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Contributions of central and systemic inflammation to the pathophysiology of Parkinson's disease

Louise M. Collins[1], André Toulouse[1], Thomas J. Connor[2] & Yvonne M. Nolan[1]*

[1]Department of Anatomy and Neuroscience, University College Cork, Ireland

[2]Trinity College Institute of Neuroscience, Department of Physiology, Trinity College, Dublin 2, Ireland

To whom correspondence should be addressed:

*Yvonne M. Nolan, Department of Anatomy and Neuroscience, University College Cork, Ireland

Tel:(353) 21-420 5476

Fax:(353) 21-427 3518

email: y.nolan@ucc.ie

Abbreviations: 1-MPP$^+$; 1-methyl-4-phenylpyridinium: 3'-UTR; Three prime untranslated region: 6-OHDA; 6-hydroxydopamine: AD; Alzheimer's disease: ALS; Amyotrophic lateral sclerosis: AP-1; Activation-protein-1: ATP; Adenosine triphosphate: BBB; Blood-brain-barrier: BP; Binding protein: BV; bacterial vaginosis: CD200; Cluster of differentiation 200: CD200R; Cluster of differentiation 200 receptor: CM; Conditioned-medium: COPD; Chronic obstructive airway disease: COX; Cyclooxygenase: COX2; Cyclooxygenase-2: DAT; Dopamine transporter: DNA; Deoxyribonucleic acid: E; Embryonic day: GDNF; Glial cell-derived neurotrophic factor: H_2O_2; Hydrogen peroxide: HD; Huntington's disease: HIV; Human immunodeficiency virus : ICAM5; Intercellular adhesion molecule 5: IFN-γ; Interferon-gamma: IKK; IkappaB kinase beta: IL-1R1; Interleukin-1 receptor type 1: IL-1RA; Interleukin-1 receptor antagonist: IL-1β; Interleukin-1 beta: IL-6; Interleukin-6: iNOS; Inducible nitric oxide synthase: IRAK1; Interleukin-1 receptor-associated kinase 1: JEV; Japanese-encephalits virus: JNK; C-Jun N-terminal Kinase: LBP; Lipopolysacharide binding protein: L-DOPA; L-3,4-dihydroxyphenylalanine: LFA-1; Lymphocyte function-associated antigen 1: LC; Locus coeruleus: LPS; Lipopolysacharide: LRRK2; Leucine-rich repeat kinase 2 : MAO; Monoamine oxidase: MAO-B; Monoamine oxidase B: MAPK; Mitogen-activated protein kinase: MARCKS; Myristoylated alanine-rich C-kinase substrate: MCP-1; Monocyte chemoattractant protein 1: MHC class II; Major histocompatibility complex class II: MIP-1α; Macrophage inflammatory protein-1 alpha: MIP-1β; Macrophage inflammatory protein-1 beta: miRNA; Micro-ribonucleic acid: MMP-3; Matrix metalloproteinase-3: MPTP; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine: MPTP; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine: MRI; Magnetic resonance imaging: mRNA; Messenger ribonucleic acid: MS; Multiple Sclerosis: myD88; Myeloid differentiation primary response gene 88: NADPH-oxidase; Nicotinamide adenine dinucleotide phosphate-oxidase: NF-κB; nuclear factor kappa

B: NO; Nitric oxide: NOD2; Nucleotide-binding oligomerizetion domain 2: NA; Noradrenaline: NRIs; Noradrenaline reuptake inhibitors: NSAIDS; Nonsteroidal anti-inflammatory drugs: O_2^-; Oxide : Oas1; 2'-5'-oligoadenylate synthetase 1: P; Postnatal day: PAMPS; Pathogen-associated molecular patterns: PCR; polymerase chain reaction: PD; Parkinson's disease: PEP; Post-encephalitic Parkinsonism: PET; Positron emission tomography: PINK-1; PTEN induced putative kinase 1: PKCδ; Protein kinase C delta: Poly I:C; Polyriboinosinic-polyribocytidylic acid: PPARγ; Peroxisome proliferator-activated receptor gamma: PRKN; Parkin: RANTES; Regulated upon activation, normal T cell expressed and secreted: ROS; Reactive oxygen species: shRNA; Small hairpin ribonucleic acid: siRNA; Small interfering ribonucleic acid: SNCA; Synuclein, alpha (non A4 component of amyloid precursor): SNpc; Substantia nigra pars compacta: SPECT; Single-photon emission computed tomography: TH; Tyrosine hydroxylase: TLR; Toll-like receptor: TNFR-1; Tumor necrosis factor receptor 1: TNF-α; Tumour necrosis factor-alpha: TRAF6; TNF receptor associated factor: TSPO; Translocator protein: UTP; Uridine-5'-triphosphate: VEGF: Vascular endothelial growth factor: VM; Ventral mesencephalon : WT; Wild-type

Abstract

Idiopathic Parkinson's disease (PD) represents a complex interaction between the inherent vulnerability of the nigrostriatal dopaminergic system, a possible genetic predisposition, and exposure to environmental toxins including inflammatory triggers. Evidence now suggests that chronic neuroinflammation is consistently associated with the pathophysiology of PD. Activation of microglia and increased levels of pro-inflammatory mediators such as TNF-α, IL-1β and IL-6, reactive oxygen species and eicosanoids has been reported after *post mortem* analysis of the substantia nigra from PD patients and in animal models of PD. It is hypothesised that chronically activated microglia secrete high levels of pro-inflammatory mediators which damage neurons and further activate microglia, resulting in a feed forward cycle promoting further inflammation and neurodegeneration. Moreover, nigrostriatal dopaminergic neurons are more vulnerable to pro-inflammatory and oxidative mediators than other cell types because of their low intracellular glutathione concentration. Systemic inflammation has also been suggested to contribute to neurodegeneration in PD, as lymphocyte infiltration has been observed in brains of PD patients and in animal models of PD, substantiating the current theory of a fundamental role of inflammation in neurodegeneration. We will examine the current evidence in the literature which offers insight into the premise that both central and systemic inflammation may contribute to neurodegeneration in PD. We will discuss the emerging possibility of the use of diagnostic tools such as imaging technologies for PD patients. Finally, we will present the immunomodulatory therapeutic strategies that are now under investigation and in clinical trials as potential neuroprotective drugs for PD.

Keywords: Parkinson's disease; Neuroinflammation; Systemic inflammation; Microglia; Cytokines; Immunomodulatory Therapies

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References

1. Parkinson's disease

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder after Alzheimer's disease (AD) with a prevalence of 0.5-1% among people older than 65 years of age (Toulouse and Sullivan, 2008). The disease is a chronic, progressive neurodegenerative motor disorder, resulting in the selective loss of dopaminergic neurons within the substantia nigra (SN) pars compacta (pc) of the midbrain. As the disease progresses there is gradual circuitry degeneration within the nigrostriatal pathway, producing motor, cognitive and psychiatric symptoms (Braak et al., 2003). Despite intensive research the aetiology of this neurodegenerative disease still remains unclear with ~10% of cases with a clear genetic origin while the rest are of idiopathic origin although a number of risk factors have been identified including age, genetic predisposition, environmental toxins, neuronal injury such as traumatic brain injury (TBI) or stroke, and bacterial or viral infections (Bekris et al., 2010; Koprich et al., 2008; Tansey and Goldberg, 2010). The most significant environmental factors implicated in idiopathic PD are pesticides and have been shown to induce oxidative stress which leads to increased lipid peroxidation, DNA damage, mitochondrial dysfunction and ultimately dopaminergic neuronal dysfunction in the SNpc (Dick, 2006; Jenner, 2003). Nigral dopaminergic neurons are particularly vulnerable to oxidative stress as they operate under high oxidant conditions due to reduced levels of the anti-oxidant glutathione and increased nigral iron content (Dexter et al., 1989; Misra and Kalita, 2010; Sian et al., 1994). Oxidative stress is also a key stimulator of microglial activation, which subsequently leads to the generation of reactive oxygen species (ROS) from microglia, and consequently further dopaminergic neuronal death to ultimately propagate and propel a feed forward cycle of neuronal cell death and inflammation underlying the progression of the disease (Block and Hong, 2005). It has recently been recognised that individuals may present with a variety of neurological or psychiatric symptoms including

constipation, impaired olfaction, sleep disturbance, pain, depression and anxiety disorders which begin five and in some instances up to 20 years before the classical motor deficits of PD are apparent (Ferrer et al., 2011; Savica et al., 2010). While evidence from neuropathological studies and genomic analysis in AD suggests that defective inflammation is a preclinical event (Hoozemans et al., 2002; Bossers et al., 2010), to date there are no biomarkers for the detection of PD in the premotor phase. However, as both of these diseases present common features (protein aggregation, oxidative stress, progressive neuronal degeneration, systemic and neuroinflammation), and as there is now strong evidence for a relationship between inflammation and nigrostriatal degeneration, we surmise that targeting inflammatory events early in the disease progression, or indeed when possible during the premotor phase, will provide us with a promising therapeutic strategy for PD.

