PET Imaging in Multiple Sclerosis

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Published in:
PET and SPECT in Neurology

DOI:
10.1007/978-3-030-53168-3_33

Publication date:
2020

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Abstract

Multiple sclerosis (MS) pathology is associated with inflammation and demyelination in the central nervous system (CNS), which leads to neurodegeneration. Various positron emission tomography (PET) tracers have been employed to image these processes. PET tracers for 18-kD translocator protein (TSPO) receptors, which are overexpressed on activated microglia, macrophages, and astrocytes, have been used to assess neuro-inflammation. PET imaging of TSPO expression depicted an increased activation of inflammatory cells in normal

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R. A. J. O. Dierckx et al. (eds.), *PET and SPECT in Neurology*,
https://doi.org/10.1007/978-3-030-53168-3_33

appearing white matter (NAWM), grey matter (GM), and MS lesions. A reduction in inflammation in MS lesions was found to be a main determinant of treatment efficacy. Recently, advances have been made in myelin visualisation with PET. The first clinical studies to visualise myelin with PET show promising results. As for other neurodegenerative diseases, [^{18}F]FDG is still the main PET tracer used to assess neuronal damage. Current clinical use of PET in MS is mainly restricted to aiding in differential diagnosis or for determining the efficacy of immune suppressive treatments. Once myelin imaging has been validated as a reliable method for characterisation of myelin integrity, it would enable the evaluation of the efficacy of a new line of therapies that aim to repair myelin.

33.1 Introduction

Multiple sclerosis (MS) is the most common neurodegenerative disease in young adults (Ramagopalan et al. 2010). MS pathology is characterised by immune attacks on the myelin sheath covering the axon (Traugott et al. 1983). The initiation of the immune response seems to be driven by peripheral activation of the adaptive immune system (Dendrou et al. 2015). After migration to the central nervous system (CNS), activated T cells cause activation of antigen presenting cells, like microglia and macrophages, which then initiate recruitment of additional inflammatory cells (Fig. 33.1). During this process, myelin-specific antibodies are produced and together with cytotoxic cytokines, excitotoxins, reactive oxygen, and nitric oxide, which are released by activated microglia and macrophages, they cause the damage to myelin (Dendrou et al. 2015; Lassmann et al. 2012). Oligodendrocytes are able to repair the myelin sheaths of axons (remyelination) and thereby restore the protective and signal enhancement function of myelin (Prineas and Connell 1979). However, when myelin damage is too severe, it will be beyond the restoration capacity of oligodendrocytes. Damaged myelin makes axons vulnerable for any exposure to environmental effects and ultimately leads to neurodegeneration (Ferguson et al. 1997; Franklin and Ffrench-Constant 2008). All these processes (i.e. inflammation, myelin degradation, and neurodegeneration) are part of the MS pathology and are involved in relapses (episodes with a temporary increase in severity of symptoms) and disease progression.

When a patient presents with a history of only one relapse, this is called a clinically isolated syndrome (CIS). Subjects with CIS have an increased risk to develop MS, and therefore CIS is considered to be a prodromal stage of MS (Baecher-Allan et al. 2018). Almost all patients with CIS develop relapsing remitting MS (RRMS), although this may take many years. RRMS is with an 85% occurrence, the most prevalent form of MS. The remaining 15% of patients have a slowly progressive disease course from disease onset without relapses, which is called primary progressive MS (PPMS). In RRMS, clinical symptoms emerge during relapses, but subsequently diminish over time during remission due to reduction of inflammation and recovery of the myelin sheaths. Incomplete repair of myelin damage leads to

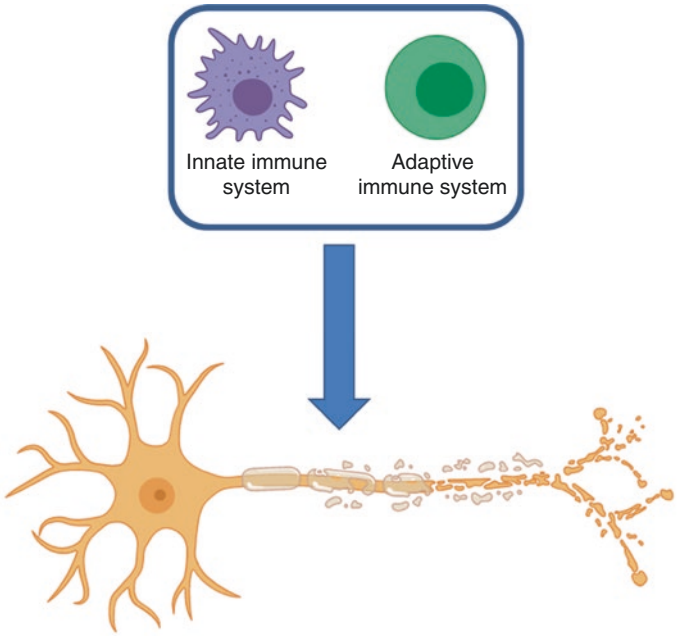

Fig. 33.1 Current view of the MS pathogenesis pathway. Inflammatory cells cause demyelination, which ultimately results in neurodegeneration

increased axonal damage and disease progression. When remissions no longer occur and axonal damage increases more gradually, MS patients are considered to have entered the secondary progressive (SP) stage of MS.

Due to the random location of inflammatory lesions occurring in the CNS, clinical symptoms in MS are highly diverse. The most typical symptoms are the ones involving the optic nerve, the urinary tract, and those resulting in sensory and motor symptoms (Huang et al. 2017; Miljković and Spasojević 2013). Disease severity is often expressed using the Expanded Disability Status Scale (EDSS) (Kurtzke 1983). The EDSS is scored from 0 (no disability or other impairments) to 10 (death due to MS). With a score of 5, the patient is hampered in his daily activities and walking distance due to symptoms of MS, and is not capable of completing full work days without special precautions.

A diagnosis of MS is based on the combination of clinical symptoms, the presence of typical lesions on MRI, and, if necessary, analysis of cerebrospinal fluid (Thompson et al. 2018). The mainstay in diagnosing MS is the demonstration of dissemination of lesions in place and in time clinically or with MRI. Current MRI protocols are very effective in supporting a diagnosis of MS and excluding other diseases. On MRI scans, the damage caused by inflammation is visualised as white matter lesions, which are hyper-intense on T2 fluid-attenuated inversion recovery (T2-FLAIR) images (Biediger et al. 2014). The visually non-affected white matter is typically called normal appearing white matter (NAWM), which does not mean

biological changes are absent. Gadolinium (Gd) contrast enhancement is a marker for blood–brain barrier breakdown. This makes it possible to distinguish with MRI between active (Gd-enhanced) and non-active (non-enhanced) lesions (Kaunzner and Gauthier 2017). However, irrespective of their activity status, these lesions depict a combination of processes including inflammation, gliosis, demyelination, and axonal loss. MRI is therefore currently not able to visualise alterations in individual biological processes. The availability of highly specific ligands would enable distinguishing between individual biological alterations in MS pathology with molecular imaging techniques, in particular positron emission tomography (PET).

