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Imaging neuroinflammation in Alzheimer's disease and other dementias: Recent advances and future directions

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Abstract Alzheimer's disease (AD), dementia with Lewy bodies, frontotemporal dementia (FTD), and Huntington's disease (HD) are the main neurodegenerative causes of dementia. Causes and mechanisms of these diseases remain elusive. Neuroinflammation is increasingly emerging as an important pathological factor in their development. Positron emission tomography (PET) using [^{11}C]PK11195 represents a method of visualizing the microglial component of neuroinflammation via the translocator protein (TSPO) and we discuss the valuable insights this has yielded in neurodegenerative diseases. We discuss the limitations of this method and the development of second generation TSPO PET ligands which hope to overcome these limitations. We also discuss other methods of visualizing neuroinflammation and review the state of current dementia treatments targeted at neuroinflammation. It is our view that a multimodal investigation into neuroinflammation in AD, Parkinson's disease dementia, FTD and HD will yield valuable pathological insights which will usefully inform development of therapeutic targets and biomarkers.

Keywords: Alzheimer's disease; Dementia; Neurodegenerative disease; neuroinflammation; Microglial activation; PET; TSPO; MRI

1. Introduction

Neurodegenerative conditions account for significant morbidity and mortality and comprise a variety of pathologies associated with aberrant protein aggregation, including Alzheimer's disease (AD)—beta amyloid and tau; frontotemporal dementias (FTD)—tau, TDP-43, fused in sarcoma protein (FUS); Lewy body spectrum disorders which include Dementia with Lewy Bodies (DLB) and Parkinson's disease with (PDD) and without (PD) later dementia—alpha synuclein; and Huntington's disease (HD)—huntingtin. Chronic neuroinflammation and, in particular, microglial activation is associated with all these conditions [1–4]. There is an intense debate on whether neuroinflammation is a primary or secondary event in neurodegenerative diseases [5].

Microglia are of myeloid origin and comprise around 15% of the non-neuronal cells in the brain. Normally they are quiescent and their processes monitor the status of the brain milieu. Invading pathogens, trauma, infection, degenerative disease and stroke can all trigger activation of microglia with the production and release of reactive oxygen and nitrogen species, cytokines, and chemokines. This intrinsic "inflammation" in the central nervous system can have both beneficial and deleterious effects [6,7]. Microglia have different phenotypes which interchange dynamically and the cells act to strip and remodel synapses [8], remove cellular debris by phagocytosis [9] and provide central nervous system innate immunity by releasing cytokines [10]. A significant amount of current evidence points to a key role for microglia in neurodegeneration. In AD, activated microglia surround amyloid plaques and resting microglia are activated by amyloid oligomers, fibrils, and amyloid precursor protein (APP) [11,12]. Knockout mice lacking the APP gene show decreased microglial activation [13]. In PD, microglia are activated by alpha synuclein fibrils [14]. This initial activation is likely an attempt to clear the protein, however due to factors specific to the misfolded protein, the microglia are unable to accomplish this and become

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chronically activated [15]. Plaque associated microglia display dilated intracellular channels of smooth endoplasmic reticulum containing amyloid fibers [16,17], suggesting a role of microglia in clearing beta amyloid. Microglia may normally be responsible for amyloid phagocytosis in health [18]. In AD it has been argued that the microglia clustered around amyloid deposits have become dysfunctional and incapable of removing amyloid [19]. One can therefore see how a deleterious loop may be established, whereby accumulation of misfolded protein leads to microglial activation and secretion of neurotoxic factors which perpetuates neurodegeneration and further microglial activation [20]. Though the precise causal relationship remains to be fully delineated, the paradigm whereby protein misfolding is the primary trigger to microglial activation has been strengthened by a post-mortem study demonstrating reduced microglial activation in AD patients treated with an active vaccine to amyloid-β42 and subsequent decreased amyloid-plaque burden [21].

