PET Imaging of Translocator Protein Expression in Neurological Disorders

30

David J. Brooks

Contents

Abstract

Microglia provide the intrinsic immune defence of the brain and are activated by any injurious process. As such they provide a non-specific marker of disease activity. Their function can be both detrimental and beneficial as they release cytokines which drive disease progression but also release restorative growth factors, help clear cellular debris and abnormal protein aggregations and can remodel connections as an adaptive response to brain damage. Activated microglia express translocator protein (TSPO), and this allows them to be imaged in vivo with positron emission tomography (PET) radioligands which are

D. J. Brooks (✉)
Faculty of Medicine, University of Newcastle Upon Tyne, Newcastle Upon Tyne, UK

Department of Nuclear Medicine, Aarhus University, Aarhus, Denmark
e-mail: David.Brooks@newcastle.ac.uk

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substrates. In this review the role of TSPO imaging with PET is discussed in neurodegenerative and inflammatory brain diseases and in focal brain injury due to trauma or stroke.

30.1 Introduction

The 18 kDa translocator protein (TSPO), previously known as the peripheral benzodiazepine receptor (PBR), is present in many peripheral organs including the liver, spleen, adrenals and myocardium (Banati 2002b). It is expressed only at low levels in a normal brain, but if microglial cells become activated, TSPO can be detected in their outer mitochondrial membrane. The TSPO serves a number of functions including transport of cholesterol, anions, nucleosides and porphyrins; maintenance of mitochondrial membrane potential; regulation of cell apoptosis and proliferation and immunomodulation (Papadopoulos et al. 2006). The protein expresses a binding site for benzodiazepines and isoquinolines such as PK11195, and this has allowed the detection of TSPO expression in vivo with (*R*)-[^{11}C]PK11195 PET. Newer PET biomarkers are now available to image TSPO expression which include phenoxyarylacetamides such as [^{11}C]/[^{18}F]DAA1106, [^{11}C]PBR28, [^{18}F]PBR06, [^{18}F]PBR111 and [^{18}F]FEPPA; pyrazolo-[1,5-a]-pyrimidines such as [^{11}C]DPA713 and [^{18}F]DPA714; the vinca alkaloid [^{11}C]vinpocetine and the imidazo-[1,2a]-pyridines [^{11}C]/[^{18}F]CLINDE (Dolle et al. 2009; Doorduin et al. 2008).

Microglia account for around 15% of the cerebral white cell population. They are normally in a resting state sending out long ramified processes which contact neighbouring neurones and astrocytes (Kreutzberg 1996; Ransohoff and Perry 2009). It is, therefore, likely that the function of resting microglia is to monitor changes in the local brain milieu—for a review see (Hanisch and Kettenmann 2007). Microglia are cells of monocyte lineage and are protected from antigens in the plasma by the blood-brain barrier. They form the natural immune defence of the brain, and exposure to plasma proteins such as fibrinogen following blood-brain barrier disruption, or to intrinsic excitotoxic agents such as raised glutamate, nitric oxide or cytokines, causes them to become activated taking on ameboid- or rod-like morphology. When activated, the microglia express MHC class 1 and 2 antigens and can release cytokines such as TNFα, IL1β and IL6, or growth factors such as TGF-β1. They may become phagocytic clearing cellular debris and stripping and remodelling synapses. It is now considered that activated microglia may exist as two primary phenotypes: M1 which is associated with the release of cidal cytokines so promoting cell damage and M2 which is associated with phagocytosis of dead tissue, synaptic remodelling and growth factor release promoting neurogenesis (Boche et al. 2013; Varnum and Ikezu 2012). These two primary phenotypes are thought to be interconvertible, have overlapping functions and predominate at different disease phases. It has been suggested that substrates binding to the TREM2 receptor on microglia promote activation of the M2 phenotype (Li and Zhang 2018). After an acute stroke, activated microglia act locally to wall off, remove dead tissue and remodel connections, while

in chronic neurodegenerative diseases, they may release cytokines where disease is locally active but remodel distant connections in the brainstem and thalamus. The advent of TSPO PET agents has allowed us to image in life the distribution of activated microglia in the brain. Current TSPO PET ligands are unable to discriminate between M1 and M2 phenotypes and provide a measure of total activated microglia load rather than indicating whether their function is protective or toxic in nature.

30.2 Imaging TSPO with PET

The PET ligand that was initially used for imaging TSPO expression in the brain and has seen the greatest use is the isoquinoline (*R*)-[^{11}C]-PK11195. The rat unilateral facial nerve crush model results in activated microglia in the disconnected ipsilateral facial nucleus. Autoradiography studies have shown that [^{3}H]PK11195 binds selectively to these activated microglia which are involved in remodelling connections to restore facial muscle function (Banati et al. 1997). A human equivalent of this rodent model is Bell's palsy where the facial nerve becomes unilaterally compressed due to local inflammation and swelling as it passes through the auditory canal. (*R*)-[^{11}C]PK11195 PET studies have demonstrated tracer uptake in the facial nerve nucleus ipsilateral to the paralysed facial muscles (Banati 2002b). Human subjects with acquired upper limb amputations develop phantom limb phenomena where the absent limb still feels present but telescoped into the stump. In these subjects one can detect thalamic inflammation contralateral to the missing limb with (*R*)-[^{11}C]PK11195 PET (Banati 2002a). These studies, therefore, reveal the microglial activation resulting from the disconnection of brain nuclei due to peripheral injury, presumably playing an active role in the remodelling of connections. It remains to be determined whether these cells are primarily expressing an M2 phenotype.