33.2 PET Tracers Used to Assess MS Pathology

PET imaging can enable imaging of individual biological processes. However, it is only possible to visualise one biological process per scan. Many tracers have been developed for specific biological processes. MS is best described using the three major biological processes involving inflammation, demyelination, and neurodegeneration. Within these processes, there are multiple aspects that can be visualised, and hence a wide variety of tracers have been used in MS. An overview of the tracers used in MS is displayed in Table 33.1. A more thorough discussion of the relevance of these tracers within MS pathology is provided in the following sections.

Table 33.1 PET tracers currently being employed for the visualisation of biological processes in MS pathology

Tracer	Imaging target	Relevant structures/cells
[^{11}C]PK11195	TSPO	Activated microglia, macrophages, astrocytes
[^{11}C]PBR28	TSPO	Activated microglia, macrophages, astrocytes
[^{18}F]PBR06	TSPO	Activated microglia, macrophages, astrocytes
[^{18}F]PBR111	TSPO	Activated microglia, macrophages, astrocytes
[^{18}F]GE-180	TSPO	Activated microglia, macrophages, astrocytes
[^{11}C]DPA713	TSPO	Activated microglia, macrophages, astrocytes
[^{18}F]DPA714	TSPO	Activated microglia, macrophages, astrocytes
[^{11}C]acetate	MCT	Activated astrocytes
[^{11}C]TMSX	Adenosine A_{2A} receptor	Cerebral stress coping mechanisms
[^{11}C]PiB	Amyloid beta and MBP	In MS pathology, assessment of myelin integrity
[^{18}F] Florbetaben	Amyloid beta and MBP	In MS pathology, assessment of myelin integrity
[^{18}F] Florbetapir	Amyloid beta and MBP	In MS pathology, assessment of myelin integrity
[^{11}C] flumazenil	Benzodiazepine receptor	Synaptic integrity
[^{11}C]DASB	Serotonin transporters	Neuronal presynaptic membrane
[^{18}F]FDG	Glucose consumption	Neurodegeneration
[^{11}C] methionine	Protein synthesis	Differential diagnosis between MS and brain tumours

MBP myelin basic protein, *MCT* monocarboxylate transporter, *MS* multiple sclerosis, *TSPO* 18-kDa translocator protein

33.3 PET Imaging to Assess Neuro-Inflammation

MS is characterised by neuro-inflammation aimed at the myelin layers around the axons. The 18-kD translocator protein (TSPO) is upregulated in activated inflammatory cells in the brain (Fig. 33.2), especially in microglia, but also in macrophages and to a lesser extent in astrocytes (Chechneva and Deng 2016). TSPO is found on mitochondrial membranes and has many functions, including the mediation of cholesterol transport from the cytosol into the mitochondria (Papadopoulos et al. 2006) and regulation of mitochondrial energy metabolism (Gut 2015). The latter function could be the reason why TSPO is upregulated in activated inflammatory cells. Thus, determination of TSPO expression is used to assess the amount of activated inflammatory cells (Fig. 33.3). Traditionally, [^{11}C]PK11195 PET imaging was the primary method for the evaluation of TSPO expression (Vowinckel et al. 1997). [^{11}C]PK11195 is currently still regularly used (Table 33.2), although a new generation of TSPO tracers with higher affinity has been developed as well. A major disadvantage of the new so-called "second generation" tracers is the genotype-dependent binding affinity. The second-generation tracers require therefore classification of patients into low- (LAB), medium- (MAB), and high-affinity binding (HAB) individuals. A single-nucleotide polymorphism in the TSPO gene (rs6971), which replaces alanine with threonine (Ala147Thr), was shown to be responsible for the variation in binding affinity resulting in LAB for homozygotes of this single nucleotide permutation (SNP) (Owen et al. 2012). A study assessing the frequency of the different TSPO binding affinities showed that 66% were HAB, 29% MAB, and 5% LAB (Owen et al. 2012). This means that, aside from the PET scan, also genotyping has to be performed for a correct analysis of the acquired images. In contrast, [^{11}C]PK11195 binding is not affected by this SNP and is therefore still a regularly used PET tracer for inflammation.

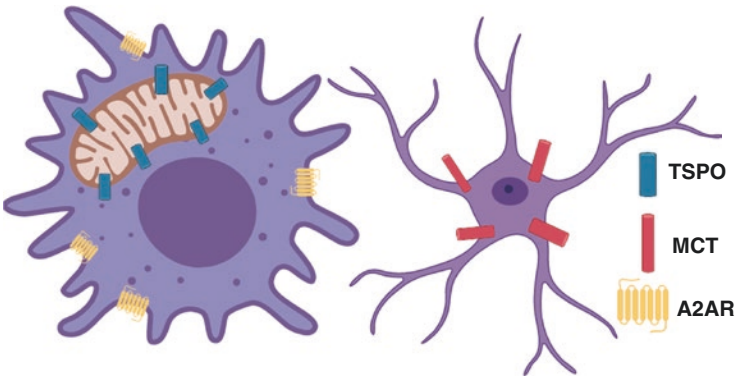

Fig. 33.2 PET imaging targets on inflammatory cells used in MS research. TSPO and monocarboxylate transporter (MCT) are markers for neuro-inflammation. Within activated inflammatory cells, TSPO is upregulated. Many PET tracers that bind TSPO have been developed to enable the visualisation of this upregulation and thus the activation status of inflammatory cells. A more specific method is imaging of MCT expression, which is upregulated in activated astrocytes. Microglial A2AR expression is supposed to modulate the inflammatory response

