both in AD patients and cognitively normal subjects.[405]

Both [^{11}C]UCB-J and [^{18}F]UCB-H seem suitable for quantification of regional SV2A availability in the human brain. [^{11}C]UCB-J shows a higher binding potential and a greater dynamic range in nonhuman primates and humans than [^{18}F]UCB-H, and may for that reason be preferred. On the other hand, [^{18}F]UCB-H has the advantage of a longer physical half-life of the radionuclide and can be distributed to remote imaging centers.[384,385,406]

Imaging Cerebral Glucose Metabolism

2-[^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG), an analog of glucose, is taken up into cells by glucose transporters and is subsequently converted to [^{18}F]FDG-6-phosphate by the

Table 6 Tracers for Novel Targets (and Novel Tracers for Established Targets)

Target	Ligand(s)	Radionuclide(s)	Reason for Interest	PET Study or Review Article
AMPA receptor	Allosteric modulators, such as BPAM121	^{11}C, ^{18}F	AMPA receptor signaling modulates Aß deposition, loss of AMPA receptors is related to memory deficits.	414,415
AMPA receptor	Agonist HMS011	^{11}C	See above.	416
Amyloid-ß	Bispecific tribody	^{124}I, ^{18}F	Antibodies may offer greater specificity than small molecules.	417,418
ß-Adrenoceptor	Isoproterenol	^{11}C	The ß-AR agonist isoproterenol is an inhibitor of tau aggregation.	419,420
Cannabinoid CB2 receptor (CB2R)	A-836339, NE40	^{11}C	Increased in AD brains, potential therapeutic target.	267,421-426
Colony-stimulating factor 1 receptor	AZ683, CPPC	^{11}C	Inhibits microglial proliferation, potential therapeutic target	263,427,428
Cyclooxygenase-1 (COX1)	Ketoprofen methyl ester, PS13, FDF, etc.	^{11}C, ^{18}F	Involved in neuroinflammation.	268,429-434
Cyclooxygenase-2 (COX2)	MC1	^{11}C	Involved in neuroinflammation.	264,429,434
Metabotropic glutamate receptor 1 (mGluR1)	ITMM, MK1312	^{11}C, ^{18}F	Increased in early stage of disease in animal models of PD, not altered in early AD, possibly changed in advanced AD.	435-441
Metabotropic glutamate receptor 5 (mGluR5)	ABP688	^{11}C	Altered in AD, FTD, and amyotrophic lateral sclerosis (ALS).	441-446
Opioid receptors (kappa and mu)	Cyclofoxy	^{18}F	Global decrease in AD.	447
Purinergic P2X7 receptor	JNJ717, JNJ739, SMW139	^{11}C, ^{18}F	Involved in neuroinflammation.	262,265,266,448-450
Purinergic P2Y12 receptor	Not yet any ligand	—	Involved in neuroinflammation.	262,450
Phosphodiesterase-5 (PDE5)	Inhibitors	^{11}C	Therapeutic target in AD.	451
Phosphodiesterase-10 (PDE10)	MP10, AQ28A, MNI-659	^{11}C, ^{18}F	Strongly reduced in striatum in early Huntington's disease.	452-455
Receptor for advanced glycation endproducts (RAGE)	RAGER, INRAGER	^{18}F	Supposed to be involved in early pathophysiological mechanisms leading to AD.	456,457
Sigma-1 receptor	SA4503, FTC-146, FBFP, fluspidine	^{11}C, ^{18}F	Therapeutic target in AD (sigma-1 agonists are cognitive enhancers).	458-464
Sigma-2 receptor	Not yet any suitable ligand	—	Therapeutic target in AD (sigma-2 antagonists are beneficial).	461,465
α-Synuclein	Not yet any suitable ligand	^{11}C, ^{18}F, ^{124}I	Forms aggregates in PD, DLB and multiple system atrophy.	466-476
Triggering receptor expressed on myeloid cells-1 (TREM1)	Not yet any suitable ligand	—	Variant of this receptor is associated with Aß deposition and AD pathology.	477
Tropomyosin receptor kinase	*(R)*-IPMICF16, TRACK	^{11}C, ^{18}F	Downregulated in AD.	478-481

enzyme hexokinase. Since a hydroxyl group in glucose has been replaced by a fluorine atom in FDG, [^{18}F]FDG-6-phosphate is not further metabolized. The return pathway, in which [^{18}F]FDG-6-phosphate is hydrolyzed to [^{18}F]FDG, has a very low activity and is hardly measurable on a PET time scale. Charged [^{18}F]FDG-6-phosphate is thus trapped inside cells and [^{18}F]FDG-PET can be used to assess regional glucose metabolism in the human brain.

