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Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease, after Alzheimer's disease. The potential causes of PD remain uncertain but recent studies suggest neuroinflammation and microglia activation play important roles in PD pathogenesis. Major unanswered questions include whether protein aggregates cause the selective loss of dopaminergic neurons in the substantia nigra that underlies the clinical symptoms and whether neuroinflammation is a consequence or a cause of nigral cell loss. Within the microenvironment of the brain, glial cells play a critical role in homeostatic mechanisms that promote neuronal survival. Microglia have a specialized immune surveillance role and mediate innate immune responses to invading pathogens by secreting a myriad of factors that include, cytokines, chemokines, prostaglandins, reactive oxygen and nitrogen species, and growth factors. Some of these factors have neuroprotective and trophic activities and aid in brain repair processes; while others enhance oxidative stress and trigger apoptotic cascades in neurons. Therefore, pro- and anti-inflammatory responses must be in balance to prevent the potential detrimental effects of prolonged or unregulated inflammation-induced oxidative stress on vulnerable neuronal populations. In this review, we discuss potential triggers of neuroinflammation and review the strongest direct evidence that chronic neuroinflammation may have a more important role to play in PD versus other neurodegenerative diseases. Alternatively, we propose that genetic deficiency is not the only way to reduce protective factors in the brain which may function to keep microglial responses in check or regulate the sensitivity of DA neurons. If chronic inflammation can be shown to decrease the levels of neuroprotective factors in the midbrain, in essence genetic haploinsufficiency of protective factors such as Parkin or RGS10 may result from purely environmental triggers (aging, chronic systemic disease, etc.), increasing the vulnerability to inflammation-induced nigral DA neuron death and predisposing an individual to development of PD. Lastly, we review the latest epidemiological and experimental evidence supporting the potential use of anti-inflammatory and immunomodulatory drugs as neuroprotective agents to delay the progressive nigrostriatal degeneration that leads to motor dysfunction in PD.

Keywords

Microglia; inflammation; neuroinflammation; neurodegeneration; Parkinson's disease

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Introduction

A broad spectrum of neurodegenerative diseases of aging are associated with chronic inflammation, including diseases that affect the CNS such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and all of the tauopathies, and age-related macular degeneration (Block and Hong, 2005; McGeer et al., 2005). Although the key molecular and cellular events underlying development of these diseases are clearly divergent, one common way in which a number of divergent molecular or cellular events (e.g., mutations, oxidation, protein misfolding, truncation, or aggregation) may all contribute over time to death of neurons is via activation of resident microglial populations in specific brain regions. If the initial stimulus that elicited microglial activation is not resolved (as in the case of a genetic mutation or a prolonged or repeated environmental exposure or immunological insult), a self-sustaining cycle of neuroinflammation can ensue and such a chronic inflammatory environment is likely to elicit neuronal dysfunction and eventual death of vulnerable neuronal populations. Therefore, timely delivery of anti-inflammatory regimens in patient populations identified to be at risk due to genetic mutations may afford neuroprotective effects.

Parkinson's disease (PD) is the most common neurodegenerative movement disorder (Schapira, 2009a). It is an age-dependent disease characterized by resting tremor, slowed movement, postural instability and muscle rigidity (Gelb et al., 1999). The motor symptoms can be treated with dopaminergic drugs, however, the effectiveness diminishes as the severity of the clinical symptoms increases due to progression of the underlying neurodegeneration (Schapira, 2009b). The most prominent pathological features are the severe loss of dopaminergic neurons in the substantia nigra (SN) and the presence of proteinaceous inclusions called Lewy bodies (LBs) primarily composed of fibrillar α -synuclein and ubiquitinated proteins within some remaining nigral neurons (Lees et al., 2009). There is debate about whether LBs directly cause neuronal death or perhaps sequester smaller neurotoxic protein aggregates to preserve neuronal viability (Goldberg and Lansbury, 2000). The recent identification of mutations in several genes linked to rare inherited forms of PD has led to speculation that these mutations promote inclusion formation, ubiquitin-proteasome system (UPS) dysfunction and nigral cell loss, although the precise molecular mechanisms are unclear and the pathology in humans and animal models bearing these mutations is highly variable (Bonifati, 2007; Lim and Ng, 2009). Nevertheless, recent studies of transgenic animals with mutations linked to parkinsonism as well as neurotoxin and virus-based animal models of PD have provided valuable insight into potential pathogenic mechanisms involving neuroinflammation. Human clinical imaging, postmortem examinations and epidemiological studies have recently highlighted the role of neuroinflammation in PD and raise the interesting possibility that chronic inflammation may act as an environmental stressor to promote progressive degeneration of dopaminergic neurons. Here, we review data from key studies in support or against a role for neuroinflammation in PD pathogenesis or progression.

