JOURNAL OF
NEUROINFLAMMATION

REVIEW   **Open Access**

Mapping neuroinflammation in frontotemporal dementia with molecular PET imaging

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Abstract

Recent findings have led to a renewed interest and support for an active role of inflammation in neurodegenerative dementias and related neurologic disorders. Detection of neuroinflammation *in vivo* throughout the course of neurodegenerative diseases is of great clinical interest. Studies have shown that microglia activation (an indicator of neuroinflammation) may present at early stages of frontotemporal dementia (FTD), but the role of neuroinflammation in the pathogenesis of FTD is largely unknown. The first-generation translocator protein (TSPO) ligand ($[^{11}C]$-PK11195) has been used to detect microglia activation in FTD, and the second-generation TSPO ligands have imaged neuroinflammation *in vivo* with improved pharmacokinetic properties. This paper reviews related literature and technical issues on mapping neuroinflammation in FTD with positron-emission tomography (PET) imaging. Early detection of neuroinflammation in FTD may identify new tools for diagnosis, novel treatment targets, and means to monitor therapeutic efficacy. More studies are needed to image and track neuroinflammation in FTD. It is anticipated that the advances of TSPO PET imaging will overcome technical difficulties, and molecular imaging of neuroinflammation will aid in the characterization of neuroinflammation in FTD. Such knowledge has the potential to shed light on the poorly understood pathogenesis of FTD and related dementias, and provide imaging markers to guide the development and assessment of new therapies.

Keywords: Frontotemporal dementia, Neuroinflammation, Microglia, Translocator protein, Molecular imaging

Background

Frontotemporal dementia (FTD) is a devastating neurodegenerative disorder, primarily affecting the frontal and/or temporal lobes of the brain. It is the second most frequent cause of presenile neurodegenerative dementia in those less than 65 years of age [1]. The prevalence is around 15 per 100,000 in people between 45 and 65 years of age, and the mean survival varies from 3 to 10 years from diagnosis [2]. There are mainly three types of FTD: behavioral variant FTD (bv-FTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA), and they are common in the aggregation of neuronal proteins such as the microtubule-associated protein tau (MAPT), the transactive response DNA-binding protein with molecular weight 43 kDa (TDP-43), and the fused in sarcoma protein (FUS) [3]. Of the FTD cases, 25% to 50% are inherited [4], and the mutations are in the genes

for MAPT, progranulin (GRN), and in the chromosome 9 open reading frame 72 (C9orf72) [3].

The clinical diagnosis of FTD is a challenge. In general, from symptom onset, it takes 4 years for bv-FTD and SD, and 3 years for PNFA to reach a correct diagnosis [5]. FTD is often misdiagnosed as Alzheimer's disease (AD) or psychiatric disorders. Abnormalities in structural imaging may be very subtle at early stages, while functional imaging changes may not be specific enough to differentiate FTD from AD at individual patient level. For example, failure to correctly diagnose FTD and AD often occurs in cases that present with temporoparietal hypometabolism [6]. Currently, there is no effective pharmacological treatment to slow the progression of FTD. Prognosis is therefore poor, and dependency on caregivers and eventual death typically occurs in a few years after diagnosis [2,3].

Leading models have highlighted the potential neurotoxic properties of tau aggregation in FTD [7] and related neurodegenerative dementias [8,9]. Recent findings have led to a renewed interest and support for an active role of inflammation in neurodegenerative processes [10]. In AD,

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chronic neuroinflammation appears to be a central process in AD pathophysiology [11,12], and there are promising targets in modulation of neuroinflammation for AD treatment [12]. Further, a link has been proposed recently between neuroinflammation and specific forms of FTD, suggesting that neuroinflammation is an important component of FTD [10,13]. Consequently, early detection of neuroinflammation in FTD may identify new tools for diagnosis, novel treatment targets, and means to monitor therapeutic efficacy.

