Neuroinflammation in Lewy Body Dementia

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ABSTRACT

Neuroinflammation is increasingly recognized as a key factor in the pathogenesis of neurodegenerative conditions. However, it remains unclear whether it has a protective or damaging role. Studies of Alzheimer's disease and Parkinson's disease have provided much of the evidence for inflammatory pathology in neurodegeneration. Here we review the evidence for inflammation in dementia with Lewy bodies and Parkinson's disease dementia.

Neuroinflammation has been confirmed *in vivo* using PET imaging, with microglial activation seen in Parkinson's disease dementia and recently in dementia with Lewy bodies. In Parkinson's disease and Parkinson's disease dementia, microglial activation suggests a chronic inflammatory process, although there is also evidence of its association with cognitive ability and neuronal function.

Alpha-synuclein in various conformations has also been linked to activation of microglia, with a broad range of components of the innate and adaptive immune systems associated with this interaction.

Evidence of neuroinflammation in Lewy body dementia is further supported by pathological and biomarker studies. Genetic and epidemiological studies support a role for inflammation in Parkinson's disease, but have yet to provide the same for Lewy body dementia.

This review highlights the need to identify whether the nature and extent of microglial activation in Lewy body dementia can be linked to structural change, progression of domain specific cognitive symptoms and peripheral inflammation as a marker of central microglial pathology. Answers to these questions will enable the evaluation of immunotherapies as potential therapeutic options for prevention or treatment of dementia with Lewy bodies and Parkinson's disease dementia.

INTRODUCTION

Lewy body dementias (LBDs) include the closely related conditions of dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). The clinical syndrome of DLB forms at least 4.2% of all dementia patients and is second only to Alzheimer's disease (AD) as a cause of degenerative dementia in older people[1]. Dementia also develops in over 80% of those with Parkinson's disease (PD)[2], a disorder where Lewy bodies play a prominent role, with PDD forming 3.6% of all dementia cases[3]. Autopsy studies of dementia cases have estimated the combined prevalence rate of LBDs to be even higher, at around 20%[4,5].

The etiology of LBDs is unclear, but a role for chronic neuroinflammation has been proposed, analogous to the emerging evidence for inflammation in the etiology of AD. The evidence to date for AD includes neuropathological studies with evidence of brain inflammation, Positron Emission Tomography (PET) imaging displaying microglial activation *in vivo*, genetic studies implicating polymorphisms in genes involved in the inflammatory response as risk factors, epidemiological studies indicating a protective effect of non-steroidal anti-inflammatory drugs (NSAIDs) and mouse models of AD in which NSAIDs reduced neuroinflammation and protein deposition[6–9].

In light of the gathering evidence for neuroinflammation in AD, we asked whether neuroinflammation is also involved in the etiology of LBDs. We review the literature for evidence of neuroinflammation in Parkinson's disease dementia and dementia with Lewy bodies, across multiple methodologies.

LITERATURE SEARCH STRATEGY

References were identified using searches of PubMed with key words. The following combinations were used in a search of titles and abstracts in June 2015 (the number of articles yielded is noted in brackets):

1. 'Lewy' and ('inflammation' OR 'neuroinflammation') (98 articles)
2. ('Parkinson's disease dementia' OR 'PDD' OR 'DLB' OR ('Dementia AND Parkinson*')) AND ('neuroinflammation' OR 'inflammation') (283 articles)
3. 'synuclein' AND 'microglia' (185 articles)

4. 'synuclein' AND ('inflammation' OR 'neuroinflammation') (210 articles)

The abstracts of these articles were screened and full texts of those potentially relevant articles to the review were obtained. In order to ensure that all relevant references were sourced, references were in turn reviewed for other relevant articles, supplemented by articles known to the authors.

MICROGLIAL FUNCTION

Neuroinflammation describes the response to injury within the central nervous system (CNS) leading to the activation of microglia and astrocytes, release of cytokines and chemokines, invasion of circulating immune cells and complement activation. Microglia are the resident macrophages of the CNS, originating from progenitors in the embryonic yolk sac[10]. They provide the innate immune response to invading pathogens and also initiate the adaptive response through antigen presentation[11].