In the majority of brain disorders, (*R*)-[^{11}C]PK11195 PET reveals microglial activation due to both local disease activity and the effects of downstream disconnection. Additionally, as endothelial cells also express TSPO, tracer binding is seen in the lateral and sagittal venous sinuses, and this signal can spill over into adjacent brain tissue—particularly the cerebellum—due to the 4–5 mm spatial resolution of most commercial PET cameras. This makes quantitative modelling of brain (*R*)-[^{11}C]PK11195 PET problematic as there is no anatomical region that provides a pure tissue reference for non-specific tracer uptake though cerebellar grey matter has been used. The use of an arterial plasma input function with this tracer is also problematic as (*R*)-[^{11}C]PK11195 sticks to plastic tubing, making it difficult to obtain blood time-activity curves which allow an accurate measurement of peak height, delay and dispersion. For these reasons, a modelling approach has been developed that uses supervised cluster analysis to identify clusters of voxels that fall into six classes of brain uptake kinetics. One of these clusters represents a collection of grey matter voxels in the subject's brain that have a time-activity curve (TAC) similar to that of a normal grey matter TAC in a population of healthy controls, while another represents vascular binding (Anderson et al. 2007). The normal grey

matter reference cluster can be used to compute non-specific (*R*)-[^{11}C]PK11195 uptake in other brain clusters where specific tracer retention is occurring. At the same time, the vascular signal due to tracer binding, which shows the most rapid uptake, can be separated from adjacent brain parenchymal signal. The (*R*)-[^{11}C]PK11195 binding potentials (BPs) are then computed using a standard simplified reference tissue model (SRTM) with brain-specific and non-specific compartments. As (*R*)-[^{11}C]PK11195 binding increases in a normal thalamus and, to a lesser degree, cortex with age, it is important to age match healthy controls to patients when assessing levels of inflammation in disease states (Cagnin et al. 2001).

Recently, second-generation TSPO tracers have been developed which can have higher affinity and/or a lower non-specific signal in order to provide a more sensitive detection of microglial activation and facilitate modelling approaches. However, with these new tracers has come the realisation that TSPO PET imaging is influenced by TSPO gene polymorphisms expressed by individuals (Owen et al. 2012). The most influential of these is the rs6971 polymorphism where Ala147Thr substitutions result in homozygous subjects becoming low affinity binders of these newer TSPO ligands while heterozygotes express a mixture of TSPO with high and low affinity for these ligands. In Caucasian populations, around 60% of individuals are high, 10% low and 30% mixed affinity binders for the newer TSPO ligands. (*R*)-[^{11}C]PK11195 affinity for TSPO, however, appears to be less influenced by genotype (Owen et al. 2012), while [^{11}C]PBR28 shows a 75-fold difference in affinity for TSPO between high (Kd 4 nM) and low (Kd 300 nM) affinity binders. The PET tracers [^{11}C]DAA1106, [^{11}C]DPA713 and [^{18}F]PBR111 show 4–5-fold differences in affinity for TSPO between high and low binders. Mixed affinity binders express high and low affinity TSPO binding sites in equal proportions. If one is to use these newer TSPO PET markers, then low affinity binders will need to be excluded by prior genetic screening and patient and control populations matched for prevalence of mixed and high affinity binders. When interrogating associations between TSPO PET signals and pathology or clinical parameters, the variance due to TSPO polymorphisms may need to be corrected by ANCOVA.

Modelling the brain uptake kinetics of second-generation TSPO PET tracers has similar problems to those described previously for (*R*)-[^{11}C]PK11195. In practice cerebellar grey matter has often been employed as a tissue reference for non-specific binding for tracers such as [^{18}F]DPA714 and [^{11}C]PBR28 although this can lead to underestimations of specific binding in regions of interest. Supervised cluster analysis has also been applied to define reference clusters for individual patients and correct spill over of vascular signals. Arterial input functions have been also used in some series (Schain et al. 2018).

30.3 TSPO Imaging in Alzheimer's Disease

Dementia affects 10% of the over 60s, the prevalence rising to 30% by the ninth decade. It is characterised clinically by progressive impairment of memory, speech and perception along with personality change in the absence of altered conscious

level. Sixty percent of dementia cases have Alzheimer pathology characterised by extracellular fibrillar β-amyloid plaques and intra-neuronal neurofibrillary tangles of hyper-phosphorylated tau at post-mortem. Activated microglia are seen surrounding the neuritic amyloid plaques which target association cortex and cingulate but are less evident in the striatum where plaques are diffuse (Braak and Braak 1997; Dickson 1997). Activated microglia are also found in brain areas surrounding neurites with tau tangle pathology such as the entorhinal cortex and hippocampus.

Raised levels of microglial activation were first imaged in vivo in clinically diagnosed Alzheimer's disease (AD) patients with (*R*)-[^{11}C]PK11195 PET, binding potentials being raised by up to 50% in association cortex (Cagnin et al. 2001; Schuitemaker et al. 2013) (Fig. 30.1a). Uptake of the TSPO ligand [^{11}C]DAA1106 has also been reported to be elevated by up to 33% in AD (Yasuno et al. 2008). The cortical distribution of raised (*R*)-[^{11}C]PK11195 uptake parallels that of β-amyloid plaque deposition revealed with [^{11}C]PIB PET, a marker of fibrillar amyloid load

