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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

In vivo PET imaging of neuroinflammation in Alzheimer's disease

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Abstract Increasing evidence suggests that neuroinflammation contributes to the pathophysiology of many neurodegenerative diseases, especially Alzheimer's disease (AD). Molecular imaging by PET may be a useful tool to assess neuroinflammation in vivo, thus helping to decipher the complex role of inflammatory processes in the pathophysiology of neurodegenerative diseases and providing a potential means of monitoring the effect of new therapeutic approaches. For this objective, the main target of PET studies is the 18 kDa translocator protein (TSPO), as it is overexpressed by activated microglia. In the present review, we describe the most widely used PET tracers targeting the TSPO, the methodological issues in tracer quantification and summarize the results obtained by TSPO PET imaging in AD, as well as in neurodegenerative disorders associated with AD, in psychiatric disorders and ageing. We also briefly describe alternative PET targets and imaging modalities to study neuroinflammation. Lastly, we question the meaning of PET imaging data in the context of a highly complex and multifaceted role of neuroinflammation in neurodegenerative diseases. This overview leads to the conclusion that PET imaging of neuroinflammation is a promising way of deciphering the enigma of the pathophysiology of AD and of monitoring the effect of new therapies.

Keywords Neuroinflammation · Alzheimer's disease · PET imaging · TSPO · Microglia

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Introduction

The existence of neuroinflammation in neurodegenerative diseases and especially in Alzheimer's disease (AD) is now well established. This inflammatory process is nevertheless different from that accompanying autoimmune diseases of the central nervous system (CNS), such as relapsing–remitting multiple sclerosis or its experimental animal model, which develops when T cells with specificity for CNS antigens infiltrate the brain and spinal cord. In contrast, the initiation of inflammatory reaction in AD is brain associated and involves activation of microglia in close proximity to Aβ plaques (Prokop et al. 2013; Schwartz and Deczkowska 2016). Microglial cells are able to bind to soluble and fibrillar Aβ via cell surface receptors such as CD36, TLR4 and TLR6, resulting in microglial activation and cytokine production (Heneka et al. 2015). Aβ clearance by microglia through receptor-mediated phagocytosis and degradation has also been shown in vitro (Heppner et al. 2015) and activates the complement system leading to inflammatory consequences in AD (McGeer and McGeer 2013). In humans, the recent discovery of risk variants of gene encoding innate immune system molecules, such as triggering receptors expressed on myeloid cells 2 (TREM2) and myeloid cell surface antigen CD33, emphasizes the impact of neuroinflammation in AD pathogenesis. TREM2

deficiency adversely affects the ability of resident microglia to surround and clear Aβ plaques (Tanzi 2015). While TREM2 mediates a protective microglial response in AD, CD33 inhibits microglial uptake and clearance of Aβ (Heppner et al. 2015). A recent study showed an association between amyloid accumulation and *IL1RAP,* a gene of the proinflammatory interleukin-1 (IL1) pathway, with mutation carriers being more likely to evolve from mild cognitive impairment (MCI) to dementia and having greater temporal cortex atrophy on MRI (Ramanan et al. 2015). These results suggest a link between microglial activation and amyloid accumulation, which could be influenced by the IL1/IL1RAP pathway. It has even been suggested that immune actions can precede AD-like pathology and could be sufficient to cause it (Heppner et al. 2015).

Molecular imaging by PET may be a useful tool to assess neuroinflammation in vivo, thus helping to decipher the complex role of inflammatory processes in the pathophysiology of neurodegenerative diseases and providing a potential way of monitoring the effect of new therapeutic approaches. PET imaging enables us to detect, quantify and specify the topography of brain inflammatory reaction.

In the present review, we will summarize and discuss the main results obtained with neuroinflammation imaging by PET in AD, as well as in neurodegenerative disorders associated with AD. Many of the new targets and PET tracers described in this review were developed in the frame of the European funded collaborative project FW7: INMiND ("Imaging of Neuroinflammation in Neurodegenerative Diseases").

TSPO radiotracers

Microglial activation

Reactive inflammation is driven primarily by CNS resident immune cells (i.e. microglia), which are resident macrophages of the brain (Heppner et al. 2015), capable of phagocytosis and antigen presentation. Under physiologic conditions, microglial cells are in a resting state, characterized by ramified morphology. Signals of potential threat are sensed by microglial receptors and induce microglial activation. The activated state is characterized by a proliferation of resident microglial cells and recruitment of monocytes, as well as by morphologic changes of the cells, with a more amoeboid phenotype, up-regulation of major histocompatibility complex II and release of cytokines and growth factors (Venneti et al. 2009).

18-kDa translocator protein (TSPO)

The 18-kDa translocator protein (TSPO), formerly known as peripheral benzodiazepine receptor (PBR), is located on the outer membrane of the mitochondria and is likely a part of the mitochondrial permeability transition pore (McEnery et al. 1992; Casellas et al. 2002; Venneti et al. 2006). It is implicated in many physiological functions, including cholesterol transport, cellular respiration and immunomodulation (Liu et al. 2014), but the exact role played by TSPO in the CNS is not elucidated. In the normal CNS, there is a low, constitutive expression of TSPO in the endothelial cells, ependyma, the choroid plexus, the olfactory bulb and some sparse glial cells (Weissman et al. 1984; Gavish et al. 1999). This expression increases markedly from a very low baseline following brain injury, and the majority of experimental studies have linked this up-regulation to the activation of microglial cells (Venneti et al. 2006; Stephenson et al. 1995; Banati et al. 2000; Banati 2002). A study in human postmortem tissues from patients presenting with various neurological disorders showed that TSPO–radioligand binding correlated with the abundance of activated microglia (Venneti et al. 2008), suggesting that TSPO could reflect both cell recruitment and changes in microglial phenotype (migratory capacity or phagocytic activity). It is nevertheless important to notice that increased TSPO expression has also been reported in reactive astrocytes (Cosenza-Nashat et al. 2009; Lavisse et al. 2012). Postmortem studies of AD patients using several tritiated ligands (Ro5-4864, PK11195) showed a highly significant increase in TSPO binding sites in the temporal cortex and a moderate increase that approached statistical significance in the frontal cortex (Owen et al. 1983; Diorio et al. 1991).

[^{11}C]-PK11195: first generation of TSPO PET radiotracer

The first TSPO PET tracer consistently used was the [^{11}C]-PK11195. This TSPO antagonist has been the reference and most widely used radiotracer for PET imaging of TSPO expression in brain tissue with either the racemic mixture or the active R-enantiomer.

However, the development of this technique for exploring brain inflammation via microglial activation was impeded because of several technical limitations and the intrinsic properties of the compound, as well as the complexity of carbon-11 radiolabelling, which has a very short period of 20 min. [^{11}C]-PK11195 has a poor signal-to-noise ratio because of its relatively poor penetration of the blood brain barrier (BBB) and low brain uptake, low bioavailability, high plasma binding and non-specific

binding due to its high lipophilicity (Ching et al. 2012). Thus, it has limited capacity to detect small changes in TSPO expression (Banati et al. 2000; Belloli et al. 2004; Lockhart et al. 2003).

These difficulties have led several groups to develop other TSPO ligands.