Cerebral glucose metabolism reflects the local intensity of glutamatergic synaptic and astrocyte activity.[407-409] [^{18}F]FDG-PET localizes and quantifies brain regions with decreased activity (hypometabolism), mirroring neuronal dysfunction and degeneration.[410] [^{18}F]FDG-PET is a marker of neuronal loss, but does not define the pathology underlying hypometabolism, since the tracer is not disease-specific.[106] However, specific regional patterns of decreased glucose metabolism are associated with certain pathologies, as discussed in another contribution to this issue of Seminars in Nuclear Medicine.[411]

[^{18}F]FDG-PET has been used inconsistently throughout Europe in the clinical diagnostic work-up for the major forms of dementia. The indications for its use vary: (1) for FTD and unexplained dementia in the Netherlands, (2) for the differential diagnosis between AD and vascular dementia or between AD and FTD in Italy, whereas (3) no criteria have been defined in Germany.[412] A recent systematic review concluded that [^{18}F]FDG-PET is unlikely to increase diagnostic certainty in case of classic forms of dementia. Good evidence was found to support its use to differentiate AD from DLB, fair evidence for its capability to discriminate AD from FTD, and poor evidence for its value in atypical forms of AD. The evidence for diagnostic value of [^{18}F]FDG-PET in other forms of dementia was inconclusive.[412] [^{18}F]FDG-PET seems to be useful also for staging of disease and has been recommended in the assessment of subjects with MCI suspected of AD pathology.[409]

[^{18}F]FDG seems to have reached the final clinical validation phase of a PET biomarker: its analytical validation has been completed (phase 1), its clinical validation is nearly completed (phases 2 and 3), and preliminary evidence for its clinical utility has been presented (phase 4 and 5).[413]

Conclusion and Future Perspectives

Significant advances in neuroimaging have been made in the last 15 years. Three tracers for ß-amyloid plaques have already been approved by the Food and Drug Administration and European Medicines Agency. Unfortunately, the development of specific tracers for Aß oligomers has remained a challenge. The development of such tracers is difficult, since the concentration of Aß oligomers in the living human brain is extremely low (<1 nM) and fibrillar Aß is usually present in a very large excess. Several tracers for tau NFTs are already applied in clinical research. For α-synuclein, a third protein that can form pathological aggregates in the human brain and plays an important role in PD, DLB and multiple system atrophy, a useful and approved tracer for in vivo studies is still lacking, although small molecules have been identified with good affinity and selectivity for α-synuclein fibrils compared to Aß and tau (see Table 6 for references). Radioligands for targets involved in other proteinopathies (such as TDP-43, prions, huntingtin) may be developed in due time.

PET allows the quantification of regional cerebral glucose metabolism that is characteristically altered in AD, DLB, and FTD. PET studies with tracers for aggregated proteins, neuroinflammation, proteins involved in neurotransmission, or several novel targets (see Table 6) may result in better classification of neurodegenerative disorders and in accurate monitoring of therapy trials which involve these targets. PET data can be combined with anatomical information (such as cortical thickness, amygdala volume, hippocampal volume) and functional information (regional cerebral blood flow) that is provided by other imaging modalities such as MRI. PET and MRI data can also be supplemented by biomarker values that have been determined by chemical analysis of cerebrospinal fluid samples. PET may play an important role in the early and differential diagnosis of neurodegenerative disease. PET data have prognostic value and may be used to assess the response of the human brain to certain interventions, or to select the appropriate treatment strategy for an individual patient. Since the number of individuals affected by dementia is expected to grow, the application of multimodal imaging including PET may become even more essential in the near future.

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