
Imaging Neuroinflammation in Neurodegenerative Disorders

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Neuroinflammation plays a major role in the etiopathology of neurodegenerative diseases, including Alzheimer and Parkinson diseases, frontotemporal lobar degeneration, and amyotrophic lateral sclerosis. In vivo monitoring of neuroinflammation using PET is critical to understand this process, and data are accumulating in this regard, thus a review is useful. From PubMed, we retrieved publications using any of the available PET tracers to image neuroinflammation in humans as well as selected articles dealing with experimental animal models or the chemistry of currently used or potential radiotracers. We reviewed 280 articles. The most common PET neuroinflammation target, translocator protein (TSPO), has limitations, lacking cellular specificity and the ability to separate neuroprotective from neurotoxic inflammation. However, TSPO PET is useful to define the amount and location of inflammation in the brain of people with neurodegenerative disorders. We describe the characteristics of TSPO and other potential PET neuroinflammation targets and PET tracers available or in development. Despite target and tracer limitations, in recent years there has been a sharp increase in the number of reports of neuroinflammation PET in humans. The most studied has been Alzheimer disease, in which neuroinflammation seems initially neuroprotective and neurotoxic later in the progression of the disease. We describe the findings in all the major neurodegenerative disorders. Neuroinflammation PET is an indispensable tool to understand the process of neurodegeneration, particularly in humans, as well as to validate target engagement in therapeutic clinical trials.

Key Words: molecular imaging; neurology; PET; Alzheimer's disease; neurodegeneration; neuroinflammation; positron emission tomography; TSPO

J Nucl Med 2022; 63:45S–52S
DOI: 10.2967/jnumed.121.263200

Neuroinflammation is being increasingly recognized as a key component of the etiopathology of neurodegenerative diseases, spanning from Alzheimer disease (AD) through Parkinson disease (PD), frontotemporal lobar degeneration (FTD) and amyotrophic lateral sclerosis (ALS) (1,2). However, while PET biomarkers for some of these disorders, such as β -amyloid and tau tracers for AD, are widely used in both clinical and research work, the use of neuroinflammation tracers remains restricted to a small number of research centers. This limited use can be explained by the lack of cellular specificity of the currently used neuroinflammation target, the translocator protein 18 kDa (TSPO); its ubiquity in the brain, which precludes

uptake quantification by comparing a brain region harboring the target with a region devoid of it (3); and the low affinity of the original neuroinflammation PET tracers. However, tracer development, improved quantification (3,4), and the increasing awareness of the importance of neuroinflammation in neurodegenerative disorders have resulted in a sharp increase in the number of publications. For instance, on clinical AD, 4 times as many articles were published between 2021 (the date of this review) and 2013 than between 2013 and 1995 (the date of the first publication). We hope that this review will encourage additional work in this important field. After a description of the characteristics of available PET tracers and their application to the study of various neurodegenerative disorders, we discuss the characteristics and applicability of potentially new PET inflammation biomarkers.

TSPO PET: CURRENT TARGET TO IMAGE NEUROINFLAMMATION

What Is TSPO?

TSPO is an ion-channel-type receptor located on the outer membrane of mitochondria. Initially reported as transporting cholesterol, porphyrin, and Ca^{2+} (5), its function is still under investigation and likely involved in steroidogenesis, apoptosis, mitochondrial respiration, and processing reactive oxygen species (6). TSPO is not selectively expressed by microglia but also by astrocytes, vascular endothelial cells, some neurons, immune cells, and some tumor cells. Thus, frequent statements in papers that TSPO PET measured an increase in “activated” microglia oversimplify the matter (7). Furthermore, some (8,9), but not all (10,11), postmortem studies of AD brains have failed to find significant increases in TSPO, fueling skepticism on the use of TSPO PET to image neuroinflammation in neurodegenerative disorders. But even the negative studies, which contained small samples, showed in some patients much higher TSPO levels in areas typically affected in AD, such as the frontal lobe, than in the cerebellum, little involved in this disorder (8). In other diseases as well, TSPO is increased specifically in areas characteristically affected by the pathology, such as the motor cortex in ALS (12). Thus, despite its limitations, TSPO PET is useful to measure neuroinflammation in neurodegeneration.

