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Imaging of neuroinflammation in Alzheimer's disease, multiple sclerosis and stroke: Recent developments in positron emission tomography☆

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ABSTRACT

Neuroinflammation is thought to play a pivotal role in many diseases affecting the brain, including Alzheimer's disease, multiple sclerosis and stroke. Neuroinflammation is characterised predominantly by microglial activation, which can be visualised using positron emission tomography (PET). Traditionally, translocator protein 18 kDa (TSPO) is the target for imaging of neuroinflammation using PET. In this review, recent preclinical and clinical research using PET in Alzheimer's disease, multiple sclerosis and stroke is summarised. In addition, new molecular targets for imaging of neuroinflammation, such as monoamine oxidases, adenosine receptors and cannabinoid receptor type 2, are discussed. This article is part of a Special Issue entitled: Neuro Inflammation edited by Helga E. de Vries and Markus Schwaninger.

1. Introduction

Neuroinflammation is thought to play a pivotal role in many diseases affecting the brain, including Alzheimer's disease (AD), multiple sclerosis (MS) and stroke. Neuroinflammation is primarily characterised by microglial activation, although astrocytosis is also linked to neuroinflammation. Microglia are the primary immune effector cells of the brain, displaying a dual role in the immune response. Upon injury and/or release of inflammatory factors, microglia switch from a resting ramified state to an activated amoeboid state. This activation can be either pro- or anti-inflammatory, or, more likely, a combination of both states [1,2]. The general hypothesis is that initial microglial activation is beneficial for recovery of the injured central nervous system (CNS), e.g. by scavenging dead cells and secretion of neuron survival factors. On the other hand, prolonged microglial activation may lead, either directly or indirectly, to neuronal cell death [3]. Ideally, one would like to be able to distinguish between pro- and anti-inflammatory phenotypes of activated microglia in vivo, as this could affect disease treatment. The best technique to study microglial activation in vivo is positron emission tomography (PET). This imaging technique requires molecules labelled with a positron emitting isotope (tracers), targeting receptors, enzymes or other biomolecules showing increased expression in activated microglia. Traditionally, the translocator protein 18 kDa (TSPO) has been the target for imaging neuroinflammation using PET, with over 80 (and counting) tracers being developed with high affinity for TSPO. Some of these tracers have been evaluated in preclinical studies using different disease models of neuroinflammation, but (*R*)-[^{11}C]PK11195 still is the tracer most used in clinical research, despite of its low brain uptake and relatively high non-specific binding [4]. This is mainly due to the fact that (*R*)-[^{11}C]PK11195, unlike most second generation TSPO tracers, is not affected by binding differences due to two existing forms of TSPO, encoded by the rs6971 single-nucleotide polymorphism (SNP). In Caucasians, this polymorphism leads to prevalence of 49% high affinity binders (HABs), 42% mixed affinity binders (MABs) and 9% low affinity binders (LABs). Difference in binding was exemplified by Kreisl et al. using second generation TSPO tracer [^{11}C]PBR28 in healthy volunteers [5]. Total distribution volume (V_T) of [^{11}C]PBR28 was reported to be 40% higher in brain of HABs than in brain of MABs. Additionally, autoradiography studies with [^{3}H]PBR28 on post-mortem samples of 45 schizophrenia patients and 47 control subjects (all genotyped) pointed out that tracer binding was increased with 16% in schizophrenia patients. Importantly, this difference in tracer binding was only statistically significant when stratifying for genotype [5]. Therefore, the effect of the polymorphism needs to be kept in mind when quantifying TSPO PET images in human. Although

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not sensitive to polymorphism, (*R*)-[^{11}C]PK11195 suffers from low signal-to-noise ratios, therefore the search for better TSPO ligands still continues. As TSPO is not only overexpressed in activated microglia, but also in reactive astrocytes [6], there is a need for novel PET ligands that could distinguish between the two. In addition, visualisation of different microglial phenotypes may elucidate their role in disease onset and progression in neurodegenerative disease. PET ligands targeting other targets of neuroinflammation are being more and more explored, e.g. monoamine oxidase B (MAO-B), adenosine receptors, cannabinoid receptor type 2 (CB2) and matrix metalloproteinases (MMP) 2 and 9. PET imaging of neuroinflammation in AD, MS and stroke has been reviewed extensively in the past few years [3,7–21]. The purpose of the present review is to summarise more recent advances (2013–June 2015) in PET imaging of neuroinflammation in these diseases (Table 1), starting with studies using tracers targeting TSPO. In addition, this review describes both existing and emerging targets with a focus on tracer development.