Evidence that neuroinflammation compromises dopaminergic neuron survival

In the past 15 years, a wealth of new information has emerged to suggest that inflammation-derived oxidative stress and cytokine-dependent toxicity may contribute to nigrostriatal pathway degeneration and hasten progression of disease in humans with idiopathic PD. The existence of ongoing inflammatory processes that may contribute to progression of PD is supported by evidence of activated microglia, accumulation of cytokines, Nuclear Factor kappa B (NF- κ B) pathway activation, and oxidative damage to proteins in the CSF and brains of individuals with PD which is also evident in post-mortem PD brains at autopsy (McGeer et al., 1988; Hirsch and Hunot, 2009) and most experimental models of PD (Czlonkowska et al., 1996; Castano et al., 1998; Kohutnicka et al., 1998; Herrera et al., 2000; Mogi et al., 2000;

Gao et al., 2002; Gao et al., 2003; Gao et al., 2008). The lateral tier of the substantia nigra (SNL) degenerates earlier and more severely in PD than the more medial nigral component (SNm), yet the cause of this brain regional vulnerability has remained unclear. Consistent with a role for inflammation-derived oxidative stress and mitochondrial dysfunction, a microarray study of PD and control brains indicated increased expression of genes encoding pro-inflammatory cytokines and subunits of the mitochondrial electron transport chain and decreased expression of several glutathione-related genes in the more vulnerable lateral tier region of SN (Duke et al., 2007). Furthermore, because many of the genes differentially regulated in this region are known to be expressed at high levels and predominantly in glial cells, these findings support the idea that glial dysregulation may be an important mechanism underlying PD pathogenesis (Chung et al., 2005). Further support for this idea comes from studies of *in vivo* imaging of microglial activation with the peripheral benzodiazepine receptor binding ligand [11C]-(R) PK11195 in positron emission tomography (PET) scans. Specifically, irrespective of the number of years with the disease, patients with idiopathic PD have markedly elevated neuroinflammation in the pons, basal ganglia, striatum, and frontal and temporal cortical regions compared to age-matched healthy controls (Gerhard et al., 2006). This surprising finding suggests that changes in microglia activation in the affected nigrostriatal pathway are likely to be occurring early in the disease and/or in parallel with loss of dopaminergic terminals. Taken together, these studies strongly suggest that brain microglia may become activated early in the disease process and remain primed, leaving them poised to respond robustly and/or aberrantly to subsequent stimuli thereby enhancing inflammation-induced oxidative stress on vulnerable neuronal populations. It has also been postulated that the course of PD may spiral out of control with excessive activation of microglia, over production of cytokines and other inflammatory mediators, as well as reactive oxygen species (ROS) (Whitton, 2007). Even if neuroinflammation does not occur in the early stages of DA neuron dysfunction, the release of chemoattractants by the dying DA neurons (Aloisi, 2001; Kim and De Vellis, 2005; Sriram et al., 2006) are likely to promote further infiltration by activated microglia to remove neuronal debris. Microglia phagocytic activities are associated with respiratory bursts and would be expected to further enhance oxidative stress for the remaining population of DA neurons.

An important feature of the oxidative stress hypothesis of PD is that a transient initiation factor (i.e., toxins, bacterial, or viral infections, particulate matter, pesticides, etc.) may trigger an active, self-perpetuating cycle of chronic neuroinflammation (i.e., increased production of chemokines, cytokines, ROS/RNS and adhesion molecules by activated microglia) which serves to further promote clustering of activated microglia around DA neurons (Bronstein et al., 1995; Banati et al., 1998; McGeer, 1998) and may contribute to irreversible neuronal dysfunction and cell death. Data in support of this idea include studies suggesting that cell death is not required to initiate microglia activation but the latter is capable of eliciting cell death if it becomes self-sustaining. For example, intranigral administration of prostaglandin J2 was recently shown to induce microglia activation, selective nigral degeneration of DA neurons, formation of ubiquitin- and α -synuclein-immunoreactive aggregates in the spared DA neurons, and locomotor deficits (Pierre et al., 2009). Another study in support of this idea involved mice expressing increased levels of human α -synuclein (such as might be expected in individuals with triplication of the α -synuclein gene) which displayed increased microglial burden and higher levels of inflammatory cytokines that preceded loss of dopaminergic neurons (Theodore et al., 2008). In light of the fact that LB formation, microglia activation and nigral DA neuron loss are features common to both familial and idiopathic PD and that mutations in α -synuclein which cause inherited parkinsonism also promote enhanced aggregation of the protein and robust microglia activation, an attractive hypothesis about the role of inflammation in idiopathic PD is that neuroinflammatory responses and microglia activation triggered by aggregated proteins in LBs and/or initial neuronal dysfunction actively promote progressive neuronal demise as a bystander effect. Another recent study supporting the notion that chronic