2. Neuroinflammation in Parkinson's disease

Initial evidence of the involvement of inflammation in the progression of PD stems from a *post-mortem* study over twenty years ago, which demonstrated the presence of activated microglia in the SNpc of a PD patient (McGeer et al., 1988). Since then an abundance of clinical and animal studies supports the role of activated microglia and increased levels of inflammatory mediators such as cytokines, chemokines and ROS in the pathology of PD (Banati et al., 1998; Barcia et al., 2011; Boka et al., 1994; Cao et al., 2011; Crotty et al., 2008; Depino et al., 2003; Dobbs et al., 1999; Hirsch and Hunot, 2009; Imamura et al., 2003; Long-Smith et al., 2010; Long-Smith et al., 2009; McGeer and McGeer, 2004; Mogi et al., 1994a, b; Mount et al., 2007; Orr et al., 2002; Tansey et al., 2007). Enzymes associated with inflammation, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), have also been identified *post-mortem* in PD brains (Hunot et al., 1996; Knott et al., 2000). Microglia become activated either directly due to a toxin, pathogen or endogenous

protein, or indirectly from dying neurons, and while mild activation of microglia has apparent beneficial effects, chronic microglial activation in response to neuronal damage as is evident in PD, results in the death of otherwise viable cells (Gao and Hong, 2008; Perry et al., 2010). Moreover, activation of microglia from dying neurons may be both long-lived and self-propelling due to positive feedback from degenerating neurons even after the initial insult has ceased. This repetitive cycle of neurotoxic activation of microglia in response to neuronal damage is referred to as *reactive microgliosis* and is a feature of several brain pathologies such as AD, multiple sclerosis (MS), frontotemporal lobe dementia and PD (Block and Hong, 2005). It is especially pertinent to PD because dopaminergic neurons in the SNpc are particularly susceptible to microglial-mediated neurotoxicity due to the high densities of microglia present (Kim et al., 2000). Thus, microglial activation and hence neuroinflammation is propagated to amplify the destruction of neurons in PD resulting in an accelerating feed-forward cycle of inflammation and neuronal death.

Activated microglia release a host of inflammatory cytokines (interleukin (IL)-1β, IL-1 receptor antagonist (IL-1RA), IL-6, IL-8, IL-10, IL-12, IL-18, tumour necrosis factor-α (TNF-α), interferon-gamma (IFN-γ), macrophage colony stimulating factor), chemokines (macrophage inflammatory protein (MIP)-1α, MIP-1β, monocyte chemoattractant protein-1 (MCP-1), Regulated upon activation, normal T cell expressed and secreted (RANTES)), and prostaglandins which can subsequently potentiate microglial activation through autocrine signalling to create a self-propagating cycle of expression (Kim and de Vellis, 2005). Pro-inflammatory cytokines IL-1β, TNF-α, IL-2, IL-6 and IFNγ are constitutively expressed at basal levels in PD patients as demonstrated in *post-mortem* brains, serum and cerebrospinal fluid *in vivo* (Boka et al., 1994; Dobbs et al., 1999; Mogi et al., 1994a, b; Mount et al., 2007; Stypula et al., 1996). Moreover, the death signalling receptor TNF receptor type-1 (TNFR-1)

is expressed on dopaminergic neurons in human SNpc (Boka et al., 1994; Mogi et al., 2000). Animal studies support an involvement of these pro-inflammatory cytokines in the dopaminergic neuronal degeneration evident in PD; blockade of the soluble form of the TNF-α receptor was found to attenuate the death of dopaminergic neurons in 6-hydroxydopamine (6-OHDA)- lesioned rats (McCoy et al., 2006), induction of chronic expression of IL-1β in adult rat SNpc using a recombinant adenovirus resulted in dopaminergic neuronal cell death starting only three weeks post-injection (Ferrari et al., 2006), and TNFα could be detected in the SN of monkeys up to 14 years after administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), (McGeer et al., 2003) suggesting that a chronic inflammatory state may be associated with progressive dopaminergic neurodegeneration. TNFα, IL-1β and lipopolysaccharide (LPS) are also known to promote oxidative stress and accumulation of ROS (Fernandez-Checa et al., 1997; Nolan et al., 2003; Vereker et al., 2001), the presence of which in the SN of PD patients plays a key role in dopaminergic neuronal death (Jenner et al., 1992; Jenner and Olanow, 1998; Mounsey and Teismann, 2010).

Substances which have been reported to be produced by dying dopaminergic neurons to activate microglia include α-synuclein-aggregates (Zhang et al., 2005), neuromelanin (Wilms et al., 2003), adenosine triphosphate (ATP) (Davalos et al., 2005) and matrix metalloproteinase-3 (MMP-3) (Kim et al., 2007a; Kim et al., 2005) (Figure 1). α-synuclein, the major constituent of Lewy bodies in PD, is nitrated by oxidative stress in the vicinity of dying dopaminergic neurons, which promotes aggregation of the protein. A growing body of evidence now suggests that nitrated, oxidised and aggregated α-synuclein released from dying dopaminergic neurons stimulates microglia and subsequent promotion of inflammation and oxidative stress (Croisier et al., 2005; Ischiropoulos and Beckman, 2003). α-synuclein

has been reported to be surrounded by activated microglia or inflammatory mediators in PD brains (McGeer et al., 1988; Yamada et al., 1992). It has also been shown to activate microglia in primary mesencephalic cultures and in mouse models of PD using adeno-associated virus vectors to overexpress the protein (AAV2-SYN), both of which in turn amplify α-synuclein-mediated neurotoxicity (Zhang et al., 2005; Theodore et al., 2008). Moreover, the phagocytosis of extracellular aggregated α-synuclein by microglia has been shown to further activate microglia and propel dopaminergic neurodegeneration (Zhang et al., 2005). Indeed a recent communication has identified glial cell-specific mitochondrial damage in a genetic mouse model of PD overexpressing doubly mutated human α-synuclein (Schmidt et al., 2011), and suggest this as a potential mechanism underlying PD pathogenesis. These data suggest that the pathological modification of α–synuclein (overexpression or nitration as observed in PD) is sufficient to trigger neuroinflammation and consequently initiate the neurodegenerative process. However, the mechanism by which α-synuclein activates and alters the function of microglia in PD is not yet understood although it has been shown from genomic and proteomic assays that nuclear factor-kappa B (NF-κB) plays a role (Reynolds et al., 2008) and more recently, Beraud et al suggested that alterations in the expression of toll-like receptors (TLRs) are involved (Beraud et al., 2011). Neuromelanin, a neuro-pigment released from stressed dopaminergic neurons has also been shown to induce microglial activation (Wilms et al., 2003). Its accumulation in human SNpc correlates with age progression, and extra neural melanin has been found in close proximity to activated microglial cells in patients suffering from juvenile idiopathic and MPTP-induced Parkinsonism (Ishikawa and Takahashi, 1998; Langston et al., 1999). Moreover, supplementation of microglial cultures with human neuromelanin *in vitro* has been shown to induce chemotactic effects and stimulate the release of TNF-α, IL-6 and nitric oxide (NO) (Wilms et al., 2003). Thus, the release of neuromelanin from dopaminergic neurons can

augment microglial activation and contribute to a self-perpetuating cycle of neuronal degeneration and chronic inflammation. Extracellular ATP, a purinergic neurotransmitter, was initially described as an activator of microglial cells (Kettenmann et al., 1993). The effects of ATP released from damaged neurons are mediated through its signalling with purinergic receptors, namely the metabotropic G-protein coupled P2Y receptors and the ligand gated ionotropic P2X receptors, both of which are expressed on microglia (Butt, 2011). Along with other pro-migratory factors such as extracellular uridine-5'-triphosphate (UTP) and members of the chemokine family, ATP facilitates the migration of microglia along a chemotactic gradient to the site of injury or inflammation from damaged cells. ATP then interacts with P2 receptors on microglia to stimulate the release of TNF-α, IL-1β, iNOS and NO (Davalos et al., 2005). Experiments by Kim *et al* have identified a pivotal role for the protease MMP-3 released from degenerating dopaminergic neurons in microglial activation (Kim et al., 2005). 1-methyl-4-phenylpyridinium (MPP^+)-stressed primary mesencephalic dopaminergic neurons induce and release active MMP-3, which is toxic to dopaminergic neurons themselves. In addition, treatment of mesencephalic neuron-glia mixed cultures with catalytically active recombinant MMP-3 has been reported to stimulate microglial cell activation, superoxide generation and to enhance dopaminergic neuronal cell death, while MMP-$3^{-/-}$ mice did not exhibit microglial activation, superoxide generation or dopaminergic degeneration after MPTP administration (Kim et al., 2007a).

