Nucl Med Mol Imaging (2017) 51:283–296
DOI 10.1007/s13139-017-0475-8

REVIEW

ISSN (print) 1869-3482
ISSN (online) 1869-3474

Recent Progress in the Development of TSPO PET Ligands for Neuroinflammation Imaging in Neurological Diseases

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Received: 11 October 2016 / Revised: 8 December 2016 / Accepted: 6 February 2017 / Published online: 16 March 2017

Abstract Neuroinflammation is heavily associated with various neurological diseases including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and stroke. It is strongly characterized by the activation of microglia which can be visualized using position emission tomography (PET). Traditionally, translocator protein 18 kDa (TSPO) has been the preferred target for imaging the inflammatory progression of the microglial component. TSPO is expressed in the outer mitochondrial membrane and present in very low concentrations in the healthy human brain, but is markedly upregulated in response to brain injury and inflammation. Due to its value as a marker of microglial activation and subsequent utility for evaluating neuroinflammation in CNS disorders, several classes of TSPO radioligands have been developed and evaluated. However, the application of these second-generation TSPO radiotracers has been subject to several limiting factors, including a polymorphism that affects TSPO binding. This review focuses on recent developments in TSPO imaging, as well as current limitations and suggestions for future directions from a medical imaging perspective.

Keywords Microglia activation · Molecular imaging · Neuroinflammation · PET radioligand · Translocator protein

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Introduction

Emerging evidence suggests that neuroinflammation is associated with a number of neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and HIV-associated dementia, as well as stroke and neuro-psychiatric disorders [1–3]. Neuroinflammation is characterized by microglial activation, although astrocytes are also associated with neuroinflammation. Microglia are a type of glial cell present throughout the brain and spinal cord, and act as the primary line of immune defense for the central nervous system (CNS) [4]. The purpose of neuroinflammation is to localize and eliminate harmful agents and initiate tissue repair. However, in some cases, the process of neuroinflammation itself contributes to the development of disease. In response to various forms of neuronal damage within the CNS, microglia become activated and migrates to the site of injury, where they can undertake phagocytic and protective roles to maintain homeostasis and prevent further impairment [5].

Inflammation can also contribute to the pathophysiology of epilepsy in the brain [6]. Epilepsy comprises a set of chronic neurological disorders characterized by seizures. Several studies have suggested that seizures promote inflammation in the brain, resulting in the upregulation of reactive microglial cells and astrocytes, and the production of pro-inflammatory cytokines such as interleukin (IL)-1, and IL-6, as well as tumor necrosis factor-alpha (TNFα) [7]. In addition, seizures can inflict damage on the blood brain barrier (BBB), which may contribute to further inflammation and hyper excitability via astrocyte involvement.

Positron emission tomography (PET) radiotracers have been developed to detect microglial activation and have proven to be useful as noninvasive molecular imaging tools to

assess neuroinflammation. Over the past decade, several neuroinflammatory targets have been identified and their corresponding tracers developed. The translocator protein 18 kDa (TSPO) has emerged as the gold standard as the best PET imaging target for neuroinflammatory events in neurodegenerative diseases. Detection of this protein allows for the evaluation of activated microglia in the brain, and it was historically known as the peripheral-type benzodiazepine receptor (PBR). Existing as a hetero-oligomeric complex present on the outer mitochondrial membrane [8], it interacts with various other proteins at the mitochondrial permeability transition pore (MPTP), including association with the voltage-dependent anion channel (VDAC) and adenine nucleotide translocase (ANT), together with which it forms a transmembrane hyper structure [9, 10].

A number of novel approaches in imaging technology have been developed for use in both animal models and humans. Among imaging modalities, PET is the most sensitive technique that can presently be used in vivo for detecting microglial activation and provides quantitative information based on a ligand-receptor interaction [11]. While the resting microglia has moderate TSPO expression in the healthly brain, it is precipitously increased in association with inflammatory disease and injury [12]. When microglia are activated in response to injury, an upregulation of mitochondrial TSPO expression typically occurs, which serves as a marker of inflammation associated with numerous neurological diseases including AD, PD, MS and stroke [13–15]. The use of selective and high-affinity TSPO radioligands together with PET represents powerful tools for visualizing the process of microglial activation in the living brain. Functionally, TSPO has been associated with several physiological processes including cholesterol transport, steroidogenesis, mitochondrial oxidation, cell growth and differentiation, neoplastic pathologies involving numerous types of cancer and neurodegenerative diseases. Therefore, TSPO has proved to be not only a therapeutic target but also a particularly relevant diagnostics target, leading to the development of specific radioligands and biomarkers of neuroinflammation of molecular imaging of PET.

The objective of this review is to summarize recent advances in PET imaging of activated microglia using TSPO ligands for the investigation of neurodegenerative diseases. A review of existing tracers, current limitations, emerging TSPO tracer development and suggestions for future direction are also explored.

PET Radioligands for TSPO

The development of new labeled TSPO ligands with short-lived positron-emitter isotopes ^{11}C and ^{18}F emerged in the mid-1980s. A number of these radiolabeled TSPO ligands have been developed for in vivo imaging, primarily in humans and mouse models [13–15] (Figs. 1 and 2).

First Generation TSPO Tracers in Neurologic Disease

Benzodiazepines

Ro5-4864 is a 4′-chlorodiazepam-class molecule, and was the first ligand able to discriminate the peripheral benzodiazepine receptor from the central benzodiazepine receptor (CBR). Initially, PET studies of [^{11}C]Ro5-4864 in patients with brain tumors did not show great promise due to its high nonspecific binding and low in vitro affinity in human brain tissue [16]. The nonspecific binding is thought to arise from lipophilic and electrostatic interactions between the radioligand and brain tissue, especially in white matter. It has also been found that the binding affinity of [^{3}H]Ro5-4864 is both temperature- and species-dependent while that of [^{3}H]PK11195 is not, resulting in markedly different results between rat models and clinical application [17, 18]. These findings clearly indicate its limitations as a tool for TSPO PET imaging.

Isoquinoline Carboxamide

PK11195 is an isoquinoline carboxamide and in 1984 was the first non-benzodiazepine-type compound to be radiolabeled ([^{11}C]PK11195) [19]. It was initially used as a racemate with high affinity ($K_i = 9.3$ nM) and selectivity to TSPO, and has since found utility in a number of animal and clinical studies [20]. Further in vivo studies determined that the (*R*)-enantiomer ([^{11}C](*R*)-PK11195) shows a twofold higher affinity in rats than the corresponding *S*-isomer, giving it superior properties for imaging studies [21]. Although both PK11195 and Ro5-4864 bind selectively to TSPO with nanomolar binding affinity, they differ substantially in their kinetics and pharmacological profiles, which exhibit saturable and reciprocal competitive binding properties. Furthermore, the maximum density and affinity characteristics of [^{3}H]PK11195 are threefold higher compared to [^{3}H]Ro5-4864 for the human binding site region [22]. These ligands are thought to bind to heterogeneous sites on TSPO either in an overlapping or allosterically-coupled manner. Subsequent studies [^{11}C](*R*)-PK11195 have been successfully conducted for diseases as diverse as MS, AD, PD, amyotrophic lateral sclerosis (ALS), HIV, Rasmussen's encephalitis, herpes encephalitis, and neuropsychiatric disorders such as schizophrenia [23] (see [13–15] for review). Quantitative analysis of [^{11}C](*R*)-PK11195 in AD patients showed significantly increased binding in the entorhinal, temporoparietal, and cingulate cortex when compared with normal controls exhibiting only an age-dependent increase in the thalamus. Activation of the