PET Ligands to Image TSPO

Since the 1980s initial PET studies on neuroinflammation used ¹¹C-PK11195. However, later, ¹¹C-PK11195 was found to have low specific binding (13,14). Around 2000, a new series of TSPO ligands with different chemical structures was published (15), and subsequently an original chemical, ¹¹C-DAA1106, and analogs such as ¹¹C-PBR28 have been used in PET studies (16,17). PET ligands with different structure have also been developed including ¹¹C-DPA-713 (18). ¹⁸F-GE180, useful for rodent studies, does not penetrate the intact blood–brain barrier in humans (19), with K_1 (rate constant for

Received Jan. 15, 2022; revision accepted May. 3, 2022.
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transfer from arterial plasma to tissue, according to Innis et al. (20) of only 0.01 mL/g/min (21). ^{18}F -GE180 is thus questionable for human studies of neuroinflammation. Radioligands developed after PK11195 are called second-generation PET TSPO ligands. Animal PET studies showed that most of the second-generation ligands have much greater specific binding to TSPO than PK11195 (13).

A limitation of nearly all second-generation TSPO ligands is that binding is affected by the single nucleotide polymorphism (SNP) rs6971 (22). Depending on the SNP they carry, subjects can be high-, mixed-, or low-affinity binders. In low-affinity binders, the low signal precludes useful PET using most ligands. The effect of the SNP needs to be included in the analysis of PET data. Therefore, a potential improvement over the second-generation ligands is to minimize the influence of the SNP.

To select a PET ligand to study changes in TSPO, several factors need to be considered including the equilibrium ratio of specific-to-nondisplaceable binding, BP_{ND} ; influences of radiometabolites in the quantification; and feasibility to measure binding in low-affinity binders. Greater BP_{ND} provides PET signals more sensitive to the changes in specific binding. BP_{ND} is typically measured in animals by comparing scans under baseline and near complete binding blockade. However, because both in vitro and PET studies show large species differences in the density of TSPO (23–25) it is necessary to measure BP_{ND} of each ligand in humans. The Lassen plot allows measurement of BP_{ND} with only partial blockade of the binding, which is unlikely to cause pharmacologic effects (26). Thus, this method has been used in humans for 4 ^{11}C -labeled TSPO ligands: ^{11}C -R-PK11195, ^{11}C -PBR28, ^{11}C -DPA-713, and ^{11}C -ER176 (14). Feasibility of measuring TSPO in low-affinity binders and possible influences of radiometabolites have also been investigated for these 4 ligands (14). On the basis of these most comprehensive investigations in humans so far, ^{11}C -ER176 is the current choice to study TSPO. ^{11}C -ER176 has an adequate BP_{ND} even in low-affinity binders and shows the least influence from radiometabolites.

In neurodegeneration, the permeability of the blood–brain barrier may be altered (27). In theory, because greater permeability increases the movement of chemical compounds both in (K_1) and out (k_2) of the brain, changes in permeability are not expected to influence equilibrium parameters such as BP_{ND} and total distribution volume (V_T).

NEUROINFLAMMATION PET IN NEURODEGENERATIVE DISORDERS

Alzheimer Disease (AD)

The discovery of AD risk genes involved in inflammation signaling (28) has emphasized the critical role of neuroinflammation for the onset and progression of AD. In AD transgenic mouse models, innate immune microglia are initial responders to neuronal release of amyloid- β (A β), activating microglial pattern recognition toll-like receptors, and intracellular NLRP3 inflammasomes, thereby inducing tau hyperphosphorylation and aggregation (1). Subsequent release of truncated phosphorylated tau also enhances immune cell activation, promoting the release of inflammatory mediators and a self-propagating cascade of synaptic dysfunction, neuronal injury, and cell death (1). Current understanding of the role of inflammation in AD stems largely from work with rodents. However, interspecies differences with humans may be large, as shown, for instance, by profiling microglial RNA from frozen AD and control brains (29). In human brain, the proportion of morphologically activated microglia in cortical tissue is associated with