microglia activation in response to protein aggregation triggers may hasten neurodegeneration was published by the group of Trojanowski and Lee. Specifically, direct nigral administration of LPS into the substantia nigra of α -synuclein (SYN)-null mice and the same mice engineered to overexpress human SYN or mutant SYN resulted in similar inflammatory reactions. However, in the presence of human SYN, neuroinflammation was associated with dopaminergic neuronal death and the accumulation of insoluble aggregated and nitrated/oxidized SYN as cytoplasmic inclusions in nigral neurons (Gao et al., 2008), suggesting a mechanistic link between protein aggregation and enhanced neurodegeneration driven by neuroinflammation. Lastly, strong evidence supporting a causal link between chronic neuroinflammation and DA neuron degeneration was provided by a recent study involving avian H5N1 influenza. Smeyne and colleagues reported that intranasal administration of the neurotropic virus H5N1 in C57BL/6J mice resulted in a short-lived infection in the peripheral nervous system that traveled into the CNS and triggered chronic microglia activation and viral encephalitis (Jang et al., 2009). The neuropathological hallmarks of infected regions included phosphorylated and aggregated α -synuclein and activation of microglia that persisted long after resolution of the infection. As predicted by multiple models, the chronic neuroinflammatory response was accompanied by a delayed loss of nigral DA neurons, suggesting that H5N1 or other neurotropic influenza viruses have the capacity to trigger proteinopathies and promote nigrostriatal degeneration, the hallmark of PD. Taken together, these data strongly support the idea that localized and chronic production of reactive and neurotoxic inflammatory mediators in the CNS may be an integral component of inflammation triggered by insults evoked by physical, chemical or infectious stimuli that are known to increase the risk for development of PD.

What is the strongest direct evidence that inflammation may have a more important role to play in PD versus other neurodegenerative diseases where it may merely represent a non-specific symptom and/or signs that brain microglia have homed to the site where neurons have died to phagocytose the remaining debris? Unlike neurons in the hippocampus or cortex, midbrain DA neurons display exquisite sensitivity to the death-inducing properties of cytokines such as TNF (McGuire et al., 2001; Block et al., 2007) and the sensitivity to inflammatory stimuli has been demonstrated to be directly related to the high degree of oxidative processes involved in the Fenton reactions as blocking TH activity lowers their sensitivity. In addition, midbrain DA neurons live in a region of the brain reported to have the highest density of microglia (Lawson et al., 1990). Therefore, if the latter become chronically activated such as may occur with formation of protein aggregates, repeated head trauma or pesticide exposure, chronic systemic disease, and/or repeated or prolonged brain infections, the additional oxidative stress generated in this microenvironment might well tip the balance between life and death for these neurons. Alternatively, we propose that genetic deficiency is not the only way to reduce protective factors in the brain which may function to keep microglial responses in check or regulate the sensitivity of DA neurons. What if chronic inflammation had the effect of downregulating expression of these factors in wild-type animals? In essence, genetic haploinsufficiency or downregulation of protective factors such as Parkin or RGS10 by environmental factors may result from purely environmental triggers (aging, chronic systemic disease, etc.) which we have shown can reveal increased vulnerability to inflammation-induced nigral DA neuron death (Frank-Cannon et al., 2008; Lee et al., 2008) and in human populations may predispose an individual to development of PD. Environmentally triggered downregulation of protective factors could also accelerate or promote cell death initiated by other causes including normal age-related loss of nigral neurons especially if microglia become and remain activated. Aging is the greatest risk factor for PD and recent evidence indicates that aging causes microglia to be primed which can result in exaggerated neuroinflammatory responses in aged brains compared to younger brains (Dilger and Johnson, 2008; Henry et al., 2009). Nevertheless, the aging process may be the least unpreventable and least well understood of all the risk factors contributing to idiopathic PD.