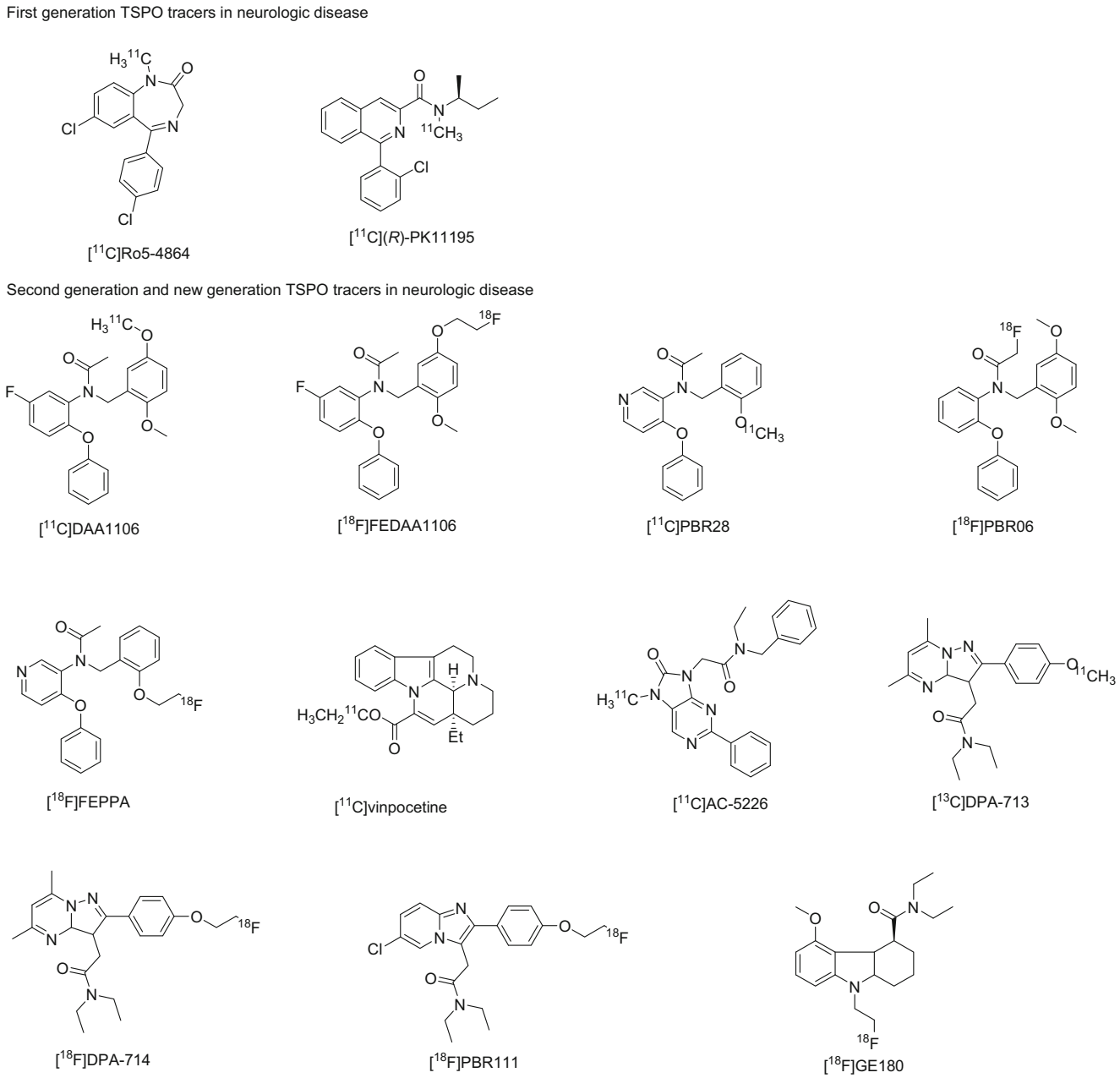

Fig. 1 First and second generation TSPO PET radioligands used for human studies

microglia, which correlates with the degree of uptake and disease progression, leads to progressive increases in TSPO binding, and is associated with early Alzheimer's pathogenesis [24].

However, several kinetic and methodological issues have restricted the interpretation and potential use of this radioligand [6]. First, PK11195 has relatively low receptor affinity and engages in a high level of nonspecific binding due to its lipophilic nature, which leads to a poor signal to noise ratio and low specificity in PET imaging. Moreover, relatively low brain uptake and poor penetration of the BBB can further exacerbate this issue. Yet another issue is that [^{11}C](*R*)-PK11195 exhibits highly variable kinetic behavior that further limits quantitative analysis of microglial activation [21]. ^{11}C also has a very short half-life compared to ^{18}F, which has negative implications for more widespread clinical use.

Second Generation TSPO Tracers in Neurologic Disease

Extensive research efforts over the past decade have led to the development of several second generation TSPO ligands that have arisen from other structural classes, with superior