Microglia are resting or "inactivated" under physiological conditions with characteristic ramified morphology and distributed within brain regions, such that rami are close but not touching, implying each cell has its own distinctive territory. But even in this inactive state, they have been shown using two-photon microscopy to be continuously monitoring the extracellular spaces with their processes and protrusions in adult mice[12]. Activation leads to morphological change to a more rounded amoeboid shape, with targeted movement of processes towards sites of injury or stimuli to initiate phagocytosis[12] and leads to production of chemokines, that amplify the response by recruiting other microglia, plus cytokines, free radicals and proteases which destroy infectious organisms and infected neurons.

Microglia appear to have an important part both in MPTP disease progression and idiopathic PD[13], suggesting a central role for these glia in nigro-striatal degeneration, irrespective of etiology. Microglia may be especially susceptible to mechanisms of aging. Their maintenance is proposed to be dependent on self-renewal rather than replenishment by peripheral blood precursors[14,15], which could be highly significant in age dependent neurodegenerative conditions such as LBD. Systemic infections or disease, which rise in number with age, could also lead to priming of microglia, such that their response is exaggerated and damaging to nearby neurons leading to cognitive decline[16]. It has

also been proposed that an initial stimulus that triggers microglial activation could persist in neurodegenerative disorders leading to repeated cyclical chronic neuroinflammation causing neuronal dysfunction and cell death[17,18]. The specificity of these changes to Lewy body dementias is unclear.

IMAGING EVIDENCE OF NEUROINFLAMMATION AND NEURONAL DYSFUNCTION

Imaging studies have shown an association between neuroinflammation *in vivo* and cognitive dysfunction. Microglial activation as a marker of neuroinflammation has been identified in PD and PDD[19] (see Table 1) using [^{11}C]-*R*PK11195 (RPK11195), a PET ligand that binds to a translocator protein found on microglia in their activated state. Extensive microglial activation has similarly been identified in another α-synucleinopathy: multiple systems atrophy[20], as well as other degenerative conditions, including AD[21,22].

An association between microglial activation in the midbrain and dopaminergic loss in the dorsal putamen has been found in the early stages of PD (less than 2.5 years), both contralateral to the clinically affected side, with levels of activation correlating with severity of motor impairment measured by the Unified Parkinson's Disease Rating Scale (UPDRS)[23]. In the later stages of disease (disease duration range 0.5 - 21 years), there is extensive microglial activation, with the basal ganglia, cortex and pons all showing significantly increased levels. The substantia nigra was however spared. Follow-up scans in eight of these subjects (after 18-28 months) showed no significant change in microglial activation from baseline despite a clear deterioration in disability as measured using the UPDRS. Cognition was however not assessed longitudinally[24]. The authors also noted a clear overlap in the areas of microglial activation and the regions proposed by Braak et al.[25] in their study of PD pathology. In PDD subjects, there is increased cortical microglial activation compared to control subjects, however levels of activation were also increased in comparison to PD cases – in the left parietal lobe[26].

In DLB, increased microglial activation in the substantia nigra and putamen, plus several cortical regions was found in a pilot imaging study of six cases of less than one year's duration[27]. That microglial activation occurs in more widespread regions in early DLB, where there is greater cognitive

dysfunction compared to early PD, strengthens the link between microglial activation and cognitive decline.

A relationship between microglial activation and cognitive function was indeed found in PDD, where cortical activation levels inversely correlated with MMSE in temporo-parietal, occipital, and frontal cortical regions[19,26]. Fan et al.[19] demonstrated a significant negative correlation between whole brain levels of microglial activation and glucose metabolism. Within the temporo-parietal cortex there was voxel by voxel significant inverse correlation between levels of microglial activation and glucose metabolism in the immediate vicinity suggesting local damage, but the areas of correlation were small. The authors however suggest distant microglial activation could be linked to cell dysfunction in the medial temporal lobe through pre-existing neuronal pathways. Neither study of PDD assessed whether areas of increased activation (such as in the hippocampus) were linked to dysfunction in specific cognitive domains (such as memory), which may have provided a stronger link between inflammation and cognitive dysfunction.