Second generation of TSPO ligands

Many second-generation TSPO ligands have emerged, which demonstrate higher affinity to TSPO and better kinetic characteristics. We will only mention those which have been the most widely studied in humans, especially in AD. [^{11}C]-PBR28 has shown higher specific signal for microglial activity, in comparison with [^{11}C]-PK11195 in the monkey brain (Kreisl et al. 2010). A study of the healthy brain showed that [^{11}C]-DPA-713 provided better sensitivity than [^{11}C]-PK11195 for evaluating increased TSPO expression (Endres et al. 2009). This assertion has been confirmed in a recent study, showing that [^{11}C]-DPA-713 reveals increased TSPO density in more widespread regions of the brain of ageing subjects and AD patients than [^{11}C]-PK11195 (Yokokura et al. 2017). Chauveau et al. (2009) compared the evaluations resulting from the use of the TSPO radioligands [^{11}C]-DPA-713, [^{18}F]-DPA-714 and [^{11}C]-PK11195 in a rat model of acute neuroinflammation. In vivo, [^{18}F]-DPA-714 performed better than [^{11}C]-DPA-713 and [^{11}C]-PK11195, with the highest ratio of ipsilateral to contralateral uptake and the highest binding potential. The ligand [^{11}C]-DAA1106 has been demonstrated to bind with high affinity (tenfold higher than [^{11}C]-PK11195) to activated microglia in neurological disorders (Venneti et al. 2008; Gulyás et al. 2009). The emergence of new compounds with high affinity, high bioavailability, high signal and the possibility to radiolabel with [^{18}F], which has a longer half-life than [^{11}C], allows easier development of the imaging of inflammation in PET centres without an on-site cyclotron. Other radioligands labelled with [^{18}F] have been developed. FEDAA1106 displays at least twofold higher affinity to TSPO than DAA1106 and preclinical studies in non-human primates have shown higher brain uptake of [^{18}F]-FEDAA1106 than of [^{11}C]-PK11195 and [^{11}C]-DAA1106 (Varrone et al. 2013). Nevertheless, a study in AD patients, which did not take genetic polymorphism into account, showed no significant difference between controls and patients, leading to the conclusion that [^{18}F]-FEDAA1106 does not enable the detection of microglial activation in AD (Varrone et al. 2013). [^{18}F]-FEMPA has also been reported to be a suitable PET tracer for TSPO (Varrone et al. 2015). [^{18}F]-FEPPA showed high affinity for TSPO, high brain penetration and good pharmacokinetics (Rusjan et al. 2011). Vinpocetine is a neuroprotective agent, which could also have anti-inflammatory properties. It has also been established that radiolabelled vinpocetine may serve as a TSPO marker. Its favourable brain penetration is reported to compensate for its moderate affinity to TSPO (Gulyás et al. 2011b). Other radioligands have been described very recently, such as, to name a few, [^{11}C]-CB184 (Toyohara et al. 2016), [^{18}F]-CB251 (Perrone et al. 2016), [^{18}F]-VC701 (Di Grigoli et al. 2015), [^{11}C]-ER176 (Ikawa et al. 2017) and the so-called third-generation TSPO ligand [^{18}F]-GE180 (Fan et al. 2016).

Methodological issues in TSPO quantification by PET

Different quantification methods have been published, according to the tracer used.

It appears that TSPO quantification by PET is very challenging (Hinz and Boellaard 2015) and that a number of factors must be taken into account when studying microglial activation with the most frequently used tracers.

Genetic polymorphism and affinity

The main limitation of the second-generation TSPO radiotracers is their sensitivity to a polymorphism of the *TSPO* gene consisting of one amino acid substitution (Ala147Thr) (Owen et al. 2012; Yoder et al. 2013). This polymorphism results in differential affinity of these ligands to TSPO, leading to three different binding patterns (Guo et al. 2013; Kreisl et al. 2013a): high (HAB) and low affinity binders (LAB) are homozygotes expressing Ala or Thr, respectively, while the so-called mixed affinity binders (MAB) are heterozygotes, expressing both Ala and Thr (Owen et al. 2010, 2012). The proportions of HAB and MAB in the Caucasian population are almost equal (about 45% each), with the LAB being rare (often less than 10%). Thus genetic polymorphism analysis is a mandatory prerequisite for imaging data analysis, and each genetic group must be analysed separately (LAB are often excluded). This is especially true for PBR28, which has a huge affinity ratio between HAB and LAB (Owen et al. 2011; Kreisl et al. 2013a). Importantly, no significant difference between the three TSPO affinity subgroups has been observed in AD patients when considering clinical phenotypes, amyloid load and rates of cognitive decline, eliminating the possibility of a biased interpretation of neuroinflammation PET imaging data when applying results obtained in TSPO subgroups to the entire AD cohort (Fan et al. 2015b; Hamelin et al. 2016).

All this means that the results of all clinical studies using second-generation TSPO tracers that have been published before the identification of this differential affinity status or performed after but without genetic

polymorphism determination must be considered with very high caution (see Table 1). Some of the second-generation tracers are less sensitive to polymorphism than PBR28, such as [^{18}F]-DPA714 and the recently developed [^{11}C]-EC176, which show an adequate sensitivity to robustly image all three affinity genotypes in the human brain (Ikawa et al. 2017; Hamelin et al. 2016).

Other factors could have an impact on TSPO affinity to PET tracers, especially the dimerization state of TSPO (Korkhov et al. 2010). The possible co-existence of monomers and dimers may further complicate the situation and especially for the heterozygote MAB subjects in which three types of dimers may be found (high–high; high–low and low–low).

Arterial plasma input function

The kinetics model analyses are based on the input function, which is the arterial free plasma kinetics of the parent radiotracer. This requires the relative traumatic placement of an arterial catheter and the development of radioanalytical methods to accurately identify the plasma metabolite fractions and the determination of the plasma-free fraction in the sequentially drawn blood samples. Besides the discomfort for the subjects, these methods introduce variability in the quantification (Lyoo et al. 2015; Lavisse et al. 2015). It has been shown that it is very difficult to obtain accurate estimates of free plasma concentrations, due to the tracers' high plasma protein binding, which is variable and subject to change in pathological conditions, with an up-regulation of certain proteins in the course of inflammation (Fan et al. 2016; Turkheimer et al. 2015).

Reference region definition

The considerations mentioned above led to the idea to employ a bloodless quantification method. Reference region analyses, which consist in quantifying the binding of the tracer in the regions of interest relative to a region devoid of targets was proposed as an alternative method. The reference region should meet two criteria: (1) be devoid (or almost devoid) of specific ligand binding to the target and only share the same free and non-specific binding with the region expressing the target (Cunningham et al. 1991) and (2) remain unaffected by the disease.

The cerebellar grey matter has been suggested to be the best reference region to study patients with AD and MCI using [^{11}C]-PK11195 (Kropholler et al. 2007). Nevertheless, this choice has been highly discussed. Most PET studies found that there is no increased microglial activation in the cerebellar grey matter in AD patients (Kreisl et al. 2013b; Lyoo et al. 2015; Hamelin et al. 2016; Suridjan et al. 2015), while others, especially when considering the whole cerebellum instead of only the grey matter, showed increased binding in this structure (Varrone et al. 2015; Yasuno et al. 2008).

Data from different studies with [^{3}H]-PK11195, [^{11}C]-PBR28 and [^{11}C]-PK11195 (Doble et al. 1987; Tomasi et al. 2008) have shown that displaceable binding has a non-negligible contribution to the distribution volume in the cerebellum. Moreover, recent studies (Cosenza-Nashat et al. 2009; Roncaroli et al. 2016) suggest that there is constitutive TSPO expressed in several cell types in the brain, including endothelial cells. A consequence of this, due to the ubiquitous distribution of vessels in the tissues, is the absence of a reference region totally devoid of non-saturable binding. This problem has been amplified by the increase in affinity of second-generation TSPO tracers, which has resulted in a disproportionate increase of the signal in the constitutive TSPO sites, due to a greater concentration of the free ligand near the blood–brain barrier (BBB), thus obscuring the signal from the tissue (Turkheimer et al. 2015). The consequence of this situation is a reduction of the sensitivity for the microglial activation detection. This is the reason why the term of "pseudo-reference region" was preferred and refers to tissue with low level of constitutive TSPO, but no or negligible amount of microglial TSPO.

The cerebellar grey matter has been used as a pseudo-reference region with [^{11}C]-PBR28 and [^{18}F]-DPA-714, after having validated the method by comparing standardized uptake value ratio (SUVR) and/or the calculation of total distribution volume with the arterial input function (Lyoo et al. 2015; Lavisse et al. 2015; Hamelin et al. 2016; Kreisl et al. 2016). This ratio method using the cerebellar grey matter as a pseudo-reference region has also been used in a longitudinal study (Kreisl et al. 2016).This approach has the advantages of limiting the coefficient of variation compared with absolute quantification and to improve subject tolerability by allowing shorter scanning time and not requiring arterial catheterization (Lyoo et al. 2015).

Nevertheless, although it could be argued that the results detailed above with [^{11}C]-PBR28 could also be applied to other second-generation TSPO ligands, it is important to notice that this methodology, consisting of using the cerebellum as a pseudo-reference region in AD patients, has only been validated for [^{11}C]-PBR28. Although methods to eliminate the need for invasive arterial blood sampling have been studied with [^{18}F]-DPA-714 in genotyped healthy volunteers (Lavisse et al. 2015), it has not been validated in AD patients.