The role of the peripheral immune cells in the neuroinflammatory responses present in PD has not been extensively investigated but merits further investigation in light of recent studies in animals and humans. Given that reduced function of efflux pumps that regulate BBB permeability has been reported for PD patients (Kortekaas et al., 2005), it is highly likely that the neuroinflammatory activity in the CNS of PD patients is partly a result of abnormal infiltration of peripheral immune cells from the systemic circulation due to a dysfunctional BBB. A recent report demonstrating that CD4⁺ and CD8⁺ populations of T cells are recruited to the SNpc of PD patients and in MPTP-intoxicated mice (Brochard et al., 2009) raise the interesting possibility that infiltration of peripheral T cells may have a modulatory role on the inflammatory response in the CNS. The identify of the molecular trigger mediating this response is unknown but another recent study demonstrated that nitrated α -synuclein may recruit peripheral leukocytes in cervical lymph nodes in an MPTP mouse model (Benner et al., 2008); transfer of T cells from syngeneic donors immunized with nitrated α -synuclein worsened DA neuron loss after MPTP in the same studies. Although it is clear that use of the MPTP neurotoxin can itself compromise BBB integrity depending on the dose used, the prevailing view is that a leaky BBB may facilitate recruitment of peripheral T cells in both the neurotoxin model and in PD but is unlikely to be sufficient for disease etiology. Nevertheless, compelling data from recent *in vivo* studies suggested that CD4⁺/CD25⁻ effector T cells promote microglia activation and neurotoxic activities in response to nitrated α -synuclein and CD4⁺/CD25⁺ regulatory T cells (Tregs) can inhibit microgliosis and induce microglia apoptosis (Reynolds et al., 2009). Taken together, these recent observations support the notion that the adaptive immune system may influence PD pathogenesis via modulation of microglia effector functions. If this is true and peripheral T cells are indeed found to infiltrate the CNS of PD patients, a worthwhile therapeutic “Trojan horse” strategy may be to deliver neuroprotective agents via these immune cells.

Is neuroinflammation a convergence point for genetic and environmental factors that promote PD pathogenesis or progression?

Neuroinflammation may be triggered by immunological challenges (bacterial or viral infections), neuronal injury (brain trauma or stroke), and other factors including chronic inflammatory syndromes (rheumatoid arthritis, atherosclerosis, type 2 diabetes, Crohn’s disease, and multiple sclerosis) and environmental toxins (pesticides, particulate matter, etc.) (Aloisi, 1999; Streit, 2000; Block and Hong, 2005; Hirsch et al., 2005; Minghetti et al., 2005). Many of these insults can increase the permeability of the blood brain barrier (BBB) to allow infiltration of lymphocytes, macrophages and perhaps environmental toxins into the brain parenchyma. Several environmental triggers known to promote neuroinflammatory responses have been implicated in idiopathic PD and include traumatic head injury, viral inflammation, exposure to heavy metals, organophosphate compounds, neurotoxins like MPTP, and certain pesticides such as paraquat and rotenone (Casals et al., 1998; Thiruchelvam et al., 2002; Liu et al., 2003a; Sherer et al., 2003; Goldman et al., 2006; Kamel et al., 2007). Additional research in gene-environment interaction studies will be necessary to establish causality and go beyond mere association between these factors and development of idiopathic PD. Nevertheless, if environmental factors have the capacity to influence disease etiology or progression of PD, one might expect that genetic mutations which increase the vulnerability of dopaminergic neurons to insult may show interactions with environmental stimuli. Evidence in support of this comes from a recent study of mice bearing mutations in the Parkin gene linked to inherited parkinsonism. Low-dose chronic systemic administration of the bacterial endotoxin lipopolysaccharide (LPS) caused significant loss of nigral DA neurons in Parkin-deficient mice but not wild-type mice even though both groups of mice showed similar increases in markers of neuroinflammation compared to control mice treated with saline (Frank-Cannon et al., 2008). LPS has been used extensively to activate microglial and

peripheral macrophage populations and study their role in degeneration of the nigrostriatal pathway (for a detailed review see (Dutta et al., 2008)) and depending on the route, dose, and frequency of administration may be modeling very different inflammatory responses in the periphery versus the CNS and activating the immune system in ways which are not yet appreciated or understood.