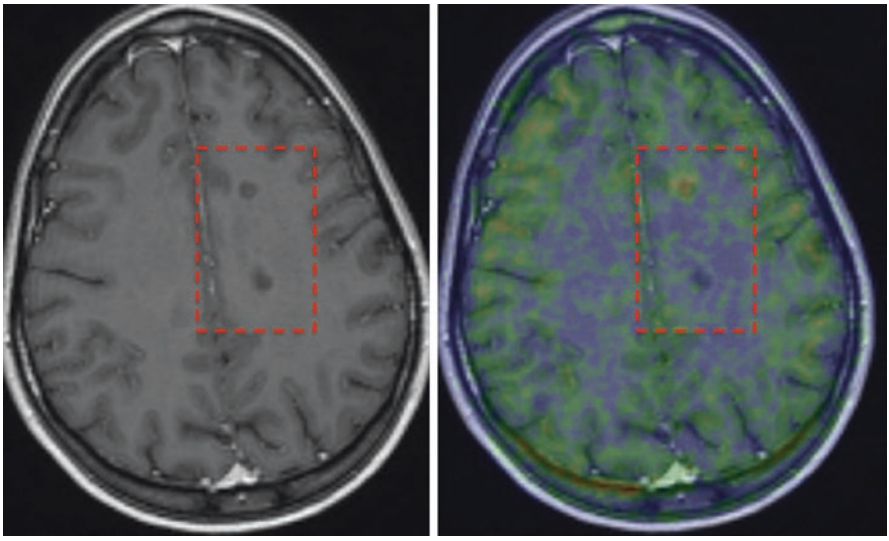

Fig. 33.3 Differentiation of two non-enhanced lesions on T1 MRI and [^{11}C]PK11195 PET. The upper lesion clearly depicts an increase in [^{11}C]PK11195 uptake, which means inflammatory activation, and thus depicts an active lesion. In contrast, the lower lesion does not show increased tracer uptake, and therefore is an inactive lesion (permission for the use of the images was obtained; source: DOI: https://doi.org/10.1007/s40336-015-0147-6) (Airas et al. 2015)

Studies assessing TSPO expression in MS with [^{11}C]PK11195 PET imaging displayed increased tracer uptake in NAWM, cortical grey matter (GM), and thalamus, which was associated with a longer disease duration and higher age (Giannetti et al. 2015; Politis et al. 2012; Rissanen et al. 2014). Other studies found only a significantly increased uptake in the whole brain, but not in individual regions (Sucksdorff et al. 2017). These findings illustrate that with advancing disease duration and age, more activated inflammatory cells are observed. More detailed analysis of the lesions themselves resulted in differential results for Gd-contrast-enhanced lesions vs. non-contrast-enhanced lesions. In general, lesions have a higher tracer uptake than NAWM, with contrast-enhanced lesions having an even higher [^{11}C]PK11195 uptake than non-enhanced lesions, supporting the concept that MRI contrast enhancement is a marker for inflammation (Vowinckel et al. 1997; Giannetti et al. 2015; Kaunzner et al. 2017). Increased [^{11}C]PK11195 uptake in cortical GM has also been observed in MS patients and was significantly correlated (r = 0.84, p = 0.0089) with EDSS scores (Politis et al. 2012). In RRMS patients, a higher [^{11}C]PK11195 uptake has been associated with smaller total black hole volumes, which are supposed to represent inactive non-remyelinated lesions with extensive axonal damage (Giannetti et al. 2014). In short, these studies show a global cerebral increase of activated inflammatory cells with disease progression, duration, and age, which corresponds to increased clinical disability. Furthermore, an increase of [^{11}C]PK11195 uptake in MS lesions corresponds with disease activity. As depicted in Table 33.2, there are also studies that do not show an increased uptake in GM

Table 33.2 Overview of the main results per study using [^{11}C]PK11195 PET to image inflammatory response in MS patients

Study	Tracer	Subjects	GM	NAWM	Non-enhanced lesions	Enhanced lesions
Giannetti et al. (2015)	[^{11}C] PK11195	8 HC 18 CIS	No differences observed	Increased [^{11}C] PK11195 uptake	n.a.	n.a.
Politis et al. (2012)	[^{11}C] PK11195	8 HC 10 RRMS	Increased [^{11}C] PK11195 uptake	Increased [^{11}C] PK11195 uptake	n.a.	n.a.
		8 SPMS	More increased [^{11}C] PK11195 uptake than in RRMS	More increased [^{11}C] PK11195 uptake than in RRMS		
E. Rissanen et al. (2014)	[^{11}C] PK11195	8 HC 10 SPMS	No differences observed	Increased [^{11}C] PK11195 uptake		Increased [^{11}C] PK11195 uptake
Sucksdorff et al. (2017)	[^{11}C] PK11195	8 HC 10 RRMS	No differences observed	No differences observed	n.a.	n.a.
Kaunzner et al. (2017)	[^{11}C] PK11195	5 HC 18 MS	n.a.	n.a.	Increased [^{11}C] PK11195 uptake	More increased [^{11}C] PK11195 uptake than non-enhanced lesions
Vowinckel et al. (1997)	[^{11}C] PK11195	2 MS	n.a.	n.a.	[^{11}C] PK11195 uptake not increased	Increased [^{11}C] PK11195 uptake

CIS clinically isolated syndrome, *HC* healthy control, *MS* multiple sclerosis, *n.a.* not applicable, *SPMS* secondary progressive MS, *RRMS* relapse remitting MS

(Giannetti et al. 2015; Rissanen et al. 2014; Sucksdorff et al. 2017), Sucksdorff et al. (2017) did not observe differences in NAWM, and Vowinckel et al. (1997) found only an increased uptake in contrast-enhanced lesions, but not in non-enhanced lesions. Giannetti et al. (2015) investigated CIS, which is a group early in the spectrum of the MS disease course, so it is logical that they found less differences in inflammation. This is in line with the findings of Politis et al. (2012) that observed increased tracer uptake in RRMS, which was further increased in secondary progressive MS (SPMS). Aside from that, the inconsistencies most likely arise from the extreme heterogeneous aspect of MS pathology and the small sample sizes in the

studies. The amount and severity of inflammation vary per person and the low affinity of [^{11}C]PK11195 for TSPO makes it difficult to find uniform group-based differences.

The most frequently studied second-generation TSPO tracer is [^{11}C]PBR28 (Table 33.3). Increased [^{11}C]PBR28 uptake has been generally observed in MS patients, including in the whole cortex, thalamus, hippocampus, basal ganglia, NAWM, lesions, and more specifically in contrast-enhanced lesions (Oh et al. 2011;

Table 33.3 Overview of the main results of studies using second-generation TSPO tracers