While numerous factors are known to activate microglia, it has been postulated that microglia can also be maintained in a quiescent state by various micro-environmental inhibitory influences, many of which are produced by neurons. Hence, microglial activation during pathological insult may be due to a "*switching-off*" of these inhibitory neuronal signals (Ransohoff and Cardona, 2010). One such neuron-cell inhibitory signalling mechanism is the

direct cell-to-cell interactions between neuronal-CD200 (OX2) and its receptor CD200R, expressed on microglia. The CD200-CD200R interaction is essential for maintaining microglial homeostasis in the unperturbed CNS. A down-regulation of CD200 expression has been observed in neurons exposed to inflammatory conditions, and inhibition of CD200 causes microglial activation (Lyons et al., 2007). Therefore, there is a direct neuronal mechanism for regulating microglial activity, and loss of this interaction during neuronal cell degeneration may stimulate up-regulation of CD200, facilitating microglial activation. We and others have provided recent evidence to implicate the impairment of CD200-CD200R interaction as a contributing factor in PD neurodegeneration (Bieschke et al., 2011; Miller et al., 2011). Blockade of CD200R was shown to selectively and significantly enhance dopaminergic neuronal cell susceptibility to rotenone and iron-induced neurotoxicity in mesencephalic neuron-glia co-cultures. This was coupled with elevated microglial activation and superoxide generation and a decrease in CD200 expression on dopaminergic neurons (Bieschke et al., 2011). Microglia have also been shown to receive inhibitory inputs from a neuronal membrane-tethered chemokine CX_3CL1, through its receptor CX_3CR1, and removal of this inhibition also unleashed microglial activity (Shan et al., 2011). Other inhibitory signals exist between CD22-CD45, CD172A-CD47 and ICAM5-LFA-1 (Ransohoff and Perry, 2009).

3. Systemic inflammation and Parkinson's disease

It has been proposed that in TBI such as cerebral ischaemia or in chronic neurodegenerative diseases like PD, systemic infections and inflammation can exacerbate symptoms and promote damage (Denes et al., 2010; Perry et al., 2007). Following infection or injury, a systemic immune response ensues comprising both acquired immunity and innate immunity. During the initial innate response, peripheral monocytes, and resident tissue macrophages

secrete pro-inflammatory cytokines IL-1β, TNFα and IL-6 as well as prostaglandins and chemokines, which contribute to the behavioural and metabolic components that induce sickness behaviour (Ferrari and Tarelli, 2011; Perry et al., 2007). Through autocrine signalling these cytokines induce self-synthesis and the synthesis of further cytokines (Dantzer, 2009) which can affect the brain via several routes; by interaction with the vagus nerve (Tracey, 2002), by activating endothelial cells and perivascular macrophages (Laflamme et al., 1999) and through circumventricular organs which lack a functional blood-brain barrier (BBB) (Blatteis, 1992). Cytokines like TNF-α can then stimulate microglia to secrete chronically elevated pro-inflammatory mediators, which in turn can induce chronic self-perpetuating neuroinflammation, resulting in a slow and progressive loss of dopaminergic neurons in the SNpc (Qin et al., 2007). It has been proposed that the brain recognises cytokines as molecular signals of sickness, and induces symptoms of malaise, lassitude, fatigue, anhedonia, apathy, numbness, coldness, and reduced appetite and body temperature (Dantzer, 2009; Perry et al., 2007). To reinforce this theory, it has been demonstrated that a systemic inflammatory challenge in an animal model of chronic neurodegeneration exhibits exaggerated brain inflammation, sickness behaviour, cognitive changes and an acceleration of neurodegeneration (Cunningham et al., 2009; Perry et al., 2007). This emerging *"two-hit hypothesis"* in the aetiology of neurodegenerative diseases such as PD, suggests that the disease is multifactorial, and possibly a consequence of *"multiple-hits"* involving a variety of inflammatory stimuli (Di Monte, 2003). Infectious agents may comprise the first *"hit",* therefore sensitising the brain to subsequent *"hits"*, which may not have been pathogenic in the absence of an already "*primed"* system (Jang et al., 2009a). In this instance, microglia in the aged or diseased brain are said to be *"primed"* and can evoke an exaggerated response contributing to disease progression (Perry et al., 2007). Another interesting "two-hit hypothesis" is that proposed by Hawkes and co-workers

who suggest that α-synuclein aggregation is triggered in olfactory structures and in enteric nerves during the premotor phase of PD (which may contribute to premotor symptoms including constipation and impaired olfaction), and then spreads slowly over time to other brain regions (Hawkes et al., 2007). They suggest that a neurotropic virus may be responsible, but given the evidence of the pathological relationship between α-synuclein aggregation, inflammation and nigrostriatal degeneration, it is tempting to speculate that systemic inflammation may be a strong contender for investigation as a culprit during the premotor phase of PD.

3.1 Epidemiological evidence

Epidemiological reports suggest a correlation between systemic inflammatory events, chronic neuroinflammation and the aetiology and progressive nature of PD (Ferrari and Tarelli, 2011; Long-Smith et al., 2009; Perry, 2010). Associations were first established towards the end of the first world war (1924-1918) when the H1N1 influenza-A pandemic was coupled with a dramatic increase in post-encephalitic Parkinsonism (PEP) (also referred to as *"sleeping sickness"* or von Economo encephalitis) (Jang et al., 2009a; Rail et al., 1981; Tansey et al., 2007). People born during this time were at a 2-3 fold increased risk of developing PD, with PEP implicated in 50% of all Parkinsonism cases (Jang et al., 2009a; Tansey et al., 2007). PEP shares cardinal symptomatology with idiopathic PD including rigidity and bradykinesia but a lack of Lewy body formation (Jang et al., 2009a). Moreover, Takahashi et al., 1995 demonstrated that the H1N1 virus preferentially targets the SNpc, the primary site of pathology in PD (Takahashi et al., 1995). It has also been shown that exposure to the highly pathogenic neurotropic H5N1 influenza virus increases susceptibility to developing PD with an observed onset of post-influenzal encephalopathies (Jang et al., 2009b). Other viruses associated with secondary Parkinsonism include coxsackie virus (Poser et al., 1969; Walters,

1960), Japanese encephalitis B (Ogata et al., 1997), St. Louis virus (Pranzatelli et al., 1994), west Nile virus (Robinson et al., 2003) and human immunodeficiency virus (HIV) (Tse et al., 2004). Infection with Japanese-encephalitis virus (JEV), which occurs predominantly in India, China and Southeast Asia, for a prolonged period is likely to induce PEP (Ogata et al., 2000; Shoji et al., 1993; Tansey et al., 2007). People with JEV have similar neuropathological and locomotor symptoms to patients with idiopathic PD (Tansey et al., 2007), and the virus has previously been used to create a pre-clinical model of PD in rats (Ogata et al., 1997). This group demonstrated that in Fisher rats infected with JEV, there was marked gliosis and dopaminergic neuronal loss in the SNpc similar to that seen in PD, and bradykinesia which could be reversed with L-3,4-dihydroxyphenylalanine (L-DOPA) and monoamine oxidase (MAO) inhibitors. More recently, in a cohort of 60 JEV patients, transient-type Parkinsonian features were observed in 16 patients, with 19 displaying Parkinsonism with additional dystonia (Misra and Kalita, 2010). Pathological and clinical evidence has also identified the involvement of the gastrointestinal tract in enhancing susceptibility to idiopathic Parkinsonism, with *Helicobacter pylori* infection proposed as a potential trigger in disease progression (Tansey and Goldberg, 2010; Weller et al., 2005). Indeed, polymorphisms in the nucleotide-binding oligiomerization domain 2 (NOD2) gene associated with Crohn's disease, a chronic inflammatory bowel disease, have been shown to be over-represented in patients with idiopathic PD (Bialecka et al., 2007).

3.2 Blood Brain Barrier permeability

As alluded to above, a disruption in neurovascular homeostasis with increased BBB permeability and infiltration of systemic inflammatory mediators into the brain has been identified as a contributing factor to the pathology of several neurological diseases including PD (Hemmer et al., 2004; Rite et al., 2007; Stolp and Dziegielewska, 2009). Indeed, positron

emission tomography (PET) and histological studies of PD patients as well as MPTP and LPS-induced models of PD reveal a pathogenic link between neuroinflammation, increased BBB permeability and the consequent infiltration of systemic inflammatory molecules, and dopaminergic neuronal death (Chung et al., 2010). It is also likely that inflammatory mediators infiltrate the brains of PD patients due to the fact that efflux pumps that regulate BBB permeability are operating at reduced function in PD patients (Kortekaas et al., 2005) or that blood vessels are dysfunctional in in the midbrain of PD patients (Faucheux et al., 1999). Moreover, activated microglia have an up-regulated expression of cellular adhesion molecules, and the subsequent induction of chemokine gradients direct peripheral leucocytes to the site of inflammation (Chung et al., 2010; Stone et al., 2009a; Tansey and Goldberg, 2010). An increased level of the vasculogenic and angiogenic protein, vascular endothelial growth factor (VEGF) has been demonstrated in PD patients and in the MPTP model (Yasuda et al., 2007). Likewise, another report provides evidence that nigral injection of VEGF to mice disrupted the BBB permeability and induced dopaminergic neuronal death in the ventral mesencephalon (VM) (Chen et al., 2008a). Acute systemic injection of LPS to rats either directly or indirectly can also cause functional breakdown of the BBB resulting in granulocyte infiltration and activation of parenchymal microglia (Banks and Robinson, 2010; Laflamme et al., 1999; Laflamme and Rivest, 1999; Perry, 2004) which contribute to the degeneration of dopaminergic neurons in the SNpc (Brochard et al., 2009; Dutta et al., 2008). Although LPS at high concentrations is used in animals to model sepsis (Mannel, 2007), to date there has only been one report of Parkinsonism as a neurological complication of sepsis; Alasia et al (2006) reported a case of a Nigerian male who developed Parkinsonism-like symptoms on a background of gram-negative sepsis which were resolved with antibiotic therapy (Alasia et al., 2006).