Pathological protein aggregation and neuroinflammatory responses may begin before patients start experiencing AD or FTD symptoms [10,11]; thus, neuroinflammation could be an early marker for neurodegenerative dementias. Since the neuroinflammatory response may mediate the outcome of brain tissue in many neurologic diseases including stroke, epilepsy, and neurodegenerative disorders, it is of great clinical interest to detect neuroinflammation accurately and reliably [14]. Positron-emission tomography (PET) imaging with radioligands that label activated microglia, a key cellular component of the neuroinflammatory response, offers a potential means to characterize neuroinflammation *in vivo*. Increases in the translocator protein (TSPO, 18 kDa) expression detected by PET imaging with radioligands of TSPO or peripheral benzodiazepine receptor (PBR) is recognized as a biomarker of activated microglia [15], which might aid in the diagnosis of early FTD. In this paper, the existing evidence on neuroinflammation in FTD and PET imaging of neuroinflammation in FTD with TSPO ligands is reviewed and related technical issues are discussed.

Neuroinflammation in FTD

Compared with healthy subjects and AD patients, an increased prevalence of related autoimmune diseases has been reported in FTD patients with semantic variant primary progressive aphasia (svPPA) who were GRN mutation carriers [13,16]. It has also been found that a proapoptotic protein (regulated partially by vasoactive neuropeptides) in astrocytes called Bax showed immunoreactivity in FTD, which suggested autoimmunity in the pathology of FTD [17]. In tau-negative FTD, neuroinflammation may play a more important role in the pathogenesis of FTD because mutations in the progranulin (GRN) genes lead to tau-negative FTD [10]. Progranulin acts as a mediator of the inflammatory response [18], and deficiency in progranulin may lead to greater microglial activation and a dysregulated inflammatory response in microglia that could cause neuron death and disease progression in FTD [10]. In addition, head trauma that triggers neuroinflammation has been associated with behavioral variant FTD [19]. Furthermore, some biomarkers of inflammation, such as elevated cytokines

(for example, tumor necrosis factor (TNF)-α) in the cerebrospinal fluid (CSF), have been observed in patients with FTD [20]. These findings support the hypothesis that neuroinflammation has a detrimental role in FTD [10]. However, the pathogenesis of FTD, in particular the role of neuroinflammation, is still poorly understood.

Microglia are the resident immune cells in the central nervous system (CNS), representing the first line of defense against pathogens: they sense subtle pathological changes and become activated before obvious functional or anatomical abnormalities occur. Normal protective microglia mediate clearance of abnormal protein (such as Aβ or tau) aggregates, remove cell debris, and promote neuroregeneration. However, activated microglia secrete inflammatory mediators (for example, interleukin (IL)-1β), coactivate astrocytes, and induce neuronal death, which further increases brain tissue damage with amplified microglial activation [14]. The neuroinflammatory reaction involves dramatic upregulation of a mitochondrial transmembrane protein, TSPO, which is a marker for microglial activation and a target for imaging neuroinflammation with PET ligands designed to bind TPSO. It has been reported that PET imaging with the widely used first-generation TSPO ligand [11C]-PK11195 detected neuroinflammation in patients with mild cognitive impairment (MCI) [21]. This and other evidence [22-25] suggests that neuroinflammation is an early and continuous process in neurodegenerative dementias [26]. It is now known that microglia detect pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs), and in neurodegenerative disorders, microglia cannot discriminate between invading pathogens and aberrant molecules (or abnormal proteins) of the host, which leads to DAMP-triggered neuroinflammation through sustained and excessive release of pro-inflammatory cytokines such as IL-1β [10]. In addition, age-related microglia priming is crucial in exaggerated neuroinflammation [27], and microglial activation may be related to dementia progression [28].

Genes related to microglial activation (for example, a variant of the triggering receptor expressed on myeloid cells 2 (TREM2)) have now been associated with FTD [29,30]. Abnormal protein aggregates such as amyloid or tau deposition could cause microglial activation. New hypothesis has suggested that microglia could be functionally impaired by abnormal protein aggregates, leading to reduced microglial motility and phagocytic activity *in vivo* [31]. There is evidence that sustained exposure to bacterial lipopolysaccharide (LPS) or other pro-inflammatory mediators restricts microglial phagocytosis of protein aggregation and suppresses axonal transportation [10]. Several animal studies and *post-mortem* studies have revealed that neuroinflammation

stimulated neuronal degeneration [32,33]. On the other hand, microglia-driven neuroinflammation could lead to the formation of tau aggregation [34]. In FTD, the neuronal and axonal degeneration are sufficient to induce microglial activation [19].