Study	Tracer	Subjects	GM	NAWM	Non-enhanced lesions	Enhanced lesions
Herranz et al. (2016)	[^{11}C] PBR28	11 HC 12 RRMS	Increased tracer uptake	Increased tracer uptake	n.a.	n.a.
		15 SPMS	More increased tracer uptake than for RRMS	More increased tracer uptake than for RRMS		
Oh et al. (2011)	[^{11}C] PBR28	7 HC 11 MS	No differences observed	No differences observed	Tracer uptake not increased	Increased tracer uptake
Singhal et al. (2018)	[^{11}C] PBR28	6 RRMS	n.a.	Increased tracer uptake	n.a.	n.a.
	[^{18}F] PBR06			Increased tracer uptake		
Datta et al. (2017b)	[^{11}C] PBR28	20 HC 24 MS	n.a.	Increased tracer uptake	Increased tracer uptake	Increased tracer uptake
	[^{18}F] PBR111	10 HC 10 MS	n.a.	Increased tracer uptake	Increased tracer uptake	Increased tracer uptake
Colasanti et al. (2014)	[^{18}F] PBR111	11 HC 11 RRMS	n.a.	Increased	Lesional uptake increased (enhancement not specified)	
Unterrainer et al. (2018)	[^{18}F] GE-180	19 RRMS	n.a.	n.a.	Increased tracer uptake	Tracer uptake increased more than non-enhanced
Bunai et al. (2018)	[^{11}C] DPA713	6 HC 6 RRMS	Increased	n.a.	n.a.	n.a.
Hagens et al. (2018)	[^{18}F] DPA714	7 HC 3 SPMS 5 PPMS	n.a.	n.a.	Tracer uptake increased (enhancement not specified)	

GM grey matter, *HC* healthy control, *MS* multiple sclerosis, *n.a.* not applicable, *NAWM* normal appearing white matter, *RRMS* relapse remitting MS, *SPMS* secondary progressive MS

Herranz et al. 2016). This increased [^{11}C]PBR28 uptake also appeared to increase with disability and disease duration (Oh et al. 2011; Herranz et al. 2016). In addition, a higher uptake of [^{11}C]PBR28 in NAWM and GM has been observed in SPMS compared to RRMS, which might be explained by the relation between increased tracer uptake and disease duration and/or elevated immune cell activation in SPMS as compared to RRMS patients in a remission phase (Herranz et al. 2016). Furthermore, [^{11}C]PBR28 uptake in both NAWM and lesions were positively correlated with T2 lesion volumes in RRMS, indicating that a higher tracer uptake corresponds with a larger total T2 lesion volume in RRMS (Datta et al. 2017a). In SPMS, a higher activation of inflammatory cells (tracer uptake) was positively correlated with brain atrophy, illustrating that neurodegenerative effects are accompanying the increased activation of inflammatory cells and further explaining the relation between disease duration and EDSS score (Datta et al. 2017a). Thus, like [^{11}C]PK11195, increased [^{11}C]PBR28 uptake, corresponding with increased activated inflammatory cells, is related to disease progression, duration, and clinical disability and an increase of [^{11}C]PBR28 uptake in MS lesions corresponds with disease activity. As stated in the previous section about [^{11}C]PK11195, inconsistencies in the literature are also found for the higher affinity second-generation TSPO tracers (Table 33.3). Oh et al. (2011) did not find any differences in tracer uptake for GM and NAWM non-enhanced lesions, but did for contrast-enhanced lesions. This is, however, the only study showing discrepancies with other studies, and illustrates the relative uniformity in the data with higher affinity TSPO tracers compared with the first-generation tracers. Heterogeneity in MS pathology may explain the remaining inconsistencies between studies.

Direct comparisons of [^{11}C]PBR28 with [^{18}F]PBR06, [^{18}F]PBR111, and [^{18}F]GE-180 have been performed, but not with [^{11}C]PK11195 (Table 33.3). Both [^{11}C]PBR28 and [^{18}F]PBR06 have a high tracer uptake in NAWM; however, only [^{18}F]PBR06 uptake was correlated to EDSS score, meaning that [^{18}F]PBR06 could be more sensitive to slight changes in immune activation in the specific population studied (Singhal et al. 2018). A comparison of [^{11}C]PBR28 with [^{18}F]PBR111 showed that [^{11}C]PBR28 has a higher binding in thalamus compared to [^{18}F]PBR111, aside from that, both tracers showed an increased uptake in NAWM, and both showed a higher tracer uptake in both contrast and non-contrast-enhanced lesions (Datta et al. 2017b). The other study analysing solely [^{18}F]PBR111 TSPO binding confirmed the higher tracer uptake in both NAWM and lesions (Colasanti et al. 2014). [^{11}C]PBR28 and [^{18}F]GE-180 TSPO binding are highly comparable (Sridharan et al. 2019). Like [^{11}C]PBR28, [^{18}F]GE-180 tracer uptake is also increased in lesions, especially in contrast-enhanced lesions (Unterrainer et al. 2018). According to these findings, all tracers seem to perform comparable, although [^{18}F]PBR06 might be slightly more and [^{18}F]PBR111 slightly less sensitive than [^{11}C]PB28.

Other second-generation TSPO tracers are [^{11}C]DPA713 and [^{18}F]DPA714 (Table 33.3). [^{11}C]DPA713 showed a global cortical increase of tracer uptake in MS patients (Bunai et al. 2018). For [^{18}F]DPA714, an increased uptake was observed in lesions compared to NAWM, and specifically for HAB patients. [^{18}F]DPA714

Table 33.4 Studies assessing MCT to image neuro-inflammation

Study	Tracer	Subjects	GM	NAWM	Non-enhanced lesions	Enhanced lesions
Takata et al. (2014)	[^{11}C] acetate	6 HC 6 RRMS	Increased tracer uptake	Increased tracer uptake	n.a.	n.a.

GM grey matter, *HC* healthy control, n.a. not applicable, *NAWM* normal appearing white matter, *RRMS* relapse remitting MS

showed also an increased tracer binding in NAWM when compared to NAWM of HAB healthy subjects (Hagens et al. 2018). These findings indicate that with [^{11}C]DPA713 PET, a global increase of activated inflammatory cells is observed in MS, and with [^{18}F]DPA714 the increase in activated immune cells was only visible in NAWM of HAB patients. This suggests that [^{11}C]DPA713 might be more suitable for visualising inflammatory changes in MS than [^{18}F]DPA714. The fact that [^{18}F]DPA714 is a TSPO agonist, whereas the other TSPO tracers are antagonists may also play a role in explaining this difference in binding.

Despite the upregulation of TSPO in microglia, macrophages, and astrocytes, TSPO imaging is primarily used to assess microglial activation (Fig. 33.2). However, astrocytes also play a role in MS pathology. In MS, there is an increased cerebral expression of the monocarboxylate transporter (MCT) (Nijland et al. 2014). MCT functions as a transporter for monocarboxylates, such as acetate. Acetate is preferentially absorbed into astrocytes by MCT (Waniewski and Martin 1998). Therefore, [^{11}C]acetate could be used to assess astrocyte activation, due to the upregulation of MCT by activated astrocytes (Table 33.4). Using [^{11}C]acetate, increased tracer uptake was observed in both WM and GM in MS patients compared to healthy subjects, and the amount of [^{11}C]acetate uptake was positively correlated to the number of lesions (Takata et al. 2014). This suggests that aside from microglia, also astrocytes are activated in MS pathology, and the amount of activation increases with disease severity. Whether the increased activation of astrocytes in MS pathology is supporting repair of neuronal damage still remains to be investigated.