Clustering approaches, supervised or not, have also been developed to extract pseudo-reference regions (Turkheimer et al. 2007; Corcia et al. 2012; García-Lorenzo et al. 2017). These data-driven methods extract selected voxels based

Table 1 Studies of neuroinflammation by PET imaging performed in AD patients, with the number of subjects, the tracer used, the method of tracer binding quantification, and the presence or absence of TSPO genotyping when applicable

	Nb of subjects	Tracer(s)	Quantification method	rs6971 TSPO polymorphism genotyping
Groom et al. (1995)	8 AD patients	[^{11}C]-PK11195	Reference region: cerebellum	NA
		[^{18}F]-FDG		
Cagnin et al. (2001)	8 AD patient, 1 MCI patient and 15 controls	[^{11}C]-PK11195	SRTM	NA
			Reference region: cluster analysis	
Versijpt et al. (2003)	10 AD patients and 9 controls	[^{123}I]-iodo-PK11195	SPECT	NA
			Reference region: cerebellum	
Kropholler et al. (2005)	2 AD patients, 5 MCI patients and 6 controls	[^{11}C]-PK11195	Compartment models: 1TCM, 2TCM, 2TCM (irreversible). Arterial input function	NA
Anderson et al. (2007)	4 AD patients, 11 Huntington patients and 12 controls	[^{11}C]-PK11195	SRTM, basis pursuit, a simple target-to-reference ratio, Logan plot, and a wavelet-based Logan plot	NA
Turkheimer et al. (2007)	4 AD patients, 3 Huntington patients, and 18 controls	[^{11}C]-PK11195	Rank-shaping exponential spectral analysis (both plasma and reference input) and SRTM	NA
Kropholler et al. (2007)	9 AD patients, 10 MCI patients, and 10 controls	[^{11}C]-PK11195	SRTM with grey matter, white matter, whole cerebellum, cerebrum, and cluster analysis as reference regions	NA
Schuitemaker et al. (2007)	9 AD patients and 20 controls	[^{11}C]-PK11195	Logan graphical analysis with plasma input, SRTM, Ichise linearizations and Logan graphical analysis with reference tissue input	NA
Edison et al. (2008)	13 AD patients and 10 controls	[^{11}C]-PK11195	SRTM	NA
		[^{11}C]-PIB	Reference region: supervised cluster analysis	
Tomasi et al. (2008)	10 AD patients and 10 controls	[^{11}C]-PK11195	SRTM with modelling of peripheral benzodiazepine binding sites vascular activity	NA
Wiley et al. (2009)	6 MCI, 6 mild to moderate AD and 5 controls	[^{11}C]-PK11195	SRTM (whole cerebellum as reference) and tissue ratio method (ROI to subcortical white matter ratio)	NA
		[^{11}C]-PIB		
			Correction for partial volume effects	
Okello et al. (2009)	14 MCI patients, 15 AD patients and 10 controls	[^{11}C]-PK11195	SRTM	NA
		[^{11}C]-PIB	Reference region: supervised cluster analysis	
Yokokura et al. (2011)	11 mild to moderate AD patients	[^{11}C]-PK11195	SRTM: input curve from young subjects	NA
	10 controls	[^{11}C]-PIB		
		[^{18}F]-FDG		
Yaqub et al. (2012)	8 AD patients, 9 MCI patients, and 17 controls	[^{11}C]-PK11195	SRTM with and without vascular correction, reference region: cerebellum or supervised cluster analysis	NA
Schuitemaker et al. (2013)	19 AD patients, 13 amnestic MCI patients and 21 controls	[^{11}C]-PK11195	Receptor parametric mapping (basis function implementation of the SRTM) and modified supervised cluster analysis	NA
Fan et al. (2015a)	10 AD patients, 10 MCI, 11 Parkinson (PD) patients, and 16 controls	[^{11}C]-PK11195	Reference region: supervised clustering method	NA
		[^{11}C]-PIB	BP mapping: unspecified method	
		[^{18}F]-FDG		
Fan et al. (2015c)	8 AD patients and 14 controls	[^{11}C]-PK11195	SRTM	NA
		[^{11}C]-PIB	Reference region: cluster analysis	
		[^{18}F]-FDG	Longitudinal study	

Table 1 continued

	Nb of subjects	Tracer(s)	Quantification method	rs6971 TSPO polymorphism genotyping
Femminella et al. (2016)	8 AD patients, 9 PD patients, and 8 controls	[^{11}C]-PK11195	SRTM	NA
		[^{18}F]-FDG	Reference region: cluster analysis	
Fan et al. (2017)	8 MCI patients (4 with negative amyloid imaging) and 14 controls	[^{11}C]-PK11195	SRTM	NA
		[^{11}C]-PIB	Reference region: cluster analysis	
			Longitudinal study	
Yokokura et al. (2017)	13 young controls, 12 elderly controls, and 7 AD patients for [^{11}C]-DPA713 and 13 young controls, 10 elderly controls, and 10 AD patients for [^{11}C]-PK1195	[^{11}C]-PK11195	SRTM (input curve from young subjects)	No (rs6971 polymorphism is considered to be rare in japanese population)
		[^{11}C]-DPA713		
Kreisl et al. (2013b)	19 AD patients, 10 MCI patients, and 13 controls	[^{11}C]-PBR28	2 TCM: with the arterial input function, corrected for plasma-free fraction of radiotracer	Yes for 10 AD patients and 12 controls
		[^{11}C]-PIB		
				In vitro binding to TSPO on peripheral leukocytes for the remaining subjects
Kim et al. (2013)	6 AD patients, 7 amnestic MCI, and 7 controls	[^{11}C]-PBR28	SUV analysis	Yes
Yoder et al. (2013)	7 AD patients, 7 MCI patients, and 18 controls	[^{11}C]-PBR28	SUV analysis	Yes
Lyoo et al. (2015)	25 AD patients, 11 MCI patients, and 21 controls	[^{11}C]-PBR28	2TCM with the arterial input function, corrected for plasma-free fraction of radiotracer	Determined by using leukocyte binding assay
			SUVR using cerebellum as pseudo-reference region	
Kreisl et al. (2016)	14 amyloid-positive patients and 8 amyloid-negative controls	[^{11}C]-PBR28	SUVR analysis using cerebellum as the pseudo-reference region	Yes for 8 patients and 7 controls
			Longitudinal study	
				In vitro binding to TSPO on peripheral leukocytes for the remaining subjects
Nair et al. (2016)	5 AD patients with HAB genotype	[^{11}C]-PBR28	Test–retest reliability of unadjusted SUV, SUV normalized to the whole brain, and normalized to the cerebellum	Yes
Kreisl et al. (2017)	11 PCA patients, 11 amnestic AD patients, and 15 controls	[^{11}C]-PBR28	2TCM with the arterial input function, corrected for plasma-free fraction of radiotracer	Determined by using leukocyte binding assay
		[^{11}C]-PIB		
		[^{18}F]-FDG	SUVR using cerebellum as the pseudo-reference region	
				Confirmed by genotyping in 21 subjects