2. Tracers targeting translocator protein 18 kDa in healthy volunteers

In a blockade study in 26 healthy volunteers (all genotyped), [^{11}C]PBR28 PET scans were acquired [22]. Total volume of distribution (V_T) was found to be 1.5-fold higher in HABs compared with MABs in all regions of interest (ROIs) examined (cortex, hippocampus, thalamus, cerebellum, brain stem, striatum). Owen et al. then determined the non-displaceable volume of distribution (V_{ND}) of [^{11}C]PBR28 by blockade with XBD173 (TSPO ligand) in 6 HAB healthy volunteers. Each volunteer received a different dose of XBD173 (10–90 mg) orally, 2 h prior to a repeat scan with [^{11}C]PBR28. Whole brain V_T in HABs was 4.33 ± 0.29 (n = 16) and a measurable occupancy of TSPO in 5 out of 6 subjects was observed. The population V_{ND} was estimated to be 1.98 (1.69–2.26) via the occupancy plot. Authors conclude that a substantial part of [^{11}C]PBR28 specific binding in healthy subjects is represented by V_T; however, V_{ND} is almost half of V_T, complicating quantification of the specific binding. Based on a polymorphism plot using V_{ND} in HABs from the occupancy study, non-displaceable binding potential (BP_{ND}) was estimated to be 2-fold higher in HABs compared with MABs [22]. In another study, focused on modelling of [^{11}C]PBR28, the two-tissue compartment model (2TCM) with irreversible vascular trapping (2TCM-1K) was compared with 2TCM, which is usually used for TSPO ligands, using two previously acquired datasets [23]. 2TCM-1K V_T showed higher correlation with gene expression than 2TCM V_T and between-subject variability of absolute V_T values across brain regions was smaller using 2TCM-1K [23]. Simulated TACs based on the obtained datasets showed 2TCM to severely underestimate increases in V_T, leading to subtle changes not being observed (e.g. neuroinflammation). Binding of TSPO tracers in the vasculature has been shown previously [24]. However, 2TCM-1K suggests irreversible tracer binding to the vasculature, whereas binding to TSPO is known to be reversible. This indicates that the vascular target may not necessarily be TSPO, or that tracer kinetics in endothelium differ substantially from kinetics in brain parenchyma. In addition, inclusion of more parameters usually provides better fits, even if the additional parameters have limited physiological meaning. Therefore this extended model should first be validated using biological data, e.g. immunohistochemical staining and demonstration of irreversible binding in the vasculature.

Guo et al. showed slower [^{18}F]PBR111 washout from brain stem in HABs than in MABs and LABs (decrease of 50% at 60 (HAB), 40 (MAB) and 20 min (LAB) p.i.) in a group of 21 genotyped healthy volunteers (9 HABs, 8 MABs and 4 LABs) [25]. Thirty minutes after [^{18}F]PBR111 injection, 40% of the tracer was still intact, which decreased to 20% at 120 min p.i. The free fraction in plasma was not significantly different between genotype groups. Substantial variability in V_T was observed within each genotype group, especially in HABs (e.g. 2TC V_T (brain stem) HAB 5.08 ± 1.80; MAB 3.10 ± 0.50; LAB 2.33 ± 0.52), which the authors partly attribute to age [25]. Microglial activation, or at least TSPO overexpression, has also been shown to be increased upon healthy ageing using other TSPO-PET tracers [26–28]. In another cohort of 33 genotyped healthy volunteers (22 HABs, 11 MABs, 19–78 years old) using [^{18}F]FEPPA, no significant correlation between age and ROI

Table 1
Tracers used for PET imaging of neuroinflammation in Alzheimer's disease, multiple sclerosis and stroke (included in this review).

Target	Tracer	Preclinical	Clinical	References
TSPO	(*R*)-[^{11}C]PK11195	APP/PS1 mice		[32]
		Demyelination rat model		[51]
		EAE rats		[52]
		MCAO rats		[62,64–66,132]
			MCI, amnestic MCI, AD patients, HC	[39]
			SPMS patients, HC	[56]
	[^{18}F]DPA-714	APPswePS1dE9 mice		[33]
		MCAO rats		[65]
		MCAO mice		[68]
			AD patients, HC	[47,48]
			Stroke patients	[75]
	[^{18}F]PBR06	$APP^{L/S}$ mice		[34]
		MCAO mice		[69]
	[^{11}C]PBR28		MCI, AD patients, HC	[40,42]
			MS patients, HC	[59]
	[^{18}F]PBR111	EAE mice		[53]
			RRMS patients, HC	[58]
	[^{18}F]FEDAA1106		AD patients, HC	[45]
			RRMS patients, HC	[57]
	[^{18}F]FEMPA		AD patients, HC	[46]
	[^{18}F]GE180	EAE rats		[54]
		MCAO rats		[66]
	[^{11}C]MBMP	MCAO rats		[70]
	[^{18}F]FEBMP	MCAO rats		[71]
	[^{18}F]FPBMP	MCAO rats		[71]
MAO-B	[^{11}C]DED	APPswe mice		[94]
			MCI patients, AD patients	[95]
$A_{2A}R$	[^{11}C]TMSX		SPMS patients, HC	[110,111]
nAChrR α2β4	2[^{18}F]-fluoro-A853380	MCAO rats		[132]

HC = healthy control.