Following degradation of the myelin sheaths, axons are susceptible to adverse environmental impact, such as exposure to oxidative stress, ultimately leading to neurodegeneration. The inflammation in MS pathology is a major source of oxidative stress. Upon neuronal damage, adenosine is released leading to the attraction of microglia. One intrinsic manner to cope with inflammation and corresponding tissue damage is the microglial upregulation of adenosine signalling via the adenosine A_{2A} receptor (A2AR) (Garcia et al. 2007). Upregulation of A2AR results in attenuation of inflammation (Fig. 33.2) and thereby limits the damage caused by inflammation (Blackburn et al. 2009). In MS, A2AR upregulation has been demonstrated by PET imaging with the A2AR tracer [^{11}C]TMSX (Rissanen et al. 2013). This indicates that in MS, microglial upregulation of A2AR expression might attenuate the inflammation, thereby reducing tissue damage and enhancing axonal survival.

33.4 PET Imaging to Assess Myelin Integrity

One of the main characteristics of MS pathology is the degradation of myelin. However, a validated and specific imaging method to directly visualise myelin in vivo and therefore to assess its integrity is still lacking. Because of high binding of amyloid tracers to white matter in healthy subjects, amyloid tracers have been recently applied for assessment of myelin integrity (Matías-Guiu et al. 2015). Amyloid tracers are designed to bind amyloid-beta deposits in the brain, which is one of the hallmarks of Alzheimer's disease pathology. More specifically, amyloid tracers bind to the beta sheets in amyloid-beta depositions (Wu et al. 2011). Myelin basic protein (MBP), one of the most prominent protein in the myelin lipid layers, also contains beta sheet structures (Ridsdale et al. 2002). Therefore, the high uptake of amyloid tracers in white matter of healthy subjects is hypothesised to correspond with binding to MBP, and thus might be used as a measurement for assessing myelin integrity (Fig. 33.4).

Amyloid tracers for assessing myelin integrity generally display a decreased uptake in the white matter lesions compared to NAWM (Table 33.5). However, none of the studies also assessed the perfusion rate of lesions. Diminished perfusion in lesions could also lead to a lower tracer uptake in the lesions, even without demyelination. Current research with amyloid tracers leads to conflicting results regarding differentiation between NAWM in MS patients and WM of healthy subjects. [^{18}F]Florbetaben, for instance, showed differences between tracer uptake in NAWM

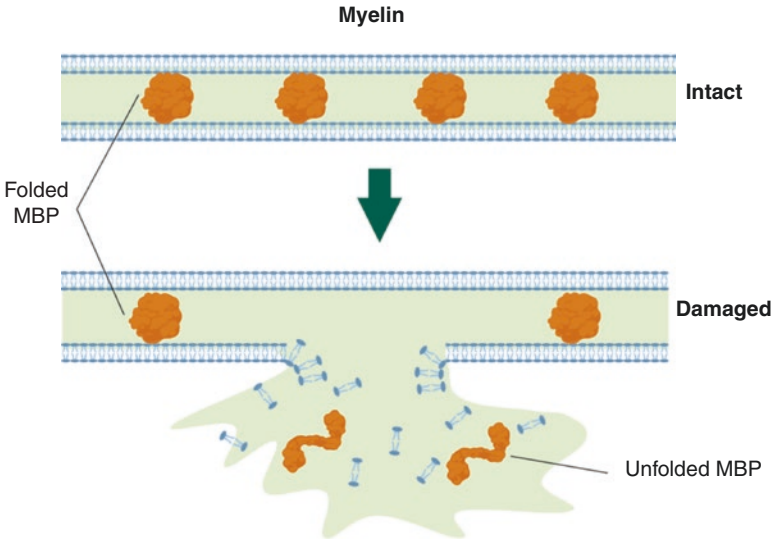

Fig. 33.4 Mechanism of action for myelin visualisation. The main target for myelin visualisation is supposedly myelin basic protein (MBP). The tracers bind to the beta sheets of intact MBP. When myelin is damaged, MBP loses its structure and thereby the tracer binding site (the figure is inspired by Stapulionis et al. (2008); Source: DOI: https://doi.org/10.4049/jimmunol.180.6.3946)

Table 33.5 Overview of studies with amyloid tracers employed for myelin imaging

Study	Tracer	Subjects	GM	NAWM	Non-enhanced lesions	Enhanced lesions
Bodini et al. (2016)	[^{11}C]PiB	8 HC 20 RRMS	No differences in tracer uptake	No differences in tracer uptake	Decreased tracer uptake	Decreased tracer uptake
Grecchi et al. (2017)	[^{11}C]PiB	20 RRMS	n.a.	n.a.	Decreased tracer uptake	Decreased tracer uptake
Zeydan et al. (2018)	[^{11}C]PiB	80 HC 12 MS	No differences in tracer uptake	No differences in tracer uptake	n.a.	n.a.
Matías-Guiu et al. (2015)	[^{18}F] Florbetaben	3 HC 5 RRMS 5 SPMS 2 PPMS	n.a.	Decreased tracer uptake	Decreased tracer uptake (enhancement not specified)	
Matías-Guiu et al. (2017)	[^{18}F] Florbetaben	1 MS	n.a.	n.a.	Decreased tracer uptake (enhancement not specified)	
Pietroboni et al. (2019)	[^{18}F] Florbetapir	7 RRMS 3 SPMS 2 PPMS	n.a.	n.a.	Decreased tracer uptake (enhancement not specified)	

GM grey matter, *HC* healthy control, *MS* multiple sclerosis, *n.a.* not applicable, *NAWM* normal appearing white matter, *PPMS* primary progressive MS, *RRMS* relapse remitting MS, *SPMS* secondary progressive MS

and WM, whereas [^{11}C]PiB did not (Matías-Guiu et al. 2015; Bodini et al. 2016). [^{18}F]Florbetaben, [^{18}F]Florbetapir, as well as [^{11}C]PiB, all showed a decreased tracer uptake in lesions relative to NAWM (Matías-Guiu et al. 2015, 2017; Bodini et al. 2016; Pietroboni et al. 2019; Zeydan et al. 2018; Grecchi et al. 2017). Furthermore, [^{11}C]PiB has shown to be able to capture remyelination and demyelination processes (Bodini et al. 2016). In contrast, [^{18}F]Florbetaben displayed differences in tracer uptake in lesions between different MS disease types, while no significant differences were observed in T2-weighted total lesion volumes between MS types (Matías-Guiu et al. 2015). This difference in [^{18}F]Florbetaben uptake in lesions between MS types might illustrate possible remyelination processes of lesions that occur in RRMS, which might not be detectable with T2 imaging. An example of [^{18}F]Florbetaben PET employed for myelin imaging is displayed in Fig. 33.5. Aside from the repurposing of amyloid tracers, recently the tracer [^{11}C]MeDAS has been specifically developed for the visualisation of myelin (Wu et al. 2010). PET studies with [^{11}C]MeDAS in preclinical models show that the tracer binds more specifically to MBP than other tracers (De Paula et al. 2014a, 2014b). Currently, the first clinical study with [^{11}C]MeDAS is still in progress (Trial register no. NL7262).