Systemic infections

Recent studies have demonstrated that LPS administered systemically to pregnant rats enters the chorioamniotic environment and this prenatal LPS exposure to the unborn pups results in a reduced number of DA neurons in the post-natal rat midbrain compared to non-LPS exposed controls (Carvey et al., 2003) through mechanisms likely to involve inflammation-enhanced oxidative stress (Gayle et al., 2002; Ling et al., 2002; Ling et al., 2006). These observations further support a role for endotoxin-induced inflammation in nigrostriatal pathway degeneration and raised the interesting possibility that pre-natal infections (i.e. bacterial vaginosis) may contribute to development of sporadic PD. Specifically, the permeability of the fetal BBB and the high sensitivity of nigral DA neurons to LPS (German et al., 1993; De Pablos et al., 2005) may act in concert to increase the probability that pre-natal neuroinflammation is a predisposing risk factor for development of PD later in life. In support of this notion, a follow-up study by the Carvey group more recently demonstrated that although pre-natal LPS exposure does not seem to robustly accelerate the loss of DA neurons that occurs with normal aging in rats, LPS-exposed rats do have reduced number of DA neurons at birth and by age 14 months they developed Lewy-body-like inclusions (Ling et al., 2009). Interestingly, bacterial vaginosis (BV) is a fairly common condition in humans that can occur during pregnancy and is associated with an excess of Gram-negative bacteria which produce the bacterial endotoxin LPS (Thorsen et al., 1998). In terms of causality, the delayed time-course will likely make it very difficult to establish a direct link between prenatal cerebral infection in humans induced by BV and idiopathic PD later in life, but the possibility that it could explain the random epidemiology of idiopathic PD cannot be ruled out.

Viral encephalitis

The influenza pandemic towards the end of the First World War (1914–1918) was associated with a dramatic increase in post-encephalitic parkinsonism (PEP; 'sleeping sickness' or von Economo encephalitis) (Dale et al., 2004) in the 1920s and 30s with PEP accounting for about 50% of all parkinsonism cases (Josephs et al., 2002). Moreover, it is well known that human populations infected with Japanese encephalitis virus (JEV) in India, China, and Southeast Asia for longer than 1 year are likely to develop postencephalitis parkinsonism which shows many of the same neuropathological and locomotor symptoms as those seen in patients with sporadic PD (Shoji et al., 1993). Experimentally, JEV has been used to create a pre-clinical model of postencephalitic parkinsonism in rats (Ogata et al., 1997) in which JEV induces brain catecholamine (dopamine and norepinephrine) depletion and severe hypokinesia (Hamaue et al., 2006). More recently, a study by Smeyne and colleagues demonstrated that administration of the neurotropic avian influenza virus H5N1 in C57BL/6J mice resulted in a short-lived infection in the peripheral nervous system that traveled into the CNS via the vagus nerve and gave rise to viral encephalitis (Jang et al., 2009). In support of a link between neuroinflammation and proteinopathies, the neuropathological hallmarks of the infected regions included α -synuclein phosphorylation and aggregation and activation of microglia that persisted long after resolution of the infection. As predicted by multiple models, the chronic neuroinflammatory response was accompanied by a delayed loss of nigral dopaminergic neurons, suggesting that H5N1 or other neurotropic influenza viruses may be involved in the etiology of CNS proteinopathies and in particular of PD. Therefore, chronic inflammation in the brain, such as that which occurs in encephalitic syndromes, may promote α -synuclein

aggregation and hasten dysfunction of vulnerable nigral DA neurons, increasing the likelihood for development of PD.

Gastrointestinal Inflammation and Infections

Because the triggering event for sporadic PD may be coming from environmental sources, it has been suggested that diseases of the gastrointestinal tract could contribute to enhanced vulnerability for PD (Przuntek et al., 2004; Weller et al., 2005b; Weller et al., 2005a). In support of this concept, three single nucleotide polymorphisms in the *CARD15* gene shown to be associated with a common chronic inflammatory disease of the intestinal tract known as Crohn's disease (Hugot et al., 2001; Ogura et al., 2001) have recently been shown to be over-represented in patients with sporadic PD (Bialecka et al., 2007). Interestingly, a recent genome-wide association study (Barrett et al., 2008) identified another susceptibility locus for Crohn's disease in the *LRRK2* gene, mutations in which have previously been causally linked to PD. In addition, parkinsonism has been loosely associated with prodromal peptic ulceration; and *Helicobacter pylori* is the most common bacterial infection in adults which is usually acquired in childhood and has been linked with peptic ulcer/non-ulcer dyspepsia, immunosuppression, and autoimmunity. Patients diagnosed with sporadic PD are more likely to be seropositive for *H. pylori* before age 75 (odds ratio 2.04 (95% CI: 1.04, 4.22) $P < 0.04$) (Dobbs et al., 2000). Nevertheless, causality has been difficult to establish and the mechanisms are not well-understood. One alternate possibility is that higher prevalence of *H. pylori* seropositivity in parkinsonism diagnosed before the 8th decade of life may be due to host susceptibility/interaction; alternatively, infection with particular *H. pylori* strain(s) may compromise catecholaminergic neuron function in the GI and predispose the individual to secondary triggers.