Small clusters of positive correlations were also found between RPK11195 binding and amyloid load (as determined by [^{11}C] Pittsburgh compound B (PIB), a marker of fibrillary amyloid load) in PDD subjects, but only in the parietal lobe and anterior cingulate, as opposed to AD subjects in whom there was a stronger correlation between amyloid load and microglial activation. There was however little amyloid deposition found in PDD cases overall[19]. Proteins other than amyloid, such as α-synuclein or tau, could be triggering microglial activation in PDD, however currently there are no α-synuclein PET ligands available to demonstrate this and tau ligands have only very recently become available.

Overall small scale studies with *in vivo* imaging have suggested that in PD, PDD and in a small preliminary report of DLB, there is early microglial activation. But, this does not appear to increase over time. Significantly microglial activation also correlates inversely with cognitive function and to an extent protein deposition, suggesting microglia may have a crucial role in the pathogenesis of these conditions.

ALPHA SYNUCLEIN AND NEUROINFLAMMATION

The evidence for extensive microglial activation in LBDs, in an immunologically privileged site such as the brain, is highly significant. Immune responses are tightly controlled and yet there is widespread

glial cell activation, present chronically during the disease. The initiation of the innate response occurs through pattern-recognition receptors (PRRs) expressed on CNS cells (for example the toll-like receptor (TLR)) through activation by pathogen associated molecular patterns or danger associated molecular patterns. However α-synuclein is the main component of Lewy bodies[28] which characterize LBDs, and the driving force behind the disease process, hence the interaction between this protein and microglia appears to be critical. Alpha-synuclein inclusions in neurons and glia are associated with DLB and PDD, as well as PD and multiple system atrophy. In DLB and PDD, the inclusions are neuronal and in the form of Lewy bodies[28]. Lewy neurites are also common in these disorders, consisting of coarse dystrophic neurites immunoreactive for α-synuclein within affected neurons. With 140 amino acids, α-synuclein's possible intracellular forms include monomeric[29,30] or relatively stable folded tetramer[31,32].

Alpha-synuclein, has been shown repeatedly to activate microglia and induce dopamine cell loss[33–35], including monomeric wild-type and mutant forms as well as extracellular oligomeric conformations. Indeed, neuron-glia cultures depleted of microglia have been shown to be resistant to α-synuclein induced dopaminergic neurotoxicity[33]. More recently the focus has moved on to possible mechanisms. Models of PD have been used to study this relationship rather than models of DLB, with overexpression of α-synuclein in the substantia nigra using viral vectors, the most common. A survey of the literature shows several possible mechanisms for this interaction (see Table 2).

A number of immunomodulatory proteins and compounds are implicated in α-synuclein microglial recognition, chemotaxis, activation and response. TLRs 1[36], 2[36,37] and 4[38] are PRRs key to the innate response machinery and have been reported as having a role in recognition of α-synuclein by microglia. Microglia exposed to higher-ordered oligomers (but not monomers) of α-synuclein changed to an amoeboid, phagocytic morphology with increased secretion of Tumor Necrosis Factor α (TNF-α) that was reduced by inhibition of the TLR 1/2 complex [36]. A separate study found only β-sheet rich oligomeric conformations of α-synuclein could activate microglia via TLR 2, but both aggregated and non-aggregated forms could activate microglia through TLR 4. Furthermore pro-inflammatory cytokine/chemokine release was completely eliminated in TLR 2 knockout mouse microglia exposed to α-synuclein, but remained unaffected in TLR 4 knockout mouse microglia[39], suggesting TLR 2 recognition of oligomeric α-synuclein leads to inflammation.

Another molecule which could feature in the initiation of microglia activation is Fractalkine, a membrane bound chemokine which acts on the CX3CR1 receptor on microglia to suppress production of inflammatory molecules. A soluble secreted form of Fractalkine had a protective function in an animal model of α-synuclein overexpression, suggesting loss of this membrane bound chemokine could lead to neuronal loss through microglia mediated cell damage[40].

Alpha-synuclein, in extracellular aggregated form, has been shown to be a chemoattractant through CD11b receptors on microglia[41]. Also, the β1-integrin subunit, which forms transmembrane adhesion molecules has been reported as being required for the morphological changes and migration of microglia seen in the presence of extracellular α-synuclein[42].