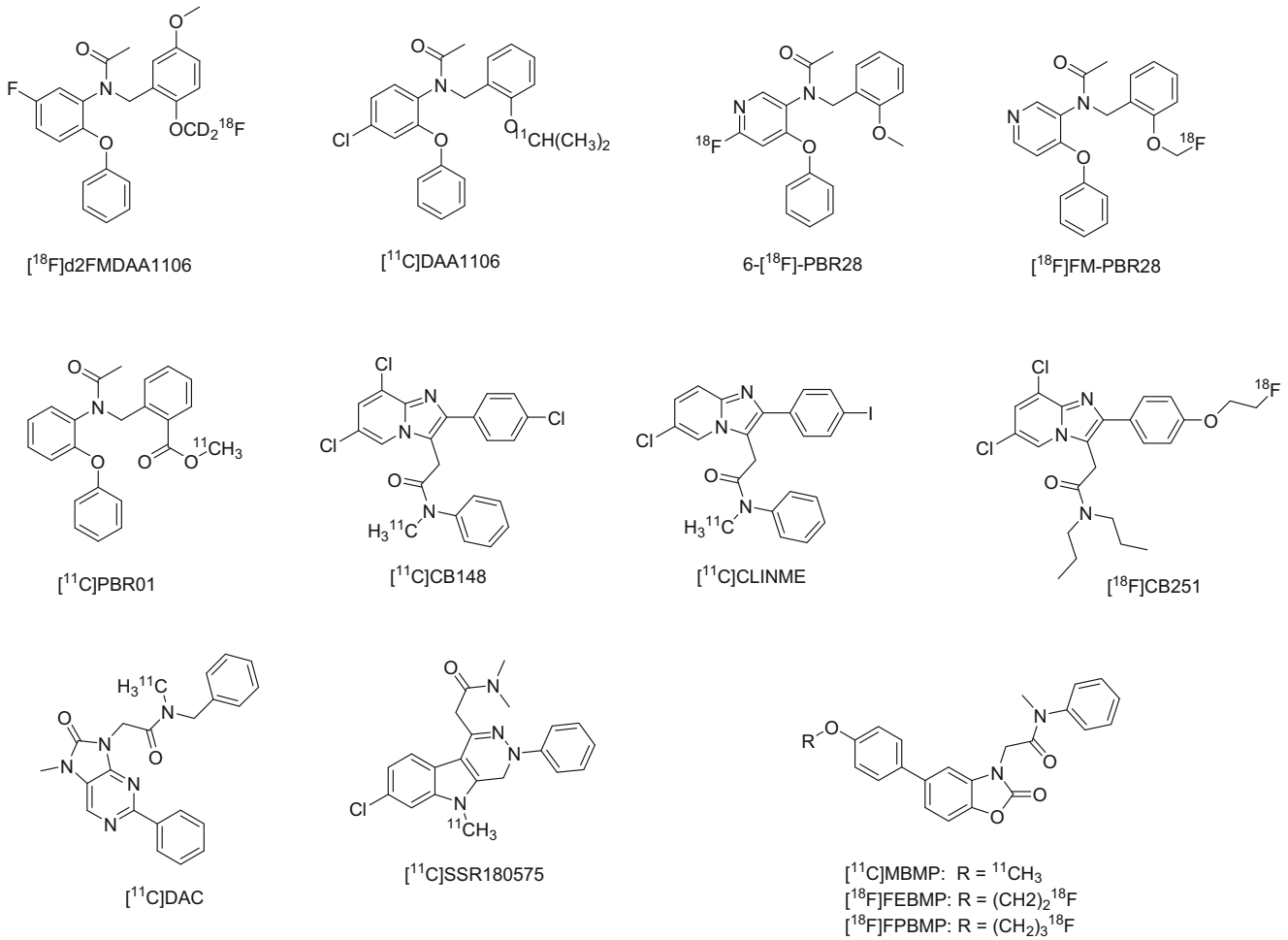

Fig. 2 Second and new generation TSPO tracers in various stages of development

imaging characteristics (higher affinity and lower lipophilicity). These radiotracers include [^{11}C]DAA1106, [^{18}F]FEDAA1106, [^{11}C]PBR28, [^{11}C]DAA1097, [^{18}F]PBR06, [^{11}C]PBR01, [^{18}F]FEPPA, 6-[^{18}F]-PBR28, [^{18}F]FM-PBR28, [^{11}C]AC-5216, [^{11}C]DAC, [^{11}C]DPA-713, [^{18}F]DPA-714, [^{18}F]VUIIS1008, [^{11}C]CLINME, [^{11}C]CB148, [^{18}F]CB251, and [^{18}F]PBR111, and are in various stages of development and are being evaluated in humans. With the purpose of improving signal to nose ratios, a number of ^{11}C and ^{18}F-labeled radiotracers have been utilized in preclinical and early clinical studies of neurologic and oncologic diseases with varying degrees of success [13], (Table 1).

Acetamides

[^{11}C]DAA1106 is a novel class of phenoxyarylacetamide derivative with high specificity for TSPO, and was derived on the opening of the diazepine ring of Ro5-4864 [25]. As a second generation ligand, it has high affinity and selectivity for TSPO over [^{11}C](*R*)-PK11195. The effects of the TSPO ligand on [^{3}H]DAA1106 binding for TSPO in the mitochondrial fraction of rat ($K_i = 0.04 \pm 0.00$ nM) and monkey ($K_i = 0.18 \pm 0.02$ nM) brain cerebral cortexes are comparable with PK11195 (rat vs monkey 0.76 ± 0.11 vs 0.73 ± 0.13 nM), although Ro5-4864 has shown poor binding with TSPO in animal models [26]. Similar studies focusing on in vivo imaging of [^{11}C]DAA1106 in healthy mouse brain [27] and kainic acid-lesioned rats [28] revealed specific binding demonstrated by blockage with [^{3}H]PK11195. Four times higher uptake in vivo than [^{11}C](*R*)-PK11195 has been demonstrated in the monkey brain, while the highest concentration of specific binding was observed in lesioned areas [28]. Mean binding potential was significantly higher in the brains of AD patients when compared to their healthy control counterparts in areas of AD pathology including the dorsal and medial prefrontal cortex, parietal cortex, lateral temporal cortex, anterior cingulate cortex, occipital cortex, striatum, and cerebellum. The widespread increase in TSPO binding was visualized using [^{11}C]DAA1106 in the brains of AD patients at a relatively early stage [29], suggesting that DAA1106 may overall be superior to PK11195. Moreover, in binding studies of AD patients [^{11}C]DAA1106 showed more promising results than in earlier studies using [^{11}C]PK11195, which could be due to the higher affinity and lower lipophilicity of

DAA1106 over [^{11}C]PK11195 for the quantification of TSPO in vivo. It has also been demonstrated that [^{11}C]DAA1106 effectively crosses the BBB and shows higher signal at lesion sites compared with [^{11}C]PK11195. Although the study did not directly compare DAA1106 and PK11195 in the same subjects, it appears that a shorter half-life limits the potential complexity of imaging protocols.

The fluorinated ethyl analogue [^{18}F]FEDAA1106 was recently developed as a potential PET ligand for the quantification of TSPO in vivo. High specific binding to TSPO in the rat brain has been reported, especially the olfactory bulb [30]. The uptake ratio of [^{18}F]FEDAA1106 into the brain was approximately 1.5 times higher than [^{11}C]DAA1106 and six times higher than that of [^{11}C]PK11195 in the monkey occipital cortex [31]. The deuterated fluoroalkyl derivative [^{18}F]d_2FMDA1106, an analogue of [^{11}C]DAA1106, was also successfully imaged in a healthy monkey brain after the nondeuterated form defluorinated rapidly in vivo, resulting in bone uptake in mouse biodistribution studies. However, deuteration does not prevent defluorination but rather slows the process in mice, resulting in bone uptake of [^{18}F]fluoride [32]. This may potentially act as a confounding factor in human imaging studies. More recently, quantification of [^{18}F]FEDAA1106 has been applied in studies of the human brain. These simulation studies have indicated that nonlinear least-squares (NLS) is a suitable method for the stimulation of [^{18}F]FEDAA1106 binding to TSPO. A sixfold higher signal to noise ratio than [^{11}C]PK11195 was observed, which was metabolically stable, representing a more suitable imaging agent with a longer half-life [33].

PBR28, an analog of DAA1106, was developed as a TSPO ligand with lower lipophilicity (cLogP = 3.01) than PK11195 (cLogP = 5.28) and DAA1106 (cLogP = 4.28) [34]. The in vivo specific binding of [^{11}C]PBR28 in monkey brain was 80-fold higher than that of [^{11}C](*R*)-PK11195, resulting in excellent signal to noise ratio and significantly more favorable pharmacokinetics [35]. It has been shown that high uptake of [^{11}C]PBR28 in specific areas of the monkey brain is consistent with known TSPO distribution in the same species [36]. Similar results have been demonstrated in a rat model of cerebral ischemia and stroke [37]. Moreover, studies with [^{11}C]PBR28 have led to a better understanding of the in vivo state of TSPO [38]. Initial studies have shown that approximately 10–20% of individual human subjects do not show appreciable specific binding for [^{11}C]PBR28 [35, 39]. This has a clear association with neuroinflammation in patients with temporal lobe epilepsy, suggesting an increased expression of TSPO. In addition, clinical studies have determined that epilepsy is associated with neuroinflammation, with brain uptake higher ipsilateral to the seizure focus in the hippocampus, parahippocampal gyrus, amygdala, fusiform gyrus, and choroid plexus, but not in other brain regions. Given the important clinical implications of this finding, further studies in a larger sample are warranted to confirm this finding and determine the clinical utility of TSPO imaging in the temporal lobe of epilepsy patients [40].