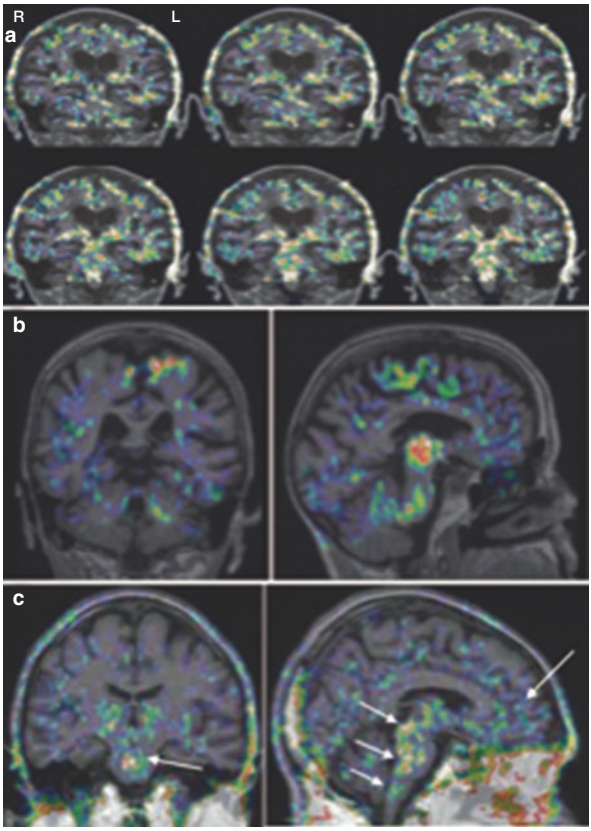

Fig. 30.1 (*R*)-[^{11}C]PK11195 PET images of microglial activation in patients with (**a**) Alzheimer's disease, (**b**) motor neuron disease, (**c**) Parkinson's disease, (**d**) multiple sclerosis

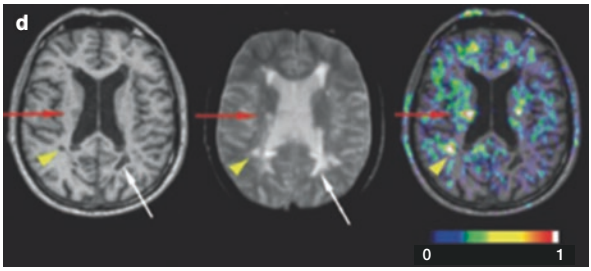

Fig. 30.1 (continued)

(Edison et al. 2007a), targeting association rather than primary areas. Levels of cortical (*R*)-[^{11}C]PK11195 and [^{11}C]PBR28 uptake in AD have been reported to correlate with cognitive impairment rated with the mini-mental state examination (MMSE) and CDR-SOB, but there was no correlation between amyloid load and cognitive status (Edison et al. 2007b; Kreisl et al. 2016; Yokokura et al. 2011). In established Alzheimer's disease, amyloid plaque load plateaus while cognitive ability declines, and these findings suggests that it may be the cortical microglial activation rather than amyloid plaques in AD that are detrimental to cognitive function, possibly due to cytokine release by cells exhibiting a cidal M1 phenotype. Along with the raised cortical TSPO signal, activated microglia can also be detected in the thalamus, cerebellum and brainstem of Alzheimer patients. As these subcortical areas are only targeted in late disease by plaques, the (*R*)-[^{11}C]PK11195 signal there is likely to reflect microglial activation either due to local tau tangle disease or in response to cortical disconnection, the cells acting to remodel connections.

(*R*)-[^{11}C]PK11195, [^{11}C]DAA1106 and [^{18}F]DPA714 PET have all been reported to detect the presence of microglial activation in a proportion of amnestic mild cognitive impairment (MCI) cases. These subjects have isolated progressive recall problems that are not severe enough to interfere with activities of daily living, but around 60% of these cases progress over 5 years to develop Alzheimer's disease (Petersen et al. 2001). In an initial small series, 60% of MCI cases showed evidence of amyloid plaque deposition with [^{11}C]PIB PET and so represented prodromal Alzheimer's disease (pAD). (*R*)-[^{11}C]PK11195 PET detected microglial activation in 40% of these amnestic MCI cases; that is two thirds of the pAD subjects (Okello et al. 2009). However, another series failed to detect microglial activation in amnestic MCI with (*R*)-[^{11}C]PK11195 PET—possibly because these workers used a cerebellar reference rather than defining normal voxels with supervised cluster analysis (Schuitemaker et al. 2013). A group of seven MCI cases showed a significant mean of 27% increase in tracer uptake across brain regions when their TSPO was imaged with [^{11}C]DAA1106 PET, and two cases individually had microglial activation elevated more than 2 SD above the control mean (Yasuno et al. 2012). Five of these seven MCI subjects with [^{11}C]DAA1106 uptake raised more than 0.5 standard deviations above the normal mean progressed to develop dementia over a 2-year follow-up period.

More recently, Parbo and colleagues scanned 42 MCI cases with [^{11}C]PiB and (*R*)-[^{11}C]PK11195 PET (Parbo et al. 2017). Twenty-six (62%) of the cases had raised cortical [^{11}C]PiB uptake, and 17 (65%) of these pAD cases had evidence of cortical inflammation. Clusters of correlated levels of amyloid and inflammation were found in the frontal, temporal and parietal cortex. In a follow-up study, tau tangle load was imaged with [^{18}F]flortaucipir PET in a subgroup of 20 MCI cases and 6 AD patients (Parbo et al. 2018). While amyloid load and inflammation levels were again correlated in cortical clusters of voxels, there was surprisingly no correlation evident between tau tangle load and inflammation. However, a 2-year follow-up study on these subjects has now detected a correlation between cortical tau and inflammation levels in the MCI and early AD cohort though this was not evident at baseline (R Ismail, Brooks DJ. Neurobiology of Disease 2020;17(1):151).