3.3 T Lymphocytes

Assessment of serum obtained from PD subjects demonstrates a role for an adaptive immune response in PD (Hirsch and Hunot, 2009). Increased levels of $CD4^+$ T-cells have been reported in the serum of patients with PD, suggesting peripheral activation of lymphocytes (Bas et al., 2001; Fiszer et al., 1994; Hirsch and Hunot, 2009). Infiltrating cytotoxic $CD4^+$ and $CD8^+$ T-cells, but not B-cells, have also been observed in the inflamed SNpc of *post-mortem* PD human specimens and in the MPTP-induced mouse model of PD during the course of neurodegeneration (Brochard et al., 2009; Ferrari and Tarelli, 2011; Stone et al., 2009a). In support of a specific role for systemic immune cells in the degeneration of nigral dopaminergic neurons, $CD4^{-/-}$ mice have been shown to be resistant to MPTP-induced neurotoxicity in the SNpc (Brochard et al., 2009), while Benner and co-workers demonstrate that mice deficient in T and B-lymphocytes were more resistant to MPTP (Benner et al., 2008). In addition, this group also report that nitrated α-synuclein was detected in the lymph nodes of MPTP-treated mice where it was associated with increased expression of the class II major histocompatibility complex. They further show that nitrated α-synuclein can also cross the BBB, enter cervical lymph nodes, activate antigen presenting cells (APCs) and stimulate naïve T-cells to expand into subsets of $CD4^+$ and $CD8^+$ effector T-cells. Mice immunised with a nitrated fragment of α–synuclein displayed strong T-cell and pro-inflammatory responses whereas the native protein did not elicit an immune response. Furthermore, the response to nitrated α–synuclein led to an increased neuroinflammatory response and accelerated neurodegeneration following treatment with MPTP. The influence of α-synuclein on the adaptive immune response and consequently on the neuroinflammatory response was also reported by Theodore et al. who showed that four and twelve weeks after an AAV2-SYN injection, mice displayed increased CD-68 positive microglia and increased infiltration of B and T-lymphocytes in the SN of injected animals compared to controls. In addition, the levels

of pro-inflammatory cytokines were elevated compared to controls (Theodore et al., 2008). These studies implicate that the adaptive immune system contributes to the progression and pathogenesis of PD (extensively reviewed by (Cao et al., 2011) and indicate that this promising line of investigation (which will be further discussed below as a potential immunomodulatory therapy) warrants additional work to determine definitive targets for PD therapies.

3.4 Systemic Cytokines

Amplified levels of the cytokines TNF-α, IL-2, IL-6 and RANTES (Brodacki et al., 2008; Dobbs et al., 1999; Rentzos et al., 2007; Stypula et al., 1996) have also been detected in serum obtained from PD patients. It has been proposed that increases in these serum cytokine levels may serve as a therapeutic marker for PD, based on a blood sample study of men with high plasma concentrations of IL-6 correlating with an increased risk of developing PD (Chen et al., 2008b). Increased serum levels of soluble TNFR-1 were also detected in PD patients, which is in agreement with an earlier study showing elevated TNFR-1 in the SNpc of PD brains (Mogi et al., 2000), although this was not associated with clinical parameters. Another group however, has demonstrated that an LPS-induced increase of MCP-1, RANTES, MIP-1α, IL-8, IL-6 and IFNγ levels secreted by peripheral blood mononuclear cells significantly correlated with the severity of PD symptoms (Reale et al., 2009). In support of the role of primed microglia, in the *"two-hit hypothesis"*, a low level of systemic inflammation induced by a non-toxic dose of LPS has been shown to increase the severity of nigral dopaminergic neuronal cell loss in response to a subsequent low-dose of 6-OHDA in the rat model of PD (Koprich et al., 2008), while chronic systemic IL-1β also exacerbated neurodegeneration and microglial activation in the SNpc of 6-OHDA-treated rats (Pott Godoy et al., 2008).

3.5 Prenatal Systemic Infection

Evidence now suggests that prenatal systemic infections may be a risk factor for the development of PD in later life. It has been suggested that prenatal infections such as bacterial vaginosis (BV) in humans may be potential risk factors for PD (Ling et al., 2002). Indeed, during pregnancy, levels of LPS and TNF-α are elevated in the chorioamniotic environment of women with BV (Menon et al., 1995; Okada et al., 1997), and evidence from animal studies have demonstrated that prenatal inflammagen exposure may hinder typical dopaminergic neuron development. In a study by Ling et al, brains from postnatal day (P) 21 rat pups born to dams that were intraperitoneally injected with LPS at the gestation window of vulnerability (embryonic day (E) 10.5), displayed reduced numbers of tyrosine hydroxylase (TH) immunoreactive cells in the SNpc and ventral tegmental area. This apparent dopaminergic neuronal loss was associated with reduced striatal dopamine and an increase in TNF-α in the striatum and mesencephalon when examined at P21. (Ling et al., 2002). It is likely that dopaminergic neurons are lost at the time of embryonic exposure of LPS, as reports from studies examining the effect of treatment with LPS or pro-inflammatory cytokines IL-1β and TNFα on TH immunoreactivity in embryonic mesencephalic cultures *in vitro* have revealed that these immunomodulatory agents reduce dopaminergic neuronal viability (Bronstein et al., 1995; Jarskog et al., 1997; Long-Smith et al., 2010). Another group has reported the loss of dopaminergic neurons up to 16 months post exposure of rats to LPS *in utero*, which corresponds to the mean age in humans at which PD symptoms are first observed, and they have suggested that prenatal exposure of rats to LPS is a potential model of PD as it induces a slow, protracted loss of nigral dopaminergic neurons (Carvey et al., 2003). Further validation for this model was demonstrated by significant dopamine and serotonin reductions observed in the frontal cortex, nucleus accumbens, striatum, amygdala, hippocampus and hypothalamus, comparable to the neurochemical alterations evident in PD

subjects (Wang et al., 2009). More recently however, suggestions of prenatal endotoxin exposure to rats as a progressive animal model of PD have been thwarted by a study demonstrating that prenatal LPS exposure to rats does not accelerate dopaminergic neuronal loss but rather that the progressive dopaminergic neuronal loss observed in these rats is due to normal aging (Ling et al., 2009). This group had previously carried out a study to examine the effect of prenatal exposure to systemic inflammation on the progression of dopaminergic neuronal loss induced by 6-OHDA at a later stage. In this study, prenatally LPS-exposed rats were subjected to a moderate dose of 6-OHDA at four-months and the data revealed that both prenatal LPS exposure and postnatal 6-OHDA-treatment produced significant dopaminergic neuron loss. However, the combined effect was additive and not synergistic. This may have been due to the young age of the animal or the toxin used (Ling et al., 2004). This model was subsequently investigated but with prenatally LPS-exposed rats treated with rotenone rather than 6-OHDA postnatally. The combined effects of LPS and rotenone produced a synergistic loss of TH^+ cells in the SNpc relative to controls, which was associated with increased striatal-dopamine activity, TNF-α and increased reactive microglia (Ling et al., 2004). To mimic a response to viral rather than a bacterial infection, challenges with polyriboinosinic-polyribocytidilic acid (Poly I:C), a TLR-3 agonist and synthetic analogue of double-stranded RNA have been used in rats. Results have revealed an increase in the production of pro-inflammatory cytokines in the brain (Cunningham et al., 2007) , an exacerbation of chronic neurodegeneration (Field et al., 2010), and an induction of nigrostriatal dopaminergic neurodegeneration in adult rats (Deleidi et al., 2010). When administered early in gestation to mice, acute poly I:C induced maternal immune activation and a subsequent increase in the numbers of dopaminergic neurons in the foetal brains during middle and late foetal development (Meyer et al., 2008a). This is in contrast to studies reporting that prenatal challenge with bacterial LPS induced a reduction in the numbers of dopaminergic neurons

postnatally, and suggests that the source of infection and immune activation may have a specific impact on dopaminergic neuronal development, or indeed that there is a gestational window of susceptibility to immunological challenge. This hypothesis that the timing of prenatal exposure to maternal infection is critical for dopaminergic neuronal development was tested by the same group who showed that early but not late foetal exposure of mice to poly I:C challenge reduced prefrontal dopamine D1 receptors in adulthood (Meyer et al., 2008b). The impact of the timing of prenatal viral exposure on the development and later viability of dopaminergic neurons in the adult nigrostriatal pathway has yet to be explored.