Another important issue to consider is heterogeneity of microglial subpopulations. Peripheral macrophages have been shown to have two distinct activated states. In the first state, described as classical activation (M1), macrophages respond to a micro-organism challenge with a robust proinflammatory cytokine response and enhanced microbial killing, which may also damage the host. The second state, alternative action (M2), is a more nuanced response to T-helper-2 cytokines and is associated with wound healing and tissue repair [22]. Microglia broadly follow this schema and the balance of neurotoxic M1 microglia and neuroprotective M2 microglia is increasingly thought to be central to AD pathogenesis, with evidence of M1 microglia localizing around amyloid plaques [23]. More recent evidence implicates the TREM2 gene, a gene involved in balancing M1 and M2 activation, with risk of AD [24]. Clearly further exploration of microglial behavior in vivo, assessing the behavior and heterogeneity of microglia, the temporal relationship between microglial activation and neurodegeneration and how exactly microglial activation correlates to clinical phenotype are critical issues to explore.

2. Imaging microglia using [^{11}C]PK11195

Given the potentially important role of activated microglia in neurodegeneration, imaging their function in vivo provides a tool which allows us to quantify and localize disease activity and potentially to evaluate novel therapeutic interventions. Positron emission tomography (PET) is the most widely used in vivo method for detecting microglial activation. When microglia are activated, there is an upregulation of mitochondrial translocator protein (TSPO) expression. TSPO is found throughout the body but at only low levels in healthy central nervous system (CNS). It is thought to have a role in cholesterol and amino acid transport, in CNS steroid production and mitochondrial membrane potential regulation, but the exact function of TSPO in the CNS is yet to be elucidated [25].

Experimental data in animal models of brain disorders show TSPO expression is associated primarily with activated microglia, but can also be seen in reactive astrocytes depending on the nature of the neuronal insult [26]. In rat models of focal ischemia, TSPO expression has been found to peak in microglia and then be followed by a rise in astrocyte activation, suggesting a temporal relationship between TSPO expression in microglia and reactive astrocytes [27]. Ex vivo human post-mortem study of patients suffering from stroke, multiple sclerosis (MS), AD, FTD and progressive supranuclear palsy (PSP) showed that there was a degree of observed TSPO-radioligand binding, with both first and second generation radioligands, to reactive astrocytes. There was no correlation, however, on quantification of this association whereas significant correlation was noted between TSPO-radioligand binding and activated microglia [28]. A recent contradictory study in rats, where specific astrocyte activation was achieved by lentiviral gene transfer in the absence of neurodegeneration or a generalized noxious stimulus, demonstrated specific and significant binding of first and second generation TSPO-radioligands to reactive astrocytes [29]. Other papers also support a role for reactive astrocytes in the TSPO-signal [30,31]. There is ongoing debate about the extent to which TSPO can distinguish between activated microglia and reactive astrocytes but it is clear there is a degree of overlap and therefore caution should be applied when interpreting TSPO-binding in humans and animals. This signal could be the result of reactive astrocytes and activated microglia, which play markedly different roles in neuroinflammation.

The PET marker most commonly used to target TSPO is [^{11}C]*(R)*PK11195 [1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinoline carboxamide], which was first reported to bind to the hearts of dogs and humans in 1986 [32]. [^{11}C]PK11195 has a half-life of 20.4 minutes due to its carbon-11 label and its extensive use in imaging human neurological diseases is explored below.

2.1. Dementia

AD represents 60% of dementia cases and its incidence is predicted to rise. Immunological studies have shown that activated microglia colocalize with amyloid plaques and hyperphosphorylated tau, both in post-mortem human AD studies [1,33] and in animals [34]. [^{11}C]PK11195 PET detects in vivo microglial activation in the brain of mouse models of AD [33] and in patients with AD [35,36]. In humans with AD, [^{11}C]PK11195 PET reveals microglial activation throughout the association cortex (Fig. 1) in a similar distribution to that of amyloid plaque deposition [36]. Increased cortical [^{11}C]PK11195 binding can be detected in around 60% of mild to moderate AD patients and around 40% of subjects with amnestic mild cognitive impairment (aMCI) [37]. Levels of cortical [^{11}C]PK11195