Using [^{18}F]DPA714 PET, Hamelin and colleagues have studied the levels of microglial activation in prodromal (38) and early clinical Alzheimer's disease (26) and its relationship with clinical progression (Hamelin et al. 2016). The presence of raised amyloid load was confirmed in all cases with [^{11}C]PiB PET, and, based on their MMSE score changes over 2 years, the AD group was divided into fast and slow decliners. The levels of TSPO binding were determined as target region:cerebellar ratios, and findings for high and mixed affinity binders were combined. TSPO binding in AD was raised relative to healthy controls, and cortical levels correlated negatively with MMSE scores and hippocampal volume and positively with CDR-SOB ratings and [^{11}C]PiB uptake. The slow and fast decliners had similar baseline levels of amyloid load, but baseline TSPO uptake was higher in the slow decliners. The authors suggested that microglial activation may be playing a protective role in early AD. In a follow-up study, these workers repeated [^{18}F]DPA714 PET in their AD patients and control subjects and found a greater increase in inflammation in AD (Hamelin et al. 2018). However, the increase in [^{18}F]DPA714 uptake was lower in those cases with higher baseline inflammation. The authors suggested that inflammation has two distinct profiles in AD, an initial protective profile followed by a detrimental effect on disease progression.

In favour of a protective role of inflammation in early AD, an [^{11}C]PBR28 PET series in 37 MCI amyloid-positive cases has reported that levels of TSPO binding correlated positively with cortical and hippocampal volumes (Femminella et al. 2019). Here an arterial input function with Logan graphical analysis was employed to measure tracer volumes of distribution. Longitudinal data is not yet available for this cohort.

Recently, our group has followed 38 MCI cases over 2 years with [^{11}C]PK11195 and [^{11}C]PiB PET (Ismail R and Brooks DJ. Neurobiology of Disease 2020;17(1):151). Twenty-two of these MCI subjects also had [^{18}F]flortaucipir PET to determine their tau tangle load. At baseline 23 MCI cases had raised and 15 cases had low/normal levels of cortical PiB uptake. Over 2 years the combined group of 38 MCI cases showed a rise in mean amyloid load but a decrease in mean cortical level of inflammation. In those 22 cases who had [^{18}F]flortaucipir PET, their cortical tau tangle load increased over time. Seven of the low PiB cohort showed increasing tracer uptake over 2 years, three crossing into the abnormal range. These cases

showed a correlation between their cortical PiB uptake and inflammation levels in the absence of tau tangle deposition. In the MCI group with raised PiB, the level of inflammation correlated with tau tangle load. These findings suggest that inflammation plays a role both in early MCI when amyloid load is rising—possibly protective—and in later MCI when tau tangles are forming, possibly toxic. The relationship between pathology and cognitive status was also followed in this MCI cohort. Amyloid plaque load and levels of inflammation across cortical regions at baseline correlated with cognitive deficit, while tau load correlated most strongly at the 2-year follow-up time point.

30.4 Imaging Inflammation in Frontotemporal Dementia and ALS

Dementia with a frontotemporal phenotype comprises around 10% of later onset dementia cases, and clinically it presents as personality change, praxis and language difficulties with memory becoming impaired subsequently. Clinical phenotypes include behavioural variant frontotemporal dementia (bvFTD), semantic dementia (SD) where subjects cannot recall the features and uses of objects and progressive non-fluent aphasia and apraxia (PNFA). The pathology targets the frontal and inferior temporal lobes and most commonly involves TDP-43 protein inclusions when it can also be associated with ALS. Less commonly Pick bodies containing three-repeat tau isoforms or spongiform degeneration are present.

25–50% of FTD cases are genetic in origin, and multiple gene mutations have been implicated. Repeat expansions of the C9ORF72 gene are the most common genetic cause and are associated with TDP-43 inclusions as are mutations of the progranulin (GRN) gene. MAPT gene mutations can cause Pick body tau inclusion disease. Mutations of TREM2 have been associated with FTD implicating a role of inflammation (Zhang 2015). Presenilin gene mutations also can rarely cause FTD as can mutations of the mitochondrial CHCHD10 gene. FTD is usually younger onset than AD and rarely associated with amyloid plaque formation.

The first PET series to study inflammation reported raised frontotemporal uptake of (*R*)-[^{11}C]PK11195 in four idiopathic PFNA and a fifth bvFTD case (Cagnin et al. 2004). In some but not all regions, the inflammation was associated with cortical atrophy. More recently, increased [^{11}C]PBR28 uptake has been documented in bvFTD cortex targeting association areas in patterns matching the clinical phenotypes of the patients (Kim et al. 2019). Larger series including presymptomatic susceptibility gene carriers are required to determine whether inflammation precedes neuronal dysfunction and aberrant protein aggregation in FTD.

There is both a clinical and pathological overlap between frontotemporal dementia and motor neuron disease (amyotrophic lateral sclerosis). The neuropathology of both can be associated with cortical TDP-43 inclusions and spongiform degeneration, and neuropsychological and imaging studies have indicated that dysfunction extends beyond the motor system in ALS. In an early series, ten probable or definite (El Escorial criteria) ALS patients without dementia had (*R*)-[^{11}C]PK11195 PET (Turner

et al. 2004). Significantly increased microglial activation was seen in the motor cortex, brainstem, thalamus, dorsolateral prefrontal cortex and occipital lobes of the ALS patients compared with 14 healthy controls (Fig. 30.1b). There was a significant correlation between the severity of upper motor neuron signs on examination and levels of motor cortex (*R*)-[^{11}C]PK11195 uptake. More recently, ten non-demented patients with probable or definite ALS were enrolled prospectively and eight healthy controls matched for age had [^{18}F]DPA714 PET (Corcia et al. 2012). A significant increase of microglial activation was found in the ALS sample in primary motor, supplementary motor and temporal cortex. Longitudinal follow-up is required in these series to determine the predictive power of TSPO PET for dementia in ALS cases.