4. Neuroinflammatory diagnostic tools for Parkinson's disease

Microglial responsiveness to injury and neurodegenerative disease suggests that it may serve as a marker for the diagnosis and progression of disease pathology in PD. Thus there is a current drive to develop non-invasive imaging tools to assess and quantify the dynamics of activated microglia in neurodegenerative diseases like PD. Advances in this technology, especially for identification of microglial biomarkers at the early stages of disease, would have important implications for PD diagnosis, assessment of progression, and therapy. Currently, the best-studied imaging paradigm for microglial activation is the radiolabelled translocator protein (TSPO) ligand using PET (Dolle et al., 2009). This line of research initially started when a correlation was observed between increased binding of Ro5-4864 (a benzodiazepine) and PK11195 (an isoquinoline) to receptors on the surface of mitochondria primarily localised in glial cells (Arlicot et al., 2008; Chauveau et al., 2008). These receptors were originally referred to as peripheral type benzodiazepine receptors and were increased in activated microglia (Park et al., 1996; Stephenson et al., 1995). The nomenclature has since been changed to TSPO as further research elucidated that these receptors are expressed throughout the brain and body (Papadopoulos et al., 2006). Gene-expression analysis in

brains of rodents, primates and humans have illustrated that TSPO expression is nearly absent in parenchyma-microglia (Winkeler et al., 2010) but is elevated in many neurodegenerative disorders including, stroke, AD, PD, MS, Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), (Arlicot et al., 2008), thus emphasising the involvement of microglial activation and neuroinflammation in these diseases. As TSPOs are the prototypical biomarkers of neuroinflammatory changes in a variety of CNS disorders, they have therefore been proposed as potential diagnostic targets for *in vivo* imaging (Arlicot et al., 2008; Chauveau et al., 2008).

Currently, functional PET and single photon emission tomography (SPECT), in conjunction with ligands for TSPO, can detect microglial activation *in vivo*. Examples of radiolabelled TSPO ligands include [^{11}C]Ro5-4864 and [^{11}C](*R*)-PK11195 (1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3 isoquinoline carboxamide) (Chauveau et al., 2008). In PD subjects, PET imaging revealed microglial activation in the pons, basal ganglia, and frontal and temporal cortical areas, and longitudinal studies of these patients revealed stable [^{11}C](*R*)-PK11195 binding potential (BP; a parameter that mixes receptor density with ligand affinity), indicative of early activation of microglia in PD pathology (Gerhard et al., 2006; Winkeler et al., 2010). However, the [^{11}C](*R*)-PK11195 tracer is limited, as it is incapable of distinguishing between phenotypic differences, and thus possibly functional differences of microglia. To overcome this, a PET tracer for the dopamine-transporter (DAT), [^{11}C]CFT, has been used in conjunction with [^{11}C](*R*)-PK11195 to examine the viability of the presynaptic dopaminergic neurons (Ouchi et al., 2009). This study of 10 drug-naïve PD patients, demonstrated changes in microglial activity in conjunction with DAT density which were investigated using PET imaging with [^{11}C](*R*)-PK11195 and [^{11}C]CFT tracers. Subjects underwent magnetic resonance imaging (MRI) prior to PET measurement to define the

regions of interest, which would allow for the evaluation of microglial activation in parallel with presynaptic neuronal degeneration *in vivo*. Elevated midbrain [^{11}C](*R*)-PK11195 BP levels were significantly inversely correlated with [^{11}C]CFT BP localised in the putamen, and the elevated [^{11}C](*R*)-PK11195 BP also correlated with motor impairment. A follow-up 4-year scan revealed increased microglial activation spread over the extrastriatal region (Ouchi et al., 2009). PET imaging and *post-mortem* analysis of the brain of a rat lesioned with 6-OHDA revealed reduced [^{11}C]CFT BP in the striatum, indicative of dopaminergic degeneration, while [^{11}C](*R*)-PK11195 BP was markedly increased in the striatum and SNpc. *Post-mortem* immunohistochemical analysis corroborated this finding by showing activated microglia in the striatum and SNpc at 4 weeks post-lesion (Cicchetti et al., 2002). Alternative SPECT imaging biomarkers for TSPO such as [^{123}I]CLINDE (2-(4′iodophenyl)-3-(N,N-diethyl)-imidazo[1,2-a]pyridine-3-acetamide) have been examined *in vivo* and also pose as potential image-guided diagnostic tools for microglial activation in neurodegenerative diseases like PD (Arlicot et al., 2008).

5. Immunomodulatory therapies

As the wealth of evidence from animal models continues to accumulate regarding the apparent role of inflammation in the pathogenesis of PD, a large number of inhibitory drugs have been investigated (Table 2). The use of broad spectrum steroidal and non-steroidal anti-inflammatory drugs (NSAIDs), specific microglial inhibitors or anti-inflammatory cytokines have not only helped decipher the role of microglial activation in neuroinflammation in PD but also indicated that inhibiting the specific processes involved in microglial activation may be a therapeutic avenue for PD.

5.1 Glucocorticoids

The glucocorticoids are well known for their broad range of anti-inflammatory effects and have long been used in clinical settings for the treatment of brain inflammation (Castano et al., 2002). Microglial cells express the glucocorticoid receptor, which is involved in the regulation of the transcription factor NF-κB and activator protein-1 (AP-1) (Scheinman et al., 1995), which in turn are key regulators of pro-inflammatory cytokine expression (Nadeau and Rivest, 2003). Of particular interest, the synthetic steroid dexamethasone was shown to provide neuroprotection against LPS or MPTP-induced toxicity in rodent models. In both models, the delivery of dexamethasone prevented the activation of microglia usually associated with neurodegeneration (Castano et al., 2002; Kurkowska-Jastrzebska et al., 2004). However, the severe side-effects associated with glucocorticoid use prevent any long-term usage in neuroprotective therapies for PD. Large scale epidemiological studies have shown that the chronic use of NSAIDs such as aspirin or ibuprofen could provide some level of protection against PD (Chen et al., 2005; Chen et al., 2003; Kurkowska-Jastrzebska et al., 2006; Mohanakumar et al., 2000). Other studies suggest that the role of NSAIDs in decreasing the risk of PD is extremely limited (Hancock et al., 2007; Hernan et al., 2006). A recent meta-analysis of studies published between 1966 and 2008 showed that while NSAIDs as a class do not modify the risk of developing PD, the chronic intake of ibuprofen may have a beneficial effect (Gagne and Power, 2010; Gao et al., 2011; Samii et al., 2009). Ibuprofen possibly mediates this effect via its inhibition of COX activity to inhibit the production of pro-inflammatory lipid mediator prostaglandins (Mitchell et al., 1993). Some of the beneficial effects observed could also be mediated via other mechanisms associated with NSAIDs such as inactivation of the pro-inflammatory nuclear receptor NF-κB (Grilli et al., 1996; Kopp and Ghosh, 1994), activation of peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear factor mediating anti-inflammatory effects in microglia (Bernardo et al., 2005) or activation of the Rho kinase pathway (Zhou et al., 2003). Results from animal models of PD

demonstrate that aspirin and indomethacin have both been shown to prevent MPTP-induced loss of striatal dopamine in the mouse (Aubin et al., 1998; Kurkowska-Jastrzebska et al., 2002). The NSAID Celecoxib reversed striatal dopaminergic neuronal fibre and nigral dopaminergic neuronal cell loss in 6-OHDA-treated rats (Sanchez-Pernaute et al., 2004) while aspirin has been shown to prevent 6-OHDA-induced striatal dopamine depletion (Di Matteo et al., 2006).

5.2 Minocycline

Other neuroimmunomodulatory strategies include the use of the second generation tetracycline analogue, minocycline. It has been shown to inhibit microglial activation and prevent iNOS and nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase) generation as well as IL-1β up-regulation (Du et al., 2001). It is a lipophilic molecule which easily crosses the BBB and is reported to have anti-inflammatory and neuroprotective activities (Kim and Suh, 2009). Some studies in experimental models of PD have shown that it is neuroprotective against MPTP-, LPS, or 6-OHDA-induced neurodegeneration (Du et al., 2001; He et al., 2001; Quintero et al., 2006; Tomas-Camardiel et al., 2004; Wu et al., 2002) while others showed that it exacerbated the deleterious effects of MPTP in rodents and non-human primates (Diguet et al., 2004; Yang et al., 2003). While the reason for the discrepancies is unknown, differences between the various studies include doses and timing of intervention and may reflect the dual role of microglia in inflammation. Indeed, results of clinical trials from various patient cohorts suffering neurological diseases have also revealed differing results; significant toxicity was found after a phase III randomised trial in patients with ALS (Gordon et al., 2007), a phase III futility study in HD recommended that further study of minocycline in HD was not warranted (Schwarz et al., 2010), while the results of a double-blind, placebo-controlled study have suggested the beneficial effects of minocycline

as a combination therapy for MS (Metz et al., 2009), and another preliminary study showed efficacy in acute ischemic stroke (Lampl et al., 2007). Despite these contradictory results, a phase II randomized double-blind futility clinical trial of minocycline in PD has been set-up. Results after 12 and 18 months suggest that minocycline is well tolerated and does not negatively impact on symptomatic treatment. It is therefore currently recommended for phase III clinical trials to assess its long-term effect on disease progression (NINDS-NET-PD-Investigators, 2006, 2008).