Other promising candidates for TSPO labeling include [^{11}C]DAA1097, [^{11}C]PBR01, and [^{18}F]FEPPA. [^{11}C]DAA1097 is a phenoxyphenyl acetamide derivative, which crosses the blood–brain barrier (BBB) in rats and accumulates in the occipital cortex of healthy monkeys. In vitro quantitative autoradiography studies have shown that DAA1097 has a similar binding affinity ($K_i = 0.19 \pm 0.02$ nM) with DAA1106 ($K_i = 0.09 \pm 0.02$ nM) and higher than PK11195 ($K_i = 0.54 \pm 0.24$ nM) for TSPO in the rat brain, suggesting that the bulky substitution is not favorable for binding affinity, and very good permeation of the BBB was observed [41]. Ex vivo autoradiography studies revealed that [^{11}C]DAA1097 is preferably distributed to the olfactory bulb and cerebellum, which are of a high density in the rat brain. The uptake of [^{11}C]DAA1097 in the monkey brain was also examined by PET, with higher radioactivity levels present in the occipital cortex providing visual evidence that [^{11}C]DAA1097 is a specific ligand for TSPO. Metabolite analysis demonstrated that [^{11}C]DAA1097 could be metabolized by debenzylation to a polar product primarily in plasma. A limited number of other studies have shown good permeation of the CNS, although these findings require further investigation.

[^{11}C]PBR01 and [^{18}F]PBR06 are phenoxyaryl acetamide derivatives that have been evaluated in rhesus monkeys as potential imaging agents for human studies. In vitro binding characteristics in the monkey brain for both compounds are approximately similar (PBR01; $K_i = 0.25 \pm 0.04$ nM and PBR06; $K_i = 0.3 \pm 0.08$ nM), with higher affinity compared to PK11195($Ki = 3.48 \pm 1.26$ nM). Both compounds show a high brain uptake, in blocking studies, [^{11}C]PBR01 was selectively blocked by using nonradioactive PBR01 and [^{18}F]PBR06 blocked with DAA1106, resulting in faster washout in each case [42]. Although the brain kinetics of the two radioligands are similar, with the exception that [^{18}F]PBR06 tracer performed slightly better relative to [^{11}C]PBR01 in quantitative analysis of the total brain uptake. The high proportion of specific to nonspecific binding should provide high sensitivity to detect small changes in TSPOs in brain, because longer half-life of the ^{18}F-tracer allowing for extended acquisition time to measure TSPOs as a biomarker of inflammation in the brain.

Combined studies of [^{11}C]PBR01, [^{11}C]PBR28, and DAA1106 were evaluated in vitro by displacement of [^{3}H]PK11195 from mitochondria derived from rat, monkey, and human brains. These three compounds showed higher affinity for TSPO than PK11195. Among them, the highest affinity was for rat-derived mitochondria and the lowest affinity was for human-derived TSPO over monkey mitochondrial fractions, with DAA1106 showing the highest overall affinity

[34, 42]. However, [^{11}C]PBR01 and [^{11}C]PBR28 exhibited more favorable properties than [^{11}C]PK11195 including higher brain entry, higher specific signal, and lower nonspecific binding and metabolism. Overall, [^{11}C]PBR28 is a more promising PET ligand than [^{11}C]PBR01 due to its highly specific signal, greater brain penetration and more easily measurable free fraction in blood. It is now under intensive investigation in an FDA-approved exploratory IND.

[^{18}F]FEPPA is the fluoroethoxy derivative of PBR28, and has been evaluated in vivo in PET imaging with an animal model [43–45] and clinical settings [46–48]. It was demonstrated that increased neuroinflammation was not associated with normal aging, but rather that regional increased FEPPA uptake was associated with AD or PD [48, 49]. FEPPA displayed higher in vitro binding affinity (K_i = 0.07 nM) compared to PBR28 (K_i = 0.22 nM), DPA-713 (K_i = 0.87 nM), and [^{3}H]PK11195 (K_i = 1.29 nM) in rat mitochondrial fractions. Upon intravenous injection into rats, moderate brain uptake and slow washout was observed. The highest uptake of radioactivity was in the TSPO-rich regions of the hypothalamus and olfactory bulb [43]. Furthermore, it showed a better association with severity of injury in the rat brain compared to [^{11}C](*R*)-PK11195, suggesting a higher affinity to TSPO and better brain transport [49]. However, quantitive interpretation of the PET signal with [^{18}F]FEPPA can be confounded by large inter-individual variability and differences in binding affinity [43].

6-^{18}F-PBR28, an alternative fluorinated analogue of the PBR28 ligand, has been evaluated in binding affinity studies in vitro of 6-^{18}F-PBR28 (K_i = 0.44 ± 0.01 & 1.19 ± 0.03 nM) with direct comparison to [^{3}H](*R*)-PK11195 (Ki = 1.80 ± 0.04 vs 7.11 ± 0.35 nM) from mitochondria derived from rat and human tissue. Ex vivo autoradiography showed that 6-^{18}F-PBR28 was preferably distributed to the olfactory bulb and cerebellum, which are of a high density in the rat brain. The uptake of 6-^{18}F-PBR28 in the rat lesion striatum remained at a plateau until the end of the imaging procedure, while [^{11}C]PK11195 underwent rapid clearance in the same region. 6-^{18}F-PBR28 has therefore demonstrated great potential as a radiotracer for in vivo imaging of TSPO with PET [50]. Comparison studies of TSPO radiotracers have shown that although [^{11}C]DAA1106, [^{18}F]FEDAA1106 and [^{18}F]PBR06 have advantages over [^{11}C]PK11195 for brain imaging and exhibit higher binding affinity to TSPO, these radiotracers are influenced by TSPO polymorphisms and can bind to cells other than activated microglia. These compounds are currently being used to investigate the role of TSPO in various brain diseases [51].

[^{18}F]FM-PBR28 is the derivatives of PBR28 and directly compared with [^{11}C]PBR28 in the same inflammatory rat model to determine the more promising TSPO PET imaging neuroinflammation. In a competition assay with (*R*)-PK11195, binding affinity and the partition coefficient of floromethyl-PBR28 are similar to those of PBR28 (IC_{50} & Log D; 8.27 & 2.85 nM verses 8.07 & 2.82 nM). The TACs of the radioactivity of both tracers showed good ipsi to contralateral ratio, but due to difference in pharmacokinetics profile the highest uptake ratio was more rapidly reached with [^{18}F]FM-PBR28 (35 min post injection for [^{18}F]FM-PBR28 verses 85 min post injection for [^{11}C]PBR28) [52]. In blocking and displacement studies indicate that [^{18}F]FM-PBR28 exhibited highly specific and selective binding for TSPO in the traumatic brain injury. The in vitro stability of [^{18}F]FM-PBR28 was shown to be stable (99%, 4 h) in human serum. This high stability indicated that [^{18}F]FM-PBR28 was stable for use in further in vivo biological studies.