Alshikho and colleagues have scanned 53 ALS and 11 primary lateral sclerosis (PLS) cases with [^{11}C]PBR28 PET and compared their findings with those of 21 healthy controls (Alshikho et al. 2018). Inflammation was measured as cortical grey matter SUVRs with a cerebellar reference for non-specific signal. ALS and PLS cases both showed increased inflammation in pre-and post-central gyri along with cortical thinning. Cortical uptake of [^{11}C]PBR28 correlated negatively with ALSFRS-R disability ratings. No significant increase in pre- and post-central cortical [^{11}C]PBR28 was apparent over a 6-month follow-up although ALSFRS-R ratings continued to decline. The authors suggested [^{11}C]PBR28 PET could provide a useful biomarker of the efficacy of neuroprotective strategies in ALS.

30.5 Parkinson's Disease and TSPO Imaging

Parkinson's disease (PD) is the second most common neurodegenerative disorder after dementia, affecting around 1% of the over 60s. It manifests as asymmetrical limb bradykinesia, rigidity and tremor, and these symptoms are usually responsive to oral levodopa. The pathology is characterised by Lewy body inclusions in neurons and Lewy neurites which contain aggregated alpha-synuclein and neurofilaments.

While the dopamine neurons of the substantia nigra pars compacta are targeted by the Lewy body pathology, it is now thought that the pathology can start peripherally in the skin and gut and then track via the vagus nerve to affect the dorsal motor nucleus in the medulla and then ascend through the brainstem to the cortex in stages (Braak et al. 2004). In stage 2 the locus ceruleus, pedunculopontine nucleus and median raphe in the pons become involved, while the dopamine neurons of the substantia nigra pars compacta in the midbrain only become targeted in stage 3 along with the cholinergic nucleus basalis. The limbic cortex and cingulate are involved by stage 4 and the association and primary neocortex in stages 5 and 6.

At post-mortem microglial activation has been reported to accompany Lewy body pathology in affected subcortical and cortical regions (Imamura et al. 2003; McGeer et al. 1993). Aggregations of alpha-synuclein as oligomers and fibrils can stimulate microglial activation in vitro, but the relationship between inflammation and disease progression remains uncertain. In an initial PET study, it was reported that levels of increased midbrain (*R*)-[^{11}C]PK11195 uptake in PD patients correlated

with reductions in putamen dopamine transporter (DAT) binding measured with [^{11}C]CFT PET (Ouchi et al. 2005). The authors suggested that this provided evidence for involvement of microglia in the dopamine loss that characterises PD.

Later (*R*)-[^{11}C]PK11195 PET series, however, have failed to detect consistent microglial activation in the substantia nigra of PD cases or to replicate an association between midbrain (*R*)-[^{11}C]PK11195 signals and loss of dopaminergic function in PD. Gerhard and colleagues noted that PD patients showed significant striatal and frontotemporal (*R*)-[^{11}C]PK11195 uptake though this did not correlate with disease severity (Gerhard et al. 2006a) (Fig. 30.1c). Iannaccone and co-workers have reported increased (*R*)-[^{11}C]PK11195 binding in the putamen and the substantia nigra of early Parkinson's disease but did not detect inflammation in the cortex (Iannaccone et al. 2013). Measuring [^{11}C]PBR28 V_T with Logan graphical analysis using an arterial plasma input function, Varnas and co-workers (Varnas et al. 2019) were unable to detect any increase in microglial activation in their group of 16 PD patients (8 HABs and 8 MABs).

In contrast, using the second-generation TSPO marker [^{11}C]DPA713 PET, increased signal was detected in the temporal, parietal and occipital cortex of PD cases which increased over 1 year (Terada et al. 2016). This finding supports the report from Gerhard and suggests that microglia activation can involve the substantia nigra, striatum and association cortex and be present in the early stages of the disease even in the absence of dementia.

It is conceivable that the dopaminergic drugs used to treat PD may have an influence on levels of microglial activation. Although none of these dopaminergic agents directly act to suppress microglial activation, it has been suggested that both dopamine agonists and monoamine oxidase B inhibitors have neuroprotective properties (Schapira and Olanow 2004). This claim is, however, controversial, and currently there is no hard evidence that therapy for PD influences levels of the inflammatory response.

The widespread microglial activation seen in PD at post-mortem and the raised (*R*)-[^{11}C]PK11195 uptake seen in the brainstem, basal ganglia and cortical regions of non-demented cases with PET are all regions which are targeted by Lewy body pathology in later Braak stages. More recently we have noted that levels of striatal (*R*)-[^{11}C]PK11195 uptake in PD correlated with disability rated with the Unified Parkinson's Disease Rating Scale (UPDRS), while impaired verbal fluency was associated with raised frontal and insular (*R*)-[^{11}C]PK11195 activity (Simpson et al. 2012). This supports a role for microglial activation in driving disease activity and is in line with the dying back theory of PD pathology which suggests that nigrostriatal terminals may become dysfunctional ahead of nigral cell body loss.

Those few longitudinal studies that have reported (*R*)-[^{11}C]PK11195 uptake in PD suggest levels remain static over a 1–2-year follow-up period despite on-going clinical deterioration and loss of putamen [^{18}F]DOPA storage of PD cases (Gerhard et al. 2004; Terada et al. 2016). It has been suggested that cortical microglial activation is an early phenomenon in PD and may act to promote the superadded dementia that usually follows although levels of inflammation remain fixed. In favour of this viewpoint, it was noted that PD cases with late dementia had similar cortical levels of microglial activation to similarly disabled non-demented cases.