Epidemiological studies in support of neuroinflammation as a contributing factor in PD pathogenesis

Perhaps the most convincing and compelling evidence to support the claim that inflammatory mechanisms are likely to contribute to PD risk comes from epidemiological studies (McGeer and McGeer, 1998; Chen et al., 2003; Chen et al., 2005). Elevated plasma concentrations of the proinflammatory cytokine interleukin-6 correlate with increased PD risk (Chen et al., 2008). A large prospective study of hospital workers indicated that the incidence of PD in chronic users of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) which scavenge free oxygen radicals and inhibit cyclo-oxygenase (COX) activity was 46% lower than that of age-matched non-users (Chen et al., 2003). Similar findings were reported for chronic users of the non-selective COX inhibitor ibuprofen in a follow-up study involving a large (~180,000) cohort of U.S. men and women (Chen et al., 2005). However, other studies showed that the effect of NSAIDs in decreasing the risk of PD is limited or of no benefit (Hernan et al., 2006; Hancock et al., 2007). Importantly, a recently published systematic review and meta-analysis of studies published between 1966 and 2008 does indicate that although NSAIDs as a class do not seem to modify risk of PD, ibuprofen may have a slight protective effect (Samii et al., 2009). Inhibition of COX-mediated DA oxidation (Teismann et al., 2003), as well as inhibition of microglial-derived toxic mediator production, are likely to be among the mechanisms that contribute to decreased incidence of PD in chronic NSAID users (Chen et al., 2003; Chen et al., 2005). This and other evidence relating to the protective effects of aspirin or other NSAIDs on DA neurons in animal models of PD as well as epidemiological data exploring the effectiveness of NSAIDs in the prevention of PD has been reviewed recently (Esposito et al., 2007; McGeer and McGeer, 2007). Mechanistically, the PD risk-lowering effects of NSAIDs (albeit modest) strongly suggests that neuroinflammatory processes contribute to DA neuron loss and development of PD in humans. Although the protective effect of NSAIDs are likely to be primarily mediated by COX inhibition, multiple mechanisms,

including the Rho kinase pathway (Zhou et al., 2003; Tang and Liou, 2007), cannot be ruled out at this time. Therapeutically, these findings raise the possibility that early intervention with NSAIDs or similar anti-inflammatory therapy may be neuroprotective and could delay or prevent onset of PD.

Potential inflammation-related targets for drug development to ameliorate PD progression

During the decade or two, there has been significant interest in developing novel anti-inflammatory agents that may help prevent or ameliorate CNS inflammation. The reader is referred to one recent review which focuses on disclosures from the patent literature of the various approaches that are being taken to try and develop more effective and selective anti-inflammatory agents to manage acute and chronic inflammation in the CNS (Nimmo and Vink, 2009). In this section, we will mention a few targets the modulation of which has yielded promising results that may be translatable to the clinic in the future.

The presence of activated microglial cells and elevated levels of inflammatory cytokines, including TNF, IL1 β , IL-2, IL-4 and IL-6 are evident in post-mortem examination of SN (Mogi et al., 1994; Mogi et al., 1996; Hunot et al., 1999). An emerging area of pre-clinical investigation involves development of strategies to inhibit the glial reaction and/or target inflammatory cytokines (Nagatsu et al., 2000; Barcia et al., 2003; Hirsch et al., 2005). IL-1 β levels have been reported to increase rapidly after nigral administration of LPS in mice and neuroprotection can be achieved with nigral administration of an anti-IL-1 β neutralizing antibody (Arai et al., 2004; Arai et al., 2006). In the case of TNF, approximately 50% of rat nigral DA neurons destined to die from oxidative neurotoxin and endotoxin-induced death can be rescued by transient (2-week) inhibition of soluble TNF signaling via nigral administration of the recombinant dominant negative TNF inhibitor XENP345 (McCoy et al., 2006). In short, it is clear that targeting specific inflammatory mediators has been a valuable approach to establish the extent to which the various factors implicated in PD pathogenesis (Table 1) contribute to loss of DA neurons in any one model of nigral cell loss. However, due to the complexity of the human disease and the interactions of inflammatory pathways, design of a successful intervention to protect the nigrostriatal pathway from death-inducing inflammatory insults will very likely require a multi-target approach during the earliest stages of PD.