Few studies to date have examined neuroinflammation *in vivo* in FTD patients. Molecular PET imaging with [11C]-PK11195 has found that compared with controls, the mean [11C]-PK11195 binding was significantly increased in patients with FTD (*n* = 5, including four patients with progressive non-fluent aphasia and one patient with behavioral variant FTD) in regions such as the left dorsolateral prefrontal cortex and the right hippocampus and parahippocampus [35]. The pattern of microglial activation partially overlapped with the pattern of brain atrophy, but there was also increased [11C](R)-PK11195 binding in regions contralateral to predominant lobar atrophy suggesting that microglial activation was present at early stages of FTD prior to anatomical changes [19]. Using *postmortem* brain tissues, Vennetic *et al.* found that [11C]-PK11195 binded specifically to activated microglia in FTD, and the binding was correlated with microglial activation identified by immunohistochemistry *in situ* [36]. *Postmortem* immunohistochemistry study further demonstrated that compared with controls, higher level of microglial activation detected by [11C]-PK11195 was found in the frontal and temporal cortex in patients with FTD (*n* = 78), and greater microglial activation was found in the temporal subcortical white matter in FTD-MART than in other FTD genetic types [37].

In neurodegenerative disorders such as FTD, there is a common pattern in the mechanisms of sensing abnormal protein aggregates, activating microglia, transducing to the release of cytokines, and amplifying the neurotoxic effects in a chronic inflammatory process [14]. A better understanding of the immune response in the brain is critical for possible modulation of microglial activity to slow down or reverse the course of neurodegeneration [14]. Further development of PET imaging with TSPO ligands represents a potential *in vivo* tool for tracking the progression of neuroinflammation in neurodegenerative disorders such as FTD.

Molecular PET imaging with second-generation TSPO ligands

The value of TSPO PET imaging is in detecting microglia activation in the diseased brain, visualizing neuroinflammation and its progression, and monitoring treatment effect, which is highly needed in the diagnosis and treatment of FTD. TSPO is an interesting target for molecular PET imaging because it is involved in a number of neurodegenerative disorders (such as AD, FTD, and Parkinson's disease (PD)) and neuroinflammatory disorders (such as

ischemic stroke and multiple sclerosis). However, there are several limitations in the first-generation TSPO ligand [11C]-PK11195, mainly high non-specific binding, low brain penetration, and high plasma protein binding, which may explain the negative findings in several studies using [11C]-PK11195 [38,39]. In recent years, novel tracers such as [11C]-DAA1106, [11C]vinpocetine, [11C]-DPA-713, [11C]-PBR28, [18F]-FEDAA1106, [18F]-PBR06, [18F]-PBR111, [18F]-DPA-714, and [18F]-FEPPA have been developed as the second-generation TSPO radioligands. Comparative studies showed that novel TSPO ligands such as [18F]-DPA-714 have higher specific binding and lower non-specific binding than [11C]-PK11195 in rodent models [40,41]. Further, Venneti *et al.* reported that [3H]-DAA1106 showed a higher binding affinity than [11C]-PK11195 in *postmortem* brain tissues of patients with neurodegenerative disorders such as FTD [36]. Similarly, Vas *et al.* found higher binding of [11C]vinpocetine than [11C]-PK11195 in patients with multiple sclerosis [42]. These findings suggest that the second-generation TSPO ligands are better than the first-generation TSPO ligand [11C]-PK11195 in imaging activated microglia *in vivo* in neurodegenerative disorders due to improved pharmacokinetic properties [36].