30.6 Atypical Parkinsonian Syndromes and TSPO Imaging

Neurodegenerative disorders that cause atypical parkinsonian disorders include multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). MSA is associated with asymmetric parkinsonism along with early autonomic dysfunction, postural instability and ataxia. The pathology is characterised by argyrophilic glial cytoplasmic inclusions (GCIs) that contain alpha-synuclein and targets the substantia nigra, putamen, ponto-cerebellar connections and the lateral columns of the spinal cord. Microglial activation is known to be associated with MSA pathology, and (*R*)-[^{11}C]PK11195 PET has revealed raised TSPO binding in the putamen, pallidum, pons, substantia nigra and the dorsolateral prefrontal cortex at higher levels than that associated with PD (Gerhard et al. 2003). In a follow-up series of 14 MSA-P cases, Gerhard and colleagues again reported significant increases in microglial activation in the putamen ($p = 0.001$), pallidum ($p = 0.002$), precentral gyrus ($p = 0.004$), orbitofrontal cortex ($p = 0.006$), presubgenual anterior cingulate cortex ($p = 0.006$) and the superior parietal gyrus ($p = 0.007$) but now also the caudate nucleus ($p = 0.002$) (Kubler et al. 2019). The increases in (*R*)-[^{11}C]PK11195 binding potentials correlated with decreases in glucose utilisation in the putamen ($r = -0.78$, $p = 0.003$) and pallidum ($r = -0.77$, $p = 0.003$). No correlations between regional (*R*)-[^{11}C]PK11195 BPs and clinical parameters were found.

A proteolipid protein-alpha-synuclein overexpression (PLP-αSYN) transgenic mouse model of MSA showed a correlation between levels of nigral microglial activation and dopamine neurone loss (Stefanova et al. 2007). Minocycline suppressed the inflammation and preserved dopamine neurones in the mouse. A human trial was subsequently set up to determine whether minocycline had neuroprotective efficacy in MSA. The drug failed to alter disease progression at clinically licensed doses though MSA cases receiving active medication showed a 30% reduction in brain (*R*)-[^{11}C]PK11195 uptake relative to placebo-treated cases (Dodel et al. 2010).

Three PSP patients with Richardson syndrome who were studied with (*R*)-[^{11}C]PK11195 PET showed significantly increased signal in their caudate nucleus, putamen, pallidum, midbrain, substantia nigra, the frontal lobe and the cerebellum (Gerhard et al. 2006b). One of these patients was rescanned after 10 months, and the level of microglial activation had remained stable.

30.7 Detecting Preclinical Huntington's Disease Activity with TSPO PET

Huntington's disease is an autosomal dominant inherited progressive neurodegenerative disorder associated with motor, cognitive and psychiatric symptoms. It arises from an abnormal CAG triplet repeat expansion of the HTT gene on chromosome 4 which leads to an elongated polyglutamine chain at the terminus of the huntingtin protein. This results in cytoplasmic and intranuclear aggregations of huntingtin and progressive loss of medium spiny striatal GABA-ergic and cortical interneurons

(Sapp et al. 1997). The striatal output neurons express either dopamine D1 or D2 receptors depending on whether they are part of the direct or indirect pathway to the internal pallidum. Striatal dysfunction can be detected prior to symptom onset as a loss of availability of D1 and D2 sites for ligand binding (Andrews et al. 1999).

The loss of striatal and cortical neurons in HD is associated with microglial activation (Sapp et al. 2001) which can be detected in vivo with (*R*)-[^{11}C]PK11195 PET. Levels of striatal microglial activation correlate with loss of dopamine D2 receptor binding measured with [^{11}C]raclopride PET and with locomotor disability rated with the Unified Huntington's Disease Rating Scale (UHDRS) (Pavese et al. 2006). This suggests that microglial activation plays a role in driving the disease process. Supporting this viewpoint, (*R*)-[^{11}C]PK11195 PET studies have detected raised microglial activation in a majority of asymptomatic adult HD gene carriers in their fourth decade (Tai et al. 2007). Those asymptomatic carriers with raised TSPO expression also showed reduced dopamine D2 availability with [^{11}C]raclopride PET. Cortical microglial activation was also evident in pre-manifesting HD carriers confirming that this is not purely a basal ganglia disorder (Politis et al. 2011). Levels of striatal (*R*)-[^{11}C]PK11195 uptake have been shown to correlate with the predicted time of clinical disease onset (Politis et al. 2011; Tai et al. 2007).

Lois and colleagues have measured translocator protein (TSPO) expression in HD using [^{11}C]PBR28 PET. Regional signals were quantitated using SUVRs normalised to whole brain uptake with emission data acquired 60–90 min after intravenous radiotracer administration (Lois et al. 2018). Significant TSPO overexpression was detected in the putamen and pallidum of all the individual HD patients. Additionally, some HD patients showed elevated [^{11}C]PBR28 uptake in thalamic nuclei, the brainstem and red nuclei. Increased cortical inflammation was not reported in this series. The authors suggested that [^{11}C]PBR28 PET might prove a useful biomarker in clinical trials evaluating therapies targeting neuroinflammation.

