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Inflammatory Responses and Regulation in Parkinson's Disease

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1. Introduction

Parkinson's disease (PD) is a slow, progressive neurodegenerative disorder affecting an estimated 6 million people worldwide (Litteljohn, Mangano et al. 2011). The etiology of the disease is characterized by increasing loss over time of dopaminergic neurons (DA-neurons) in the substantia nigra (SN) as well as the depletion of dopamine in the striatum, which eventually leads to pathological and clinical symptoms (Jenner and Olanow 2006). PET imaging and post-mortem analyses of the brains of PD patients indicate that the appearance of symptoms, including tremor, bradykinesia, rigidity, slowness of movement, and postural instability (Jellinger 2001), generally are manifest once 60% of DA-neurons have died and a 70% threshold decrease in normal DA activity has been reached (Klockgether 2004; Litteljohn, Mangano et al. 2011). Epidemiological studies indicate that only about 10% of PD cases are early onset , i.e. prior to the age of 50 and occur mainly in familial clusters (Mizuno, Hattori et al. 2001). These cases have established genetic bases due to mutations in several recently identified genes, including parkin, leucine-rich repeat kinase 2 (LRRK2), α-synuclein, PINK-1, or DJ-1 (Polymeropoulos, Lavedan et al. 1997; Lucking, Durr et al. 2000; Abou-Sleiman, Healy et al. 2003; Farrer, Haugarvoll et al. 2006; Sun, Latourelle et al. 2006; Jiang, Wu et al. 2007; Weng, Chou et al. 2007; Bonifati, Wu-Chou et al. 2008). The majority of PD cases (approximately 90%) are late onset and idiopathic (Tanner 2003). Although the etiology of idiopathic PD is uncertain, this form of PD particularly affects the elderly, with average onset of clinical symptoms between 60 and 65 years of age (Litteljohn, Mangano et al. 2011). Idiopathic PD is thus age-associated, with approximately 1% of the population being affected by 65-70 year of age, increasing to 4-5% at 85 years (Fahn 2003; Tansey, McCoy et al. 2007). However, the causes of idiopathic non-familial PD are probably multifactorial, with some form of genetic predisposition, environmental insults and/or aging all likely to be important factors in disease initiation and progression (Nagatsu and Sawada 2006; Dickson 2007; Vilar, Coelho et al. 2007; Singh, Singh et al. 2008).

While the exact cause of chronic neurodegeneration of PD is not known, increasing evidence suggests that chronic inflammation is the fundamental process mediating the progressive nature of the neurodegeneration characteristic of PD (McGeer, Yasojima et al. 2001; Hirsch and Hunot 2009). In animal PD models, long-term inflammation induces progressive loss of DA neurons within the SN brain region (Gao, Jiang et al. 2002; Dauer and Przedborski 2003; Bartels and Leenders 2007). Neuroinflammation, which is characterized by activation of

both the innate and adaptive immune response, has been demonstrated in PD patients by the preponderance of activated microglia within the SN, and the increased production in the CNS of inflammatory mediators, such as cytokines, chemokines, reactive oxygen species (ROS) and reactive nitrites (Cicchetti, Lapointe et al. 2005; Loeffler, Camp et al. 2006; Ghosh, Roy et al. 2007; Cicchetti, Drouin-Ouellet et al. 2009). Post mortem analyses of brains from PD patients provide clear evidence of large numbers of human leukocyte antigen (HLA-DR) and CD11b-positive microglia in the SN, the brain region in which the degeneration of DA neurons is most prominent (McGeer, Itagaki et al. 1988). Expression of the inflammatory markers MHC II, TNFα and cyclooxygenase (COX-2) is also higher in SN tissue of patients with PD than in comparable tissue from unaffected controls (McGeer, Itagaki et al. 1988; Boka, Anglade et al. 1994; Knott, Stern et al. 2000). Additionally, levels of proinflammatory mediators, including TNFα, IL-1β, IL-6, (ROS), and eicosanoids, are all elevated in the SN, striatum, cerebrospinal fluid (CSF) and/or peripheral blood mononuclear cells (PBMC) of PD patients (McGeer, Itagaki et al. 1988; Qureshi, Baig et al. 1995; Mogi, Harada et al. 1996; Nagatsu, Mogi et al. 2000; Imamura, Hishikawa et al. 2003; Teismann and Schulz 2004; Nagatsu and Sawada 2006; Sawada, Imamura et al. 2006; Hirsch and Hunot 2009; Pisani, Moschella et al. 2010). Nitric oxide (NO) free radicals are also elevated in PD as indicated by increased nitrite (an indicator for NO) present in the CSF, as well as increased expression of inducible nitric oxide synthase (iNOS) within the SN of PD patients (Qureshi, Baig et al. 1995). Oxidative damage measured by the presence of nucleoside oxidation product 8-hydroxyguanosine, is approximately 16-fold higher in SN of PD patients and post-mortem analysis of the brains of PD patients also show evidence of the oxidation of lipids, DNA and proteins (Owen, Schapira et al. 1996; Spencer, Jenner et al. 1998; Halliwell 2006). Reduced levels of antioxidant glutathione (GSH) concomitant with increased concentrations of oxidized GSH, are found in the surviving SN neurons of PD patients compared to normal controls, indicating these neurons were undergoing increased oxidative stress (OS) at the time of death (Sofic, Lange et al. 1992; Pearce, Owen et al. 1997).

In addition to direct evidence for increased inflammatory activity within the CNS of patients with PD, other aspects of the etiology of PD suggest this is primarily an inflammatory disorder. For example, PD patients display decreased activity in mitochondrial complexes I and I/III (Krige, Carroll et al. 1992), and the inhibition of mitochondria respiratory complex-I after exposure to MPTP gives rise to PD-like pathologies in humans (Tetrud, Langston et al. 1989; Langston, Forno et al. 1999), primates, mice and rats (Yazdani, German et al. 2006; Jackson-Lewis and Przedborski 2007). This is because DA neurons appear to have an intrinsic sensitivity to complex I defects based on studies that demonstrate the selective neurotoxic effects of the pesticide rotenone on DA neurons only, despite the fact that rotenone inhibits complex I throughout the brain (Sherer, Betarbet et al. 2002). However, even direct inhibition of complex-I by MPTP in DA neurons results in neurodegeneration that is primarily inflammatory in nature (Ghosh, Roy et al. 2007; Qian, Gao et al. 2007; Qian and Flood 2008). Further evidence of the key role of inflammation in PD is seen in other features of the disease. For example, blood-brain-barrier (BBB) leakage has been found in positron-emission tomography (PET) images of the brains of PD patients (Kortekaas, Leenders et al. 2005), and is likely caused by increased inflammation in PD. In addition, increased angiogenesis also occurs in PD patients (Faucheux, Bonnet et al. 1999) , and in the SN of a monkey-model of PD (Barcia, Bautista et al. 2005). Increased expression of the angiogenic-stimulant vascular endothelial growth factor (VEGF) and its major receptor

VEGFR1, have been found post mortem in the SN of PD patients (Wada, Arai et al. 2006), and this is consistent with increased angiogenesis found in PD brains (Faucheux, Bonnet et al. 1999). Excess VEGF induces increased macrophage migration mediated by VEGFR1 (Huusko, Merentie et al. 2009) and VEGF also induces BBB disruption in animal models after brain injury (Zhang, Zhang et al. 2000; Nguyen, Julien et al. 2002; Rite, Machado et al. 2007; Argaw, Gurfein et al. 2009) as well as in a rat model of PD (Rite, Machado et al. 2007). The VEGFR antagonist, Cyclo-VEGI, reduces inflammation and vascular leakiness, and is neuroprotective against excitotoxin-induced neurodegeneration in rats (Ryu and McLarnon 2008). This suggests dysregulated VEGF expression in the PD brain is also a key part of the neuroinflammatory response and increased edema in PD (Kirk and Karlik 2003; Suidan, Dickerson et al. 2010) (Nguyen, Julien et al. 2002; Nguyen, Tatlipinar et al. 2006; Zhang, Wang et al. 2006).