Once microglia are activated, Interleukin-1 (IL-1) appears to be a key cytokine in promoting an inflammatory response. IL-1α and β knockout mice did not show loss of dopamine neurons or behavioral deficits seen in wild-type mice in a mouse model of PD, utilizing lipopolysaccharide(LPS) injections into the substantia nigra. LPS injections have been shown to produce microglial activation, cytokine release and subsequent dopaminergic cell loss in the substantia nigra[43]. TNF-α knockout mice however showed similar results to wild-type mice[44], indeed TNF-α may have role in promoting α-synuclein accumulation[45]. Galectin-3 has also been shown to be important for the inflammatory effect of α-synuclein. Its inhibition significantly reduced cytokine release by microglia in response to aggregated α-synuclein[46].

Leucine-rich repeat kinase 2 (LRRK2) is a protein expressed on microglia when they are in their inflammatory state and has been shown to have a significant role in α-synuclein mediated microglial activation and subsequent cell loss, with LRRK2 knockout mice being protected from α-synuclein overexpression[47]. Another protein involved is NRF2, which is a transcription factor for a number of cell protection proteins and appears to have a protective role in the interaction[48].

Several studies suggest the adaptive immune response is engaged by microglia following their activation. Knockout mice without Fc gamma receptors (FcγR), which are found on microglia and involved in facilitating phagocytosis through binding of IgG, showed reduced pro-inflammatory signaling in the presence of aggregated α-synuclein. Suggesting the latter could be triggering inflammation and antibody mediated cell damage through FcγR[49]. In addition, a knockout of all four

murine MHC II complex genes prevented α-synuclein induced dopaminergic cell loss in a mouse model, strongly suggesting that CD4 T lymphocytes are critical to α-synuclein cell damage. Microglia, as the only resident cells expressing MHC class II in the CNS, would be candidates for their recruitment, although infiltrating antigen presenting cells such as macrophages may also be involved[50]. Furthermore, mice with microglia deficient in Prostaglandin E2, which is thought to have a role in lymphocyte proliferation, have increased resistance to MPTP mediated pathology[51].

PATHOLOGICAL EVIDENCE OF INFLAMMATION

Pathological studies further support a role for inflammation. Large numbers of HLA-DR-positive microglia, indicating reactive states, have been reported in the substantia nigra of PD and PDD cases together with Lewy bodies in association with a reduction in dopaminergic cells. In the PDD cases HLA-DR positive microglia were also found in the hippocampus, though this was associated with neuritic plaques and tangles suggestive of AD pathology[52]. Involvement of the transenterohinal, cingulate and temporal cortices in PD has also been identified. Activated microglia in these regions also expressed MHC Class II molecules, HLA-DP, DQ and DR[53]. The presence of CD4 (as well as CD8) T lymphocytes within the substantia nigra of PD cases at post-mortem has subsequently been confirmed[54]. In addition, concentrations of interleukin-1β, interleukin-6 and transforming growth factor-α are higher in the striatal regions of post-mortem PD brains compared to controls[55]. Complement proteins are also found with Lewy bodies within this region in PD[56].

In DLB, both complement proteins and microglial interaction are associated with Lewy body containing degenerated neurons on autopsy, suggesting microglial involvement[57]. An increase in activated microglia has also been reported in DLB cases, positively correlating with the number of Lewy bodies also seen regionally[58]. However this was not as high as in those cases with concomitant senile plaques and a second study has shown a lack of significant microglial activation in the absence of tau neuritic plaques in DLB[59]. The link between microglial activation and pathological protein deposition in both PDD and DLB is therefore not fully established.

EVIDENCE FROM GENETIC STUDIES

Genetic studies have identified polymorphisms in genes coding IL-1β, TNF-α and Triggering Receptor Expressed on Myeloid cells 2 (TREM2) as risk factors for PD. Up to a doubling of risk has been reported amongst carriers of a genotype of IL-1β that is associated with increased gene expression[60,61]. Those carrying the homozygous variant genotype TNF-α-308, a variant which is thought to be a stronger transcriptional activator, experience doubled risk[60]. Overall the results from these two small studies are consistent with a gene dosing effect for these two powerful cytokines. A rare variant of the microglial receptor TREM2, that leads to loss of function, was found to be another risk factor for PD in a study of 1493 cases compared to 1957 controls[62].