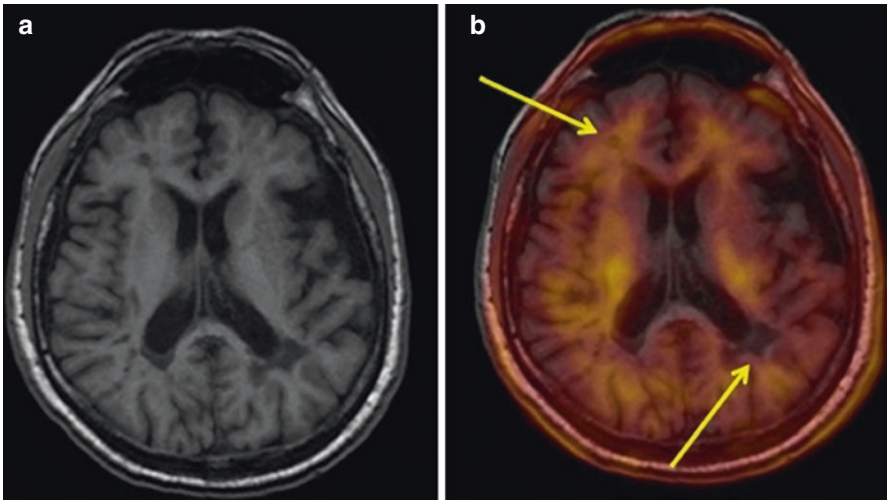

Fig. 33.5 A [^{18}F]Florbetaben PET image illustrating its ability to depict demyelination. On the left, a T1 MRI scan is displayed, with on the right a PET-MRI fusion image, illustrating both normal tracer uptake (left top corner) and a decreased tracer uptake (right bottom corner) at the lesion location as detected by T1 MRI (permission for the use of the images was obtained; Source: DOI: https://doi.org/10.1186/s12883-015-0502-2) (Matías-Guiu et al. 2015)

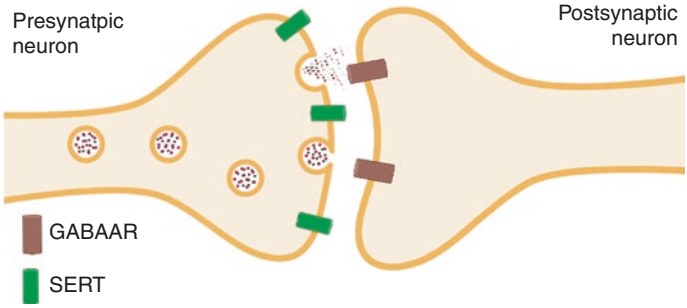

Fig. 33.6 Neuronal targets used for PET imaging in MS. $GABA_A$ receptor is essential for the propagation of action potentials, a reduced expression indicates a reduced synaptic density. SERT upregulation increases serotonin re-uptake and thereby enhances depressive symptoms

33.5 PET Imaging to Assess Neuronal Integrity

As a result of neurodegeneration, the amount of synapses decreases. One of the most important synaptic receptors is the γ-aminobutyric $acid_A$ ($GABA_A$) receptor. $GABA_A$ receptors (Fig. 33.6) are essential for propagating action potentials, and thus responsible for signal transduction (Mohler 2009). One of the sub-components of the $GABA_A$ receptor is the benzodiazepine receptor. Benzodiazepines enhance the effect of GABA binding to the $GABA_A$ receptor (Sigel and Ernst 2018). In MS, imaging with [^{11}C]flumazenil, an antagonist for the benzodiazepine receptor,

resulted in a lower cortical tracer uptake compared to healthy subjects, indicating a reduction of synapses in MS (Freeman et al. 2015).

Depression and mood disorders can occur in MS, possibly as a direct result of the disease. Depression is associated with a decreased availability of serotonin. Serotonin is a major contributor to feelings of well-being and happiness (Mitchell and Phillips 2007). One cause for the decreased availability of serotonin is an increase of serotonin transporters (Fakhoury 2016). Serotonin transporters transport serotonin from the synaptic cleft to the presynaptic neuron, and thereby counteract the effects of serotonin (Fig. 33.6). Therefore, a decrease or inhibition of serotonin transporters increases serotonin concentrations in the synapses and thus stimulates serotonin functions. [^{11}C]DASB is a tracer binding to serotonin transporters. In MS, a study with [^{11}C]DASB showed a reduced tracer uptake in the cingulate cortex, the thalamus, and the insula and an increased uptake in the orbitofrontal cortex (Hesse et al. 2014). This indicates a reduction of serotonin transporters in limbic and paralimbic regions and an increase in frontal regions. This study also assessed the correlation between [^{11}C]DASB uptake and depression. In line with expectations, there was a positive correlation between insular tracer uptake and depression, which means the higher the amount of serotonin transporters in the insula, the more prominent the depressive symptoms.

Like in all other neurodegenerative diseases, [^{18}F]FDG, a tracer for imaging glucose consumption is also used in MS to study neuronal integrity (Roelcke et al. 1997). As neurons are the major consumers of glucose in the brain, a decreased uptake of [^{18}F]FDG depicts dysfunction or degeneration of neurons. Reduced cortical [^{18}F]FDG uptake has also been found to be associated with a reduced cortical *N*-acetylaspartate concentration normalised to creatine (NAA/Cr) in RRMS (Blinkenberg et al. 2011). NAA/Cr is another method to assess neuronal deterioration and thus further illustrates the ability of [^{18}F]FDG to capture neurodegenerative processes in MS. However, as MS is a quite heterogeneous disease, there is a wide variety of regions showing neurodegeneration (Table 33.6). The hypometabolism in those regions was also positively correlated with both the duration and severity of MS (Bakshi et al. 1998). The clinical effects of neurodegeneration studied with [^{18}F]FDG in MS are mostly related to mobility or fatigue, but also to some extent to cognition.