It is also worth noting that the innate immune cells of the brain, including microglia, become more reactive with age and that this might contribute to increased neuroinflammation in the elderly at some time point after activation of the peripheral immune response (Godbout and Johnson 2009). It has been suggested that prolonged exposure over a lifetime to inflammatory cytokines in the brain might eventually lead to various neurologic disorders (Godbout and Johnson 2009). This increased susceptibility to chronic inflammation in the elderly could contribute to the increased risk of PD associated with age. With growing elderly populations in many countries, PD is potentially an expanding public health problem. It is therefore critical that therapeutic interventions be identified and developed, that can halt and eventually reverse the neurodegeneration characteristic in PD. Treatments that focus on reducing chronic inflammation and pro-inflammatory microglial cell activation offer great promise for this sort of therapy. Therapies that foster microglia phenotypes which are non-inflammatory and supportive of neuroregeneration, could also prove beneficial in treating PD in the future.

In this chapter, we will discuss inflammatory mechanisms that play a crucial role in the progression of PD, and the therapeutic efficacy of using several anti-inflammatory compounds to treat progressive PD. We will also discuss the biology of microglial cells, including the cellular and molecular mechanisms that activate and regulate their inflammatory response, the evidence that implicates their different inflammatory mediators in the destruction of DA-neurons, and the efficacy of using different anti-inflammatory cytokines such as IL-10 and 1β, natural anti-inflammatory compounds such as *sinomenine*, *luteolin,* and *curcumin*, and the anti-inflammatory drugs morphinans and cyclosporine A, cell-based treatments such as Treg therapy, and specific anti-inflammatory therapies such as NF-κB inhibitors and β2-Adrenergic Receptor (β2AR) agonists. in halting or reversing the degenerative effects of inflammation within the SN. Finally, we will propose a model for PD as it relates to chronic inflammation, and discuss some possible future directions for the therapeutic treatment of PD.

2. Neuroinflammation in Parkinson's Disease

2.1 Microglia and chronic inflammation in neurodegeneration

Over two decades ago, high levels of activated microglia were discovered in the SN of PD patients (McGeer, Itagaki et al. 1988), first suggesting a connection between inflammation and PD. Since then, a wide range of inflammatory mediators produced by active microglia

have been identified post mortem in PD tissue samples (Hirsch 2000; Orr, Rowe et al. 2002). The presence of activated microglia has also been verified in the SN of PD animal models (rodents and primates) (Akiyama and McGeer 1989; Barcia, Sanchez Bahillo et al. 2004; Gao, Miao et al. 2011). Studies using animal models of PD have begun to elucidate the inflammatory mechanisms that underlie the neurodegeneration of DA neurons and loss of DA production which are hallmarks of the disease. It has been found that intranigral injection of the pathogen product lipopolysaccharide (LPS) induces increased levels of CD11b+ and microglia and neutrophils in the SN of rats when compared to levels found in the cortex (Ji, Kronenberg et al. 2009). This same study also observed pronounced damage to endothelial cells and BBB permeability within the SN of the LPS-injected rats (Ji, Kronenberg et al. 2009). In this model, direct intranigral injection LPS or administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced PD-like symptoms accompanied by increased activation of microglia in the SN. Of particular significance is another finding that activated microglia and elevated levels of pro-inflammatory TNFα could be detected in the SN of monkeys from 1 to 14 years after an initial brief administration of MPTP (McGeer, Schwab et al. 2003; Barcia, Sanchez Bahillo et al. 2004; Barcia, de Pablos et al. 2005). These observations suggested that a brief insult to the brain by toxins could induce a chronic inflammatory state with concomitant progressive neurodegeneration. Additional support for sustained inflammation after insult is provided by an unfortunate human example of accidental exposure to MPTP in contaminated illegal street-drugs. Post-mortem evidence of activated microglia and degeneration in the SN of these human patients remained evident from 3 to 16 years after intravenous injection of the toxin (Langston, Forno et al. 1999).

Among the many inflammatory factors produced by microglia, superoxide is one of the major mediators of neurodegeneration. DA neurons are especially vulnerable to oxidative insults and this strongly supports the association of microglia activation with progressive PD (Block and Hong 2007). It is known that the normal midbrain region encompassing the SN contains nearly five times more microglia than other areas of the brain (Kim, Mohney et al. 2000). Understanding the progressive nature of microglia-mediated neurotoxicity, and the common mechanism of microglia activation by various diverse toxins or insults, thus has prime therapeutic importance for treating PD (Nguyen, Julien et al. 2002).

2.2 Inflammatory mechanisms and dopaminergic-neuron death

Several different animal models of PD have found that both systemic inflammation and direct dopaminergic neurotoxicity can initiate or exacerbate the neuroinflammation and neurodegeneration that are hallmarks of the disease. Injection of MPTP results in chronic neuroinflammation and progressive neurotoxicity in humans (Langston, Forno et al. 1999) and other primates (McGeer, Schwab et al. 2003). In the former case, an accidental intravenous injection of MPTP-contaminated street-drugs left several patients ill with progressive motor-dysfunction which was shown in post mortem analysis to be mediated by DA-neuron loss in the SN, very similar to what is observed following MPTP injection in both rodent and primate models of neurodegeneration (Langston, Forno et al. 1999; Qin, Wu et al. 2007). Similarly a single systemic injection of LPS in an rodent model results in significant loss (23%) of DA neurons in the SN beginning at 7-months post treatment, increasing to a 47% loss at 10-months post injection (Qin, Wu et al. 2007). This delayed, progressive loss of DA neurons in the SN recapitulates some of the hallmark characteristics

of PD. This model is further supported as a model for PD by a clinical case report that a patient displayed PD-related symptoms after accidental peripheral exposure to LPS (Niehaus and Lange 2003). However, the underlying mechanism that advances the progressive nature of the disease remains unclear. It is known that systemically injected LPS cannot readily cross the blood-brain barrier, and studies have shown that pro-inflammatory cytokines, actually mediate the mechanism of systemic LPS-induced DA neurotoxicity (Qin, Wu et al. 2007). Interestingly, systemic administration of LPS enhances motor neuron degeneration in animal models of another neurodegenerative disease, amyotrophic lateral sclerosis (ALS), 6 months after LPS injection (Nguyen, D'Aigle et al. 2004), suggesting this may be a common etiology for a number of chronic neurodegenerative conditions. In addition, systemic exposure to LPS was also shown to significantly exacerbate neuronal-cell death associated with ischemic insult in neonatal rats (Lehnardt, Massillon et al. 2003). The effects of systemic inflammation on neuronal survival may depend upon several factors such as brain region affected, length of time to allow cumulative effects, age of exposure to the inflammagen, presence of systemic TNFα, and severity of the inflammatory stimulation.

It now appears that it is the inflammatory cytokines TNFα, IL-1β and IL-6 which play major roles in the etiology of PD both systemically and within the CNS. First, TNFα produced in the periphery after systemic LPS injection is transported across BBB to enter the brain through a TNFα-receptor dependent mechanism (Gutierrez, Banks et al. 1993; Pan and Kastin 2002; Qin, Wu et al. 2007). TNFα then initiates an inflammatory cascade by interacting with TNFα receptors on the microglia, leading to the activation of transcription factor NF-κB within microglial cells, and resulting in the production of additional TNFα and other pro-inflammatory factors, and thus creating a persistent and self-perpetuating neuroinflammatory response that drives delayed and progressive loss of DA neurons in the SN (Park and Bowers 2010). In addition, TNFα is one of the primary pro-inflammatory cytokines that promote overproduction of ROS (Fernandez-Checa, Kaplowitz et al. 1997), a key player in DA-neurodegeneration (Gao and Hong 2008) (Qian, Flood et al. 2011). Another pro-inflammatory cytokine, IL-1β, is also under transcriptional control of NF-κB and is consequently up-regulated in neuroinflammation. Direct injection of recombinant IL-1β into the brains of rats induces astrocytic expression of hypoxia inducible factor (HIF-1α) which contributes to the induction of oxidative stress (Argaw, Zhang et al. 2006). IL-1β also induces the HIF-1α-VEGF pathway that results in increased BBB permeability and increased angiogenesis (Argaw, Zhang et al. 2006; Argaw, Gurfein et al. 2009), which are all found to be increased in PD patients (Kortekaas, Leenders et al. 2005). Similarly, IL-6 expression is controlled by NF-κB (Lappas, Permezel et al. 2002) and is increased under a variety of inflammatory conditions (Van Snick 1990; Dendorfer 1996), including an MPTP-induced mouse model of PD (Kohutnicka, Lewandowska et al. 1998). IL-6 expression from activated microglia coincides in the SN with loss of TH+ DA neurons after MPTP injection but is absent from the SN in uninjected controls (Kohutnicka, Lewandowska et al. 1998). Neuronal levels of IL-6 are also increased by oxidative stress which is another mediator of microglia activation, neuroinflammation and degeneration (Lee, Cho et al. 2010; Naik and Dixit 2011; Negi, Kumar et al. 2011).