Genome wide association studies (GWAS) provide further evidence for inflammatory pathology in PD. Polymorphisms in HLA regions that code segments of the MHC class II molecule present increased risk. A strong association was found within noncoding intron 1 of HLA-DRA (in a study of 2000 cases and 1986 controls) by Hamza and colleagues[63], with subsequent large-scale meta-analyses of single nucleotide polymorphisms(SNP) confirming associations amid the HLA-DR locus, with both HLA-DRB5[64] and HLA-DQB1[65] identified. Wissemann and colleagues[66] found loci that predisposed to, as well as protected from, PD within the same 2000 PD and 1986 control GWAS dataset initially analyzed by Hamza et al. [63], and replicated these in a further 843 cases and 856 controls. The strongest association was again intron 1 of the HLA-DRA region, which regulates gene expression and linked to increased risk. This suggests HLA expression levels may play a key role in determining risk for PD. Indeed subjects homozygous for the G allele in this SNP, were found to have significantly increased MHC class II expression, compared to subjects who did not have a single G allele. In addition, exposure to a common insecticide, pyrethroid, when combined with possession of the GG allele, significantly increased PD risk[67], suggesting a combination of environmental triggers and inflammatory processes may play a part in PD pathology.

Notwithstanding the accumulated genetic evidence in the context of PD, the equivalent associations in DLB have not been established, although methods of investigation may need to be broadened, as studies have been limited so far[68]. Polymorphisms in genes associated with inflammation are also yet to be identified as risk factors for PDD specifically.

EVIDENCE FROM BLOOD BIOMARKERS

Elevated peripheral inflammatory markers both before and after the onset of PD, suggest inflammation is concurrent with the disease. Increased plasma interleukin-6 (IL-6), measured on average 4.3 years before diagnosis, is associated with increased risk of developing PD, with higher levels associated with higher risk[69]. After disease onset, levels of IL-6[70,71], IL-1β[71] and TNF-α[70] are elevated compared to controls in PD, as is RANTES (regulated on activation, normal T cell expressed and secreted), a chemokine which attracts T-cells. RANTES levels also correlated with motor symptom severity[72]. A change in peripheral blood lymphocyte subsets further suggests a role for the adaptive immune system. A decrease in the overall level of T-helper CD4 cells but a rise in the subset of activated T-helper cells is reported in PD cases compared to controls[73].

In PDD, high sensitivity CRP is increased compared to controls, but a significant elevation was not found in PDD compared to PD[74]. Peripheral markers suggestive of inflammation are yet to be found in DLB. Therefore the blood biomarkers evidence for inflammation in LBDs is inconclusive.

EVIDENCE FROM CEREBROSPINAL FLUID BIOMARKERS

Attempts to identify a reliable cerebrospinal fluid (CSF) biomarker for PD or PDD have so far been inconsistent. The main candidates include total α-synuclein, Aβ42, and β-Glucocerebrosidase[75]. Inflammatory cytokines TNF-α[76], IL-6[77,78] and IL-1β[71,77] have also been investigated with raised levels seen in the CSF of PD cases compared to controls. IL-1β levels in the CSF were associated with raised α-synuclein oligomers also in the CSF, suggesting a direct link with protein deposition[71].

In a study of 22 cases of PD, IL-6 was found to associate inversely with disease severity as assessed by the UPDRS[78]. In a larger study of 62 cases, IL-6 was elevated in cases of PD with cognitive impairment compared to those without, the levels being negatively correlated to cognitive function. TNF-α and Interferon γ levels were however reduced in those with cognitive impairment in PD compared to control subjects[79]. A rise in the fractalkine:Aβ42 ratio in CSF is also associated with motor severity of PD (again measured by UPDRS) but not with disease duration[80]. An increase in this ratio could suggest increased inflammatory signaling and microglial activation. An increase in

Leucine rich α2-glycoprotein (LRG), thought to be a marker of inflammation, is reported in the CSF and post-mortem tissue of PDD and DLB cases, compared to controls[81].

The focus in DLB has been on the variations of Aβ peptides and tau as well as α-synuclein; a combination of biomarkers may be the best route to increase specificity and sensitivity[82,83]. The inflammatory marker Procalcitonin has been found to be significantly raised in dementia subjects within the CSF, compared to controls, with the highest median level found in DLB cases[84].