5.3 Regulatory T cells

One of the mechanisms whereby the immune response can be modulated to prevent the prolonged cytotoxic effects of inflammation on endogenous tissue involves regulatory T-cells (Tregs), and it is currently under investigation as a potential target for immunomodulatory therapies for PD and other neurological disorders including ALS and CNS injury (for reviews see Appel et al., 2010; Walsh and Kipnis, 2011). Tregs are capable of inhibiting an immune response by suppressing $CD4^+$ and $CD8^+$ effector T-cells (Teffs) and B-cell responses, counteracting the actions of myeloid and APCs, including microglia, and promoting release of anti-inflammatory IL-10 and TGF-β. They also promote neurotrophic factor production (brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF)) from astrocytes (for review see Qian et al., 2010; Stone et al., 2009b) suggesting a capacity of Tregs for promotion of dopaminergic neuronal cell development. A number of studies by Reynolds and co-workers have demonstrated that Treg alters the microglial response in response to nitrated α-synuclein (Reynolds et al., 2009a, b). Specifically, $CD4^+CD25^+$ Treg were shown to suppress nitrated α-synuclein microglial-induced ROS and NF-κB activation, while $CD4^+CD25^-$ Teffs exacerbated microglial activation and induced neurotoxic responses (Reynolds et al., 2009a). This group also show that Treg alters the

microglial proteome in response to nitrated α-synuclein and suggest that this mechanism of Treg-mediated microglial response can slow the momentum and course of PD (Reynolds et al., 2009b). Interestingly, the neuropeptide vasoactive intestinal peptide (VIP), which is a potent inducer of Treg (Delgado et al., 2005), has been reported to prevent MPTP-induced loss of nigral dopaminergic neurons and striatal dopaminergic fibres in the mouse, while also down-regulating IL-1β and TNF-α expression and iNOS generation (Delgado and Ganea, 2003). In a more recent study, the adaptive immune response and nigrostriatal dopaminergic neurodegeneration generated as a result of immunization of MPTP-treated mice with nitrated α-synuclein was attenuated by VIP-induced Tregs (Reynolds et al., 2010). This effect was mediated in part through Tregs suppression of Th17-mediated inflammatory response and the mechanism has been proposed as a potential immunisation strategy for PD (Cao et al., 2011; Reynolds et al., 2010). Thus manipulating this adaptive response by redirecting the harmful T-cell response towards an anti-inflammatory and protective immune response by means of an antigen-based immunisation could be a successful approach for neuroprotection in PD. Preclinical results using glatiramer acetate (a random amino acid polymer composed of alanine, glutamine, lysine and tyrosine amino acids, also known as copolymer 1 and copaxone) as an immunisation agent showed that this approach could be successful. Glatiramer-acetate primed T-cells transferred to MPTP-treated mice were shown to reach the brain where they suppressed microglial activation and provided neuroprotection to the nigrostriatal neurons by inducing the neurotrophic factor GDNF. Furthermore, specific depletion of the donor T-cells abrogated this neuroprotective effect confirming that the effect is donor T-cell dependent (Benner et al., 2004). Moreover, the donor T-cells were shown to secrete high levels of anti-inflammatory cytokines IL-4, IL-10 and TGF-β (Benner et al., 2004). Interestingly, there is also evidence to suggest that glatiramer acetate is an inducer of Tregs (Arnon and Aharoni, 2004). As glatiramer acetate has already been shown to be safe

and tolerable in clinical trial and has had significant reduction effects on disability in MS patients (Comi et al., 2011), it represents a very attractive possibility. The complex interactions between infiltrating lymphocytes, glial cells and neurons is not fully elucidated and further research is necessary for the development and advance of novel effective adaptive cell-based therapies for PD. However, if the above results are indicative of outcomes that could be achieved through Treg based therapeutics, then the future for neuroprotection in PD is encouraging.

5.4 Cytokines

Alternatively, the delivery of anti-inflammatory cytokines such as IL-10 could be considered as an anti-inflammatory therapeutic strategy for PD. Pre-treatment of mesencephalic neuroglial cultures with IL-10 inhibited LPS-stimulated microglial activation and degeneration of dopaminergic neurons (Qian et al., 2006). Similar neuroprotective effects were observed *in vivo* after chronic infusion of IL-10 into the SNpc of rats that were challenged with LPS (Arimoto et al., 2006). More recently, gene therapy approaches have been developed to deliver IL-10 into the rat SNpc, and have proved effective in attenuating the neuronal loss and behavioural deficits in the 6-OHDA rat model of PD (Johnston et al., 2008). It has been suggested that targeted delivery of IL-10 such as by gene delivery to CNS tissue in order to maintain effective levels of the cytokine over a sustained period of time would yield more effective results in progressive neurological disorders such as MS or PD (O'Garra et al., 2008). This reasoning has come about due to the lack of efficacy as well as the pro-inflammatory and cytotoxic effects of systemic administration of IL-10 in clinical studies for patients with psoriasis, Crohn’s disease and rheumatoid arthritis (Asadullah et al., 2003; Lauw et al., 2000; Tilg et al., 2002), and from preclinical studies showing that experimental autoimmune encephalomyelitis mice (a model of MS) intracerebrally injected

with an adenovirus inducing expression of IL-10 in the brain can inhibit disease pathology (Cua et al., 2001). Thus, the potential of targeted delivery of anti-inflammatory cytokines like IL-10 to CNS tissue for the treatment of brain inflammation and the consequent associated neurological deficits is ripe for exploration. Furthermore, the blockade of pro-inflammatory cytokines should be considered as a potential therapeutic avenue. Blocking the soluble TNF signalling by delivery of a dominant-negative form has been shown to promote neuronal survival and reduce the behavioural deficits in the hemi-Parkinsonian rat model of PD (McCoy et al., 2006; McCoy et al., 2008). While these pre-clinical results are interesting, the availability of a broad spectrum of compounds acting on TNF signalling makes this molecule a very attractive target. Etanercept and Infliximab are a new generation of engineered inhibitors of TNF that are broadly used for the treatment of rheumatoid arthritis and other peripheral inflammatory diseases. Their use in CNS diseases is however limited by their general inability to cross the BBB (Tweedie et al., 2007). While direct intrastriatal delivery or long-term gene transfer as illustrated above are possibilities, other inhibitors of TNF synthesis may prove useful such as the infamous antiemetic compound thalidomide. Thalidomide is a sedative, immunosuppressive and anti-inflammatory drug that has teratogenic effects (Smithells and Newman, 1992) and inhibits the synthesis of TNF-α (Sampaio et al., 1991). Thalidomide was shown to protect nigrostriatal neurons and prevent striatal dopamine depletion in the early stages of MPTP-induced neurodegeneration (Boireau et al., 1997; Ferger et al., 2004).

As mentioned above, NF-κB plays an important role in the regulation of chronic diseases through the promotion of inflammation and of cell survival. Activated NF-κB (which requires the activity of the IκB kinase (IKK) complex (Kim et al., 2006)) has been detected in neurons and activated microglia in the SNpc of PD patients and MPTP-treated animals suggesting that

some of the pro-inflammatory mechanisms regulated by the NF-κB pathways may play an important role in the pathogenesis of PD (Ghosh et al., 2007; Hunot et al., 1997). Recent studies have shown that blockade of NF-κB activity either directly or through IκB can inhibit components of the inflammatory pathways in microglia namely, the oxidative stress pathway and the production of pro-inflammatory cytokines (Anrather et al., 2006; Gauss et al., 2007). Selective inhibition of NF-κB activity by a peptide blocking the IKK complex prevented dopaminergic neuronal loss in MPTP-treated mice and suppressed microglial activation (Ghosh et al., 2007). Finally, a selective pharmacological IKKβ inhibitor has demonstrated neuroprotective properties in LPS- and MPTP-induced models of PD. Treatment with this compound prevented neuronal damage in a process dependant on the presence of microglia. Particularly, it prevented the activation of microglial oxidative pathways and the release of pro-inflammatory cytokines by specific blockade of the NF-κB signalling pathway (Zhang et al., 2010).