In addition to inflammatory cytokines, oxidative stress appears to play a crucial role in the DA-neurodegeneration seen in PD. Oxidative stress occurs because of intracellular accumulation of reactive oxygen and nitrogen species (ROS & RNS) and, along with

mitochondrial dysfunction and inflammation, has been identified as central in the mechanism underlying the inflammatory pathogenesis of PD (Bartels and Leenders 2007; Monahan, Warren et al. 2008). Impaired mitochondrial function has been observed in PD (Schapira, Cooper et al. 1989; Schapira 1994; Jenner and Olanow 1996; Sherer, Betarbet et al. 2002; Keeney, Xie et al. 2006; Schapira 2006), in which mitochondria generate ROS as by-products of molecular oxygen consumption in the electron transport chain. Oxidative stress is hypothesized to initiate DA neuron loss in the SN (Jenner and Olanow 1998; Lin and Beal 2006). The brain is hypersensitive to oxidative damage in part due to the fact that oxygen consumption by brain cells constitutes 20% of total oxygen consumption in body. Brain tissue is also enriched in peroxidizable fatty acids and has low levels anti-oxidant defenses (catalase, SOD, glutathione, glutathione peroxidase) (Floyd 1999; Floyd 1999). Within the brain, the SN is amongst regions most vulnerable to oxidative insult. The SN is characterized by a pro-oxidative state, and has a high metabolic rate with high levels of the oxidizable species DA, DA-derived ROS, neuromelanin and other molecules that render the SN vulnerable to the possible effects of peroxynitrite and sulfite (Marshall, Reist et al. 1999).
Oxidative stress is part of the pro-inflammatory response of microglia within the CNS, and it has been found that NADPH oxidase (PHOX), is the major superoxide-producing enzyme of microglia. It is a molecular complex of membrane-associated cytochrome b558 (composed of 2 subunits: gp91phox and p22phox) and the cytosolic components: p47phox, p67phox, p40phox, and a small GTPase rac2 (Groemping and Rittinger 2005). Upon activation, the cytosolic subunits translocate to the membrane and form a functional enzyme to generate superoxide. Therapy directed against the oxidative stress response has proved beneficial in treatment for PD (Smith and Zigmond 2003; Jackson-Lewis and Smeyne 2005). Anti-inflammatory agents that inhibit NADPH oxidase activity are neuroprotective (Liu and Hong 2003; Qian, Block et al. 2006; Qian, Gao et al. 2007), and reduced DA neurotoxicity induced by LPS or MPTP has been demonstrated in PHOX-/- compared to wild-type mice (Gao, Liu et al. 2003; Qin, Liu et al. 2004). Pharmacological inhibition of PHOX by the specific inhibitor diphenyliodonium (DPI), also shows potent DA-neuroprotection *in vitro* (Qian, Gao et al. 2007). PHOX activity also regulates production of pro-inflammatory cytokines, such as TNFα, by activated microglia *in vitro* following LPS stimulation (Qin, Liu et al. 2004). This suggests that PHOX not only mediates superoxide production, but also controls the levels of other pro-inflammatory neurotoxic factors produced by activated microglia. Cell signaling pathways that regulate PHOX activity are still being elucidated but it has been shown that a microglial adhesion molecule, the integrin MAC1 (macrophage antigen complex 1), is closely linked with PHOX and plays an important role in microglia-mediated neuroinflammation and neurotoxicity (Hu, Zhang et al. 2008). Microglial- cell expressed MAC1 is indispensable for the enhanced neurotoxicity induced by LPS, a-synuclein, or MPTP in neuron-glia mixed cell cultures (Pei, Pang et al. 2007; Zhang, Dallas et al. 2007; Hu, Zhang et al. 2008). Furthermore, MAC1-deficient mice show resistance to MPTP-induced DA neurotoxicity *in vivo*. NADPH oxidase-generated oxygen free radicals are also required for MAC1-mediated phagocytosis in neutrophils (Coxon, Rieu et al. 1996). Therefore, the dual activity between MAC1 and NADPH oxidase might be a central mechanism underlying the reactive microgliosis that mediates oxidative damage and consequent progressive neurodegeneration after microglia activation.

2.3 Peripheral inflammation, microglial-cell activation and neurodegeneration

Neuroinflammation is an important defense mechanism against pathogens and environmental toxins damaging the brain. Under normal conditions, the central nervous

system (CNS) and the brain especially are considered to be immune privileged (Neuwelt and Clark 1978; Smith, DeGirolami et al. 1992; Lotan and Schwartz 1994). Any immune response is very highly regulated with a finely balanced anti-inflammatory environment within the CNS combined with vigilant immune surveillance by circulating immune cells and those that are resident in the CNS. Under pathological conditions, the brain mounts an aggressive, acute inflammatory response to invading pathogens, infection, trauma, stroke or any other threat to homeostasis. These perturbations trigger the activation of microglia, the brain resident macrophages (Ransohoff and Perry 2009), as well as local invasions of circulating immune cells and the production of ROS and RNS (Mosley, Benner et al. 2006; Tansey, McCoy et al. 2007; Whitton 2007). The resident microglia aid in functional regulation of other immune cells particularly the helper T-cells and dendritic cells (DC) which also play critical roles in the initiation and maintenance of any neuroinflammatory response to pathological threats. However, inflammation in the brain is a 'two-edged sword' (Wyss-Coray and Mucke 2002) because if the tight regulation of the inflammatory process breaks down in any manner, the inflammatory response can switch from being beneficial to highly detrimental to brain function. In acute situations short-lived inflammatory mechanisms limit injury and promote healing (Wyss-Coray and Mucke 2002; McGeer and McGeer 2004). Microglia are the critical elements in an acute neuroinflammatory response that minimize tissue damage, restore tissue to homeostasis and promote would healing processes. Conversely, when inflammation is chronically sustained at high levels, this can lead to brain-tissue damage with concomitant initiation and progression of neuroinflammatory diseases such as PD.