Table 1 continued

	Nb of subjects	Tracer(s)	Quantification method	rs6971 TSPO polymorphism genotyping
Golla et al. (2015)	10 AD patients and 6 controls	[^{18}F]-DPA-714	Plasma input models and SRTM with cerebellar grey matter as reference tissue	No
Golla et al. (2016)	9 AD patients and 6 controls	[^{18}F]-DPA-714	Logan graphical analysis and spectral analysis using plasma input function	No
			Five versions of Ichise, Logan plot, and 2 basis function implementations (receptor parametric mapping and SRTM2, all using cerebellar grey matter as the reference region	
Hamelin et al. (2016)	64 AD patients and 32 controls	[^{18}F]-DPA-714 [^{11}C]-PIB	SUVR analysis using cerebellar grey matter as pseudo-reference region	Yes
Suridjan et al. (2015)	21 AD patients and 21 controls	[^{18}F]-FEPPA	2-TCM with arterial plasma input function	Yes
Varrone et al. (2015)	10 AD patients and 7 controls	[^{18}F]-FEMPA	2-TCM and Logan graphical analysis with arterial input function	Measured by using a competition assay with [^{3}H]PK11195 and PBR28 on platelet membrane suspension
Varrone et al. (2013)	9 AD patients and 7 control subjects	[^{18}F]-FEDAA1106	2-TCM, with blood volume parameter and Logan graphical analysis	No
Yasuno et al. (2008)	10 AD patients and 10 controls	[^{11}C]-DAA1106	2-TCM with arterial input function	No
Yasuno et al. (2012)	7 MCI patients, 10 AD patients, and 10 controls	[^{11}C]-DAA1106	2-TCM with arterial input function	No
Gulyás et al. (2011b)	6 AD patients and 12 controls	[^{11}C]-vinpocetine	SUVR and Logan graphical analysis using cerebellum as reference region	No
Esposito et al. (2008)	8 AD patients and 9 controls	1-^{11}C-AA	Study of regional K^* for AA	NA
Hirvonen et al. (2009)	4 AD patients and 16 controls	^{11}C-L-DED	2-TCM	NA
Santillo et al. (2011)	9 AD patients, 1 mixed dementia, and 11 controls	^{11}C-L-DED [^{11}C]-PIB	Patlak analysis with cerebellum as reference region	NA
Carter et al. (2012)	7 AD patients, 8 MCI patients, and 14 controls	^{11}C-DED [^{11}C]-PIB [^{18}F]-FDG	Patlak analysis with cerebellar grey matter as reference region	NA
Choo et al. (2014)	7 AD patients and 13 MCI patients	^{11}C-DED [^{11}C]-PIB [^{18}F]-FDG	^{11}C-DED slope value ratio analysis with cerebellar values as reference	NA
Schöll et al. (2015)	7 AD patients, 11 MCI patients, 6 presymptomatic mutation carriers, 3 symptomatic mutation carriers, and 12 mutation non-carriers	^{11}C-DED [^{11}C]-PIB [^{18}F]-FDG	Patlak analysis with cerebellar grey matter as reference region	NA
Rodriguez-Vieitez et al. (2016a)	8 AD patients, 17 MCI patients, and 16 controls	^{11}C-DED [^{11}C]-PIB [^{18}F]-FDG	Patlak analysis with cerebellar grey matter as reference region	NA

Table 1 continued

	Nb of subjects	Tracer(s)	Quantification method	rs6971 TSPO polymorphism genotyping
Rodriguez-Vieitez et al. (2016b)	8 sporadic AD patients, 17 MCI patients, 7 presymptomatic mutation carriers, 4 symptomatic mutation carriers, and 16 mutation non-carriers	^{11}C-DED [^{11}C]-PIB [^{18}F]-FDG	Patlak analysis with cerebellar grey matter as reference region	NA
Sturm et al. (2016)	10 AD patients and 6 controls	^{11}C-DED	2-TCM irreversible	NA
Ohnishi et al. (2016)	3 PIB positive dementia patients, 2 PIB-positive MCI patients, and 4 controls	^{11}C-ketoprofen methyl ester ([^{11}C]-KTP-Me)	Study of cortical retention and washout rate	NA
Ahmad et al. (2016)	9 AD patients and 8 controls	[^{11}C]-NE40 [^{11}C]-PIB	A one-tissue (*K1*, *k2*) kinetic model and two-tissue (2T) reversible (*K1*, *k2*, *k3*, *k4*) and irreversible (*K1*, *k2 k3*) kinetic models with input functions corrected for blood volume and arterial metabolites	NA

AD Alzheimer's disease, *MCI* mild cognitive impairment, *PD* Parkinson disease, *HAB* high affinity binder, *ROI* region of interest, *SRTM* simplified reference tissue model, *SPECT* single photon emission tomography, *SUVR* standardized uptake value ratio, *1-TCM*, *2-TCM* one, two tissue compartmental analysis, *BP* binding potential, *PCA* posterior cortical atrophy, *K** incorporation coefficient, *AA* arachidonic acid

on their time activity profiles, rather than their spatial proximity. Thus, the values of the selected voxels are neither altered by partial volume effect that affect the anatomically drawn region nor by the tissue heterogeneity within ROI. Some caveats have recently been discussed about a possible underestimation of the reference region kinetics in patients as it is defined in controls. This may lead to an overinterpretation of the results in patients (Raffel et al. 2017; Herranz et al. 2017).

Another method consisting in the determination of a distribution volume ratio (distribution volume in a ROI/distribution volume in whole brain) has also recently been proposed for the quantification of [^{11}C]-PBR28 binding (Turkheimer et al. 2015; Bloomfield et al. 2016). It must be noticed that this approach is expected to underestimate group differences, since the target region is a subset of the reference region. In addition, it is hypothetically possible to get completely erroneous results—e.g. if binding is globally reduced but to a disproportionately lower amount in the target region, one might falsely get the impression that target binding is increased.

Recent works, using [^{11}C]-PK11195 and [^{11}C]-PBR28, developed new strategies, which added extra compartment in the kinetics model to account for the endothelial cell binding, allowing an enhanced quality of the kinetic parameter determination (Tomasi et al. 2008; Yaqub et al. 2012; Rizzo et al. 2014). Further validation of this approach using other second-generation TSPO tracers and clinical cohorts is in progress (Wimberley et al. 2016).

It is also important to consider other factors that could have an influence on microglial activation, especially drug therapies (cholinesterase inhibitors, NSAIDs) and white matter hyperintensities on MRI (Hommet et al. 2014).

Thus, further work is needed to validate new quantification methods and to independently determine a reference region for each tracer and in each disease, because the affinity of the ligands can be different, as is TSPO distribution in diseases (Vivash and O'Brien 2016), and then apply these validated methods to larger cohorts of patients. It is also important to develop new types of radioligands, such as the so-called third-generation TSPO tracers or new analogues of [^{11}C]-PK11195, like [^{11}C]-ER176, which could be less sensitive to TSPO binding affinity status (Fan et al. 2016; Ikawa et al. 2017), or the alternatives to TSPO imaging mentioned in "Other radiotracers" and "Imaging neuroinflammation with MRI", either with PET or with other techniques like MRI, and to use the complementary information provided by each method, to better understand the multiple aspects of neuroinflammation, by developing a multimodal approach (Pasternak et al. 2016).

The results obtained by TSPO PET imaging of neuroinflammation in AD

We will describe the main results obtained in the studies of neuroinflammation by PET in AD. By contributing to a better understanding of the mechanisms of the disease, these works could lead to new therapeutic approaches whose effects could also be monitored by TSPO PET imaging. As we will see later, the difficulties in the interpretation of the results obtained up to now raise the question of how the beneficial effect of a drug would be expressed in PET imaging.

[^{11}C]-PK11195 PET imaging in AD

This tracer was used in 20 studies involving AD patients (Table 1)—some of which had a methodological purpose (Anderson et al. 2007; Schuitemaker et al. 2007)—and showed contradictory results. The first study of AD patients using [^{11}C]-PK11195 failed to detect TSPO binding sites associated with microglial activation in patients with mild to moderate dementia (Groom et al. 1995). This lack of increased binding in AD was also reported by Wiley et al. (2009), who concluded that either microglial activation is limited to later stages of severe AD or [^{11}C]-(*R*)-PK11195 is too insensitive to detect microglial activation in mild to moderate AD. In a more recent study, voxel-wise statistical parametric mapping (SPM) analysis showed only small clusters of significantly increased [^{11}C]-(*R*)-PK11195 binding in occipital lobes in AD dementia patients and no difference between clinically stable prodromal AD patients and those who progressed to dementia (Schuitemaker et al. 2013).

Other studies demonstrated the interest of [^{11}C]-(*R*)-PK11195 to detect neuroinflammation in AD. An increased PK11195 uptake was found in AD patients in two studies: in the frontal and right mesotemporal regions using SPECT (Versijpt et al. 2003), and in the frontal, temporal, parietal, occipital and cingulate cortices, as well as in the striatum using PET with region-of-interest analysis (Edison et al. 2008). Interestingly, Cagnin et al. (2001) found an increased regional [^{11}C]-(*R*)-PK11195 binding in the entorhinal, temporoparietal and cingulate cortex in mild and early AD. These data were congruent with Okello's work, showing an increased cortical [^{11}C]-(*R*)-PK11195 binding, which remained significant in the frontal cortex after a correction for multiple comparisons in AD at the MCI stage defined by positive [^{11}C]-PIB-PET imaging (Okello et al. 2009).