Vinyl Alkaloids

Vinpocetine, a vinca alkaloid, was initially used in the treatment of acute and chronic shock patients [53]. It was found to interfere with various stages of the ischemic cascade, and was thus developed as a carbon-11 PET ligand with more favorable pharmacokinetic characteristics and affinity toward TSPO. Vinpocetine binds to TSPO in brain tissue with low affinity in vitro (IC_{50} = 0.2 μM) and was used for the pretreatment of two cynomolgous monkeys with vinpocetine reducing the uptake of [^{11}C](*R*)-PK11195. In contrast, the uptake of [^{11}C]vinpocetine is increased in the brain after pretreatment due to the blockage of TSPO in the periphery, but with reduced binding potential for [^{11}C]vinpocetine [54]. These findings supported the hypothesis that the clinical neurological effects of vinpocetine may be due to its effect on microglial cells. It was also noted that it binds to other nonspecific receptors with a similar affinity to TSPO, raising questions about its in vivo specificity for TSPO [55]. A PET imaging study with four MS patients showed that, when compared with [^{11}C](*R*)-PK11195, [^{11}C]vinpocetine exhibits greater global and regional brain uptake and increased binding potential for all four MS patients whereas [^{11}C]PK11195 showed increased binding in only one of the patients [56]. However, in an additional study in six AD patients and 12 healthy volunteers, there were no statistically significant differences between these uptake values in Alzheimer's patients and age-matched control subjects [57]. Another study comparing [^{11}C]vinpocetine with [^{11}C](*R*)-PK11195 in stroke did not find evidence of any significant difference between the uptake of these two ligands in the peri-infarct zone, an area of established microglial activity [58]. This could be due to a low affinity of [^{11}C]vinpocetine for TSPO, which may limit its future clinical use.

Aryl-Oxodihydropurines

AC-5216 is an oxopurine and another second generation candidate with high affinity for the TSPO ligand [59]. It has more suitable lipophilicity (cLogP = 3.5) than PK11195

Table 1 Summary of new generation of TSPO radiotracers

Chemical class	Ligand	Binding affinity K_i (nM)	Ref.
Benzodiazepines	[^{11}C]Ro 5–4864	>40 nM in human	[17]
Isoquinoline carboxamide	[^{11}C]PK11195	9.3 nM in rat	[21]
	[^{11}C](*R*)-PK11195	3.0 nM in rat	[8]
		3.5–4.5 nM in rhesus	[8]
		2.1–28.5 nM in human	[14]
Phenoxy acetamide	[^{11}C]DAA1106	0.04 nM in rat	[26]
		0.18 nM in monkey	[26]
		0.2–13.1 nM in human	[8]
	[^{18}F]FEDAA1106	0.078 nM in rat	[31]
	[^{11}C]PBR28	0.68 nM in rat	[34]
		0.94 nM in monkey	[34]
		2.2–52 nM in human	[8]
	[^{11}C]DAA1097	0.19 nM in rat	[41]
	[^{11}C]PBR01	0.09 nM in rat	[34],
		0.24 nM in monkey	[42]
		1.40 nM in human	[34]
	[^{18}F]PBR06	0.30 nM in monkey	[42]
	[^{18}F]FEPPA	0.07 nM in rat	[43]
	6-^{18}F-PBR28	0.44 nM in rat	[50]
		1.19 nM in human	[50]
	[^{18}F]FM-PBR28	8.27 nM* in rat	[52]
Vinyl alkolids	[^{11}C]vinpocetine	200 nM* in rat	[53]
Aryl-oxodihydropurines	[^{11}C]AC-5216	0.29 nM in rat	[60]
	[^{11}C]DAC	0.23 nM in rat	[65]
Pyrazolopyrimidine0073	[^{11}C]DPA-713	4.7 nM in rat	[60]
		1.3 nM in mouse	[14]
		15.0–66.4 in human	[8]
	[^{18}F]DPA-714	7.0 nM in rat	[71]
	[^{18}F]VUIIS1008	0.3 nM in rat	[77]
Imidazopyridineacetamides	[^{11}C]CLINME	–	[79]
	[^{11}C]CB148	0.20 nM	[80]
	[^{18}F]CB251	0.27 nM in rat	[81]
	[^{18}F]PBR111	3.70 nM in rat	[83]

The half maximal inhibitory concentration (IC_{50})*

(cLogP = 5.1), which is required for a favorable PET ligand, guaranteeing high uptake and low nonspecific binding in the brain. AC-5216 showed potent displacement of [^{3}H]PK11195 binding in rat C6 (IC_{50} = 3.04 nM) and human Hs638 (IC_{50} = 2.73 nM) glioma cell-derived mitochondrial fractions [60]. The binding affinity of AC-5216 for TSPO in whole rat brain (K_i = 0.297 nM) was higher than PK11195 (K_i = 0.602 nM) [60] but lower than DA11106 (K_i = 36~108 pM) [61]. It has been successfully evaluated in several tumor models including a kainic acid rat model [59, 62] and murine fibrosarcoma models [63]. PET studies in monkey brain showed a high uptake of [^{11}C]AC-5216 in the occipital cortex, a rich TSPO-dense area in the primate brain [59]. PET studies in humans have demonstrated that the highest binding potential compared with undisplaceable uptake (BP_{ND}) is in the thalamus (4.6 ± 1.0) and the lowest is in the striatum (3.5 ± 0.7) [64]. The total distribution volume (V_T) obtained by nonlinear least-squares fitting (NLS) showed regional distribution similar to BP_{ND}. However, there was no correlation between BP_{ND} and V_T due to inter-individual variation in *K1/K2*. BP_{ND} data by NLS with a 60-min scan time were in good agreement with that from a scan time of 90 min (r = 0.87). Thus, BP_{ND} is more appropriate for the quantification of [^{11}C]AC-5216 binding compared with V_T and [^{11}C]AC-5216 is a promising PET ligand for the in vivo quantification of TSPO in the human brain.

[^{11}C]DAC is a novel derivative of AC-5216 that has been recently developed and demonstrates a high signal to noise

ratio for TSPO in unilateral kainic acid (KA)-induced striatum lesion rats and brain ischemia [65]. It has lower lipophilicity (cLogP = 3.0) compared to AC-5216, suggesting that it may exhibit decreased nonspecific binding and rapid kinetics. The binding affinity and selectivity of DAC for TSPO were similar to AC-5216 (K_i = 0.23 vs 0.20 nM) and higher than PK11195 (K_i = 0.30 nM in rat). The in vivo binding of [^{11}C]DAC for TSPO in KA-lesioned rats exhibited a similar brain uptake in the lesioned and non-lesioned striatum. In vitro autoradiography showed that the binding of [^{11}C]DAC to TSPO was increased to 1.8 fold in the lesioned striatum and good contrast between lesioned and non-lesioned striatum was observed. TACs of [^{11}C]DAC in the rat brain were similar to [^{11}C]AC-5216, suggesting that the brain kinetics of the two ligands could be related within the primate brain. Therefore, [^{11}C]DAC has been acknowledged as a useful PET ligand for TSPO imaging, and its in vivo specific binding is sufficiently sensitive as a biomarker in brain imaging. Moreover, it may have applications in determining the function and expression of TSPO in the brain and elucidate the relationship between TSPO and brain disease.