While microglial cells are the major immunocompetent cells in the CNS and are important mediators in the pathogenesis of PD (Herrera, Tomas-Camardiel et al. 2005; Smeyne, Jiao et al. 2005; Zhou, Wang et al. 2005), up-regulation of humoral response and other peripheral immune components has been identified in both idiopathic and genetic cases of PD (Orr, Rowe et al. 2005). Elevated levels of IL-1β, TNFα, IL-6 have been described in post mortem tissue from PD patients (Mogi, Harada et al. 1994; Mogi, Harada et al. 1994; Mogi, Harada et al. 1996), and PD patients show higher levels of IL-1β, TNFα, Il-1, CD4+ and CD8+ cells in serum and CSF (Dobbs, Charlett et al. 1999; Bas, Calopa et al. 2001; Hisanaga, Asagi et al. 2001; Reale, Greig et al. 2009). CD8+ T cells have also been found associated with degenerating SN neurons (McGeer, Itagaki et al. 1988), and classical complement components have been isolated in the Lewy bodies that form in the SN of PD patients (Yamada, McGeer et al. 1992). Significantly, compromised BBB integrity has also been observed in PD patients (Kortekaas, Leenders et al. 2005), indicating that factors in peripheral inflammation have ready access to the brain and may also be involved in the neurodegenerative process probably via an effect on the activation of microglia. Complement proteins normally circulate in the blood in an inactive state, but in response to pathogenic threat, these proteins become activated in cascades of events that precipitate destruction and removal of the threat. Importantly for PD, studies have shown that complement factors C1q and mannose-binding lectins (MBL), participate in microglial cell activation and could be important in pathogenesis of neurodegeneration (Yamada, McGeer et al. 1992; Webster, Galvan et al. 2001; Whitton 2007). The importance of the classical complement pathway in PD has been established (Yamada, McGeer et al. 1992; Yamada, Chong et al. 1993), and MBL infiltration into the brain accompanies degeneration of TH+ neurons in MPTP-injected mice up to 28 days post MPTP administration in an animal model of PD (Chao, He et al. 2009). In the latter study, clear evidence of BBB breakdown was also

documented, providing further evidence that peripheral immunity probably participates in the activation of microglia and consequent DA-neuron destruction.

Normally, immune surveillance protects the healthy brain from pathogen assault and damage. Memory T-cell surveillance of the CNS is first regulated via migration from the blood into the cerebral spinal fluid (CSF) through the choroid plexus barrier (Engelhardt and Ransohoff 2005), while the recruitment and infiltration of immune cells into brain tissue occurs through the post-capillary venules into the perivascular space that surrounds microvascular endothelial cells (MVEC) which are joined together by tight-junctions that form the blood-brain-barrier (Carrithers, Visintin et al. 2000; Pachter, de Vries et al. 2003). MVEC in the brain closely interact with astrocytes, pericytes, perivascular microglia and neuronal cells such as DA-producing neurons to form the neurovascular unit. Thus, at these crucial checkpoints the specific microenvironment within the CNS tissues determines whether the immune cells survive to mount antigen-specific inflammatory response or if they will be eliminated. CD4+ T cells play a critical role in the initiation and maintenance of any immune response in the CNS including the brain, but to survive in this normally anti-inflammatory environment, they need additional stimulatory signals. Generally, CD4+ must be activated in the peripheral lymphoid system prior to migration into the CNS. Activated CD4+Th cells differentiate into distinct effector subsets that express unique suites of cytokines that perform different immunoregulatory functions. For example Th1 and Th2 produce predominantly INF-γ and IL-4 respectively which have differential effects on the activation state of microglia amongst other disparate outcomes (Appel, Beers et al. 2009)

T cells express many sensor receptors with which they assess the microenvironment milieu. CD+4 interact with other immune cells such as antigen presenting cells (APC) that take-up, process and present antigens via the major histocompatibility complex molecules (MHC). MHCII is expressed mainly in cells of the lymphoid system such as T cells, B cells, macrophages, and DC (Matarese, De Rosa et al. 2008). Under non-inflammatory conditions, cells of the CNS express low levels of MCH and in the absence of histocompatibility molecules the survival or further differentiation of activated T cells is low. Constitutively expressed mediators also help prevent differentiation of Th cells, and conversely promote development of Tregs. For example, the neuropeptide Vasoactive Intestinal Peptide (VIP) up-regulates Treg function which has an inhibitory effect on microglia and macrophages (Delgado, Chorny et al. 2005; Fernandez-Martin, Gonzalez-Rey et al. 2006). Additionally, anti-inflammatory cytokines secreted by astrocytes and glial cells, such as IL-10 and TGFβ1, induce differentiation of Tregs (Chen and Wahl 2003). However, during inflammation TGFβ1 works with IL-6 or IL-21 to induce differentiation of pro-inflammatory IL-17-producing T cells (Th17) indicating the distinction between anti-inflammatory and pro-inflammatory is not always straight forward. In an animal model of PD, the DA-neuron neurodegenerative effects of MPTP administration were Th17-cell mediated, and the induction of Tregs by VIP attenuated this effect (Reynolds, Banerjee et al. 2007; Reynolds, Stone et al. 2010). However, as it has also been shown that TGFβ1/IL-6 increases production of IL-10 as well as IL-17, this IL-10 is then capable of suppressing the degenerative effects mediated by Th17 cells (McGeachy, Bak-Jensen et al. 2007).

3. Efficacy of anti-inflammatory agents halting or reversing degeneration

Mounting evidence indicates that numerous types of inflammatory mediators such as TNFα, prostaglandin (PGE2), NO, free radicals, and other products of activated immune

cells can also play a role in the DA-neuron degeneration in several models of PD (Gao, Jiang et al. 2002; Dauer and Przedborski 2003; Bartels and Leenders 2007). Treatment using anti-inflammatory agents directed at a number of different pro-inflammatory targets could potentially halt, slow or even reverse PD disease progression. For example, steroidal anti-inflammatory drugs (SAIDS) such as dexamethasone have been used to stimulate neuroprotection against MPTP or LPS-induced toxicity (Kurkowska-Jastrzebska, Wronska et al. 1999; Castano, Herrera et al. 2002; Kurkowska-Jastrzebska, Litwin et al. 2004). In addition, non-steroidal anti-inflammatory drugs (NSAIDS), e.g. aspirin and ibuprofen, can reduce inflammation by inhibition of COX activity (Sairam, Saravanan et al. 2003)(Sairam et al. 2003). A prospective study found a significantly lower risk of developing PD in users of ibuprofen compared to non-users, and that the efficacy of taking ibuprofen was dose-dependently related to the number of weekly tablets of the drug taken (Gao, Chen et al. 2011). Microglial cell inhibitors such as minocycline have also shown neuroprotective characteristics in PD animal models (Du, Ma et al. 2001; Wu, Jackson-Lewis et al. 2002). Recently, strategies that directly inactivate the activation of the pro-inflammatory transcription factor NF-κB (Ghosh, Roy et al. 2007; Zhang, Qian et al. 2010), and/or activate the peroxisome proliferator-activated receptor-c (PPARc) (Bernardo, Ajmone-Cat et al. 2005), have produced beneficial modulation of inflammatory responses. Other strategies, including inhibition of ion channels in microglial cells (Thomas, Chartrand et al. 2007) can also be effective treatments aimed at halting progressive PD in an animal model of the disease. We will focus on five relatively new approaches in anti-inflammatory therapy for PD: (1) the use of exogenous anti-inflammatory cytokines IL-10 or TGFβ1, (2) the use of cell-based therapies such as regulatory T cells (Tregs), which are the major source of IL-10 or TGFβ1 in the resolution of neuroinflammation; (3) the use of morphinan-related compounds; (4) the targeting of NF-κB, the major transcriptional regulator of inflammation, and (5) the administration of beta2-adrenergic receptor (β2AR) agonists.

3.1 Therapies using anti-inflammatory cytokines: IL-10 and TGFβ

When acute inflammation is not resolved, i.e. the agent or event that originated the inflammatory response has not been eliminated, chronic inflammation can become entrenched and lead to neuroinflammation and degeneration. Normally, endogenous anti-inflammatory cytokines provide a negative-feedback mechanism which controls the continued activation of immune cells from potentially pathological effects (Moore, Lahiri et al. 2001; Strle, Zhou et al. 2001). Therefore, replacing or elevating the level of these anti-inflammatory regulators could be a therapeutic means to halt the chronic, pathological aspects of inflammation. IL10 and TGFβ1 are two major anti-inflammatory cytokines that are normally produced by Treg cells. Studies using exogenously supplied IL10 and TGFβ1 have shown potent effects in reducing neurotoxicity induced by either LPS or MPTP in PD models. In an *in vitro* model of PD, application of IL-10 to a mixed glial cell-neuron cell culture abrogated the degeneration of the neuron cells induced by either LPS or MPTP (Qian, Block et al. 2006). This inhibitory effect of IL10 was mediated through its inhibition of the production of TNFα, nitric oxide, and extracellular superoxide in the microglia cells within the mixed cell culture (Qian, Block et al. 2006). These *in vitro* effects of IL-10 are confirmed by *in vivo* results from a 6-OHDA rat model of PD. In this model, sustained administration of IL10 via a viral-vector, significantly protected DA-neuron from death and ameliorated behavioral deficits induced by intra-striatal delivery of 6-OHDA (Johnston, Su et al. 2008).