Analyses of correlations between microglial activation and cognitive functions led to conflicting results. While some studies found significant negative correlations (i.e. increased microglial activation and decreased cognitive abilities) between tracer binding and cognitive functioning (Versijpt et al. 2003; Edison et al. 2008; Yokokura et al. 2011; Fan et al. 2015a), other studies found no correlation between [^{11}C]-PK11195 retention and cognitive function (Schuitemaker et al. 2013; Yokokura et al. 2017).

The analyses of the relationship between microglial activation and amyloid deposition assessed by [^{11}C]-PIB showed inconsistent results. No correlation between cortical microglial activation and amyloid load was sometimes reported (Edison et al. 2008; Okello et al. 2009), while other works found significant correlations between [^{11}C]-(*R*)-PK11195 and [^{11}C]-PIB binding, which were either negative in the posterior cingulate cortex (PCC) (Yokokura et al. 2011) or positive (Fan et al. 2015a, c).

Interestingly, a very recent study showed a negative correlation between hippocampal volume and microglial activation within the hippocampus or parahippocampus and with cortical and subcortical areas of projections from the hippocampus (Femminella et al. 2016).

Two longitudinal studies provided information about the course of neuroinflammation in AD using [^{11}C]-(*R*)-PK11195. The first one shows an increase of tracer binding in AD patients (Fan et al. 2015c). Conversely, another recent longitudinal study by the same team reports the evolution of [^{11}C]-(*R*)-PK11195 binding over time in eight MCI patients, four of whom had a negative amyloid imaging, and finds a longitudinal reduction of microglial activation in this population (Fan et al. 2017).

Taken together, these data, although sometimes conflicting, suggest an early and persistent neuroinflammation in AD. The small sample sizes, the different methods used, and the limits of the tracer itself could explain these contradictory results.

Second generation of TSPO ligands

The development of second generation of TSPO ligand permitted to continue this work by improving the specificity of the tracers.

Summary of the main results

In this paragraph, we will first summarize the main results observed in AD according to the tracers used. Note that the conclusions of the studies that do not take the genetic status of TSPO binding into account (mentioned in Table 1) must be considered with caution and will not be discussed in detail.

Many studies with second-generation TSPO ligands found increased binding in AD patients compared to controls:

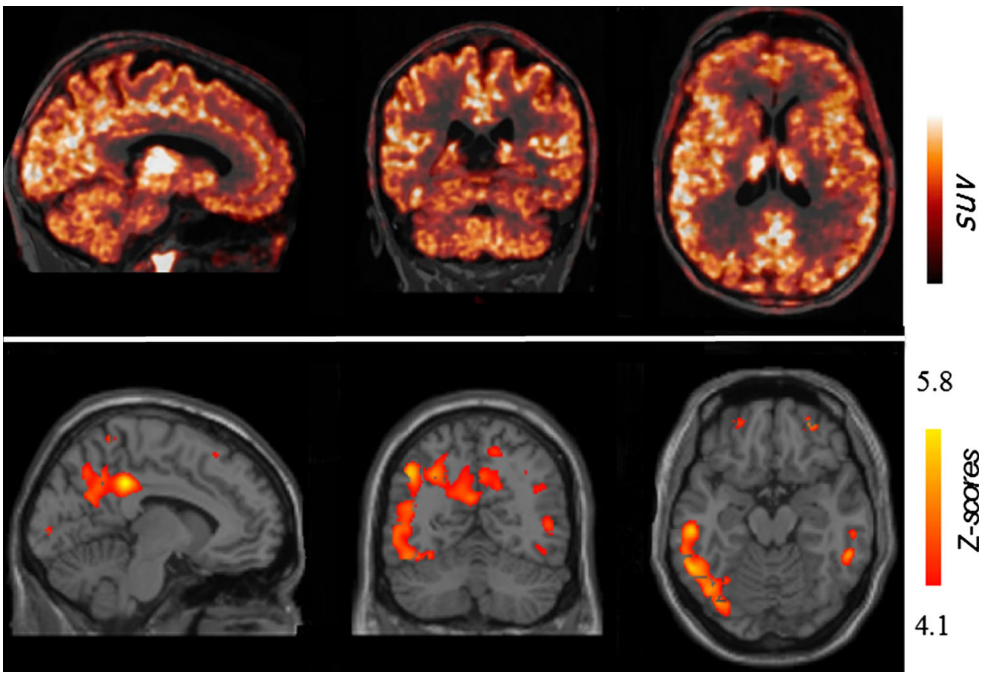

Fig. 1 TSPO PET imaging in Alzheimer's disease. Top: [^{18}F]-DPA-714 brain distribution in an AD patient. Bottom: statistical parametric mapping analysis of [^{18}F]-DPA-714 binding (SUVr) between AD patients and controls. Significance threshold set at $P < 0.05$ family-wise error (FWE) corrected, with TSPO genotype as covariate (modified from Hamelin et al. 2016)

(a) using [^{11}C]-PBR28 in the parietal and temporal cortices (more specifically in the inferior parietal lobule, precuneus, occipital cortex, hippocampus, entorhinal cortex) (Kreisl et al. 2013b; Lyoo et al. 2015; Kreisl et al. 2016),
(b) using [^{18}F]-DPA-714: in the frontal, temporal, and parietal cortex (Hamelin et al. 2016) (Fig. 1),
(c) using [^{18}F]-FEPPA: in the grey matter of the hippocampus, prefrontal, temporal, parietal and occipital cortex, in the white matter of the posterior limb of the internal capsule, and the cingulum bundle (Suridjan et al. 2015),
(d) using [^{18}F]-FEMPA: in the medial and lateral temporal cortex, posterior cingulate, caudate, putamen, and thalamus (Varrone et al. 2015).

Other positive results reported with other tracers are only listed here, as they did not take the genetic TSPO status into account: [^{11}C]-DAA1106, [^{18}F]-FEDAA1106, [^{11}C]-DPA713, [^{18}F]-DPA-714 and [^{11}C]-vinpocetine (Yasuno et al. 2008, 2012; Varrone et al. 2013; Yokokura et al. 2017; Golla et al. 2015, 2016; Gulyás et al. 2011b).

Early stage of AD

In the early stage of AD, defined as amnesic MCI associated with positive amyloid PET, increased [^{11}C]-DAA1106 binding was found in widespread areas when compared to healthy controls (Yasuno et al. 2012). In a larger cohort of subjects, an increased [^{18}F]-DPA-714 binding was observed in the frontal, temporal, and parietal cortex (Hamelin et al. 2016). These positive results were not confirmed by using [^{11}C]-PBR28, for which no increased binding in AD-MCI patients was found (Kreisl et al. 2013b).

It is important to highlight here that the methods used for the quantification of tracer binding were different between the studies, which could explain some discrepancies (see "Methodological issues in TSPO quantification by PET").

Taken together, the data obtained with second generation of TSPO ligands showed more consistent results than those found with [^{11}C]-PK11195 and demonstrated the possibility of using these PET tracers to assess neuroinflammation in AD.

Age of onset

An effect of the age of onset was observed using [^{11}C]-PBR28 with early-onset AD patients having greater TSPO binding than late-onset patients (Kreisl et al. 2013b), while no correlation with age was observed in a larger cohort of subjects using [^{18}F]-DPA-714 (Hamelin et al. 2016).

Different AD variants

A very recent study compared TSPO binding by using [^{11}C]-PBR28 in posterior cortical atrophy (PCA) and in amnestic AD. When compared to controls, [^{11}C]-PBR28 binding was greater in occipital, posterior parietal, and temporal regions in PCA patients, and in inferior and medial temporal cortex in amnestic AD patients,

suggesting distinct binding patterns that mirror neurodegeneration assessed by MRI and FDG PET (Kreisl et al. 2017).

The second step to analyse these data was based on the correlations with different clinical parameters. It is difficult to bring out a simple message, due to differences in the sample sizes and in the methods of quantification used.

Correlations with cognitive deficits

Negative correlations between TSPO binding and cognitive testing were found using [^{11}C]-PBR28 binding (scores on Folstein Mini-Mental State Examination, Clinical Dementia Rating Scale Sum of Boxes, Logical Memory Immediate (Wechsler Memory Scale Third Edition), Trail Making part B and Block Design (Wechsler Adult Intelligence Scale Third Edition) tasks) (Kreisl et al. 2013b), and using [^{11}C]-DPA713 or [^{18}F]-FEPPA (visuospatial function and language ability with the parietal cortex and posterior limb of the internal capsule) (Yokokura et al. 2017; Suridjan et al. 2015). A recent study in a larger number of subjects did not confirm these data, showing that DPA-714 binding was positively correlated with MMSE scores (Hamelin et al. 2016). In this latter study, the neuroinflammation in the MCI-AD patients was higher than in the demented-AD patients, reinforcing the idea that the level of neuroinflammation is greater at the early stage of the disease.