Pyrazolopyrimidines

[^{11}C]DPA-713 is a high-affinity, selective TSPO ligand in the pyrazolopyrimidine group [66]. It has a lower lipophilicity (logP = 2.4) compared to [^{11}C](*R*)-PK11195 (logP = 3.4), and good in vitro affinity for TSPO (K_i = 4.7 vs 9.3 nM in rat kidney tissue). It was successfully evaluated in a variety of animal inflammation models and clinical studies [66]. In a PET study using an AMPA (amino-3-hydroxy-5-methyl-4-isoxazolepropionate) lesioned rat model of neuroinflammation, it was demonstrated that [^{11}C]DPA-713 exhibits a higher signal to noise ratio than [^{11}C](*R*)-PK11195 as a result of less nonspecific binding in the brain that is likely related to the lower lipophilicity of [^{11}C]-DPA-713 and lower binding affinity with plasma protein [67]. In vivo imaging in baboon brain has demonstrated a higher specific uptake of [^{11}C]DPA-713 than the more widely used [^{11}C](*R*)-PK11195, which could be due to its highly specific binding with TSPO, which is useful in detecting changes in TSPO density [68]. PET studies in healthy human subjects showed that high uptake was observed throughout the brain and the dose-normalized uptake was up to three times greater than that of [^{11}C](*R*)-PK11195 [66]. Accordingly, TACs showed that [^{11}C]DPA-713 provides a greater signal in the brain and consistent biodistribution and dosimetry similar to the TSPO ligands [^{11}C]PK11195 and [^{11}C]PBR28, which was expected due to its similar pharmacokinetics. Moreover, human PET studies have characterized the radiation dosimetry of [^{11}C]DPA-713 with single administration dose limit of 67.3 mCi, making multiple tracer injection for test–retest and longitudinal studies quite feasible [69].

[^{18}F]DPA-714 is a close analogue of [^{11}C]DPA-713, which shows excellent biodistribution and low levels of metabolic breakdown in vivo [70]. It has an inherent advantage for clinical studies as it is radiolabeled with ^{18}F and has a longer half-life (110 min) allowing more versatility in usage. [^{18}F]DPA-714 exhibits in vivo affinity for TSPO (K_i = 7.0 nM) in rat models, which is slightly smaller than [^{11}C]DPA-713 compared with [^{3}H]PK11195 (K_i = 9.3 nM) and excellent selectivity for TSPO, respectively, to the CBR [71]. A direct comparison of [^{18}F]DPA-714, [^{11}C]DPA-713, and [^{11}C](*R*)-PK11195 was made in unilateral, striatal-AMPA-lesioned rat, in which it was found that [^{18}F]DPA-714 was better than [^{11}C]DPA-713, [^{11}C](*R*)-PK11195 (ipsi/contralateral ratio = [^{18}F]DPA-714 (4.30 ± 0.30) vs [^{11}C]DPA-713 (3.31 ± 0.31), and [^{11}C](*R*)-PK11195 (2.27 ± 0.08). Furthermore, this finding suggests that [^{18}F]DPA-714 appears to be an attractive alternative to [^{11}C](*R*)-PK11195 due to its increased bioavailability in brain tissue and reduced nonspecific binding [72]. Recently, [^{18}F]DPA-714 has been evaluated for neuroinflammation in ALS patients and the results showed increased uptake in the primary, supplementary, and temporal cortex, suggesting that it could be a surrogate marker of treatment efficacy with regards to microglial activation [73]. Moreover, it has also been successfully demonstrated for the quantification of TSPO in healthy humans for several brain diseases including AD [74] and stroke [75]. Uptake of [^{18}F]DPA-714 in nonspecific binding is lower compared to [^{11}C](*R*)-PK11195, which leads to a better signal to noise ratio [70]. As such, [^{18}F]DPA-714 is an emerging potential PET tracer for diagnosis and investigation of neurological diseases associated with microglial activation [76]. The biodistribution of [^{18}F]DPA-714 was shown to be similar in different cortical regions compared to [^{11}C](*R*)-PK11195, [^{11}C]DPA-713, [^{11}C]PBR-28 and [^{18}F]FEPPA. However, TACs were always higher in the thalamus than in the other cerebral regions.

[^{18}F]VUIIS1008 is a candidate in a new generation of novel TSPO ligands, and has exhibited a 36-fold enhancement in binding affinity (K_i = 0.3 nM) compared to its parent molecule, [^{18}F]DPA-714 (K_i = 10.9 nM) [77]. It also exhibited lower uptake in healthy brain tissue, superior tumor to background ratio (V_T), and higher binding potential compared to [^{18}F]DPA-714. Moreover, despite improved affinity for TSPO, the perfusion rate (K_1) was significantly lower than [^{18}F]DPA-714, suggesting that more tracer crosses the BBB which indicate that [^{18}F]DPA-714 can perform slightly better uptake.

Imidazopyridineacetamides

[^{11}C]CLINME is an analogues of imidazopyridineacetamide and new TSPO ligand that compares favorably with [^{11}C](*R*)-PK11195 in PET imaging of rodents with induced local acute neuroinflammation [78, 79]. [^{11}C]CLINME exhibits higher

binding potential than [^{11}C]PK11195 (1.07 ± 0.30 vs 0.66 ± 0.15). This results demonstrated that [^{11}C]CLINME perform better than [^{11}C](*R*)-PK11195 in terms of specific to nonspecific ratio and hence sensitivity. However, although the uptake of [^{11}C]CLINME was identical to that of [^{11}C](*R*)-PK11195 in brain lesions, it was significantly lower in the contralateral intact hemisphere [79].

[^{11}C]CB148 is another analogue of imidiazo pyridineacetamide, which is selective for TSPO. It shows higher binding affinity (K_i = 0.20 nM) compared to PK11195 (K_i = 4.26 nM) in rat models, while distribution studies in mice show accumulation of radioactivity in TSPO-rich regions of the brain [80]. Moreover, the co-injection of either PK11195 or CB148 reduced the accumulation of this radioactivity in the brain. These results demonstrate that [^{11}C]CB148 maybe a useful radioligand and for the in vivo imaging of TSPO.

[^{18}F]CB251 is the imidazopyridineacetamide derivative that have been evaluated in animal models as potential imaging agents for human studies. CB251 display higher in vitro binding affinity (*Ki* = 0.27 nM) which was 22 and five times higher than the observed for PBR28 (*Ki* = 6.1 nM) and [^{3}H]PK11195 (Ki = 1.38 nM) in rat model. Furthermore, binding to CBR was below the detection limit, indicating the high selectivity of CB251 for TSPO. In PET imaging studies in neuroinflammatory rat model, [^{18}F]CB251 rapidly approaches the highest target to background ratio (2.7 times) at early imaging time and was selective accumulated in the ipsilateral striatum. The binding potential of the specifically bound ration ligand relative to the non-displaceable radioligand in tissue (BP_{ND} = 1.83 ± 0.18) compared to that of [^{11}C]PBR28 (BP_{ND} = 1.55 ± 0.41) in neuroinflammation rat model [81]. Furthermore, in PET imaging studies, [^{18}F]CB251 displayed moderate tumor uptake (1.96 ± 0.11%ID/g at 1 h post injection) in human glioblastoma U87-MG xenograft. These result suggested that [^{18}F]CB251 could serve as novel TSPO probes for PET imaging agent for neuroinflammation and TSPO rich cancers.