β -amyloid, tau-related neuropathology, and the rate of cognitive decline (30). However, neuroinflammation may be neuroprotective or harmful in neurodegeneration (31). It is possible that the predominant role of inflammation may shift at various stages of AD, being neuroprotective at earlier stages and neurotoxic at advanced stages, but this is yet to be proven in human AD. TSPO PET provides a tool to characterize brain inflammation at the various stages of human AD (Fig. 1). A preclinical stage, when the person is still cognitively unimpaired, but brain β -amyloid is already high, may be most amenable to therapy but has been least studied by PET. As the disease worsens, the patient has mild cognitive impairment, already with some degree of memory or language impairment, but not enough to interfere seriously with activities of daily living as it is in the next stage, clinical AD. Clinical AD, still not severe enough to render the patient uncooperative for brain PET, is the stage at which most early TSPO PET studies were performed and will be described first below. Although single photon emission tomography has been used to image TSPO in AD, most groups have used PET. The 2 tracers most often used have been ^{11}C -PK11195, in 28 publications, and ^{11}C -PBR28, in 16 publications. The first article (32) using ^{11}C -PK11195 in AD was published in 1995 and the first ones (33,34) using ^{11}C -PBR28, in 2013. Several studies have used an arterial input function (Supplemental Table 1; supplemental materials are available at <http://jnm.snmjournals.org>), but in AD the cerebellum is spared until the disease is very advanced and may serve as a pseudoreference region, that is, a region with TSPO receptors but no change in patients (4).

TSPO PET at the Clinical Alzheimer Disease (AD) Stage. At the clinical AD stage, most studies have detected significant neuroinflammation. Brain regions most often affected have been the medial temporal region, including the entorhinal cortex; temporoparietal association cortex, including precuneus; and cingulate cortex (35–37). The localization of inflammation matched the clinical syndrome (37) and correlated negatively with metabolism measured with ^{18}F -FDG PET (35–37). Furthermore, the degree of TSPO uptake correlated with worse cognition (33,38,39), better than the degree of amyloid deposition and, together with the degree of tau deposition, predicted the degree of cognitive worsening over 3 y (40). Inflammation correlated with white matter changes (41) and impaired large-scale functional connectivity on MRI (42).

TSPO PET at the Mild Cognitive Impairment (MCI) Stage. Abnormal TSPO density (43) has not been found as consistently in MCI as in AD, with some studies reporting no difference with controls (33). Most cross-sectional studies reported greater neuroinflammation in the AD than in the MCI stage (36,44), although greater inflammation at the MCI stage has also been reported (45). To this variability may contribute the behavior of neuroinflammation at the MCI stage. A biphasic inflammation peak has been postulated by following MCI patients longitudinally with repeated TSPO PET over 2 y. Some patients with greater initial inflammation had decreased inflammation in the second scan, although their β -amyloid levels continued to rise (31,46). This observation supported the notion that initial inflammation may be neuroprotective (31), a concept supported by slower decline in patients with more initial inflammation at the MCI stage (47) and the inverse correlation between inflammation and neurofilament light levels (48). As at the AD stage, in MCI a negative correlation has been found between regional inflammation and metabolism (49). The relation of TSPO density to a marker of neurodegeneration, cortical atrophy on MRI, is complex. At the AD and MCI stages, inflammation was associated with decreased cortical thickness in the neocortex but