Several *in vitro* studies have shown that TGFβ1 can also protect neurons from cell death induced by oxidative stress (Prehn and Krieglstein 1994), glutamate excitotoxicity (Zhu, Yang et al. 2002), or chemical-induced hypoxia (Ruocco, Nicole et al. 1999). TGFβ1 suppresses the progression of neurodegeneration *in vivo* in an EAE model of MS (Szczepanik, Tutaj et al. 2005). Additionally, recombinant TGFβ1, intracerebrally delivered by a viral-vector, protects against brain injury induced by ischemia (Unsicker and Krieglstein 2002), excitotoxic-induced death (Ruocco, Nicole et al. 1999), and oxidative stress (Henrich-Noack, Prehn et al. 1996). Although exogenous TGFβ1 has thus been strongly suggested as a neuroprotective treatment, the molecular mechanisms underlying its neuroprotection have not been clearly elucidated. Recent evidence indicates that the neuroprotective effects of both IL10 and TGFβ1 are mainly due to their inhibition of ROS production in microglia during initial activation or in reactive microgliosis (Qian, Block et al. 2006; Qian, Wei et al. 2008). In mixed glial cell-neuronal cell cultures, application of TGFβ1 blocked neuron cell death through the inhibition of PHOX activity in cultures exposed to either LPS or MPTP. TGFβ1 prevented the ERK-dependent phosphorylation on p47phox in the microglial cells and blocked translocation and assembly of the PHOX molecular complex to the plasma membrane. Inhibition of PHOX activation consequently reduced oxidase activities induced by LPS (Qian, Wei et al. 2008). While the complete *in vivo* roles of IL10 and TGFβ1 in the regulation of chronic CNS inflammation in PD remain to be determined, both may provide promising basis for therapeutic use in PD treatments.

3.2 Morphinan-based anti-inflammatory therapeutics

Dextromethorphan (DM) is a well established drug that is used as the active ingredient in many cough suppressants. Over twenty years ago, it was recognized that DM and the metabolite dextrorphan (DX) could have anti-seizure effects in models of convulsive disorders such as epilepsy (Tortella, Ferkany et al. 1988). Dextrorphan was also shown to antagonize the *in vitro* excitation of spinal neurons by application of N-methyl-D-aspartate (NMDA), a glutamate receptor ligand (Church, Lodge et al. 1985). In addition, DX was found to block cortical neuron injury induced by NMDA or by glutamate (Choi 1987; Choi, Maulucci-Gedde et al. 1987; Choi, Peters et al. 1987; Koh and Choi 1987). Because NMDA receptors were known to mediate hypoxic injury in neuronal cell cultures, it was suggested that morphinan drugs, especially DX and DM, might be potential therapeutic treatments for brain injury from hypoxia of ischemia (Goldberg, Weiss et al. 1987). Additionally, since the loss of DA-neuron in PD leads to the secondary effect of hyperactive glutamatergic function, it was postulated that DM and DX might also be useful as adjunct therapies in treating PD (Albin, Young et al. 1989; Greenamyre and O'Brien 1991).

Several studies using PD animal models or *in vitro* cell cultures have shown that dextromethorphan and its metabolites are neuroprotective due to their anti-inflammatory properties and inhibitory function towards microglia activation (Liu, Qin et al. 2003; Zhang, Wang et al. 2004; Zhang, Qin et al. 2005). In the first of these studies, DM treatment protected DA-neurons from LPS-induced neuron death in mixed glial-neuronal cell cultures (Liu, Qin et al. 2003). Furthermore, the neuroprotective effects of DM were mediated through inhibiting microglial cell activation (Liu, Qin et al. 2003). Similarly, DM inhibited microglia activation and was neuroprotective when administered daily to mice that had been injected with MPTP (Zhang, Wang et al. 2004). Another metabolite of DM, 3-hydroxymorphinan (3-HM), was shown to have the greatest potency (of several tested

methorphinans) for attenuating the loss of DA-neurons in the SN, as well as restoring motor functions in an MPTP-injection mouse-model of PD (Zhang, Qin et al. 2005). 3-HM also protected neuronal cells in mixed glial-neuronal cells cultures by reducing MPTP-induced microgliosis and decreasing the production of ROS. In addition to this neuroprotective property, 3-HM was also found to have neurotrophic effects. The neurotrophic effects of 3-HM were mediated by induction of increased expression of neurotrophic factors, including GDNF, EGF, NTF and TGFβ1, by astroglial cells in mixed cultures with neuronal cells (Zhang, Wang et al. 2004; Zhang, Shin et al. 2006). In another study using mixed neuron-glia cultures, both l-morphine and it synthetic steroenantiomer, d-morphine, reduced LPS or MPTP-induced DA-neuron death with similar efficacy (Qian, Tan et al. 2007). These results indicated that morphine exerts anti-inflammatory effects either by inhibition of direct microglial cell activation via LPS or through attenuating reactive microgliosis induced by MPTP. A naturally occurring d-morphinan, sinomenine, also has neuroprotective effects and will be discussed below (Qian, Xu et al. 2007).

While DM and other morphinan compounds appear to have strong neuroprotective properties in animal model systems of PD, early human trials using DM to treat PD patients were contradictory. While one study found daily high doses of DM could improve some motor-behavioral deficits in PD patients (Bonuccelli, Del Dotto et al. 1992), another similar trial using the same dose regimen reported no beneficial effects on PD motor-associated symptoms (Montastruc, Fabre et al. 1994). Significantly, more recent double-blind trials have confirmed that DM can improve motor function in PD patients, especially the dyskinesia associated with long-term levadopa treatment (Verhagen Metman, Blanchet et al. 1998; Verhagen Metman, Del Dotto et al. 1998). It has been suggested that the uncertainty over the true effects of DM might be due to the relatively rapid metabolism of DM *in vivo* (Werling, Lauterbach et al. 2007). Although, DX and other DM metabolites have shown similar neuroprotective properties in preclinical studies, only DM seems to function through multiple mechanisms rather than simply blocking activity of the NMDA-receptor (Werling, Lauterbach et al. 2007). In situ DM concentrations can be increased if given in conjunction with a low dose of the drug quinidine which retards metabolism of DM and leads to increased DM concentrations in plasma, resulting in greater bioavailability (Pope, Khalil et al. 2004). Clearly, DM presents an attractive potential for use in combinatorial treatment for at least ameliorating the motor deficits characteristic of PD and possibly for attenuating the activation of microglia and chronic inflammation also prominent in PD.

3.3 Sinomenine, luteolin and curcumin as treatments for Parkinson's disease

Several natural compounds isolated from plants, including sinomenine, luteolin and curcumin, are also being investigated for their ability to attenuate inflammation and provide neuroprotection against the loss of DA neurons. Although these three agents belong to different families of organic compounds, they have all shown anti-oxidant, anti-inflammatory and neuroprotective qualities *in vitro* cell-culture models of neurodegenerative diseases including PD. The first of these is sinomenine, a morphinan related alkaloid compound purified from a medicinal plant (Sinomenine acutum) that has been traditionally used to treat inflammatory disorders (Liu, Resch et al. 1994; Liu, Buchner et al. 1996). In a study using rat midbrain mixed glial cell-neuron cell cultures, sinomenine protected the neuronal cells from both LPS and MPP+ induced cell death (Qian, Xu et al. 2007). Sinomenine protected neurons by reducing release of extracelluar ROS and inhibiting PHOX/p47 from translocation to the plasma membrane where the complex becomes

activated. These effects were mediated by inhibition of microglial cells since sinomenine failed to protect neuronal-cell enriched cultures which lacked microglia from MPP+ induced damage and death (Qian, Xu et al. 2007).