Several brain regions are involved in the initiation of movement, and therefore neurodegeneration in any of those regions can affect mobility. The combination of regions responsible for movement is called the motor network. For the initiation of movement, first the parietal and temporal lobes receive sensory information and then initiate the motor network by stimulation of the prefrontal cortex (Gray and Bjorklund 2014). The prefrontal cortex then creates a general plan of action, which is then converted by the premotor area into neural programmes for movement. The primary motor cortex propagates this to the cerebellum and basal ganglia for fine tuning. The optimised plan of action is then sent down the spinal cord for execution of the movement.

Table 33.6 Overview of studies assessing CNS glucose metabolism in MS using [^{18}F]FDG PET

Study	Subjects	Metabolism quantification method	Hypermetabolism
Bakshi et al. (1998)	6 HC 25 MS	Absolute	Whole brain, cortex, WM, subcortical
Derache et al. (2013)	17 RRMS	CMRglu	Negative correlations with fatigue
Roelcke et al. (1997)	16 HC 47 MS	Normalised to mean uptake (CMRglu)	Whole brain, prefrontal cortex, premotor cortex, putamen, supplementary motor area, basal ganglia
Kindred et al. (2014)	8 HC 8 RRMS	SUVmean	Spinal cord
Blinkenberg et al. (2001)	9 HC 23 MS	CMRglu	Cortex, prefrontal cortex, orbitofrontal cortex, caudatus, putamen, thalamus, hippocampus

CMRglu cerebral metabolic rate of glucose, *HC* healthy control, *MS* multiple sclerosis, *RRMS* relapse remitting MS, *SUVmean* mean standardised uptake value, *WM* white matter

Several studies found changes in metabolism in regions of the motor network (Table 33.6). For instance, a reduction in cortical glucose uptake was found to be associated with disease severity expressed as fatigue (Roelcke et al. 1997; Derache et al. 2013). This might be explained by the increased muscular demands caused by a decreased CNS efficacy, and therefore leads to earlier muscular exhaustion, hence fatigue (Rudroff et al. 2014). Also negative correlations have been observed between physical score and metabolism in left parietal regions, right frontal regions, and right temporal regions (Derache et al. 2013). This means the higher physical score, the lower the [^{18}F]FDG uptake in those regions, which might illustrate network disruptions in patients with fatigue. In addition, a decreased [^{18}F]FDG uptake was observed in the spinal cord of MS patients (Kindred et al. 2014). This might indicate that the autonomic nervous system and walking/motor dysfunctions that are often seen in patients with MS could originate from spinal cord neurodegeneration.

While assessing cognitive effects of MS pathology, a negative correlation was observed between cognition and metabolism in thalamus (Derache et al. 2013). This means lower cognitive performance, relates to higher [^{18}F]FDG uptake in the thalamus, and thus may illustrate cerebral compensation for maintaining cognitive function. A more thorough assessment of the effects of MS pathology on cognition revealed a relation between lesion-affected regions, adjacent cortical hypometabolism, and corresponding diminished cognitive performance (Blinkenberg et al. 2001). This study found no other clinical deterioration aside from cognition and therefore illustrates that cognitive deterioration may occur without any other signs of disease progression, most likely resulting from white matter lesion-induced neurodegeneration.

33.6 PET Imaging as a Tool to Aid in Differential Diagnosis

MRI lesions can show a pattern specific for MS. In some cases, lesions seem to resemble tumours, both radiologically and clinically (Di Patre et al. 2003). This type of MS is therefore called tumefactive MS. For the differentiation of the lesions of tumefactive MS from brain tumours, [^{11}C]methionine PET imaging might be employed. Tumours are associated with a high proliferation and protein synthesis (Waarde and Elsinga 2008). For PET imaging of protein synthesis, radiolabelled amino acids, like [^{11}C]methionine, are used. Methionine was shown to have a low uptake in the healthy brain, but in tumours methionine uptake is increased (Jager et al. 2001; Coope et al. 2007). Therefore, [^{11}C]Methionine PET is widely used to aid in the diagnosis of brain tumours, and thus might be used to differentiate between tumefactive MS and cerebral tumours. However, at the moment there is only evidence from case studies to support this concept.

For instance, in a case for which it was not possible to differentiate between a tumefactive MS lesion and a tumour with MRI, [^{11}C]methionine PET displayed no significant uptake in the lesion (Ninomiya et al. 2015). The diagnosis of this specific patient was therefore tumefactive MS, which significantly influenced the selection of treatment strategies. In another case, [^{11}C]methionine PET was used to differentiate a low-grade glioma from a suspected diagnosis of tumefactive MS (Tarkkonen et al. 2016). In this patient there was actually significant [^{11}C]methionine uptake in the lesion, which suggested a possible tumour (Fig. 33.7). In addition, a [^{11}C]PK11195 PET scan was performed, which showed no increased uptake, arguing against MS and leading ultimately to a glioma diagnosis. These cases clearly illustrate that the important contribution PET could potentially have in differential diagnosis in cases where other techniques are inconclusive.

33.7 PET Imaging to Assess Treatment Effects in MS

To study therapy effects on MS pathology, PET imaging can play an important role due to visualisation of alterations in individual biological processes (Table 33.7). Currently, the primary treatment strategy of MS is inhibition of the immune attacks on the myelin sheaths. Current disease modifying therapies are all anti-inflammatory. For example, treatment with fingolimod inhibits the migration of lymphocytes from the lymph nodes (Matloubian et al. 2004; Mandala et al. 2002). Due to the reduction of lymphocytes, the severity of inflammatory responses in MS is reduced. In a [^{11}C]PK11195 PET imaging study, increased tracer uptake in NAWM and GM areas was observed in MS patients prior to fingolimod treatment, as compared to healthy subjects (Sucksdorff et al. 2017). After 6 months of fingolimod treatment patients displayed a decrease in tracer uptake in lesions, but not in other brain areas. Therefore, the inhibition of lymphocyte migration by fingolimod has globally limited effects on the activation of microglia and macrophages outside of the lesions. The observed clinical improvements are therefore probably primarily caused by the reduction of activation of inflammatory cells within the lesions. This illustrates the