5.5 PPARγ

PPARγ has been shown to exert anti-inflammatory functions in both the periphery and the CNS where it is detected in glial and neuronal cells. Following activation by its naturally occurring ligands eicosanoids and prostaglandin J2, it regulates the expression of pro-inflammatory molecules such as iNOS, COX-2, and indirectly of a broad array of cytokines through its interactions with the transcription factor NF-κB (Chaturvedi and Beal, 2008; Chung et al., 2008). Pioglitazone and rosiglitazone are two synthetic agonists of PPARγ that are approved for the treatment of type II diabetes. In the CNS they exhibit neuroprotective effects in models of neurodegenerative disorders, including PD, by preventing inflammation, oxidative damage and apoptosis (Chaturvedi and Beal, 2008). Specifically, pioglitazone prevents MPTP-induced activation of microglia and dopaminergic neuronal cell loss in

murine SNpc *in vivo* (Dehmer et al., 2004). This has been shown to occur through inhibition of monoamine oxidase B (MAO-B), the enzyme responsible for conversion of MPTP to its toxic metabolite MPP^+ (Quinn et al., 2008). When pioglitazone was administered to rats that were also injected intrastriatally with LPS, the resultant LPS-induced microglial activation and dopaminergic degeneration was attenuated (Hunter et al., 2007). Recently, the neuroprotective effects of rosiglitazone have been shown in the MPTP mouse model of PD; chronic administration of the drug prevented behavioural deficits, dopaminergic neuronal loss and microglial activation in the SNpc *in vivo* (Schintu et al., 2009).

5.6 β2-adrenoceptor agonists

Noradrenaline (NA) is a neurotransmitter which is present throughout the body and is known to elicit anti-inflammatory actions in the brain by stimulating glial β_2-adrenoceptors. For instance, NA suppresses production of neurotoxic substances including TNF-α, IL-1β and NO from activated microglia (Feinstein et al., 2002; McNamee et al., 2010a). In fact, NA plays a key role in keeping brain microglia in a quiescent state, and loss of NA sensitises the brain to inflammatory damage (Heneka et al., 2003, 2010). The locus coeruleus (LC) is the primary source of NA cell bodies and their axons innervate almost all parts of the brain including the SN and striatum, and LC cell numbers are reduced by approximately 60% at autopsy in PD patients compared to normal age-matched controls (Marien et al., 2004). Consequently, NA inputs into the SN are depleted in the brains of PD patients (Gesi et al., 2000), and it has been suggested that loss of LC NA neurons is a significant contributor to the progression of PD, and that pharmacotherapies aimed at restoring normal NA tone are likely to have therapeutic potential (Rommelfanger and Weinshenker, 2007). The idea that NA loss contributes significantly to pathology in PD is supported by the observation that depletion of NA exacerbates DA loss in animal models of PD including the MPTP and 6-OHDA models

(Fornai et al., 2007). It has also been demonstrated that treatment with NA reuptake inhibitors (NRIs); a class of drugs that enhance availability of the neurotransmitter NA, the endogenous ligand for β_2-adrenoceptors in the CNS inhibit microglial activation and production of inflammatory mediators TNF-α and NO, and inhibit activation of NF-κB (O'Sullivan et al., 2009), and that treatment with β_2-adrenoceptor agonists elicits anti-inflammatory and neuroprotective effects in the CNS (Gleeson et al., 2010; McNamee et al., 2010a, b). Moreover, a recent report indicates that β_2-adrenoceptor agonists inhibit dopaminergic neuron loss induced by LPS *in vitro* and *in vivo* (Qian *et al.,* 2011). In further support of the idea that NRIs may be successful in ameliorating the progression of PD, it has been demonstrated that NA transporter knockout mice display reduced toxicity to MPTP (Rommelfanger et al., 2004). In this regard, both NRIs and β2-adrenoceptor agonists are lipophillic compounds and readily penetrate the CNS. Moreover, long-term treatment with NRIs represent a clinically feasible neuroprotective strategy in PD, as these agents are currently used in the treatment of depression and attention deficit hyperactivity disorder, and clinical data demonstrates that these agents are safe when taken for prolonged periods. Similarly, long-acting β2-adrenoceptor agonists are already in widespread therapeutic use for the treatment of asthma and chronic obstructive airway disease (COPD).

5.7 microRNAs and RNA interference

Although microRNAs (miRNAs) are expressed in the brain, only a limited number of studies have examined the biological role of miRNAs in brain disorders including PD (Hebert and De Strooper, 2007; Saugstad, 2010). These small RNA molecules (21-23 nucleotides) are non-protein coding transcripts that play an important function in post-transcriptional regulation of gene expression in the development, function and survival of mammalian midbrain dopaminergic neurons, and so their expression may be a potential therapeutic

marker for disease progression of PD. For example, miR-133b, which is specifically expressed in midbrain dopaminergic neurons, is deficient in patients with PD and it has also been shown to regulate the maturation and function of midbrain dopaminergic neurons within a negative feedback circuit that includes the transcription factor Pitx3 (Kim et al., 2007b). MiR-7 which is expressed mainly in neurons binds to the α-synuclein mRNA 3'-UTR to repress protein expression and therefore protect cells against oxidative stress. Analysis of the MPTP model of PD indicates decreased expression of miR-7, which results in elevated α-synuclein expression (Junn et al., 2009). Single nucleotide polymorphisms within the fibroblast growth factor 20 gene disrupts a binding site for miR-433, resulting in increased fibroblast growth factor 20 and subsequent α-synuclein expression (Wang et al., 2008). It is feasible then to suggest that miRNAs that regulate inflammatory mediators such as cytokines, which are participating players in the progression of PD, may contribute to the pathogenesis of sporadic PD. For instance, recent work by Bauer and colleagues have shown that a miR-30-based shRNA construct (which can activate cellular immune responses) prevented IFN-stimulated gene expression of oligoadenylate synthetase 1 (Oas1) and was concomitant with accelerated apoptosis and neuronal loss (Bauer et al., 2009). Thus, it would be interesting to investigate the role of miR-30 in inflammation-induced changes in dopaminergic neuronal development and survival. Ultimately, miRNAs may be a potential therapeutic target for PD, although the practicalities of manipulating miRNAs as therapeutic targets may yet be a long way from the clinic.

A relatively recent technological advance which is considered an attractive therapeutic option for the treatment of CNS diseases is RNA interference. This post-transcriptional gene silencing mechanism allows for selective and efficient gene silencing which can be used for functional analysis of individual genes. Small interfering RNA (siRNA) is now widely

applied in mammalian cell cultures and in animal models of CNS disorders (Paddison et al., 2002; Thakker et al., 2006). Thus in PD research, the advent of RNA interference is a prospective useful approach for silencing target genes to increase our understanding of dopaminergic cell mechanisms, provide us with potential therapeutic targets for manipulation of genes *in vivo,* or in cultured cells for transplantation to the brain (Porras and Bezard, 2008). For example, using an *in vitro* model of PD, Yang and colleagues have previously demonstrated that the application of siRNA against protein kinase Cδ (PKCδ) abolished the MPP^+- induced PKCδ activation, DNA fragmentation and dopaminergic neuronal cell loss (Yang et al., 2004). More recently, it has been reported that siRNA directed against α-synuclein and infused into the SNpc of primates caused a significant reduction in nigral α-synuclein expression (McCormack et al., 2010). Considering that inflammation in the host brain is a contributing factor to the progression of dopaminergic neuronal demise as well as to the functional outcome of neural transplantation procedures in PD (Piccini et al., 2005), it is conceivable that silencing of host or transplanted inflammatory mediators using RNA interference is a therapeutic avenue which is worthy of investigation.

6. Conclusion

Although the precise role of inflammation in the pathogenesis of PD remains unclear, an array of evidence from the clinic and from animal models now points to its involvement in fuelling progression of the disease. Moreover, the assertion that both systemic and central inflammation contributes to the demise of nigral dopaminergic neuronal function is rapidly gaining momentum. Therefore, in order to develop strategies to counteract the consequences of inflammation on the susceptible Parkinsonian brain, it is essential that research is undertaken to better understand how the brain and systemic immune system communicate, as well as to decipher the fundamental mechanisms of how dopaminergic neuronal cells die in

an inflammatory environment. The immunomodulatory approaches described here show both limitations and promise for therapeutics for PD. For example, Tregs currently show particular promise in light of the fact these cells can promote the development of dopaminergic neurons and so have potential in cell replacement strategies, as well as the fact that they have shown capacity to form the basis of immunisation strategies. We hypothesise that the emerging information on the role of the immune system in PD, especially early in the disease progression will provide us with a window of opportunity to target early symptoms of this debilitating disease.