Another plant extract, the flavonoid luteolin, has also been used for its anti-oxidant and anti-inflammatory properties. Luteolin was demonstrated to have neuroprotective effects by inhibiting oxidative stress-induced cell death in the DA-producing SH-SY5Y cell line (Kang, Lee et al. 2004). In mixed glial-neuron midbrain cell cultures from rats, luteolin attenuated the loss of TH+ DA-neurons after addition of increasing concentrations of LPS. The protective effect of luteolin in these experiments was shown to be mediated through the inhibition of microglial cell activation, and reduced production of TNFα, NO and ROS (Chen, Jin et al. 2008). Similarly, curcumin, the active anti-inflammatory isolate from turmeric (Curcuma longa), is known to have anti-inflammatory neuroprotective effects in CNS disorders. In an experimental allergic encephalomyelitis (EAE) mouse model of MS, curcumin inhibited EAE development by attenuating microglia activation and IL-12 production as well as Th1 cell differentiation (Natarajan and Bright 2002). Curcumin also has shown protective effects against LPS-induced DA neuron cell death in mixed rat neuron-glial cell cultures which were mediated by inhibition of the production of proinflammatory factors in microglia (Yang, Zhang et al. 2008). Taken together, the neuroprotective results from these three natural plant products suggest an interesting possibility for PD therapeutics. Since these and other similar plant-based isolates can cross the BBB and have anti-inflammatory as well as anti-oxidant properties, they may provide new directions for adjunct therapy.

4. Anti-inflammatory cell-based strategy for Parkinson's disease therapy: Regulatory T-cells

An anti-inflammatory strategy currently being studied as a cell-based therapy in PD involves the therapeutic introduction of Treg cells. It is now believed that Tregs suppress immune reactivity through multiple mechanisms, such as release of IL-10 and TGFβ, induction of apoptotic tolerance, and suppression of metabolic functions in effector immune cells such as microglia and effector T-cells. As the primary source IL10 and TGF1β *in vivo*, Tregs have been shown to be the major cells which regulate the inflammatory response in a number of disorders through their effects on the innate and adaptive immune responses that have escaped normal pathways of control. Recent studies using models of neurodegeneration demonstrated that induction of an anti-inflammatory Treg response inhibited microglial activation, and promoted neuronal survival (Reynolds, Banerjee et al. 2007; Liu, Gong et al. 2009; Reynolds, Stone et al. 2009). In another report, adoptively transferred Treg cells attenuated a Th17-mediated inflammatory response in mice that had been injected with MPTP and concomitantly vaccinated with nitrated (N) α-synuclein. In this model, injection of N-α-synuclein elicited an adaptive immune response in conjunction with the MPTP-induced neurotoxicity both of which were ameliorated by the transfer of natural or VIP-induced Treg cells in these mice (Reynolds, Stone et al. 2010). Tregs have also been shown to promote neurotrophic factor production from astrocytes (Reynolds, Banerjee et al. 2007; Reynolds, Stone et al. 2010), indicating their potential for neuroregeneration of DA neurons.

Strategies that use Th2 cells are also being employed. Th2 cells inhibit microglial cell activation through the production of IL4 and IL10, and stimulate the production of GDNF by astrocytes,

thereby providing neuroprotection against MPTP-induced neuronal death (Benner, Mosley et al. 2004). Copaxone, a peptide-based therapy approved for patients with MS, is thought to promote the development of Th2 cells which function to decrease CNS inflammation through the release of anti-inflammatory cytokines and neurotrophic factors (Kipnis and Schwartz 2002; Angelov, Waibel et al. 2003; Benner, Mosley et al. 2004; Schwartz 2004). Copaxone-induced T-cells also have neuroprotective effects in animal models of ALS and PD (Angelov, Waibel et al. 2003; Benner, Mosley et al. 2004). However, because the interactions amongst regulatory T cells, glial cells, neurons and other infiltrating leukocytes within the SN is incredibly complex and not well understood, further studies to elucidate the regulatory pathways involved are necessary to develop Th2-cell based therapies for PD patients.

5. Specific anti-inflammatory therapies

5.1 Therapies targeting pro-inflammatory transcription factor NF-κB

Many of the inflammatory mediators involved in inflammation and DA-neurodegeneration in PD are expressed in microglial cells and their regulation is primarily mediated by the transcription factor NF-κB. NF-κB was first described in 1986 as a transcription factor which is essential for the expression of mouse kappa light chain genes (Sen and Baltimore 1986; Sen and Baltimore 1986). It has since been shown that NF-κB functions to control gene expression of many of pro-inflammatory mediators (Tsoulfas and Geller 2001). Inflammatory cytokines such as TNFα and IL-1α and β, bacterial products such as lipopolysaccharide (LPS), and products of cellular damage strongly activate inflammatory responses through the activation of NF-κB. NF-κB subsequently plays an essential positive-feedback role in the inflammatory response through regulation of genes encoding inflammatory cytokines IL-1β, TNFα, and IL-12/23, as well as chemokines IL-8, MIP-1α, and MCP-1(Xia, Pauza et al. 1997; Roebuck 1999; Roebuck, Carpenter et al. 1999). NF-κB also mediates nitric oxide production (iNOS), expression of NADPH oxidase subunits p47 and p67 (Gauss, Nelson-Overton et al. 2007; Lawrence 2009), and adhesion molecules ICAM-1, VCAM, and E-selectin (Chen and Manning 1995; Tak and Firestein 2001). Activation of NF-κB is a key event in many chronic inflammatory diseases such as cardiovascular disease (Van der Heiden, Cuhlmann et al.), tissue reperfusion injury (Latanich and Toledo-Pereyra 2009), experimental autoimmune encephalomyelitis (EAE) (Vandenbroeck, Alloza et al. 2004), rheumatoid arthritis (Criswell 2010), and inflammatory bowel disease (IBD) (Atreya, Atreya et al. 2008). A large number of the therapeutic agents for treating human inflammatory conditions, including sulfasalazine, 5-aminosalicylates, and corticosteroids, as well as some natural anti-inflammatory compounds such as IL-10, TGFβ1, β2AR agonists, glutamate, and curcumin, may owe their anti-inflammatory effects to inhibition of NF-κB (Lawrence and Fong ; Wang, Boddapati et al. ; Pereira and Oakley 2008; Lawrence 2009). These anti-inflammatory agents are potent inhibitors of microglial activation, and are neuroprotective to DA neurons *in vitro* and *in vivo*. Clearly, NF-κB activity presents a key target to ameliorate chronic inflammation in humans. Therapeutic strategies to inhibit NF-κB activity in microglial cells may lead to more effective treatments for PD (Zhang, Qian et al. 2010; Flood, Qian et al. 2011).

The NF-κB family consists of dimeric transcription factors which include five members: c-Rel, RelA (p65), RelB, NF-κB1 (p50/p105), and NF-κB2 (p52/p100) (Flood, Qian et al. 2011). There are two major activation pathways: (1) the classical or canonical pathway, and (2) the

alternate or noncanonical pathway. While the non-canonical pathway does not appear to play a major role in the activation of inflammation, the classical pathway is thought to regulate the production of most pro-inflammatory mediators and is characterized by activation of a dimer of Rel proteins p50 and p65. In the inactive state this Rel dimer is complexed within the cytosol to the inhibitory protein IκBα complex (Lawrence 2009). The classical NF-κB pathway is initiated upon phosphorylation, ubiquitination, and subsequent proteasome-dependent degradation of IκBα. The phosphorylation of IκBα on serine residues is mediated by IκB kinase (IKK), which is a molecular complex of three proteins consisting of a heterodimer of the two catalytic subunits IKKα and IKKβ, along with IKKγ (the NF-κB essential modulator, NEMO) (May, Marienfeld et al. 2002; Huxford and Ghosh 2009; Oeckinghaus and Ghosh 2009). Embryonic cells derived from genetic knock-out mice lacking IKKβ, IKKγ, or p65 are unresponsive to classical NF-κB inducers such as TNFα and IL-1β (Reuther-Madrid, Kashatus et al. 2002; Sizemore, Lerner et al. 2002; Sizemore, Agarwal et al. 2004). Activation of IKK in response to inflammatory mediators such as TNFα, IL-1β, and LPS, depends critically on the presence of the IKKγ (NEMO) subunit of the IKK complex (Rudolph, Yeh et al. 2000; May, Marienfeld et al. 2002), which results in the phosphorylation of the IκB by the kinase activity of IKKβ (Huxford and Ghosh 2009; Oeckinghaus and Ghosh 2009). An N-terminal region of NEMO associates with a hexapeptide sequence within the C-terminus of both IKKα and IKKβ (NEMO binding domain or NBD), and disruption or mutation of this NEMO-NBD interaction site on either IKKβ or IKKγ results in a loss of responsiveness of cells to pro-inflammatory signaling (Flood, Qian et al. 2011). Agents that block the activation of NF-κB are capable of inhibiting the two major inflammatory pathways in microglia—activation of oxidative stress and production of inflammatory mediators, including cytokines TNFα, IL-1β, IL-6, as well as chemokines associated with inflammation (Qian, Flood et al. 2010).