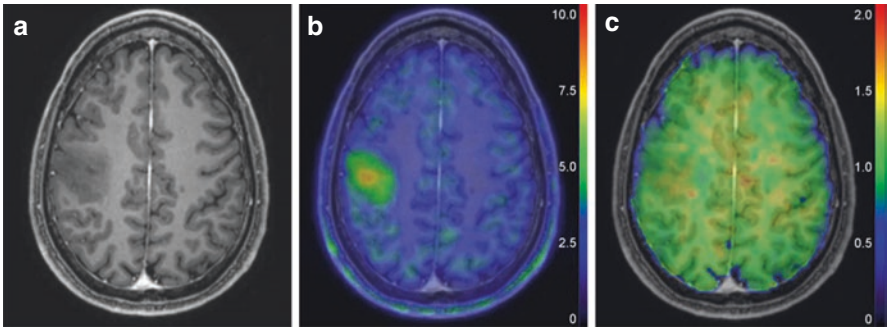

Fig. 33.7 MS differential diagnosis with PET imaging. (**a**) depicts a T1 MRI image with a hypointense lesion. (**b**) is a [^{11}C]methionine PET image, which clearly illustrates an increased uptake at the lesion. (**c**) [^{11}C]PK11195 PET image, illustrating no significant differences in uptake, and thus supported glioma diagnosis, which was confirmed by brain biopsy (permission for the use of the images was obtained; Source: DOI: https://doi.org/10.1016/j.msard.2016.07.016) (Tarkkonen et al. 2016)

Table 33.7 Overview of studies using PET to analyse therapy effects in MS

Study	Tracer	Subjects	Treatment	Treatment response
Sucksdorff et al. (2017)	[^{11}C] PK11195	10 RRMS	Fingolimod	Reduced lesional tracer uptake after 6 months of treatment, but not in other brain areas
Baumgartner et al. (2018)	[^{18}F]FDG	10 HC 9 RRMS	Interferon beta therapy	6 months IFN-beta. After treatment, decreased metabolism in cerebellum, increased metabolism in left inferior parietal cortex, right insula, left temporo-occipital cortex, left frontal cortex, and left striatum
Bunai et al. (2018)	[^{11}C] DPA713	6 HC 4 RRMS	Fingolimod	After 1 year treatment, a broad increased tracer uptake, especially in temporal and parietal cortex
		2 RRMS	Interferon beta therapy	
Ratchford et al. (2012)	[^{11}C] PK11195	9 RRMS	Glatiramer acetate	After 1 year of treatment, whole brain tracer uptake decreased, cerebral white matter, cortical grey matter. No change in binding in lesions
Kaunzner et al. (2017)	[^{11}C] PK11195	5 HC 18 MS	Natalizumab	After 6 months of treatment, decreased tracer uptake in both non- and enhanced lesions. No changes observed in NAWM, thalamus, and cortex

HC healthy control, *IFN-beta* interferon beta, *MS* multiple sclerosis, *NAWM* normal appearing white matter, *RRMS* relapse remitting MS

importance of reducing the inflammatory status within lesions. In another study on the effect of interferon (IFN)-beta therapy, [^{18}F]FDG PET showed no differences between patients and healthy subjects at baseline (Baumgartner et al. 2018). However, after 6 months of treatment, using relative regional glucose metabolism (rCMRglu) as outcome measure, a decreased [^{18}F]FDG uptake was observed in the cerebellum and an increased [^{18}F]FDG uptake in various brain regions in MS patients compared to healthy subjects. Although this might suggest that IFN-beta would lead to a decrease in cerebellar neuronal integrity, due to the use of relative measurements instead of absolute, this effect could also represent a global increase in cerebral metabolic rate of glucose (CMRglu), combined with no increase in cerebellum and, thus, a relative decrease in cerebellum. Nevertheless, these results do not depict any effects of the efficacy of IFN-beta therapy on modulation of the inflammatory response. Another study, which analysed the effects of both fingolimod and IFN-beta, showed an increased [^{11}C]DPA713 uptake at baseline in patients, which was even further increased at follow-up (Bunai et al. 2018). Traditionally, TSPO tracers are used to visualise activated inflammatory cells, however, aside from the pro-inflammatory status (e.g. M1 microglia), activated inflammatory cells can also have a protective function (e.g. M2 microglia) and thus depict protective mechanisms. Nevertheless, the results of these studies show the complexity of disentangling the mechanisms of action of disease modifying therapies in MS.

[^{11}C]PK11195 PET has also been used for the analysis of the effects of glatiramer acetate, which is commonly used in MS treatment. Glatiramer acetate putatively binds to the major histocompatibility complex receptors and thereby inhibits the T-cell response to myelin antigens (Schrempf and Ziemssen 2007). The reduction of adaptive immune system activation should also reduce the activation of the innate immune system. A study analysing the effects of glatiramer acetate with [^{11}C]PK11195 displayed a decreased tracer uptake after 1 year of treatment compared to baseline (Ratchford et al. 2012). Therefore, these results support the concept of a decreased activation of the innate immune system over time due to glatiramer acetate treatment and thus illustrate its mechanism of action.

Antibodies are also commonly used in the treatment of MS. One of these antibodies is natalizumab, which very specifically binds to integrins expressed on the cerebral vasculature, and strongly decreases the influx of lymphocytes into the CNS (Peterson et al. 2002; Yednock et al. 1992). The influx reduction limits the effects of the adaptive immune system in the CNS and subsequently the activation of innate immune cells (Del Pilar Martin et al. 2008). [^{11}C]PK11195 PET imaging showed a decrease of tracer uptake in lesions after 6 months of treatment with natalizumab, but no changes were detected in NAWM, the thalamus, and GM (Kaunzner et al. 2017). These results illustrate that natalizumab treatment also has its main effect on inflammation in lesions compared to non-lesional tissue. While both fingolimod and natalizumab have proven clinical efficacy, this seems to be mainly caused by the reduction of the inflammation within lesions. Therefore, a more thorough assessment of the lesions with PET imaging instead of whole brain analysis would be more indicative for the efficacy of therapies.

33.8 Clinical Notes

The clinical application of PET scanning in MS at this moment is restricted to aiding diagnosis in difficult cases. PET imaging in MS has been mainly used in a research setting so far. If myelin binding ligands can deliver on their promise and quantifying myelin loss in lesions becomes feasible, such scan techniques can probably be used in phase II and III trials to aid in identifying drugs promoting myelin repair. Further down the road, myelin imaging using PET may be used to inform clinicians and patients about the individual treatment effect of myelin restoring treatment protocols. The place of inflammation imaging using PET in MS is more difficult to predict. MRI protocols are already capable of imaging inflammation in MS and do not have the disadvantage of using ionising radiation.

33.9 Conclusion

The use of PET imaging in MS is increasing, in particular, in a research setting. Currently, its primary role in clinical practice is in aiding with differential diagnosis between MS and brain tumours. PET imaging of activation of the innate immune system could be of particular interest in drug development, as the technique would enable objective efficacy evaluation of immune suppressive therapies. Due to the increasing interests in myelin imaging, a method to assess myelin integrity may soon become available. As myelin repair is likely the next target of interest in the treatment of MS, myelin PET could initially be used to determine the efficacy of various remyelination therapies, and in the end to monitor individual remyelination treatment responses.

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