Although numerous studies from animal models support a role for the NF κ B pathway in preventing neuronal death induced by oxidative stress, excitotoxicity, ischemia, or glucose deprivation (for review, see Mattson et al., 2000; Kaltschmidt et al., 2005), there is also evidence supporting a dual role of NF κ B in neurodegenerative diseases. Specifically, activation of NF κ B in neurons generally promotes their survival, whereas NF κ B mediates proliferation and activation of glial cells some of which may promote pathological inflammatory processes (Mattson, 2005; Mattson and Meffert, 2006; Pizzi and Spano, 2006). In the anti-inflammatory phase of inflammation, NF κ B promotes apoptosis and expression of mediators such as TGF β 1 and cyclopentenone prostaglandins as well as transcription of genes such as Bax and p53 (Lawrence et al., 2001). Activation of the NF κ B pathway, as measured by nuclear translocation of the transactivating subunit NF κ B RelA (p65), has been reported to be as much as 70-fold higher in the SN of PD patients compared to that of age-matched healthy controls (Hunot et al., 1997). A possible relationship between the nuclear localization of NF κ B in nigral DA neurons of PD patients and oxidative stress in such neurons is supported by recent *in vivo* studies in which 6-OHDA-induced oxidative stress in rat DA neurons in SN was shown to be mediated through an NF κ B-dependent p53-signaling pathway (Liang et al., 2007). On the other hand, Nemo-Domain Binding (NBD) peptides which block activation of NF κ B signaling, have been shown to attenuate the glial response and attenuate MPTP-induced nigral degeneration (Gosh et al., PNAS 2007). Similarly, the synthetic triterpenoid CDDO-Me, a

potent activator of the Nrf2 anti-oxidant pathway and inhibitor of NF κ B, attenuates production of TNF and other glial-derived inflammatory mediators thereby reducing the neurotoxicity of activated microglial cultures on dopaminergic neuron-like cells (Tran et al., 2008) and its brain-permeant methyl amide derivative (CDDO-MA) was recently shown to afford neuroprotection *in vivo* against MPTP and 6-OHDA-induced nigral degeneration in mice and rats (Yang et al., 2009). Additional research will be needed to conclusively demonstrate whether NF- κ B itself or other pathways which modulate its activity are exerting oxidant-mediated apoptogenic transduction pathways in the nigrostriatal pathway that could contribute to development of PD.

Immunomodulatory effects have also been described in animal models and *in vitro* for two anti-parkinsonian drugs commonly used in humans: the monoamine oxidase B (MAO) inhibitor drug pargyline (Kohutnicka et al., 1998) and selegiline (Deprenyl) (Klegeris and McGeer, 2000). In addition, the immunosuppressants cyclosporine A and FK-506 (tacrolimus) as well as the non-immunosuppressant derivatives of FK-506 referred to as immunophilin ligands including pentoxifylline (Wersinger and Sidhu, 2002; Liu and Hong, 2003), and the non-selective COX-2 inhibitor sodium salicylate have all shown neuroprotective activity in either MPTP-induced nigral injury (Liu and Hong, 2003) or the 6-OHDA rat model of PD (Sanchez-Pernaute et al., 2004). Similarly, the glucocorticoid dexamethasone was shown to be protective against MPTP (Kurkowska-Jastrzebska et al., 2004) and intranigral LPS (Castano et al., 2002). Other anti-inflammatory regimens such as steroids, which have been shown to be effective at arresting DA neuron loss in rodents are not likely to be suitable for long-term use in humans. But clinical trials in PD patients using short-term administration of immunophilin ligands (which lack the immunosuppressive properties of the parent compounds) have had limited success (Gold and Nutt, 2002); although this could be due to a number of other reasons including the advanced nature of disease in the patient population. The semi-synthetic second generation tetracycline antibiotic derivative minocycline which readily crosses the BBB, has been investigated in rodent and non-human primate models of PD with mixed outcomes. For example, in some studies it was shown to be neuroprotective against MPTP-, LPS- and 6-OHDA-induced nigral DA neuron loss (Du et al., 2001; He et al., 2001; Wu et al., 2002; Tomas-Camardiel et al., 2004) while in others it exacerbated the effects of MPTP in rodents and non-human primates (Yang et al., 2003; Diguett et al., 2004). The reason for these discrepancies is unknown but may have to do with differences in dosing and timing of the intervention regimen. Nevertheless, because minocycline is well-tolerated in humans, it was in fact tested in a randomized, double-blind, futility clinical trial in patients with early PD. The recommendations at the completion of Phase II was for advancement to Phase III clinical trials to determine if minocycline could alter long-term progression of PD (The National Institute of Neurological Disorders and Stroke Neuroprotective Exploratory Trials in Parkinson's Disease Investigators, 2006). Chemical modification of minocycline using structure-activity relationship analysis is also being explored in order to develop safer drugs that can protect nigral DA neurons at low doses with reduced toxicity to increase their desirability for clinical use in PD patients (for a general review of minocycline in neurodegenerative diseases see (Kim and Suh, 2009)).