30.8 Measuring Inflammation in Multiple Sclerosis

Multiple sclerosis (MS) is a disease characterised clinically by relapsing and remitting neurological episodes followed by a progressive phase of disability. Pathologically central inflammatory demyelination is seen as white matter plaques associated with axonal degeneration. MS targets young adults and is their most common cause of non-traumatic disability in the Western world (Compston and Coles 2008). Active plaques of demyelination contain blood-borne B and T lymphocytes and macrophages that have invaded via the disrupted blood-brain barrier. However, there is also an intrinsic immune reaction to the disease process manifested as involvement of activated microglia (Benveniste 2007). Post-mortem investigations have detected activated microglia not just in white matter plaques but also in cortex and apparently normal-appearing brain areas (De Groot et al. 2001; Peterson et al. 2001). In progressive MS activated microglia are seen surrounding the degenerating myelinated axons (Magliozzi et al. 2010).

(*R*)-[^{11}C]PK11195 PET has been used to demonstrate the extent of microglial activation in MS patients (Banati et al. 2000; Debruyne et al. 2003; Politis et al. 2012) (Fig. 30.1d). PET findings have been validated with [^{3}H]PK11195 autoradiographic studies on human brain slices which showed that this tracer binds to activated microglia rather than activated astrocytes or lymphocytes in plaques of demyelination (Banati et al. 2000). PET reveals that not only can raised (*R*)-[^{11}C]PK11195 uptake be seen in active plaques which show raised T2 signal and gadolinium enhancement on MRI but also in normal-appearing white and grey matter (Banati et al. 2000; Debruyne et al. 2003; Versijpt et al. 2005; Politis et al. 2012). This finding supports the hypothesis that in early MS microglial activation may initiate the inflammatory process prior to invasion of the damaged blood-brain barrier by lymphocytes. The activated microglial load at baseline may well be the critical factor when predicting outcome in MS patients (Confavreux et al. 2000). (*R*)-[^{11}C]PK11195 uptake has been reported to be higher in secondary progressive than relapsing-remitting MS. Additionally, a significant correlation was reported between levels of (*R*)-[^{11}C]PK11195 binding in cortical grey matter and locomotor disability in patients with secondary progressive MS (Politis et al. 2012).

TSPO expression in MS has also been examined with [^{11}C]PBR28, [^{18}F]DPA714 and GE180 PET. Oh and colleagues reported that global brain [^{11}C]PBR28 uptake was increased in their MS cohort and focal increases in binding, corresponding to areas of active inflammation and blood-brain barrier breakdown on gadolinium contrast-enhanced magnetic resonance imaging (MRI), were evident (Oh et al. 2010). Increases in [^{11}C]PBR28 binding preceded the appearance of contrast enhancement on magnetic resonance imaging in some lesions, suggesting that glial activation is an early phenomenon in MS lesion formation. In this series global levels of brain [^{11}C]PBR28 binding correlated with disease duration but not with locomotor disability. Herranz and colleagues have imaged nine relapsing-remitting multiple sclerosis (RRMS) and ten secondary progressive multiple sclerosis (SPMS) patients with [^{11}C]PBR28 PET and 7-Tesla (7 T) MRI (Herranz et al. 2019). Normal white matter signal was used as a reference tissue to compute SUVRs. Raised [^{11}C]PBR28 uptake was found in cortical lesions in both RRMS and SPMS but in the latter inflammation was also evident in normal-appearing cortex. It was noted that patients with higher levels of cortical inflammation had a worse clinical outcome. The same group also used [^{11}C]PBR28 PET to demonstrate significant cerebellar inflammation in RRMS and SPMS patients (Barletta et al. 2019). Levels of cerebellar [^{11}C]PBR28 uptake correlated with both physical disability and cognitive deficit.

The utility of the TSPO ligand, [^{18}F]DPA-714, has been evaluated in primary and secondary progressive multiple sclerosis (PMS) (Hagens et al. 2018). Eight PMS cases and seven healthy controls had [^{18}F]DPA-714 PET, and non-binders were excluded by prior genotyping for the presence of the rs6971 polymorphism. Regional time-activity curves (TACs) were kinetically modelled using a brain two-compartment model and a metabolite corrected plasma input function. Regional V_Ts were higher for high affinity (HABs) than mixed affinity binders (MABs) in both patient and normal groups, but [^{18}F]DPA-714 PET was not able to discriminate

patients from healthy controls. The patients, however, only showed focally increased tracer uptake where T2 white matter lesions were seen on MRI. A drawback with [^{18}F]DPA-714 as a TSPO marker was felt to be its large non-displaceable background signal, rather similar to the situation seen with (*R*)-[^{11}C]PK11195.

30.9 Traumatic Brain Injury

Recovery from concussive traumatic brain injury (TBI) is highly variable. (*R*)-[^{11}C]PK11195 PET can detect the presence of microglial activation in many of these cases years after the original injury. In a recent series, ten patients had (*R*)-[^{11}C]PK11195 PET at least 11 months after moderate to severe TBI, and binding was calculated in and around the site of focal brain damage, and in selected distant and subcortical brain regions (Ramlackhansingh et al. 2011). Microglial activation was significantly raised in the thalami, putamen, occipital cortices and the posterior limb of the internal capsules after TBI though there was no increase in binding at the original site of the focal brain injury. Levels of thalamic (*R*)-[^{11}C]PK11195 uptake correlated with impairment on executive tasks but not with either time since the injury or the amount of structural brain injury. The authors concluded that increased microglial activation can persist up to 17 years after TBI in distant brain areas from the original focal lesion, particularly in subcortical regions. They suggested that a chronic inflammatory response to TBI develops over time and that anti-microglial strategies may still be beneficial months to years after the original insult. In a follow-up article, these workers showed that levels of thalamic inflammation correlated with levels of thalamo-cortical fibre damage measured with diffusion tensor imaging rather than cortical or thalamic lesions (Scott et al. 2015). Whether the persistent inflammation was beneficial to recovery or toxic remained uncertain.