EVIDENCE FROM EPIDEMIOLOGICAL STUDIES

There is limited support for neuroinflammation in PD from epidemiology studies. A meta-analysis of the association of NSAIDs and the risk of developing PD, showed a 15% reduction in incidence among users of non-aspirin NSAIDS, with analysis of ibuprofen alone showing a stronger protective effect. This effect was more pronounced among regular users[85]. Whether PDD incidence was lower in those who developed PD despite taking NSAIDS was not considered.

A further meta-analysis showed conflicting results with no overall protective effect, however there were methodological differences including the inclusion of aspirin and studies where NSAID exposure was entirely within a 1 year of the diagnosis of PD. Nevertheless a slight protective effect for ibuprofen in lowering the risk of PD was still confirmed[86]. The evidence from these studies is however difficult to interpret because of variations in the drugs investigated, the duration of the drug treatment and the timing of administration in relation to disease onset.

Whether NSAIDs could reduce the risk of developing DLB or protect those with PD from developing dementia, has not yet been established.

A ROLE FOR THE ADAPTIVE IMMUNE SYSTEM

Despite the evidence of microglial activation and an interaction between α-synuclein and microglia, the precise mechanism and whether it is always detrimental to neurons remains unclear. A paucity of the relationship between Lewy bodies and antigen presenting activated microglia in post mortem

studies was reported by Imamura et al.[53], indeed there was only a 20% association. This would suggest that Lewy bodies alone are not sufficient in themselves to trigger antigen presentation by microglia. In addition, increasing neuronal loss in the substantia nigra with lengthening disease duration was not associated with an increase in microglial activation, implying a steady rather than escalating inflammatory response[87].

Orr and colleagues[87] also demonstrated that substantia nigra neurons were immunopositive for IgG in PD, whereas control cases' substantia nigra neurons as well as the visual cortex of PD cases showed negative immunoreactivity. Neuronal IgG labelling related to the degree of neuronal loss and microglial activation, with the authors suggesting humoral immune system involvement in the selective destruction of substantia nigra neurons.

Given that the MHC class II complex has also been shown to be key in dopamine neuronal cell loss in mouse models[50], it may be that an adaptive immune response is the final path to neuronal loss, following a switch in microglia function from protective to deleterious. Consistent with this theory is the genetic risk associated with HLA class II gene variation previously described, as well as the alteration in peripheral lymphocyte subsets found in PD cases[73], and the evidence that B and T lymphocyte infiltration of the substantia nigra is found at post mortem[54] and in a mouse model of α-synuclein overexpression[35].

It is possible initial protein clearance by microglia could be switched to a more harmful toxic function involving recruitment of the adaptive response ultimately leading to neuronal degeneration. For example due to peripheral inflammation or increased vulnerability of microglia through ageing. The timing of treatment initiation would be key in such circumstances.

CONCLUSION AND FUTURE DIRECTIONS

Evidence for the role of neuroinflammation in LBDs continues to accumulate, building on the evidence of neuroinflammation in AD and PD. Imaging studies lead the way in supporting neuroinflammation as a key part of the pathogen process in LBDs, supported by pathological and biomarker evidence,

though mostly in PDD. Future studies are required to further establish the presence of inflammation in DLB including imaging, genetic and biomarker studies.

Involvement of microglia in LBDs is signified by the presence of activation years before neuronal death as revealed by *in vivo* imaging, as well as after cell loss in pathology specimens. Microglial involvement is also supported by evidence of the activation of microglia by α-synuclein. Levels of activation however appear to remain relatively stable, which could indicate initiation and propagation of the disease process by microglia or alternatively a protective function that is eventually overcome. In order to understand how inflammation affects disease progression in Lewy body dementia, studies need to try and link the nature and extent of microglial activation with important indicators of disease severity such as structural brain changes, protein deposition and the onset and progression of key cognitive and non-cognitive symptoms through longitudinal studies in established disease and in those at risk.