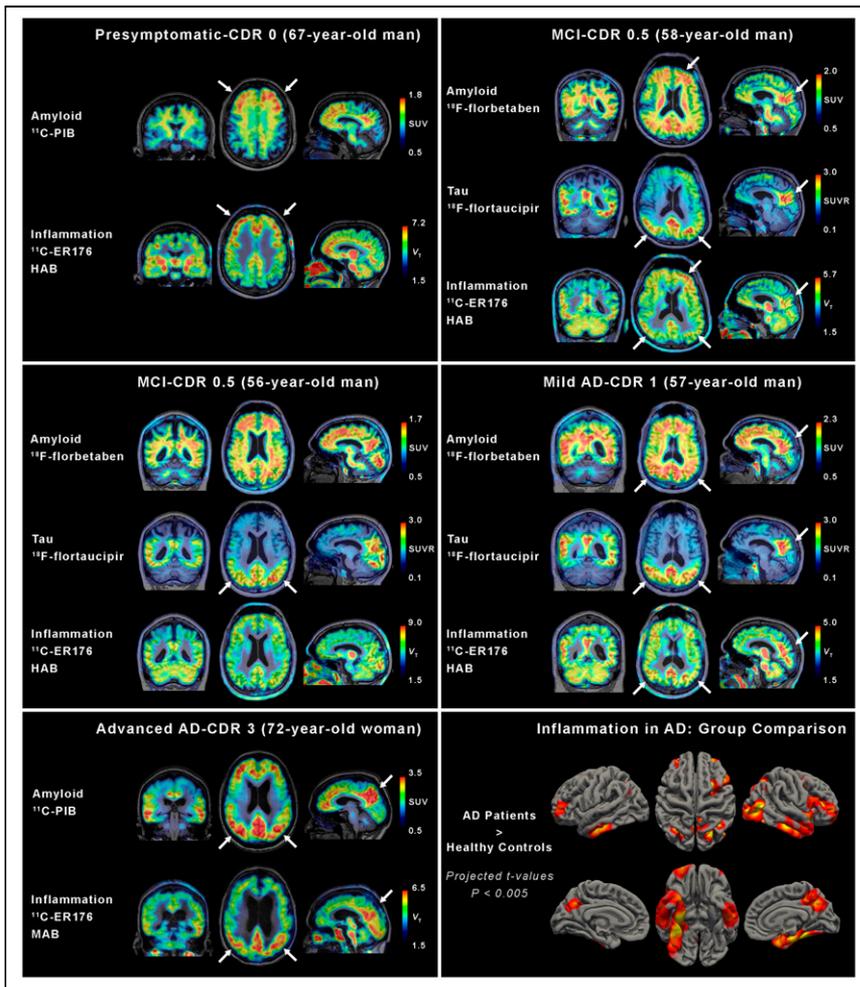


FIGURE 1. Translocator protein 18 kDa (TSPO) PET in AD. Inflammation imaging at presymptomatic, MCI, and dementia stages of AD process. In each subject, multimodal imaging is shown, to illustrate spatial correlation of inflammation, in bottom row of every individual scan, with amyloid and tau imaging. CDR = clinical dementia rating scale; HAB = TSPO-high-affinity binder subject; MAB = TSPO-mixed-affinity binder subject; SUVR = standardized uptake value ratio; V_t = volume of distribution.

not in the hippocampus (50). However, at the early MCI stage, inflammation was associated with increased gray matter volume, including in the hippocampus (51).

TSPO PET at the Presymptomatic Stage. A few studies at the presymptomatic stage, defined by normal cognition but abnormal amyloid brain deposition, have reported variable findings. Although an association of inflammation with amyloid deposition, but not with tau, has been reported in presymptomatic individuals (52), a closer correlation of inflammation with amyloid has been reported at the stage when amyloid PET is still negative, rather than when it becomes positive, although then the absolute level of inflammation is higher (53). This intriguing finding suggests that inflammation may be a very early factor in the neurodegenerative cascade (44), just as shown in experimental animal models.

TSPO PET in Normal Aging. Initial PET studies, when amyloid imaging was not consistently performed, found increased TSPO binding in subcortical structures and, particularly, in the thalamus of cognitively unimpaired older people (54,55). This aging effect may interfere with the interpretation of studies in diseases that affect the basal ganglia, such as corticobasal degeneration or

progressive supranuclear palsy unless controls are closely matched by age. Increased inflammation with aging has also been reported in cortical regions (44,52).

TSPO Versus β -Amyloid and Tau Brain Density. To ensure that the cognitive impairment is due to AD, most groups are currently reporting the β -amyloid and tau status of the subjects studied. Thus, the relation of neuroinflammation to the proteins characteristic of AD is being clarified (Fig. 1). The scant studies at the presymptomatic stage are discussed in the previous section. At the MCI and AD stages, the degree and location of neuroinflammation are correlated with both amyloid and tau deposition but reported r values oscillate around 0.35 for both associations (44), reflecting in part that amyloid and tau deposition are only partially colocalized (45). Inflammation may correlate more closely with amyloid at the MCI stage and with tau at the AD stage (45,46).

Dementia with Lewy-Bodies (DLB)

DLB is characterized clinically by progressive cognitive impairment with fluctuating cognition; visual hallucinations; REM sleep behavior disorder, which may precede cognitive decline; and one or more cardinal features of parkinsonism (56). Pathologically, the protein α -synuclein is present in intraneuronal Lewy bodies and neurites spread throughout the cortex, hippocampus, and amygdala (57). About 50% of DLB patients have associated AD pathology (58). This association is more frequent with advancing age and confers a worse prognosis (58). Several studies have reported increased neuroinflammation (59,60) and a negative correlation between inflammation and metabolism (35,61). A positive correlation with

tau has also been reported (62). Individuals with glucocerebrosidase mutations are predisposed to DLB (63). They have been reported to have increased neuroinflammation (64).