Correlation with brain atrophy

Using different tracers and different methods of quantification, opposite results were found in correlations between microglial activation and grey matter volume. [^{11}C]-PBR28 binding was negatively correlated with grey matter volume (Kreisl et al. 2013b, 2017), while DPA-714 binding was positively correlated with grey matter volume, even when the analysis was restricted to the MCI-AD patients (Hamelin et al. 2016). An inverse relationship between PBR28 binding and brain atrophy (i.e. increased binding and decreased atrophy or increased volume) has also been suggested in another study (Kim et al. 2013).

Correlation with amyloid deposit

The three studies, which analysed correlations between amyloid burden and TSPO binding in AD, reached similar conclusions. A positive relationship was observed between [^{11}C]-PIB and TSPO binding ([^{11}C]-PBR28 or [^{18}F]-DPA-714) in the inferior parietal lobule, superior temporal cortex, precuneus, hippocampus and parahippocampal gyrus (Kreisl et al. 2013b, 2017; Hamelin et al. 2016).

Whether microglial activation assessed by PET could have a prognostic value in early AD remains controversial. While higher [^{11}C]-DAA1106 binding was associated with a risk of dementia within 5 years (Yasuno et al. 2012), suggesting a detrimental effect of microglial activation in a study without TSPO polymorphism genotyping, another recent study using [^{18}F]-DPA-714 suggested a clinical protective effect of microglial activation on the measure of CDR change after 2 years of follow-up (Hamelin et al. 2016).

After the stability and reproducibility of [^{11}C]-PBR28 binding over 12 weeks were verified by Nair et al. (2016), Kreisl et al. performed one longitudinal study showing an increasing TSPO binding in temporoparietal regions from 3.9 to 6.3% per year in patients vs. 0.5–1% per year in controls. The increase in TSPO binding correlated with cognitive worsening on clinical dementia rating scale sum of boxes and with reduced cortical volume. The annual rate of increased TSPO binding in temporoparietal regions was about fivefold higher in patients with clinical progression compared with those who did not progress (Kreisl et al. 2016), suggesting not only that neuroinflammation in AD is a dynamic process, but also that this process plays a negative, toxic role.

In conclusion, the second generation of TSPO PET tracers demonstrate more consistent results regarding the increased expression of TSPO in AD, but there are diverging interpretations of the meaning of microglial activation, which is reported to be either detrimental or protective. These conflicting conclusions must be discussed in the light of the heterogeneous populations included and methods of quantification applied (see "Methodological issues in TSPO quantification by PET").

Overview of the results obtained with TSPO PET imaging in other diseases

PET imaging of neuroinflammation has been used in a great variety of disorders, among which are multiple sclerosis (Hagens et al. 2016), epilepsy (Gershen et al. 2015), stroke (Gulyas et al. 2012) or brain tumours (Su et al. 2013). We will briefly focus on the main results obtained in neurodegenerative disorders associated with AD, as well as in psychiatric disorders and ageing.

A study showed increased binding of [^{11}C]-(*R*)-PK11195 in frontotemporal lobar degeneration in the frontotemporal brain regions, suggesting that microglial activation may occur independently from increased amyloid plaque formation (Cagnin et al. 2004), and could also be an intrinsic process in other pathways, such as tau pathology (Zhang 2015).

Parkinson's disease (PD) was also studied with TSPO tracers. One study using [^{11}C]-PK11195 showed a statistically significant increase in microglial activation in the temporal, parietal, and occipital regions in PD patients compared with controls, which also concerned the anterior and posterior cingulate, striatum, and frontal cortex in patients with dementia (Edison et al. 2013). Another study using [^{11}C]-DPA713 reported a significant increase in tracer binding in the occipital, temporal, and parietal cortex, which became much higher in the temporal and occipital cortex after 1 year in PD patients (Terada et al. 2016); a lack of increase of striatal TSPO expression was nevertheless reported with [^{18}F]-FEPPA (Koshimori et al. 2015). Significant negative correlations were found between microglial activation and glucose metabolism (rCMRGlc) (Fan et al. 2015a), and between microglial activation and Mini-Mental State Examination (MMSE) score (Fan et al. 2015a; Edison et al. 2013).

Increased [^{11}C](*R*)-PK11195 binding was also reported in atypical parkinsonian syndromes and reflected the known distribution of neuropathologic changes: in the dorsolateral prefrontal cortex, putamen, pallidum, pons, and substantia nigra in multiple system atrophy (Gerhard et al. 2003); in the caudate nucleus, putamen, substantia nigra, pons, pre- and postcentral gyrus, and the frontal lobe in corticobasal degeneration (CBD) (Gerhard et al. 2004; Henkel et al. 2004); in the basal ganglia, midbrain, the frontal lobe, and the cerebellum in progressive supranuclear palsy (PSP) (Gerhard et al. 2006); in the substantia nigra, putamen, and in several associative cortices in dementia with Lewy bodies (DLB) (Iannaccone et al. 2013).

Significantly increased [^{11}C]-(*R*)-PK11195 binding was found in the motor cortex, pons, dorsolateral prefrontal cortex, and thalamus in amyotrophic lateral sclerosis (ALS) patients, with a significant correlation between binding in the motor cortex and the severity of upper motor neuron clinical signs (Turner et al. 2004). Similar results were found in the motor cortices and corticospinal tracts with [^{11}C]-PBR28 (Zürcher et al. 2015). Increased [^{18}F]-DPA-714 binding was also found in the primary motor, supplementary motor and temporal cortices (Corcia et al. 2012).

The results obtained when studying ageing are conflicting: while one study using [^{11}C]-(*R*)-PK11195 found increased tracer binding in the frontal lobe, anterior and posterior cingulate cortex, medial inferior temporal lobe, insula, hippocampus, entorhinal cortex, thalamus, parietal and occipital lobes, and cerebellum (Schuitemaker et al. 2012), another study reported no association between [^{18}F]-FEPPA binding and normal ageing (Suridjan et al. 2014).

Imaging of neuroinflammation was also applied to psychiatric diseases. Regarding psychosis and schizophrenia, some studies found no significant increase of [^{18}F]-FEPPA in first-episode psychosis (Hafizi et al. 2017) or in treated schizophrenia patients in the midst of a psychotic episode (Kenk et al. 2015), while others found elevated [^{11}C]-PBR28 binding, which was positively correlated with symptom severity in patients with schizophrenia and in persons at ultrahigh risk of psychosis (Bloomfield et al. 2016), and increased [^{11}C]-(*R*)-PK11195 binding in the hippocampus of schizophrenic patients (Doorduin et al. 2009). These results suggest that inflammation could be a subtle phenomenon in schizophrenia, which is more extensive at the early stages of the disorder and could be reduced by antipsychotic medication (Pasternak et al. 2016).

Except in one study using [^{11}C]-PBR28 (Hannestad et al. 2013), raised binding of [^{11}C]-PK11195 (Su et al. 2016b; Haarman et al. 2014) or [^{18}F]-FEPPA (Setiawan et al. 2015) has also been reported in depression.

Other radiotracers

Tracers targeting microglial activation

In this section, we mention other ligands aiming at imaging activated microglia by using other targets than TSPO. Further work is needed to develop new targets linked to the migratory capacity of microglia or their ability to phagocytose Aβ rather than just looking for proteins up-regulated on or in "activated microglia". Such targets could be identified and prioritized for further investigation, by using new approaches such as cell type-specific transcriptional profiling of human plaque-associated vs. parenchymal microglia, which could lead to the identification of numerous cell type-specific changes undetected in whole tissue RNA (Srinivasan et al. 2016).