Other compounds with anti-inflammatory actions that have been shown to rescue nigral DA neurons from a variety of neurotoxic insults (LPS, MPTP, etc.) include vasoactive intestinal peptide (VIP) (Delgado and Ganea, 2003a, b), the polyphenolic flavanoid silymarin (Wang et al., 2002), the NMDA receptor antagonist dextromethorphan commonly used in non-prescription anti-tussives (Liu et al., 2003b), and agonists of peroxisome proliferator-activated receptor- γ (PPAR γ) (Breidert et al., 2002). The selective iNOS inhibitors S-methylisothiourea and L-N(G)-nitroarginine were shown to exert neuroprotective effects on DA neurons in rats against LPS (Hemmer et al., 2001; Le et al., 2001; Iravani et al., 2002; Arimoto and Bing, 2003), suggesting that free radical scavengers or iNOS inhibitors may have potential therapeutic effects in PD. Copolymer-1 (Cop-1) immunization, which has been used effectively in patients with chronic neuroinflammatory disease such as relapsing remitting MS, has

recently been shown to have neuroprotective effects in the nigrostriatal pathway against MPTP by several immunomodulatory mechanisms, including promotion of CD4+ T cell accumulation within the SNpc, suppression of microglial activation, and increased local expression of the potent dopaminergic survival factor GDNF (Benner et al., 2004; Laurie et al., 2007). In summary, keen interest in development of new technologies to manipulate the immune response via immunomodulatory drugs and therapeutic immunization to treat neurological diseases and control neuroinflammatory responses has emerged (for an in-depth review see (Hirsch and Hunot, 2009); but it is clear that important considerations must be acknowledged before moving ahead with such approaches to avoid untoward side-effects to both the immune system and the brain.

Conclusions and Challenges Ahead

The link between inflammation, oxidative stress and PD has become less controversial due to an overwhelming number of proof-of-principle studies that strongly implicate inflammatory processes in the progressive loss of nigral DA neurons. However, despite the promising data emerging from animal studies on neuroprotective effects of compounds with anti-inflammatory properties, it remains to be determined whether anti-inflammatory therapy in humans could have a beneficial effect in preventing or slowing down progression of PD. Because cytokines such as TNF and IL-1 β are potent drivers of proximal cell death pathways, combined therapies that target their activity (perhaps in combination with anti-oxidants and neurotrophic factors) may in fact yield significant therapeutic effects and slow down progressive neuronal loss even if the initiating trigger of the disease is never identified (Golde, 2009). Possible reasons for the failure of past clinical trials with anti-inflammatory compounds may include the advanced state of the patients enrolled in the studies, the dosing regimens chosen for the trials, or simply the wrong anti-inflammatory compound; therefore, further clinical investigation in this area is warranted before dismissing the possibility of potential long-term benefits of anti-inflammatory drugs. In addition, it will be important to identify other promising candidates as well as small molecules that can cross the blood-brain barrier or to devise safe and efficient modes of delivery for those that cannot cross. A successful outcome may indeed modify the course of the disease and afford therapeutic benefit in PD patients.

Importantly, it should be noted that most of the currently available drugs to treat inflammation, including NSAIDs, are not truly “anti-inflammatory” because they don’t stimulate or trigger the anti-inflammatory response; rather, they halt the pro-inflammatory response. Moreover, given that the innate pro-inflammatory response often represents a beneficial event (Wyss-Coray, 2006), long-term global inhibition of pro-inflammatory responses may not be the most effective strategy to treat the inflammatory condition associated with neurodegenerative diseases (Wyss-Coray and Mucke, 2002; Marchetti and Abbracchio, 2005). Therefore, the challenge ahead lies in our ability to carefully dissect out which inflammatory mediators are beneficial and which are neurotoxic in specific parts of the brain where neuronal loss is occurring. Only such an approach will enable rational design and selection of anti-inflammatory therapy for targeted delivery to specific brain regions. Lastly, identification of cell type-specific differences in the proteins that activate complex signaling cascades that can either promote or interfere with neuronal survival, such as the NF- κ B pathway, will be needed before such pathways can become successful pharmaceutical targets in the treatment of specific neurodegenerative diseases (reviewed in (Camandola and Mattson, 2007).

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Table 1

Microglial-derived factors implicated in PD pathophysiology

TNF
IL1- β
IL-6
IL-4
IL-2
IFN γ
Prostaglandin E ₂
Prostaglandin J ₂
Reactive Oxygen Species (Superoxide, hydrogen peroxide, and hydroxyl radicals)
Reactive Nitrogen Species (nitric oxide, peroxynitrites)