Parkinson Disease (PD)

Clinically, PD presents with bradykinesia, rigidity, and resting tremor. Pathologically, while there are neuronal loss and Lewy bodies in the substantia nigra, these changes are not widespread in the cortex, hippocampus, and amygdala, as they are in DLB. PET TSPO findings have not been uniform. Increased inflammation in the midbrain or other regions of the brain has been found in some studies (61,65) but not in others (66,67). In a large study, it was reported that multiple-system atrophy, which presents with parkinsonian clinical findings, was associated with increased brain ^{11}C -PBR28 uptake, which PD is not, thus allowing for a ready differentiation of either disease (66).

Frontotemporal Dementia (FTD)

This heterogeneous group of diseases, known also as frontotemporal lobar degeneration, encompasses disorders that begin with behavioral, language, or motor impairment and are associated with

tau or TDP-43 deposition in the brain. Neuroinflammation plays a major role in FTD (2) and it has been shown to be increased in the likely location of pathology (68–70), which differs among FTD variants. Thus, inflammation is greatest in the frontal and temporal poles in behavioral variant, premotor cortex in nonfluent primary progressive aphasia, in superomedial convexity in corticobasal degeneration, and temporal lobe in semantic dementia (Fig. 2). Although in semantic dementia the damage begins and is greatest in the temporal tip, inflammation is greatest at the periphery of the affected region, suggesting a major role for inflammation in damage propagation (Fig. 2) (71). In progressive supranuclear palsy, greater neuroinflammation may predict faster worsening (72).

Amyotrophic Lateral Sclerosis (ALS)

Inflammation has been found in the paracentral cortex, which is most affected in ALS (73). Although an abnormal signal was detected with the TSPO tracers ¹¹C-PBR28 and ¹⁸F-DPA714 (12), in a small study no signal was detected in ALS using the purine receptor P2 × 7 tracer ¹¹C-JNJ54173717 (74).

Other Neurodegenerative Disorders

Huntington's Chorea. Genetic testing allows for the determination of the carrier state at the presymptomatic stage of the fully penetrant autosomal dominantly inherited disorder. Some (75) but not others (76) have found increased neuroinflammation in subjects at risk, whereas there is consensus on the presence of neuroinflammation in symptomatic patients (76,77).

Nieman–Pick Disease. In adult Nieman–Pick disease, neuroinflammation was increased in the white matter and correlated with decreased fractional anisotropy (78).

Chronic Traumatic Encephalopathy. Chronic traumatic encephalopathy may be considered to have a neurodegenerative component, as have many other diseases, such as multiple sclerosis. Although these disorders are not covered in this review, some of

the studies of neuroinflammation in chronic traumatic encephalopathy are listed in Supplemental Table 1.

LIMITATIONS OF TSPO PET

As a marker of neuroinflammation, TSPO has 2 major limitations: it is not specific for activated microglia and does not differentiate between microglia that protect or harm neurons.

No Selectivity to Cell Type

Although activated microglia are often considered as the main neuroinflammatory cell, astrocytes play critical roles in neuroinflammation. Both microglia and astrocytes respond to Aβ plaques but the response is different, possibly because microglia respond to the chemotactic effects of Aβ whereas astrocytes respond to neuritic damage (79). Astrocytes are heavily involved in the clearance of Aβ (80). However, close interactions between these 2 types of glia may be linked to neurodegenerative pathology. Activated microglia induce neurotoxic reactive astrocytes (81). The interaction of the microglial receptor TREM2 with lipoparticles is integral for the transfer of cholesterol from astrocytes to microglia (82), and mutations in *TREM2* increase AD risk (83). All these rich interactions are not identifiable by TSPO PET, which provides a snapshot of the regional density in the brain of both microglia and astrocytes.