[^{18}F]PBR111 is a metabolically-stable imidazo pyridineacetamide derivative which shows specificity for TSPO in a rodent model of acute neuroinflammation [82]. [^{18}F]PBR111 is a potent and selective TSPO inhibitor (K_i =3.7 ± 0.4 nM) and has very low affinity for CBR (800 ± 0.4 nM) [83]. In vitro autoradiography of an AMPA-lesioned brain showed that the target to background ratio (TBR) of [^{18}F]PBR111 (3.9 ± 1.5) was double that of [^{11}C]CLINME. The uptake values of [^{18}F]PBR111 are relatively higher than these two tracers, resulting in a significantly higher binding potential for [^{18}F]PBR111(2.5 ± 0.7) compared to both [^{11}C]CLINME (1.7 ± 0.3) and [^{11}C]PK11195 (1.1 ± 0.2). In vitro studies of PBR111 have shown that it binds to human tissue in HABs, LABs and MABs. The binding potential (BP_{ND}) of [^{18}F]PBR111 in the normal human brain is 2.78 ± 0.46 in HABs, 1.48 ± 0.46 in MABs and 0.51 ± 0.71 in LABs compared with [^{11}C]PK11195, which, relative to cortical gray matter, is 0.19 ± 0.14 in healthy brain. In silico modeling predicted that [^{18}F]PBR111 would exhibit a high specific to nonspecific ratio in the normal human brain [80]. Compared with other TSPO tracers which have been evaluated for human studies including [^{11}C](*R*)-PK11195 and [^{11}C]PBR28, [^{18}F]PBR111 shows similar uptake. Results indicate that [^{18}F]PBR111 is a promising biomarker for neuroinflammatory imaging and that ^{18}F labels provide an advantage for application in future clinical trials. Although [^{18}F]PBR111 and [^{18}F]FEPPA show favorable properties for imaging in healthy humans [82, 83], [^{18}F]FEPPA is known to be rapidly metabolized.

Despite the discovery of these second generation TSPO radiotracers, significant issues have emerged that limit their application for routine clinical use, including a low sensitivity and limited capacity to quantify suitable TSPO expression in vivo. Another concern for TSPO PET imaging is the lack of specificity of TSPO binding for activated microglia, which has necessitated the development of a new generation of radiotracers that target alternative markers of microglial activation.

New Generation TSPO Tracers in Neurologic Disease

Tricyclic Radiotracers

Recent studies have shown that the indoleacetamide [^{11}C]SSR180575 is an effective TSPO PET tracer for the in vivo imaging of neuroinflammation. Moreover, its binding and imaging contrast are higher than that obtained with [^{11}C]PK11195 when distinguishing inflammatory tissue from healthy tissue [84]. The uptake ratio of ipsilateral to contralateral for [^{11}C]SSR180575 (2.75 ± 0.13) was higher than [^{11}C]PK11195 (1.70 ± 0.05), while the binding potential as well as the ratio of tracer delivery (R_1) were significantly higher for [^{11}C]SSR180575 compared to [^{11}C]PK11195 (BP = 1.65 ± 0.36 vs 0.66 ± 0.15; R_1 = 1.26 ± 1.18 vs 1.10 ± 0.05). Further investigations are warranted to determine whether [^{11}C]SSR180575 could be used as a biomarker of neuroinflammation in neuropathological conditions [85].

The tricyclic compound, [^{18}F]GE180 is another novel PET tracer for the imaging of TSPO expression in response to neuroinflammation. Initially, [^{18}F]GE-180 was identified and evaluated as a racemate, but subsequent evaluations of the resolved enantiomers have shown that the *S*-enantiomer ([^{18}F]GE180) has a higher affinity for TSPO and better brain uptake and clearance compared to *R*-enantiomers and the racemate, due to differences in pharmacokinetics, efficacy, and potential toxicity. Furthermore, the *S*-enantiomer or ([^{18}F]GE-

180) has also been shown to be enantiomerically stable in vivo and a promising agent for imaging neuroinflammation [86]. Its ability to bind selectively with high affinity to TSPO is important for the assessment of neuroinflammation in disease states, with significantly better TSPO imaging signal to noise ratio and lower nonspecific signal compared to the current gold standard [^{11}C](*R*)-PK11195 [87].

Recently, Dickens AM, et al. reported that [^{18}F]GE-180 is superior to the [^{11}C](*R*)-PK11195 PET radiotracer for imaging TSPO expression in response to neuroinflammation in a rodent model, which was generated by unilateral striatal injection of lipopolysaccharide (LPS) [88]. The superiority of the tracers was apparent for both in vivo and ex vivo imaging techniques, in which [^{18}F]GE180 had significant higher binding potential compared to [^{11}C](*R*)-PK11195. In an autoradiography experiment, both tracers showed significantly increased binding in the LPS injected striatum ($BP_{ex\ vivo} = 0.76 \pm 0.31$ for [^{11}C](*R*)-PK11195 and 1.32 ± 0.13 for [^{18}F]GE-180) compared with saline-injected animals ($BP_{ex\ vivo} = 0.05 \pm 0.02$ for [^{11}C](*R*)-PK11195 and 0.05 ± 0.01 for [^{18}F]GE-180). Through an in vivo PET experiment, the binding potential was also shown to be significantly increased for both tracers ($BP_{in\ vivo} = 0.47 \pm 0.06$ for [^{11}C](*R*)-PK11195 and 0.92 ± 0.07 for [^{18}F]GE-180) compared with saline injected animals ($BP_{in\ vivo} = 0.00$) [88]. Therefore, the $BP_{in\ vivo}$ for [^{18}F]GE-180 was higher than [^{11}C](*R*)-PK11195, enabling the visualization of sites of activated microglia in both gray and white matter. However, the signal increases in the presence of activated astrocytes.

A direct comparison of both TSPO tracers [^{18}F]GE180 and [^{11}C](*R*)-PK11195 was performed for in vivo preclinical studies in a rat model of stroke. The in vivo binding characteristics of [^{18}F]GE180 demonstrated an improved signal to noise ratio (1.5 fold higher) and lower non-specific binding compared with [^{11}C](*R*)-PK11195. These results demonstrate that [^{18}F]GE180 is a strong candidate to replace [^{11}C](*R*)-PK11195 [89].