Selective IKKβ and IKKγ inhibitors that do not target IKKα or the non-canonical P100/p52 pathway, should be promising therapeutic agents for treating chronic inflammatory disorders including PD. Such specific NF-κB inhibitors have recently been used in murine models of PD to halt the progression of neurodegeneration induced by the neurotoxin MPTP (Ghosh, Roy et al. 2007), or by activation of CNS inflammation by the intracranial injection of LPS (Zhang, Qian et al. 2010). Pretreatment of animals with a peptide against the NEMO-binding domain (NBD peptide) prior to injection of MPTP into mice, significantly inhibits the activation of NF-κB within the midbrain region. This inhibition of NF-κB activation is accompanied by a concomitant reduction in inflammatory mediator mRNA expression within the SN, as well as the expression of microglial cell activation marker CD11b. Mice receiving the NBD peptide prior to MPTP injection also showed highly significant protection of the nigrostriatum from MPTP-induced neurodegeneration of the TH+ neurons and the loss of dopamine production, as well as improvement in their locomotor function compared with MPTP-injected mice given mutant peptide. More importantly, administration of NBD peptide 2 days after injection of MPTP showed substantial protection of TH+ neurons, suggesting that NBD peptide can be used therapeutically to slow down or halt the progression of DA-neurodegeneration in MPTP-treated animals (Ghosh, Roy et al. 2007). In addition, infrared analysis of the brains of NBD-treated animals determined that significant levels of the NBD peptide localized within the brain tissue, suggesting that the NBD peptide could cross the BBB and reach sites of

neuroinflammation. The nature of the mechanism of NF-κB inhibition within the SN remains to be determined, but these data suggest NF-κB is a viable target for therapy for PD patients (Ghosh, Roy et al. 2007).

A second approach to inhibit inflammation has been to use small molecule inhibitors that specifically block function of IKKβ. One such specific inhibitor, called Compound A, is a small molecule inhibitor of the kinase activity of IKKβ but not IKKα. Compound A, also known as BAY-65-1942 (7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]–5-[(3S)-3-piperidinyl]-1,4-dihydro-2Hpyrido [2,3- d] [1,3]–oxazin-2-one hydrochloride), has been shown to specifically and effectively block the catalytic activity of IKKβ, inhibiting its ability to phosphorylate IκB and activate the cytosolic p50/p65 NF-κB heterodimers (Moss, Stansfield et al. 2007; Zhang, Qian et al. 2010). In one recent study, Zhang and colleagues (2010) used Compound A in an LPS-induced neurodegeneration model to inhibit the canonical NF-κB pathway and halt inflammation-induced DA-neurodegeneration. In this model, LPS was injected directly into one side of the midbrain of rats, leading to inflammation-induced degeneration of DA-neurons (Zhang, Qian et al. 2010). It was found that Compound A strongly inhibited the activation of NF-κB *in vitro* and *in vivo*, as well as the mRNA expression and subsequent release of pro-inflammatory mediators. Compound A also significantly inhibited LPS- and MPTP-induced DA-neurotoxicity *in vitro*, and this neuroprotective activity required the presence of microglial cells. Most importantly, administration of Compound A to animals injected intranigrally with LPS, attenuated LPS-induced DA neuronal loss and microglia activation within the SN ((Zhang, Qian et al. ; Zhang, Qian et al. 2010). These data provide strong evidence that NF-κB offers a promising potential therapeutic target to halt DA-neurodegeneration, and that much additional work needs to be performed to determine the optimal approach and agent best suited for the treatment of PD.

5.2 β2-AR agonists as PD therapeutics

A family of compounds that have recently been shown to potentially reduce inflammation and DA-neurodegeneration in animal models are the β2 adrenergic receptor agonists. The β2 adrenergic receptor (β2AR) is a G-protein coupled receptor (GPCR) which is known to regulate of smooth muscle function in the airway and vasculature. Interestingly, β2AR expression has also been identified on immune cells such as macrophages, microglia, T cells, and B cells, and signaling through this receptor can inhibit the inflammatory response of these cells (Koff, Fann et al. 1986; Severn, Rapson et al. 1992; van der Poll, Jansen et al. 1994; Sekut, Champion et al. 1995; Panina-Bordignon, Mazzeo et al. 1997; Farmer and Pugin 2000; Kin and Sanders 2006). Both short-acting and long-acting β2AR agonists have been used for pharmacological studies and clinical therapy, and results have indicated that they possess the ability to inhibit the inflammatory responses by immune cells. Several of these long-acting agonists such as salmeterol (Advair®) and formoterol (Symbicort®) are currently being used as anti-inflammatory therapeutics to treat asthma and chronic obstructive pulmonary disease (COPD) (Koto, Mak et al. 1996; Tashkin and Cooper 2004; McKeage and Keam 2009). However, potential use of β2AR agonists in neurodegenerative diseases in the CNS has not been well studied. Since most long-acting β2AR agonists are highly lipophilic and should readily cross the BBB, it is likely that these compounds could have an immunomodulatory effect on the progression of inflammation in PD patients by inhibiting

the activation of microglia that normally express high levels of β2AR (Tanaka, Kashima et al. 2002).

When long-acting β2AR agonists were tested for DA-neuroprotective properties, it was found that the compounds can inhibit DA-neurodegeneration *in vitro,* even if used at extremely low doses. Furthermore, administration of the long-acting β2AR agonist salmeterol significantly protects DA neurons against LPS- and MPTP-induced cytotoxicity *in vivo* (Qian, Wu et al. 2011). Mechanistic studies using primary midbrain neuron-glia cultures demonstrated that salmeterol, as well as several other long-acting β2AR agonists, have potent neuroprotective effects through their inhibition of microglial inflammatory mediator production. These anti-inflammatory effects of salmeterol require the presence of β2AR, are mediated through the inhibition of both MAPK and NF-κB signaling pathways in activated microglia, and function independently of the canonical GPCR/cAMP/PKA signaling pathway. It was further determined that this inhibition is dependent on the expression of β-arrestin 2, which suggests a novel mechanism for the long-acting β2AR agonists in regulating CNS inflammatory conditions (Qian, Wu et al. 2011). Therefore, the high specific activity and effectiveness of β2AR agonists such as salmeterol at inhibiting inflammation and DA-neurodegeneration within the CNS in these animal models suggests they have potential for the treatment of chronic inflammatory disorders and in particular, Parkinson's disease.