No Differentiation Between Beneficial and Detrimental Effects of Inflammation

Neuroinflammation has both protective and damaging effects. Although activation of microglia at early stages facilitates phagocytosis of Aβ plaques and maintains neuronal survival, chronic inflammation becomes skewed toward a proinflammatory pattern, which might be neurotoxic (84). Ongoing inflammation may also facilitate phosphorylation and truncation of tau, causing further damage to neurons (85). TSPO PET studies in both humans (reviewed in the section “TSPO PET at the Mild Cognitive Impairment [MCI] Stage”) and mice suggest that TSPO presents 2 peaks in the AD process: an earlier peak, associated with neuroprotection, and a later peak as the disease worsens, associated with neurotoxicity (31,86,87). The 2 facets of inflammation indicate that simple suppression of inflammation may not help AD. Therefore, novel therapies are being developed to shift microglia from neurotoxic to neuroprotective (88).

NEW INFLAMMATION IMAGING TARGETS TO OVERCOME THE LIMITATIONS OF TSPO PET

To overcome these limitations, new and improved imaging markers are being investigated.

Cell-Type Selective Imaging

Colony-stimulating factor 1 receptor (CSF1R) is predominantly expressed by microglia and macrophages and plays a key role in differentiation and survival of immune cells (89). Inhibitors of CSF1R

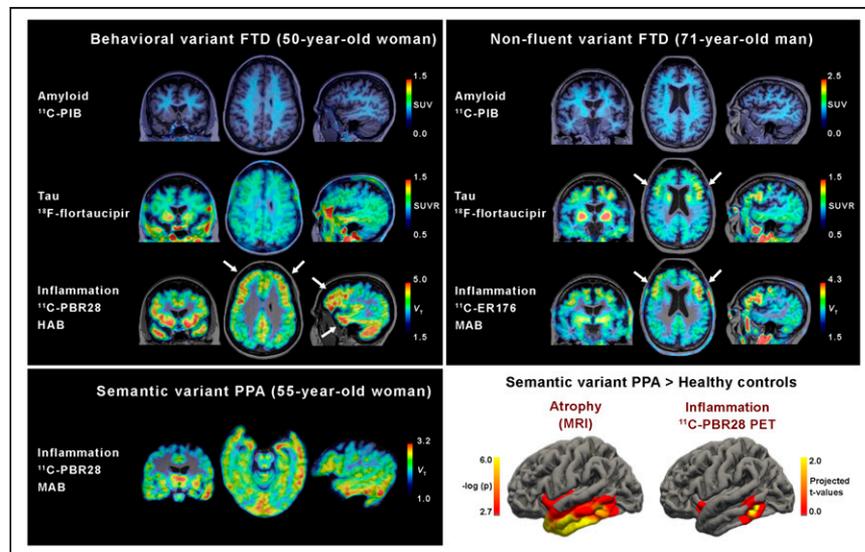


FIGURE 2. TSPO PET in FTD. Inflammation imaging in behavioral variant of FTD and in the nonfluent and semantic variants of primary progressive aphasia (PPA), also categorized as FTD. Amyloid PET was negative in all subjects. In semantic variant PPA, peak of inflammation is at periphery of most affected area, which has atrophy on MRI. HAB = TSPO-high-affinity binder subject; MAB = TSPO-mixed-affinity binder subject; SUVR = standardized uptake value ratio; V_T = volume of distribution. (Lower 2 panels are adapted with permission of (71)).

decrease microglia and prevent loss of neurons and memory (90). A novel ligand, ^{11}C -CPPC, successfully detected an increase in CSF1R in rodent and nonhuman primate after bacterial lipopolysaccharide was administered (91), but it had off-target and low specific binding (92). Another ligand, ^{11}C -GW2580, detected increased microglia in a rodent model of neuroinflammation with greater sensitivity than ^{11}C -CPPC (93).

Monoamine oxidase-B (MAO-B) is a potential PET marker of astrocytes. MAO-B is highly expressed by astrocytes and serotonin (5-HT)-releasing neurons but not by microglia (94). MAO-B is upregulated in reactive astrocytes (95) and correlates with glial fibrillary acidic protein (96). To image MAO-B, L- ^{11}C -deprenyl has been used since the 1980s (97). The irreversible nature of tracer uptake makes the PET measurement more sensitive to blood flow than to the enzyme activity, especially in areas with high MAO-B activity (98). To cope with this limitation, a deuterium-substituted PET tracer, L- ^{11}C -deprenyl-D₂, was developed (97). Still, the specific-to-nondisplaceable ratio of L- ^{11}C -deprenyl is only 1.5 in humans (99). Semiquantitative analyses in healthy humans indicated that a new ligand to image MAO-B, ^{18}F -SMBT-1 (100), has a BP_{ND} of approximately 6, which is about 4 times greater than that of L- ^{11}C -deprenyl (101).