Cannabinoid type 2 receptor (CB_2R)

CB_2R is part of the endogenous cannabinoid system and is an alternative membrane marker of microglial activation, which leads to its increased expression. A number of PET tracers showing high affinity for CB_2R have been developed. The first tracer used in human studies is [^{11}C]-NE40, which showed lower CB_2R availability in vivo in AD patients, contrary to that expected from preclinical and postmortem studies. This inconsistency is probably due to the very low level of CB_2R expression and an insufficient selectivity for CB_2R vs. CB_1R (Ahmad et al. 2016). Other high affinity CB_2R agonists are under development, such as [^{11}C]-MA2, [^{18}F]-MA3 (Ahamed et al. 2016) or [^{18}F]-RS126 (Slavik et al. 2016).

P2X7 receptor

The ionotropic purinergic receptors P2X are expressed in the cell surface membranes of hematopoietic cells including macrophages and microglia. Receptor subtype 7 (P2X7) has been implicated in microglial proliferation, phagocytosis, and release of pro-inflammatory cytokines (Territo et al. 2017). PET tracers targeting P2X7 receptor are under development: [^{11}C]-GSK1482160 (Territo et al. 2017), [^{11}C]-A-740003 (Janssen et al. 2014), [^{11}C]-JNJ-54173717 (Ory et al. 2016).

COX-1 inhibitor [^{11}C]-ketoprofen methyl ester ([^{11}C]-KTP-Me)

Ketoprofen is a selective inhibitor of COX-1, which is expressed in activated microglia. [^{11}C]-KTP-Me is a pro-radiotracer of ketoprofen, which increases its penetration through the blood–brain barrier. Animal studies suggested that [^{11}C]-KTP was retained in inflammatory lesions because of the expression of COX-1. A first-in-human study on healthy volunteers showed that [^{11}C]-KTP-Me was a stable and safe PET tracer with a good penetration in the human brain (Ohnishi et al. 2014). Nevertheless, no difference in the washout rate was found between controls and AD patients in a recent study, warranting further works and improvement before being considered a potential biomarker of neuroinflammation (Ohnishi et al. 2016).

COX-2 inhibitors

COX-2 has been reported to be up-regulated in activated microglia (Temel and Kahveci 2009). Radiolabelled COX-2 inhibitors have been used to visualize COX-2 expression and activity (Laube et al. 2013). However, despite some promising results in in vitro experiments, in vivo results with candidate PET/SPECT tracers have been disappointing (perhaps due to species difference in the role of COX-2 and COX-1).

Nicotinic acetylcholine receptors (nAChRs)

The nAChRs have been recently associated with neuroinflammation, and the ligand 2[^{18}F]-fluoro-A85380 (2-FA), which targets α4β2 nAChR, has been demonstrated to have similar patterns of uptake as [^{11}C]-PK11195 and to be up-regulated to the same extent as TSPO in activated microglia and astrocytes (Albrecht et al. 2016). Other tracers like [^{18}F]-flubatine, with more favourable kinetic profile than 2-FA have been developed and could be tested to better understand the role of nAChRs in neuroinflammation, as previous studies have demonstrated decreased receptor binding in neurological disorders (Albrecht et al. 2016; Lagarde et al. 2016).

The homomeric α7 nAChRs are co-localized in neuritic plaques in human brains with AD, and Aβ1-42 has been shown to bind with high affinity to the α7 nAChRs (Wang et al. 2000). α7 nAChRs are also strongly expressed on CNS immune cells such as astrocytes and microglia. Activation of α7 nAChRs on these cells has been shown to suppress inflammatory processes (Kalkman and Feuerbach 2016). Several α7 nAChR PET tracers have been developed with limited success. Recently, new compounds such as [^{18}F]-ASEM and [^{18}F]-DBT-10 show more promising results (Hillmer et al. 2017).

Tracers targeting other processes than microglial activation

Astrocytosis

High concentrations of monoamine oxidase B (MAO B) are present in astrocytes, while they are low in other glial elements such as microglia. During neuroinflammatory processes, MAO B is up-regulated in reactive astrocytes. L-deprenyl is an irreversible MAO B inhibitor with high affinity for the MAO B enzyme. [^{11}C]-L-deprenyl has been used to study the distribution of MAO B in the brain and sometimes to assess its occupancy by other MAO B inhibitors (Hirvonen et al. 2009; Sturm et al. 2016). A post-mortem study showed that the increased regional binding in Alzheimer brains coincided with the presence of an increased number of activated astrocytes (Gulyás et al. 2011a). The deuterium substituted compound [^{11}C]-deuteriodeprenyl (DED) has been demonstrated to have kinetic advantages to be used as a PET tracer and its binding is independent from brain perfusion (Rodriguez-Vieitez et al. 2016a). Astrocytosis has also been imaged by using [^{11}C]-acetate or ligands for the I2-imidazoline receptor, especially in multiple sclerosis (Takata et al. 2014; Matthews and Datta 2015).

Phospholipase A_2 (PLA_2) activity

Inflammatory cytokines released from microglia can bind to astrocytic receptors, which are coupled to PLA_2. When this enzyme is activated, it hydrolyses esterified arachidonic acid (AA) from the membrane. By injecting [^{11}C]-AA intravenously and determining its regional brain incorporation coefficients, it is possible to determine metabolic loss of AA in the brain, as it cannot be synthesized de novo or converted from its precursor (Esposito et al. 2008). Thus, increased incorporation of [^{11}C]-AA could represent up-regulated AA metabolism due to neuroinflammation.

Adenosine A2A receptors (A2AR)

The binding of adenosine on A2ARs tends to attenuate inflammation, leading to an up-regulation of these receptors at sites of inflammation and tissue damage to endogenously limit inflammatory response. The ligand [^{11}C]-TMSX binds selectively to adenosine A2ARs and has been used in vivo in healthy controls, Parkinson's disease (Mishina et al. 2011) and multiple sclerosis (Rissanen et al. 2013).

Results obtained in AD with non-TSPO ligands

Although some studies have failed to reveal significant differences between AD patients and controls by using [^{11}C]-KTP-Me (Ohnishi et al. 2016) or significantly lower CB_2R binding with [^{11}C]-NE40 in AD patients in contrast to preclinical and postmortem data showing opposite results (Ahmad et al. 2016), other studies have showed a significantly higher [^{11}C]-L-DED retention in the frontal, parietal, temporal, and medial temporal lobes in AD patients compared to healthy controls (Santillo et al. 2011) or significantly elevated incorporation coefficient for AA in regions reported to have high densities of senile plaques with activated microglia (Esposito et al. 2008).

Significant differences were reported in MCI patients, with elevated regional [^{11}C]-DED binding in the bilateral frontal and parietal cortices and increased [^{11}C]-DED binding in most cortical and subcortical regions in MCI patients with positive [^{11}C]-PIB binding relative to controls, MCI patients with negative [^{11}C]-PIB binding, and AD patients, suggesting that astrocytosis is an early phenomenon in AD development (Carter et al. 2012). In the same line of idea, [^{11}C]-DED binding was highest in presymptomatic autosomal dominant Alzheimer's disease (ADAD) mutation carriers (Schöll et al. 2015). A longitudinal study of astrocyte activation using [^{11}C]-DED showed significantly elevated binding in presymptomatic ADAD carriers, which then steadily declined, while it remained globally stable over time in patients with sporadic [^{11}C]-PIB positive MCI (Rodriguez-Vieitez et al. 2016b).

One study showed a significant negative correlation between [^{11}C]-DED binding and grey matter density in the parahippocampus in PIB-positive MCI patients (Choo et al. 2014).

A positive correlation was found between PIB retention and [^{11}C]-DED binding in AD patients (Santillo et al. 2011; Choo et al. 2014), while no correlation was reported between astrocytosis and CSF tau levels (Choo et al. 2014).

Taken together, these results suggest that astrocytosis is an early phenomenon in AD, occurring from the preclinical stage, with a potential influence on cellular tissue loss and a possible (causal?) link with amyloid pathology.

Imaging neuroinflammation with MRI

The sensitivity of PET targets in human study is sometimes debated and the need for radiolabelling of the tracers may limit the availability of this technique. Furthermore, PET exposes the subjects to ionizing radiations and has a relatively poor spatial resolution. The use of MRI might be easier in clinical practice and has the advantage of avoiding the exposition to ionizing radiations and to offer better spatial resolution for anatomical MRI. It has the advantage of widening the spectrum of available techniques, each of which have their limitations and could be complementary if used in a multimodal approach (Pasternak et al. 2016). We will propose a brief overview of the available and emerging techniques aiming at imaging neuroinflammation by MRI.