6. Proposed model of neuroinflammation in PD

Inflammation associated with PD can be initiated in the brain by internal factors such as a brain injury, a genetic mutation or some other brain insult or dysfunction (Nagatsu and Sawada 2006; Tansey, McCoy et al. 2007; Hirsch and Hunot 2009; Qian, Flood et al. 2010)(Figure 1). These sorts of intracerebral inflammatory stimuli activate the microglia which then up-regulate production of inflammatory factors including inflammatory cytokines such as TNFα, IL-1β or IL-6, as well as NO and ROS (Nagatsu, Mogi et al. 2000; Nagatsu and Sawada 2006; Tansey, McCoy et al. 2007). These in turn stimulate a further inflammatory response which results in a self-perpetuating chronic inflammatory condition (Qian and Flood 2008; Qian, Flood et al. 2010). Alternatively, inflammation in the periphery might induce the initial inflammatory response within the brain. Normally, the microvascular endothelial cells that line the blood vessels in the brain are tightly joined to each other through cell-cell tight junctions, and thus form the blood-brain-barrier which excludes most substances or cells from entry into the brain (Zlokovic 2008). A chronic peripheral inflammatory response can work to disrupt the cell-cell junctions and the blood-brain barrier, allowing access of inflammatory factors and cells into the brain (Stamatovic, Keep et al. 2008; Zlokovic 2008). These can then activate microglia and initiate the perpetual round of pro-inflammatory factor production leading to chronic neuroinflammation. Once microglia are activated, from whatever the source of initial inflammatory stimulus, the microglial response increases secretion of inflammatory cytokines and release of NO (Qian and Flood 2008). Microglial activation also precipitates an enhanced respiratory burst and release of ROS (Colton and Gilbert 1987). These various inflammatory mediators can trigger cell death in neurons (Chao, Hu et al. 1992; Colton and Gilbert 1993; Taylor, Jones et al. 2005), including DA neurons which seem to be especially vulnerable. Dying neurons then stimulate an intensified inflammatory response as the brain attempts to restore stasis (Qian, Flood et al. 2010). Therapies aimed at halting neurodegeneration are increasingly based on

intervention to top the chronic inflammatory response, including introduction of anti-inflammatory drugs, compounds, cytokines and Treg cells, which inherently release anti-inflammatory cytokines such as TGFβ1 and IL-10.

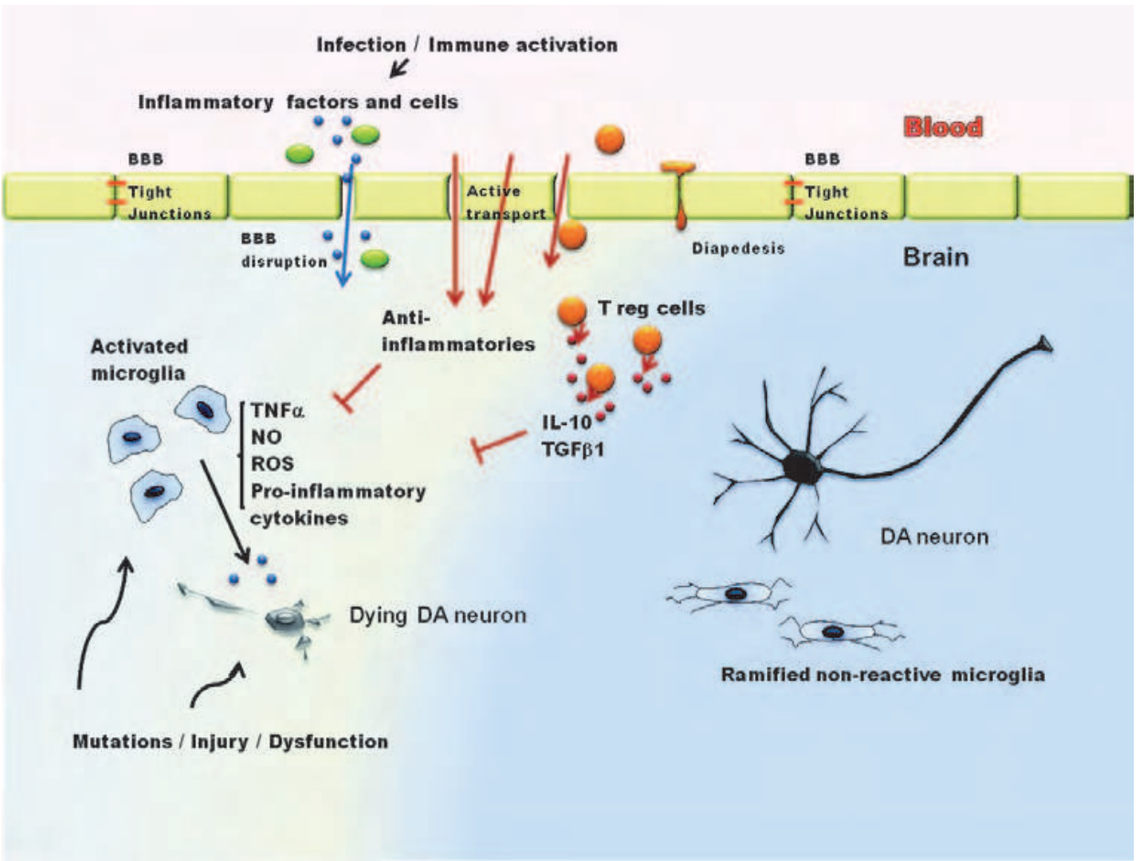

Fig. 1. Model relating chronic inflammation to dopaminergic (DA)-neuron death in Parkinson's Disease.

7. Future directions for PD therapy

Five relatively new approaches in anti-inflammatory therapy described above all show some promise for short-term or long-term therapeutics in PD. The use of exogenous anti-inflammatory cytokines such as IL10 or TGFβ1, has been shown to have potent effects in reducing neurotoxicity in both *in vitro* and in animal models of PD. However, although both cytokines are considered to be predominantly anti-inflammatory, they each can have pro-inflammatory effects in certain contexts. More thorough functional studies are needed for these anti-inflammatory cytokines, especially in the context of PD models before these might be readily used in human therapy. Particularly important factors include what form and what mode of delivery will optimize the anti-inflammatory effects of the cytokines as therapy and ameliorate any unintended negative effects. Cell-based therapies such as regulatory T cells (Tregs) offer great promise for long-term therapy in many degenerative disorders including PD. Both the use of T cells and stem cell transplantation focus on regeneration as well as intervening in neuronal death processes. However, some of the

potential problems with these cell-transplant strategies are obvious since these are invasive therapies and as such carry the attendant problems associated with transplants in general as well as the specific consequences of introducing these cells into PD patients. Much remains to be determined before they become readily applicable for PD therapy. Anti-inflammatory therapies have already been developed in animal models of PD and are being used to a limited extent in human studies. The finding that the chronic use of certain NSAIDs seems to lower the risk of PD is promising for possibly reducing PD incidence. Additionally, NSAIDS (or SAIDS) might be used profitably in combinatorial therapy for PD, but the long-term use of these drugs already has well documented potential health problems. Careful determination of the potential risks to PD patients as compared to what benefits may be gained from long-term use of NSAIDS or SAIDS needs to be addressed. This is particularly important since these drugs might be well suited to combinatorial therapy in conjunction with existing PD treatments. Similarly, morphinan-based drugs, or other drugs already used for treatment of other diseases such as beta2-adrenergic receptor agonists, hold the most immediate potential for development as therapeutics to treat PD. The normal pharmacokinetics and safety profiles have already been established for some of these drugs such as salmeterol, and although preclinical studies indicate potential efficacy in PD, again the specific pharmacokinetics and safety for treating the neuroinflammation underlying PD must be determined. Orally available NF-kB inhibitors are equally attractive as PD therapies and are currently being studied in preclinical applications in a variety of diseases including PD.

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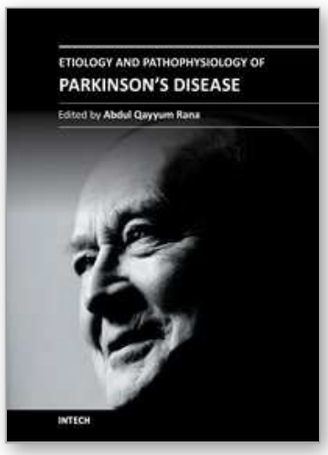

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This book about Parkinsonâ€™s disease provides a detailed account of etiology and pathophysiology of Parkinsonâ€™s disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinsonâ€™s disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinsonâ€™s disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinsonâ€™s disease.

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