Acetamidobenzoxazolone

A new TSPO tracer, [^{11}C]MBMP with high affinity ($K_i = 0.29$ nM) and specificity has been evaluated in ischemic rat brain, showing a higher BP_{ND} than [^{11}C](*R*)-PK11195. Biodistribution studies in mice showed high accumulation of radioactivity in the TSPO-rich organs, e.g., blood, heart, lung, and brain, which may be due to the lower lipophilicity of [^{11}C]MBMP (cLogP = 3.5) compared to [^{11}C](*R*)-PK11195. Moreover, although this tracer may not have significant advantages over second generation TSPO radioligands, it has similar in vitro binding affinity for TSPO. Metabolite analysis in mice brain homogenate showed that $80.1 \pm 2.7\%$ remained intact at 60 min after injection, hindering its further evaluation and optimization [90]. Therefore, in an effort to overcome its rapid metabolism, the same group developed two fluorinated analogues of MBMP ([^{18}F]FEBMP and [^{18}F]FPBMP). These compounds have lower lipophilicity compared to PK11195, and the TACs data showed high initial brain uptake (2.5–3.0% ID/g) for [^{18}F]FEBMP and [^{18}F]FPBMP which was comparable to [^{11}C](*R*)-PK11195. In an autoradiography study of ischemic rat brain, a high ipsi- to contralateral ratio was observed (3.1 for [^{18}F]FEBMP and 2.1 for [^{18}F]FPBMP). Metabolite analysis was only performed for [^{18}F]FEBMP, showing rapid metabolism in plasma, whereas in brain it remained intact in the range of 85–90% at 15–30 min [91], so an improvement in metabolic stability relative to [^{11}C]MBMP was not achieved.

Limitations of New TSPO Radiotracers

Despite intensive efforts to explore neuroinflammation in clinical studies over the last decade, several limitations specifically associated with three properties of TSPO as a molecular biomarker of neuroinflammation have emerged.

Firstly, the investigation of second generation TSPO radioligands in human clinical studies has revealed the existence of 'non binders', referring to binding targets other than TSPO. Further studies have demonstrated that, with the exception of PK11195, all second-generation TSPO ligands in clinical use were influenced by the presence of non-binders in brain tissue in vitro, resulting in a lower affinity for TSPO. A common single nucleotide polymorphism (rs6971) in exon 4 of the TSPO gene causes an alanine to threonine substitution at A^{147}T [92]. This polymorphism affects the ligand-binding affinity of TSPO and subsequent pregnenolone biosynthesis [93]. Three forms are expressed in relation to this polymorphism: Ala/Ala is associated with high affinity binding (HABs = 66% of the Caucasian population), whereas Ala/Thr is associated with mixed affinity binding (=29%), while Thr/Thr is associated with low-affinity binding (LABs, = 5%), which determines the binding affinity of the ligands and causes large inter-subject variation in comparison to [^{11}C]PK11195. Importantly, this polymorphism can be identified by genetic analysis of leukocytes, allowing for the quantification of TSPO in PET studies using second generation radiotracers. This polymorphism was initially identified using non-radiolabeled PBR28 [92] and this has also been confirmed for [^{18}F]PBR111 [94]. Furthermore, polymorphism affects the predictions of [^{18}F]FEPPA total distribution volumes in the human brain. In addition, it results in clear differences between features in the shape of TACs and genetic binding groups [43].

A second concern for the utility of TSPO is its non-specificity for activated microglia, as it is also expressed by multiple types of immune cell including astrocytes. PET TSPO radiotracers are not able to distinction between pro- and anti-inflammation microglia, as it is expressed similarly

in both activated astrocytes and microglia [95]. These two distinct activated states create significant limitations for data interpretation and in defining the role of microglia in neurologic disease. Therefore, the further development of new radiotracers that can target alternative markers of microglia activation are needed. Another issue with the development of these new generation radioligands in terms of optimal imaging results are the ^{11}C-labeled structures. Recent studies suggest that [^{11}C]PBR28 and [^{18}F]PBR06 are similar in terms of sensitivity to the accumulation of radiometabolites in the brain and binding affinity, suggesting that in future studies, [^{18}F]PBR06 can be substituted for [^{11}C]PBR28 [93].

The third major limitation of TSPO quantification in PET imaging studies using the reference tracer [^{11}C](*R*)-PK11195 is that the quantification of data is a complex task. Microglia are distributed ubiquitously throughout the entire brain and in a disease state such neurodegenerative regions with a priori pathology may exist. Therefore, advanced methods using cluster analysis can be performed with dynamic PET scans of each individual to determine a suitable reference region.

Conclusion and Future Perspectives

Although TSPO has been a target of considerable focus in multiple studies over the past few decades, its mechanistic role in the pathophysiology of neurologic diseases remains to be fully understood. Recent evidence suggests that neuroinflammation plays a vital role in neurodegenerative disease including AD, PD, MS, and stroke [96]. TSPO expression in the brain has been considered a reliable marker of neuroinflammation, and is correlated with tissue damage such as neuronal loss. Microglial activation results in several molecular changes that affect both the structure and function of the TSPO. Although these studies provide evidence that physiological changes occur, including an increase in binding site density, as well as increased expression and polymerization, it may also result in additional site-binding interactions when considering those expressed by resting microglia. Therefore, the visualization of activated microglia based on PET is becoming increasingly important.

Several new high affinity and selective TSPO ligands labeled with the short-lived positron-emitter isotopes ^{11}C and ^{18}F have been developed. These PET radioligands enable the visualization of TSPO expression, overcoming many of the limitations of [^{11}C](*R*)-PK11195. [^{11}C]DAA1106, [^{18}F]FEPPA, [^{11}C]PBR01, [^{13}C]SSR180575, [^{11}C]MBMP, and [^{11}C]DPA-713 have demonstrated significantly increased binding affinity in the human brain. Recent studies have shown that [^{18}F]DPA-714 is a promising PET tracer with high affinity for TSPO with better uptake and higher binding potential compared to other TSPO radiotracers. Further comparative studies will determine the role of these new radioligands relative to [^{11}C](*R*)-PK11195 and [^{11}C]PBR28, which will enable superior methods for human clinical research. [^{18}F]FEDAA1106, [^{11}C]PBR06, [^{18}F]PBR111, [^{11}C]AC-5216, [^{18}F]PBR28 and [^{18}F]GE-180 are currently more extensively studied as PET ligands for the quantification of TSPO in humans. General opinions on the issue are that the TSPO polymorphism results in additional binding, namely high-, low-, and mixed-affinity in vivo in the brain, which needs to be addressed when developing new PET radioligands. Furthermore, almost all TSPO PET ligands in clinical use have recognized high affinity for TSPO with better uptake compared with [^{11}C](*R*)-PK11195. Further comparisons with novel TSPO radiotracers will provide fascinating insights into the pathology of neuroinflammation.

The identification of new targets specific for either pro-inflammatory or anti-inflammatory microglial phenotypes will provide further information on the role of these immune cells, and provide mechanistic rationale for the development of more effective neuroprotective drugs. More efforts for preclinical and clinical evaluation are needed to develop these radiotracers as therapeutic agents for the assessment of neurological and psychiatric disorders, to enable the development of novel drugs for the treatment of human disease.

Compliance with Ethical standards

Conflict of Interest Md. Maqusood Alam, Jihye Lee, and Sang-Yoon Lee declare that they have no conflict of interest. This work was supported by a grant of the Korea Health Technology R&D project through the Korea Health Industry Development Institute (KHIDI), funded by the ministry of health and welfare, Korea (HI14C1135).

Ethical Approval This work does not contain any studies with human participants or animals performed by any of the authors.

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