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Table 1:

Inflammatory processes involved in Parkinson's disease

Process	Location	Reference
Activated microglia	Brain	(Banati et al., 1998; Imamura et al., 2003; McGeer et al., 1988; Sawada et al., 2006)
COX-2	Brain	(Knott et al., 2000)
IFN-γ	Brain	(Mogi et al., 2007; Reale et al., 2009)
IL-1β	Brain/CSF	(Blum-Degen et al., 1995; Hunot et al., 1996; Mogi et al., 1994a)
IL-2	Brain/Serum	(Mogi et al., 1996; Stypula et al., 1996)
IL-6	Brain/Serum/CSF	(Blum-Degen et al., 1995; Dobbs et al., 1999; Mogi et al., 1994a; Muller et al., 1998; Reale et al., 2009)
IL-8	Serum	(Reale et al., 2009)
iNOS	Brain	(Hunot et al., 1996; Knott et al., 2000)
MCP-1	Serum	(Reale et al., 2009)
MIP1- α	Serum	(Reale et al., 2009)
RANTES	Serum	(Reale et al., 2009; Rentzos et al., 2007)
TNF-α	Brain/Serum/CSF	(Boka et al., 1994; Dobbs et al., 1999; Hunot et al., 1996; Mogi et al., 1994b)
TNF-R1	Brain	(Boka et al., 1994; Mogi et al., 2000)

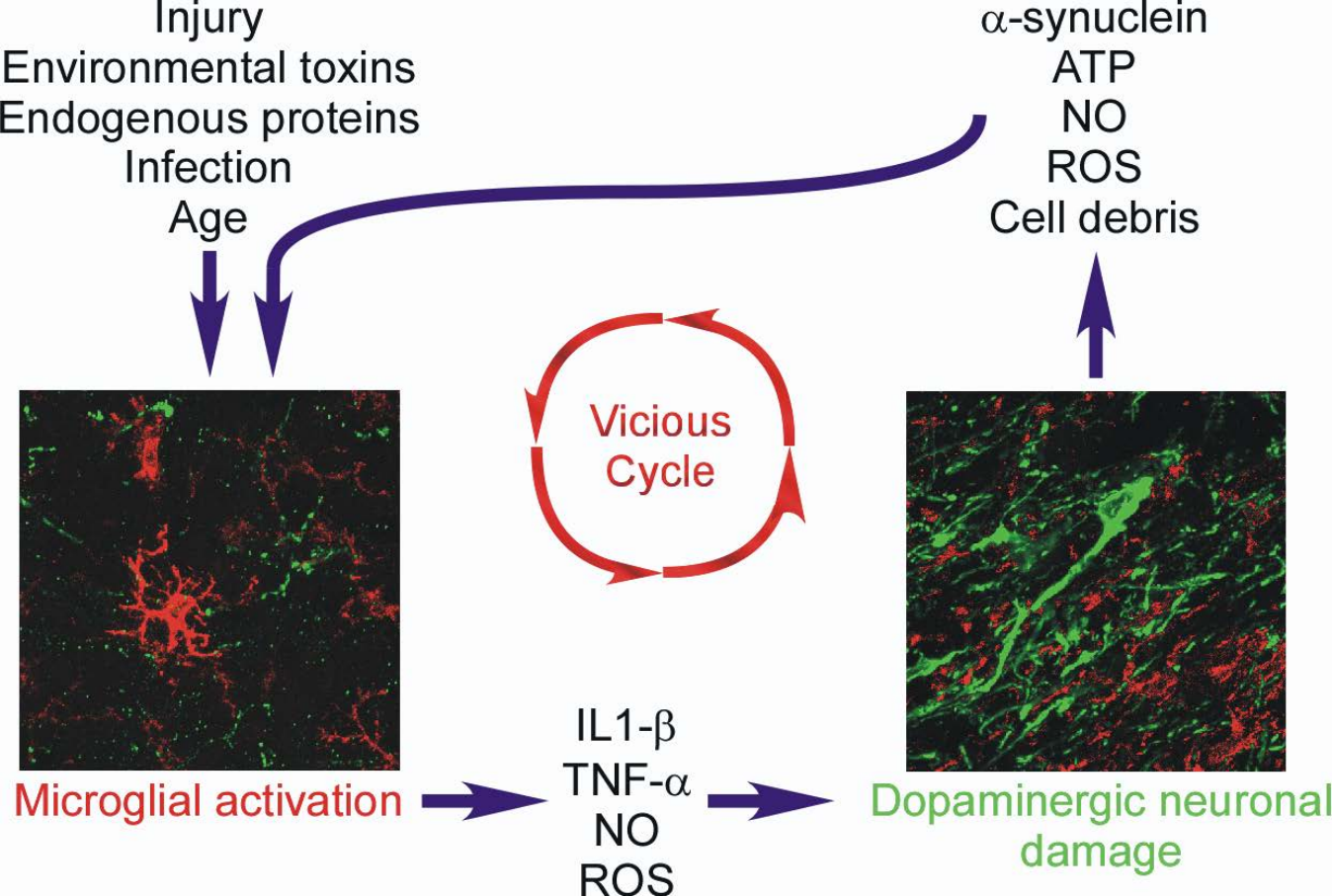
Table 2:

Anti-inflammatory agents in animal models of Parkinson's disease

Agent	Mode of action	Species	PD model	Effects	References
Dexamethasone	SAID	Mouse	MPTP	1. Prevented striatal DA depletion 2. Protected DA neurons in SN	Kurkowska-Jastrzebska et al., 2004
		Rat	LPS	1. Prevented striatal DA depletion 2. Protected dopaminergic neurons in SN	Castano et al., 2002
Aspirin	NSAID	Mouse	MPTP	Prevented striatal DA depletion	Aubin et al., 1998
		Rat	6-OHDA	Prevented striatal dopamine depletion	Di Matteo et al., 2006
Salicylic acid	NSAID	Mouse	MPTP	1. Attenuated akinesia and catalepsy 2. Prevented DA depletion and changes in DA turnover in nucleus caudatus putamen	Mohanakumar et al., 2000
Ibuprofen	NSAID	Mouse	MPTP	1. Partially prevented striatal DA depletion	Kurkowska-Jastrzebska et al., 2006
Indomethacin	NSAID	Mouse	MPTP	1. Prevented striatal DA depletion 2. Protected DA neurons in SN	Kurkowska-Jastrzebska et al., 2002
Celecoxib	NSAID	Rat	6-OHDA	Reversed striatal DA neuronal fibre and nigral DA neuronal cell loss	Sanchez-Pernaute et al., 2004
Minocycline	Microglial activation inhibitor	Mouse	MPTP	1. Protected DA neurons in SN 2. Prevented DA depletion in thestriatum and nucleus accumbens	Du et al. 2001; Wu et al., 2002
		Rat	6-OHDA	1. Reduced apomorphine-induced rotations 2. Protected DA neurons in SN	He et al., 2001; Quintero et al., 2006
		Rat	LPS	Protected dopaminergic neurons in SN	Tomas-Camardiel et al., 2004
Interleukin-10	Anti-inflammatory cytokine	Rat	LPS	Protected DA neurons in SN	Arimoto et al., 2006
		Rat	6-OHDA	1. Protected dopaminergic neurons in SN	Johnston et al., 2008

				2. Prevented striatal DA depletion 3. Reduced apomorphine-induced rotation	
Pioglitazone	PPARγ agonist	Mouse Rat	MPTP LPS	Protected DA neurons in SN 1. Prevented striatal DA depletion 2. Protected DA neurons in SN	Dehmer et al., 2004 Hunter et al., 2007
Rosiglitazone	PPARγ agonist	Mouse	MPTP	1. Prevented errors in beam traversal test 2. Protected DA neurons in SN 3. Partially prevented striatal DA depletion	Schintu et al., 2009
Glatiramer acetate	Immunisation	Mouse	MPTP	1. Prevented striatal DA depletion 2. Protected DA neurons in SN	Benner et al., 2004
Vasoactive intestinal peptide	Anti-inflammatory molecule	Mouse	MPTP	1. Protected DA neurons in SN 2. Protected striatal DA fibres	Delgado and Ganea, 2003
Thalidomide	TNF inhibitor	Mouse	MPTP	1. Prevented striatal DA depletion 2. Protected DA neurons in SN	Boireau et al., 1997; Ferger et al., 2004
IKK inhibitor	Blockade of NF-κB signalling	Rat	LPS	1. Protected DA neurons in SN	Zhang et al., 2010
Nisoxetine	NA transporter inhibitor	Mice	MPTP	1.Protected DA neurons in Striatum	Rammelfanger et al., 2004
Salmeterol	β-2-adrenoceptor agonist	Mice	LPS MPTP	1.Inhibits LPS-induced microglial activation	Qian et al., 2011

Figure 1. Microglial activation and dopaminergic neuronal damage. Schematic representation of the impact of microglial activation (induced by injury, environmental toxins, endogenous proteins, infection or age) on dopaminergic neuronal deterioration through the release of inflammatory mediators, and the consequent precipitating effect of substances released from dying dopaminergic neurons on microglial activation.


Injury
Environmental toxins
Endogenous proteins
Infection
Age
α-synuclein
ATP
NO
ROS
Cell debris
Vicious Cycle
Microglial activation
IL1-β
TNF-α
NO
ROS
Dopaminergic neuronal damage