Table 1: Evidence of *in vivo* microglial activation in PD, PDD and DLB from RPK11195 PET imaging studies

STUDY	PARTICIPANT NUMBERS (controls)	PARTICIPANT AGE (years)	PARTICIPANT MMSE	DISEASE DURATION (years)	REGIONS WITH INCREASED MICROGLIAL ACTIVATION COMPARED TO CONTROLS
Ouchi et al. 2005 [23]	10 PD (10 controls)	Range: 43-72; Mean: 59.6	Range: 26-30; Mean: 28.3	Range: 0.4-2.5; Mean: 1.4	Midbrain contralateral to the clinically affected side
Iannaccone et al. 2013 [27]	6 PD (11 controls)	Range: 60-74 ; Mean: 70.2	Range: 27-30; Mean: 29	Range: 0.6-1; Mean: 0.8	Putamen, substantia nigra
Gerhard at al. 2006 [24]	18 PD (11 controls)	Range: 50-69; Mean: 59.2	Not specifically stated, screening tests normal in PD group	Range: 0.5-21; Mean: 8.6	Striatum, pallidum, thalamus, cortex (precentral gyrus, frontal lobe, anterior cingulate gyrus, posterior cingulate gyrus) and pons
Edison et al. 2013 [26]	8 PD (10 controls)	Range: 58-75; Mean: 68.2	Range: 27-30; Mean: 28.8	Mean: 9.2	Cortex (temporal, parietal, and occipital regions)
Fan et al. 2014 [19]	11 PDD (8 controls)	Range: 55-75; Mean: 68.4	Mean: 22.1	Not stated	Anterior cingulate gyrus, posterior cingulate gyrus, frontal lobe, temporal lobe, parietal lobe, occipital lobe, medial temporal lobe, amygdala and hippocampus
Edison et al. 2013 [26]	11 PDD (10 controls)	Range: 56-80; Mean: 69.3	Range: 16-26; Mean: 21.8	PD duration mean: 10.6; Dementia duration mean: 3.5	Striatum, cortex (frontal, temporal, parietal, anterior and posterior cingulate gyrus, and occipital cortical regions)
Iannaccone et al. 2013 [27]	6 DLB (11 controls)	Range: 62-82 ; Mean: 72	Range: 19-30; Mean: 24	Range: 0.7-1; Mean: 0.8	Caudate, putamen, thalamus, substantia nigra, cortex (frontal lateral, parietal lateral, temporal lateral, temporal pole, precuneus, occipital medial, occipital lateral, anterior cingulate, posterior cingulate) and cerebellum

Table 2: Potential mechanisms of interaction between α-synuclein and microglia

INTERACTION/ RECEPTOR	PROPOSED MECHANISM OF MICROGLIAL INTERACTION WITH α-SYNUCLEIN	PD MODEL	REFERENCES
TLR 1&2 complex	**Oligomeric α-synuclein induces a pro-inflammatory microglial phenotype through TLR 1/2 complex:** microglia exposed to oligomers of α-synuclein changed to an amoeboid, phagocytic shape, with increased secretion of TNF-α and interleukin-1b. TNF-α secretion was reduced by the addition of a TLR-1/2 complex inhibitor or by a MyD88 inhibitor.	Primary microglia cultures derived from mouse cortices were exposed to high-order oligomeric forms of purified human wild-type α-synuclein	[36]
Fractalkine receptor (FKN), an immune regulatory protein	**Secreted form of FKN is neuro-protective**: Soluble secreted form of FKN prevents reduction in tyrosine hydroxylase cell staining compared to controls and membrane bound FKN models when exposed to overexpression of α-synuclein, despite increased MHCII expression on microglia	Overexpression of human α-synuclein via viral vector combined with a variety of viral constructs of FKN	[40]
CD11b receptor	**Alpha-synuclein binds to CD11b on microglia to direct microglial migration:** neuronal α-synuclein overexpression led to microglial migration toward neurons, which was reduced by antibodies to the CD11b receptor and diminished in CD11b knockout mice	Overexpression of human α-synuclein via viral vector in rat primary neuron-enriched cultures	[41]
Galectin-3 (carbohydrate-binding protein and inflammatory mediator)	**Galectin 3 mediates microglial cytokine release**: Release of Interleukin-2 and Interleukin-12 after exposure to monomeric and aggregated forms of recombinant α-synuclein reduced by genetic down regulation or pharmacological inhibition of galectin-3	Microglia from wild-type and galectin-3 knockout mice	[46]
Leucine-rich repeat kinase 2 (LRRK2)	**LRRK2 required for microglial activation and dopaminergic degeneration**: Rats lacking LRRK2 demonstrated a significant reduction in microglial activation compared to wild type mice rats, when exposed to lipopolysaccharide (LPS) and were protected from dopaminergic neurodegeneration from α-synuclein overexpression.	Rats exposed to intracranial LPS injection or overexpression of human α-synuclein via viral vector	[47]
β1-integrin	**Migration of microglia to disease affected regions is via β1-integrin**: β1-integrin inhibition reduced microglial morphological changes and motility (as shown by reduced wound healing)	Rat primary microglia exposed to α-synuclein conditioned medium (αSCM)	[42]