In recent years, PET imaging with novel TSPO radioligands has been applied to visualizing neuroinflammation in neurodegenerative disorders, although there is very limited data on *in vivo* PET imaging with the second-generation TSPO tracers in FTD. Using PET imaging with [11C]-DAA1106, Miyoshi *et al.* examined patients with FTD (*n* = 3) who were presymptomatic MART gene carriers with parkinsonism linked to chromosome 17 (FTDP-17) and found increased microglial activation in regions such as frontal cortex in patients compared with controls, although such increase was not overt throughout the diseased brain in FTD [43]. In addition, regional increased [11C]-DAA1106 binding has been found in patients with MCI (*n* = 7) compared to healthy controls [22], and patients with AD (*n* = 19) had greater regional [11C]-PBR28 binding than controls, which was correlated with severity of the disease [44]. These findings suggest that neuroinflammation is an intrinsic process in tau pathology, which exists even at a presymptomatic stage.

However, research on imaging neuroinflammation with the second-generation TSPO ligands is still in its infancy, and the sample sizes of such research are usually small. *In vivo* and *in vitro* studies with the second-generation TSPO ligands have shown significant inter-subject variability because of differences in binding affinity in individual subjects [44-47]. Three affinity patterns of binding variations have been reported: high-affinity binders (HABs), low-affinity binders (LABs), and mixed-affinity binders (MABs) [47,48]. A single polymorphism (rs6971) located in the exon 4 of the TSPO gene determines the binding affinity

of the second-generation ligands and causes large inter-subject variation [44,49,50], while for the first-generation TSPO ligand [11C]-PK11195, the inter-subject variation in binding affinity is little.

Compared with carbon-11-labeled TSPO ligands (for example, [11C]-PK11195), tracers labeled with fluorine 18 have a longer half-life ([18F] vs. [11C]: approximately 110 min vs. approximately 20 min), which is suitable for long-distance dissemination and larger clinical studies. Among the fluorine-18-labeled second-generation TSPO ligands, [18F]-FEDAA1106 has proved ineffective [51,52] and [18F]-PBR06 produces a metabolite that confounds quantification of TSPO binding [53], but [18F]-FEPPA (FEPPA) and [18F]-DPA-714 (DPA714) may be promising [54-56]. FEPPA PET imaging has been applied to animals [54,57-62] and humans [63-70] and has demonstrated that increased neuroinflammation was not associated with normal aging, but regional increased FEPPA uptake was associated with AD or PD [67-70]. Similarly, there are a number of PET imaging studies with [18F]-DPA-714 [40,56,71-79], and focal increase in DPA714 uptake has been found in patients with neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) [78].

Taken together, although in its infancy, research on PET imaging with the second-generation TSPO ligands is in progress and has shown increased uptake in brain regions associated with neuroinflammation in early FTD and other neurodegenerative disorders such as those of tau pathology (even at a presymptomatic stage), suggesting that TSPO imaging is useful in detecting neuroinflammation *in vivo* from the early stage of the disease.

Discussion

In neurodegenerative and neuroinflammatory disorders, microglia activation may be an early phenomenon, which can be visualized by PET imaging with TSPO ligands, and the second-generation TSPO ligands have shown improved pharmacokinetic properties. However, to image neuroinflammation in FTD using PET with the second-generation TSPO ligands, several practical issues or technical details need to be considered.

First, since PET imaging with the second-generation TSPO ligands display inter-subject variability in binding affinity, the genotype at the polymorphism (rs6971) in the TSPO gene needs to be determined. Subjects may need to be screened for LABs because the second-generation TSPO ligands do not provide a measureable signal in PET studies involving LABs. The ratio of LABs in healthy subjects varies from 0% [66] to 13.3% [80], and the ratio of LABs in one sample of AD patients was 15.4% [67]. Therefore, genotype analysis for polymorphism

(rs6971) in the TSPO gene is needed before PET imaging scan, and a small portion of subjects with LABs may need to be excluded from PET imaging with the second-generation TSPO ligand.

Second, most of the human studies with fluorine-18-labeled second-generation TSPO ligands used scan acquisition times of 1.5 to 2 h which might be long for patients with FTD. In attempts to reduce FEPPA PET scan time, Rusjan *et al.* have found increased variability and decreased identifiability (with the average coefficient of variance ratio 14% for total distribution volume V(T)) with 1.5-h scan time [64]. However, the average of V(T) were not significantly biased compared with those of 2-h scanning, and the V(T) values at 1.5 h were correlated with the values at 3 h ($r^2 = 0.91$) [64], suggesting that 1.5-h or shorter scan time might be possible if relative measures (for example, distribution volume ratio) are used.