Differentiating Beneficial and Detrimental Effects of Neuroinflammation

Because TSPO PET imaging does not differentiate between beneficial and detrimental effects of neuroinflammation, better PET markers are needed to monitor novel immunomodulatory therapies. For this purpose, potential markers are two adenosine diphosphate (ADP) / adenosine triphosphate (ATP) receptors with markedly different functions, P2X₇ and P2Y₁₂. Both P2X₇ and P2Y₁₂ are highly expressed by microglia. P2X₇ has proinflammatory functions. Increased ATP and ADP in the extracellular space activates P2X₇ and leads to proinflammatory cytokines (102). On the contrary, in basic studies, P2Y₁₂ is used as a marker of homeostatic microglia and may protect neurons by regulating somatic microglia-neuron junctions (103). Postmortem studies on AD showed increased P2X₇ (104,105) and decreased P2Y₁₂ (106), consistent with greater detrimental than neuroprotective effects of neuroinflammation in moderate-advanced stages of AD. To image P2X₇, ^{18}F -JNJ-64413739 (107) and ^{11}C -JNJ54173717 (108) have been successfully used in humans. PET ligands to image P2Y₁₂ are still under development.

OTHER PET MARKERS TO STUDY NEUROINFLAMMATION

In the following, we list a few additional markers of neuroinflammation, for which PET scans have detected specific binding.

Type 2 Cannabinoid Receptor (CB2)

CB2 is involved in immunomodulatory functions and expressed by microglia, astrocytes, and neurons (109). Activation of CB2 shows protective effects against A β (110). Several PET ligands are being developed to image CB2 (111). Among these, the most tested is ^{11}C -NE40, which has been used to compare healthy controls and AD patients and showed a decrease in AD (112). Because type 1 cannabinoid receptor (CB1) is highly and widely expressed in brain, high selectivity against CB1 is required to interpret CB2 PET results.

Mitochondrial Function and Reactive Oxygen Species

Because mitochondrial dysfunction has been reported in neurodegenerative disorders such as AD and PD and linked to neuroinflammation (113), there have been attempts to image mitochondrial activity. The most explored imaging target is mitochondrial complex I (MC1) imaged with ^{18}F -BCPP-EF (114). MC1 is the first enzyme complex in the electron transfer chain, having a critical role in oxidative phosphorylation in mitochondria. AD patients had reduced ^{18}F -BCPP-EF binding in the medial temporal cortex, which negatively correlated with tau (113). Recent attempts to image reactive oxygen species detected an increase induced by the local injection of bacterial lipopolysaccharide (115).

Phosphodiesterase Type 4B (PDE4B)

Cyclic nucleotide phosphodiesterases are enzymes that hydrolyze the second messengers, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate. Among 11 families of PDE, phosphodiesterase type 4, expressed by neurons and immune cells, is one of the main enzymes hydrolyzing cAMP. Among the 4 subtypes, A, B, C, and D, subtype B (PDE4B) is involved in microglial functions in neuroinflammation (116). Proinflammatory cytokines such as IL-1 β and TNF- α increase PDE4B. A PET ligand, ^{18}F -PF-06445974, has been developed to selectively image PDE4B (117).

LINKAGE BETWEEN PERIPHERAL AND CENTRAL INFLAMMATION

In addition to inflammation within the brain, inflammation in peripheral tissue and organs and interactions between peripheral and central inflammation are increasingly being recognized as important in pathogenesis. A pathogen of periodontitis was found in the brain of AD patients (118), and A β protects against microbial infection (119). Gut bacteria are involved in the production of α -synuclein, which accumulates in PD and DLB brain. Newly developed total body scanners allow for the gathering of full dynamic data in both brain and peripheral tissues and organs and open new opportunities to explore interactions between peripheral and central inflammation. In the brain, the choroid plexus is the major component of the blood-cerebrospinal fluid barrier, which may be a major player to connect peripheral and central inflammation (120). The function of the choroid plexus in neuroinflammation and neurodegeneration can be studied by brain imaging.

DISCLOSURE

Joseph Masdeu is a consultant and received research funding from Eli Lilly, parent co. of Avid Radiopharmaceuticals, manufacturer of ^{18}F -flortaucipir. No other potential conflict of interest relevant to this article was reported.

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