30.10 Stroke and Microglial Activation

Stroke is associated with microglial activation both around the infarct, which develops within hours of the event, but also later in disconnected brain regions including the thalamus and brainstem. In an early series, six patients were examined with (*R*)-[^{11}C]PK11195 PET between 3 and 150 days after their infarct, and increased microglial activation was present in all the patients examined (Gerhard et al. 2005). In the first 6 days following the stroke, the focus of inflammation was generally smaller and found adjacent to the MRI lesion with little spatial overlap. The size of the local area of microglial activation then increased over the next months overlapping with the MRI lesion as the blood-brain barrier became disrupted and invasion by macrophages binding (*R*)-[^{11}C]PK11195 alongside local microglial activation occurred. By 6 months after the initial stroke, local microglial activation was subsiding, whereas distant areas of (*R*)-[^{11}C]PK11195 uptake could be seen beyond the

primary infarct site involving disconnected areas of the ipsilateral hemisphere including the thalamus and brainstem. The lesioned cortical area with high initial (*R*)-[^{11}C]PK11195 binding became atrophic during that 6-month interval as local inflammation regressed.

Thiel and colleagues used (*R*)-[^{11}C]PK11195 PET to prospectively image activated microglia in vivo 2 weeks and 6 months after acute subcortical stroke in humans to investigate their temporal dynamics and relate local and remote inflammation to pyramidal tract (PT) damage detected using diffusion tensor imaging (DTI) (Thiel et al. 2010). As reported previously, microglial activation increased and then regressed around the local lesion. In contrast, brainstem inflammation was only seen in cases with pyramidal tract damage on DTI and occurred later. The brainstem (*R*)-[^{11}C]PK11195 signal correlated positively with clinical outcome.

Recently Morris and co-workers used diffusion and perfusion MRI to define the ischemic penumbra around acute stroke and examined neuronal integrity with the GABA marker [^{11}C]flumazenil PET and microglial activation with (*R*)-[^{11}C]PK11195 PET (Morris et al. 2018). They found evidence of viable neurons in the penumbra in the absence of microglial activation. These workers concluded that viable penumbra may not require the presence of activated microglia during the stroke recovery phase.

30.11 Psychosis

Lewy body dementia and Parkinson's disease are associated with secondary psychosis related to their cortical pathology and possibly the presence of the cortical and limbic inflammation that can be detected in these disorders. Schizophrenia is a primary psychosis but has also been reported to be associated with brain inflammation at post-mortem. In an early series, seven schizophrenic patients in the recovery phase from a psychotic episode were studied with (*R*)-[^{11}C]PK11195 PET (Doorduin et al. 2009). Conventional T1- and T2-weighted MRI showed no significant abnormalities. PET revealed a 51% increase in mean hippocampal and a 30% increase in global cortical (*R*)-[^{11}C]PK11195 binding in the schizophrenic subjects compared with age-matched cortical controls. Three of the subjects individually showed significantly raised levels of cortical inflammation. Low-level inflammation in the cortex of schizophrenic cases in remission has also been reported (van Berckel et al. 2008). Doorduin and co-workers suggested that active episodes of psychosis may be related to increases in background inflammatory activity.

In contrast, using the second-generation TSPO marker [^{11}C]PBR28 with PET, Collste and colleagues detected reduced levels of binding (V_T) in 16 untreated schizophrenics recovering from their first psychotic episode (Collste et al. 2017). Brain tracer uptake was kinetically modelled using a two-compartmental approach with an arterial plasma input function. These workers suggested that the function of immune cells may be depressed in schizophrenia.

30.12 Conclusions

Microglial activation is a non-specific reaction to all forms of brain injury and can be detected with PET in inflammatory, vascular, traumatic, degenerative and, possibly, psychotic brain disorders. The role of activated microglia after stroke and trauma appears to be primarily restorative, the cells adopting a phagic phenotype removing debris and remodelling connections to disconnected regions. However, the ischemic penumbra surrounding infarcted tissue may not require activated microglia for its revival. In neurodegenerative diseases, the role of activated microglia is less certain. Initially these cells could act to ingest misfolded proteins and release growth factors, but in later disease this action could fail and local release of toxic cytokines predominate leading to neuronal death and disease progression. In downstream disconnected areas, microglia could be beneficial leading to remodelling of connections as an adaptive response.

Currently PET imaging of activated microglia relies on the use of TSPO radioligands. While these provide a valuable in vivo tool for detecting disease activity and tracking the progression of neuroinflammation, binding of second-generation ligands is influenced by the TSPO polymorphisms expressed by subjects—10% of Caucasians are non-affinity binder, 30% mixed affinity binders and 60% high affinity binders. As a consequence, despite its higher non-specific signal and rapid washout, (*R*)-[^{11}C]PK11195 PET still provides a reasonable approach for measuring brain inflammation as it is little affected by the TSPO polymorphisms expressed. While TSPO imaging reflects disease activity, it does not have diagnostic potential as raised microglial activation is not specific to any one neurological disorder. However, the early detection of microglia with PET provides a potential biomarker for establishing the presence of disease activity in at risk subjects and testing the efficacy of neuroprotective strategies designed to suppress the inflammatory response to local injury or neurodegenerative processes. In the future, hopefully, there will be development of both better TSPO tracers uninfluenced by the genotype along with other markers of microglial activation, such as cannabinoid CB2 expression, allowing us to improve our understanding of the role of activated microglia in CNS disease.

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