In spite of a poor spatial resolution and a limited coverage of the brain, ^{1}H MRS has been used to visualize neuroinflammation by targeting metabolites, which are elevated in cases of inflammation or gliosis, such as myoinositol (MI), a putative glial marker, total creatine (tCr), which reflects the level of energy metabolites, or choline (Cho). It is nevertheless important to notice that the current results suggest that it is difficult to interpret Cho, tCr, or MI elevation as representing a single underlying mechanism that reflects neuroinflammation, and that MRS markers alone are insufficient for indentifying neuroinflammation (Zahr et al. 2014). Other metabolites like glutathione (GSH) could emerge as new indirect neuroinflammatory markers (Pasternak et al. 2016). Another limitation of MRS is the absence of standardized methodology, which makes it difficult to achieve consistency across studies (Zahr et al. 2014). Keeping these caveats in mind, we can mention a recent study using ^{1}H MRS in AD and DLB patients, which, although showing an unexpected overall decrease in most metabolites in patients, also found higher occipital MI/Cr, NAA/Cr, and Cho/Cr levels and significant correlation between MI/Cr level in the temporal lobe and cognitive performance in the DLB group (Su et al. 2016a).

Anatomical MRI can also be used, with a high spatial resolution. Gadolinium-enhanced T1-weighted images showing hypersignal outside of blood vessels is suggestive of blood–brain barrier (BBB) breakdown, which is a marker of severe inflammation (Stefaniak and O'Brien 2016). Other techniques of molecular MRI have been developed, such as myeloperoxidase imaging, autologous cell tracking, or targeted iron oxide particles (USPIOs, MPIOs). Although these methods are limited to endothelial proteins, to diseases with compromised BBB and to cells capable of crossing the BBB, and still remain for some of them (especially MPIOs, which, unlike USPIOs agents, allow endovascular specificity) restricted to preclinical imaging,

the combination of targeted MPIOs and MRI cell tracking appears as a promising approach to non-invasively study immune cells trafficking (Gauberti et al. 2014). Quantitative T2 images may be another option for identifying neuroinflammation.

Diffusion MRI enables to calculate extracellular volume, which is sensitive to neuroinflammation, particularly in the white matter, but its utility remains equivocal (Pasternak et al. 2016). Emerging techniques in diffusion MRI could prove helpful in identifying inflammation, such as neurite orientation dispersion and density imaging (NODDI) (Zhang et al. 2012), which could provide a better evaluation of the extracellular space.

A recent study of 7T ex vivo MRI in AD showed hypointensities with iron deposits inside of microglia in the subiculum, suggesting that activated iron containing microglia could be identified by MRI (Zeineh et al. 2015).

What do PET imaging data of neuroinflammation mean?

As the choice of the tracers and the methodological considerations mentioned above could have an important influence on the results obtained and explain the numerous inconsistencies in the studies involving AD patients (Kincaid 2016), it is important to ask ourselves the question of the meaning of the data generated by imaging neuroinflammation with PET (van Dyck 2008).

First, we must remember the lack of specificity of TSPO tracers for activated microglia, as TSPO is expressed in a variety of immune cells, including astrocytes (Vivash and O'Brien 2016). Increased TSPO expression has been described in relation to reactive astrocytes (Cosenza-Nashat et al. 2009; Lavisse et al. 2012). Although activated microglia and astrocytes play probably different roles in AD, it remains difficult to differentiate each cell type. Thus, new radioligands targeting alternative markers of microglial activation have been developed (see "Tracers targeting microglial activation"), as well as strategies to image other aspects of neuroinflammation than microglial activation (see "Tracers targeting other processes than microglial activation"), with the aim of providing novel and complementary results illuminating our understanding of this complex process.

Second, the beneficial and detrimental effects of inflammation on neurons continue to be discussed, especially according to the stage of the disease. Until recently, the prevalent view was that neuroinflammation in AD was harmful and drove the pathology (McGeer and McGeer 2013), and microglial activation was considered neurotoxic by generating a sustained proinflammatory response that can cause neuronal death. However, both recent animal and human studies suggested a dynamic and contrasted role of neuroinflammation in AD: beneficial in the early (MCI) stage and toxic later. Microglial activity emerges as beneficial to prevent plaque formation in the early stages of amyloid deposition and could promote removal of existing Aβ deposits. Inflammation in later stages of AD could be rather detrimental (Prokop et al. 2013) due to the persistent production and accumulation of proinflammatory cytokines (Thériault et al. 2015), favouring accumulation of Aβ (Cai et al. 2014) by the loss of microglial Aβ clearing capabilities and by increased activities of Aβ generating enzymes gamma secretase complex and beta secretase (Hickman and El Khoury 2014) and may even promote tau pathology (Prokop et al. 2013).

These considerations have led to expend to microglia the concept of diverse functional phenotypes of immune cells, ranging from pro-inflammatory M1 phenotypes to immunosuppressive M2 phenotypes (Tang and Le 2016). The "M1/M2 paradigm" is now applied to a number of neurodegenerative diseases: the situation known as classical activation is associated with the production of pro-inflammatory cytokines and corresponds to "M1 microglia", while "M2 microglia" corresponds to the states of both alternative activation and acquired deactivation and uses the anti-inflammatory cytokines IL-4, IL-13, IL-10 and TGFβ to antagonize the pro-inflammatory response (Tang and Le 2016). The balance of M1 and M2 microglial activation is highly complex, especially in AD, in which microglia may exhibit mixed activation phenotypes. The phagocytic activity of microglia surrounding Aβ plaques, which exhibits M2 activation phenotype, is attenuated by pro-inflammatory cytokines, leading to a shift into M1 state, which may be induced by oligomeric Aβ or by tau phosphorylation, thus inducing microglia-induced neurotoxicity (Tang and Le 2016). In addition, peripheral macrophages may also interfere with the role of microglia. Up to now, no PET tracer is able to distinguish between the microglial subtypes and there is no clear target to develop PET tracers, which could be specific of either of these subtypes of activated microglia (Vivash and O'Brien 2016).

In addition to enabling a better understanding of the role of neuroinflammation in neurodegenerative diseases, the use of PET imaging is thought to provide a way of monitoring the effect of new therapeutic approaches (Zimmer et al. 2014). By taking into account the considerations mentioned above, one can wonder how the beneficial effect of a drug would be expressed in PET imaging. Would it correspond to a decrease or an increase of tracer binding? If it is assumed, as stated by the prevalent view, that neuroinflammation in AD is harmful and drives the pathology (McGeer and McGeer 2013); a decreased binding would be suggestive of therapeutic efficacy, but the reverse could

also be true. For now, we have no way of choosing between these two alternatives (van Dyck 2008), which could in fact both be appropriate according to the disease stage or the clinical presentation/progression.

Conclusion

In the present review, we have detailed the different strategies used to image neuroinflammation by PET and summarized the main results obtained in the studies involving AD patients. There are many different approaches, which are validated or promising for the exploration of neuroinflammation. While the fact of detecting neuroinflammation by PET in AD is without debate, the results obtained up to now are often conflicting as to whether microglial activation and neuroinflammation in general is beneficial and could have a protective effect on the evolution of the symptoms of the disease, or detrimental, by precipitating neuronal damage and cognitive deficits. Beyond the challenges in the development of accurate tracers and in the methodology of binding quantification, these discrepancies are probably due to the complexity of neuroinflammation in AD and its multifaceted roles according to the disease stage. PET imaging of neuroinflammation is a promising way of deciphering the enigma of the pathophysiology of AD, by clarifying the interactions between amyloid and/or tau pathologies on the one hand, and neuroinflammation, which could influence, at least in part, the heterogeneous clinical presentation and progression of AD on the other hand, and of monitoring the effect of new therapies. Nevertheless, further works are needed to optimize the methods for the quantification of the binding data obtained with the current tracers and to develop new innovative tracers, which could provide additional and complementary information. It is important to try to form a consensus to harmonize and standardize the PET data analysis of imaging protocols. This is a prerequisite to perform multicentric large-scale clinical trials, which are the only ways to elucidate the complex role of the neuroimmune response in AD.

Compliance with ethical standards

Conflict of interest Hoffmann-La Roche Ltd partly supported a study conducted by the authors. During the last 2 years, M.S. has received speaker honorarium from Société Générale.

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