Interleukin-1 (IL-1)	**IL-1 is required for microglial activation**: behavioral deficiencies that occurred in wild-type mice, following LPS administration did not occur in IL-1 knockout mice. Tyrosine Hydroxylase gene expression was similarly preserved in in IL-1 knockout but not wild-type mice.	Mouse model using intracranial LPS injection into wild-type and IL-1 (α and β) knockout mice	[44]
MHCII Complex	**MHCII complex mediates microglial activation and dopaminergic cell loss**: overexpression of synuclein leads to induction of MHCII expression on microglia and genetic knockout of MHCII prevents microglial activation, IgG deposition and dopaminergic cell loss *in vivo*	Mouse model using overexpression of human α-synuclein via viral vector in wild-type and MHCII knockout mice	[50]
TLR 4	**TLR 4 mediates microglial phagocytic activity and cytokine release in the presence of α-synuclein:** Microglial phagocytic activity was significantly reduced in TLR4 knockout microglia mice after treatment with different forms of α-synuclein; knockout mice also showed significantly reduced TNF- α production following treatment with α-synuclein.	Mouse primary microglia from wild type and TLR4 knockout mice challenged with cloned human α-synuclein from spinal cord cDNA	[38]
TLR 2	**TLR 2 mediates microglial activation by oligomeric α-synuclein**: TLR2 knockout mice exhibited significantly lowered microglial activation compared with wild type mice when exposed to α-synuclein overexpression; cytokine/chemokine gene induction following exposure to αSCM, was prevented by antagonizing TLR2 and by depletion of the TLR2 gene; and TLR2 was only activated by oligomeric alpha synuclein not the dimer or monomer forms.	Mouse model using overexpression of human α-synuclein via viral vector in wild-type and TLR 2 knockout mice; oligomeric human α-synuclein proteins released from dSY5Y cells	[37]
Fc gamma receptors (FcγR)	**FcγR mediates α-synuclein intracellular localization to autophagosomes and NF-κB pro-inflammatory signaling**: microglia internalized α-synuclein in a dense aggregated form in wild-type mice but a diffuse manner in FcγR knockout mice; FcγR knockout mice treated with α-synuclein also failed to trigger the enhancement of nuclear NF-κB p65 seen when wild-type mice are exposed to α-synuclein.	Primary microglial cultures from wild-type and FcγR knockout mice, treated with human α-synuclein	[49]
NRF2 (NF-E2-related factor	**NRF2 protects against α-synuclein mediated microglial**	Mouse model using overexpression of human α-	[48]

2), a transcription factor	**activation and dopaminergic cell loss:** NRF2 knockout mice showed increased microglial activation and greater nigral dopaminergic neuronal loss than wild-type mice when exposed to α-synuclein overexpression; NRF2 knockout neurons were characterized by thick dendrites loaded with α-synuclein, similar in appearance to Lewy neurites and this was associated with reduced levels of the beta subunit (PSMB7) of the catalytic core 20S proteasome compared to wild-type mice	synuclein via viral vector in wild-type and NRF2 knockout mice	
Prostaglandin E2 receptor subtype 2 (PGE2)	**PGE2 is key to regulation of aggregated α-synuclein levels:** microglia isolated from PGE2 knockout mice exhibited enhanced clearance of aggregated α-synuclein and showed increased resistance to MPTP with less aggregated α-synuclein in the substantia nigra and striatum.	Aggregated α-synuclein from human DLB cases incubated with wild-type and PGE2 knockout mice microglia	[51]

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