Third, current PET imaging with the second-generation TSPO ligands usually requires arterial blood sampling to determine the blood radioactivity time-activity curve (TAC) and plasma radioactivity curve so that the input function for the kinetic analysis can be created to compute the ligand uptake and binding potential. Such invasive kinetic analysis is technically demanding, and uncomfortable and potentially painful to patients. To avoid the need for arterial blood sampling, it is necessary to apply non-invasive quantitative models that use radioactivity concentration in a reference region (that is, brain area with negligible binding) to approximate concentration of tracer in the non-displaceable compartment as an indirect input function [80-86]. However, microglia cells and the TPSO ligand binding sites are distributed throughout the entire brain, and a reference region can hardly be found in the brain.

In the past, the first-generation TSPO ligand [11C]-PK11195 (PK11195) faced similar difficulties. Turkheimer *et al.* developed a non-invasive analysis method for PK11195 PET using reference and target region modeling where predefined kinetic classes were used to extract a gray matter reference tissue [87]. They found that binding potential values obtained by a plasma input were highly correlated with those of a reference input [86]. Since then, non-invasive kinetic analysis has been increasingly adopted in PK11195 PET imaging, and arterial blood sampling is no longer needed. Therefore, it is possible to apply non-invasive kinetic analyses such as the reference approach to PET imaging with the second-generation TSPO ligands [87]. However, there are mainly two challenges: (1) Since the kinetics of HAB and MAB genetic groups may differ, a database of reference for both HAB and MAB groups may be needed; (2) The second-generation TSPO ligands show high level of vascular binding [88], which may

make it difficult to separate the normal gray matter from other tissue classes.

Finally, it is unclear how accurate TSPO PET imaging is in detecting neuroinflammation in neurodegenerative dementias. There are on-going clinical trials with TSPO ligands such as FEPPA [89-91], [^{11}C]PBR28 [92], and [^{18}F]PDA-714 [93] in neurodegenerative disorders (one study including FTD). However, published results of these studies are not available yet. There is a need not only for tracking neuroinflammation in FTD with TSPO PET imaging, but also for assessing the accuracy of TSPO imaging in detecting neuroinflammation in FTD. This is especially needed for subtypes within FTD that may have unique molecular mechanisms related to neuroinflammation (that is, progranulin mutations).

Conclusions

Recent molecular advances in the pathophysiology of the FTD have led to new disease models highlighting the potential role of pathologic neuroinflammation in disease onset and progression. PET imaging with the second-generation TSPO ligands offers a potentially powerful means to identify neuroinflammatory patterns *in vivo* across the FTD subtypes. More studies are needed to image and track neuroinflammation in FTD, which may aid in the diagnosis of early FTD. It is anticipated that the advances of molecular imaging of brain TSPO will overcome technical difficulties and that molecular imaging of neuroinflammation could aid in the characterization of neuroinflammation in FTD, increase our understanding of disease pathogenesis, and inform development and testing of novel therapeutic interventions.

Abbreviations

AD: Alzheimer's disease; ALC: acetyl-L-carnitine; ALS: amyotrophic lateral sclerosis; bv-FTD: behavioral variant FTD; CNS: central nervous system; DPA714: [^{18}F]-DPA714; FEPPA: [^{18}F]-FEPPA; FTD: frontotemporal dementia; FUS: fused in sarcoma protein; GRN: progranulin; HAB: high-affinity binders; IL: interleukin; LAB: low-affinity binders; MAB: mixed-affinity binders; MAPT: microtubule-associated protein tau; MCI: mild cognitive impairment; MS: multiple sclerosis; PD: Parkinson's disease; PNFA: progressive non-fluent aphasia; svPPA: semantic variant primary progressive aphasia; TDP: transactive response DNA-binding protein; TNF: tumor necrosis factor; TSPO: translocator protein.

Competing interests

The author declares no competing interests.

Author's contributions

JZ contributed to the drafting of the main text and producing the references. The author read and approved the final manuscript.

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