

Neuroinflammation in Parkinson's disease: Is there sufficient evidence for mechanism-based interventional therapy?

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1. ABSTRACT

The inflammatory response in the brain associated with most chronic neurodegenerative diseases is termed neuroinflammation. Neuropathological and neuroradiological studies indicate that in certain neurodegenerative disorders neuroinflammation may be detectable years before significant loss of neurons occurs. In this review, we discuss the evidence from human studies and experimental models that implicate neuroinflammatory processes in the progressive neurodegeneration of the nigrostriatal pathway, the hallmark of Parkinson's Disease (PD). We discuss the neurotoxic role of microglia-derived inflammatory mediators which are suspected to hasten the death of nigral dopaminergic neurons, in particular the pro-inflammatory cytokine Tumor Necrosis Factor (TNF) and its downstream signaling pathways. We also entertain the possibility that chronic microglia activation links proteinopathies to neurodegeneration. The rationale for current and future use of anti-inflammatory approaches to protect vulnerable neuronal populations in PD is also reviewed.

2. OVERVIEW

An overwhelming amount of evidence now refutes the idea that the brain is an immune-privileged organ. It was once believed that the blood-brain barrier (BBB) prevented access of immune cells to the brain and, as a result, the immune and central nervous system were relatively independent of each other. However, it has become clear that the BBB can be regulated under normal conditions and may become dysregulated in disease states. Specifically, an inflammatory reaction can occur in the brain in response to pathogenic events, traumatic injury and environmental toxins. Neuroinflammation in the CNS consists is associated mainly with an innate immune response involving activation of brain-resident glial cells as well as central production of cytokines, chemokines, prostaglandins, complement cascade proteins, and reactive oxygen and nitrogen species (ROS/RNS) in response to a central or peripheral immune challenge (1, 2). The four cardinal signs of inflammation—fever (calor), swelling (tumor), pain (dolor), and redness (rubor) often manifested in peripheral inflammation are not observed in

neuroinflammatory responses in the CNS. The presence of reactive astrocytes and activated microglia in the central nervous system (CNS) is the hallmark of neuroinflammation. Infiltration of lymphocytes (B and T cells) and polymorphonuclear cells occurs when there is extensive breakdown of the BBB (1, 2). Neuroinflammation is associated with many chronic neurodegenerative conditions, including multiple sclerosis (MS), Alzheimer's Disease (AD), Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS), and Huntington's Disease (HD). Neuropathological and neuroradiological studies indicate that in certain neurodegenerative diseases neuroinflammatory responses may begin prior to significant loss of neuronal populations. The current prevailing theory is that idiopathic PD is caused by a combination of genetic susceptibility and environmental risk factors (3, 4). Putative environmental factors that may predispose individuals to idiopathic PD include increased age, gender, reduced estrogen status, ethnicity, exposure to pesticides and heavy metals, rural living, head trauma, viral encephalitis, not smoking, not drinking alcohol, and not drinking coffee (reviewed in (5)). These multiple putative risk factors do not appear to share an obvious common pathophysiologic mechanism; yet it could be argued that a salient feature associated with several of these risk factors (aging, exposure to pesticides and heavy metals, head trauma, viral encephalitis) is their association with inflammation. Interestingly, over the last decade, a great wealth of new information has emerged to suggest that inflammation-derived oxidative stress and cytokine-dependent neurotoxicity are likely to contribute to nigrostriatal pathway degeneration and lead to idiopathic PD in humans (reviewed in (6-11)). The purpose of this review is to examine the available evidence implicating inflammatory processes in the pathophysiology of PD in order to determine whether clinical investigations and timely delivery of anti-inflammatory therapy are warranted and whether they are likely to impact the course of disease in humans afflicted with this progressive neurodegenerative disorder.

3. CLINICAL AND EPIDEMIOLOGICAL EVIDENCE FOR INFLAMMATION IN PARKINSON'S DISEASE

Classically, the neuropathological hallmark of idiopathic PD includes the presence of α -synuclein-positive inclusions in the cell body (Lewy bodies) and processes (Lewy neurites) of specific neurons of the brainstem and a classic motor phenotype resulting from substantial loss of dopaminergic neurons from the substantia nigra pars compacta (SNpc) associated with (reviewed in (5)). A number of studies have confirmed the presence of inflammatory mediators in the cerebrospinal fluid (CSF) of patients with PD as well as in the brains of PD patients post-mortem in the area of substantia nigra pars compacta (SNpc) where maximal destruction of vulnerable melanin-containing dopamine (DA)-producing neurons occurs in PD patients (12-16). Signs of inflammation include activation of microglia and accumulation of cytokines (including TNF, IL-1 β , IL-6, and IFN γ). The genes for various cytokines, chemokines and acute phase proteins have been

surveyed and individual reports demonstrate that specific single nucleotide polymorphisms associated with overproduction of cytokines are over-represented in specific cohorts of individuals affected with PD and may confer increased susceptibility for the disease (17-21). However, most of these findings have not been replicated in independent studies and a meta-analysis of multiple association studies is needed to assess the overall genetic effect of cytokine gene polymorphisms on neurodegenerative disease. Nevertheless, the advent of such technologies as positron emission tomography (PET) brain scans has enabled clinicians to image microglial activation in living patients. Importantly, recent PET studies confirm that patients with idiopathic PD have markedly elevated microglia activation in the pons, basal ganglia, striatum, and frontal and temporal cortical regions irrespective of the number of years with the disease compared to healthy age-matched controls (12). The neurotoxic effects of glial-derived cytokines (including TNF, IL-6, and IL-1 β) on DA neurons as well as the unique vulnerability of these neurons to neuroinflammatory insults that enhance oxidative stress is well-documented (22-26). Persistent activation of the abundant number of microglia in the midbrain region are likely the direct result of elevated levels of cytokines acting in an autocrine manner to potentiate inflammatory responses (e.g., auto-amplification of reactive oxygen species, nitric oxide, and superoxide radicals to form highly oxidizing peroxynitrite species) (9, 27-31). Given that DA neurons in the midbrain have an inherently elevated oxidative intracellular environment as a result of oxidation reactions required for the synthesis of the neurotransmitter dopamine, chronic neuroinflammation is likely to further enhance oxidative stress, hasten dysfunction, and eventual death of DA neurons.

3.1. Cell types involved in neuroinflammation

Both microglia and astrocytes participate in and modulate the neuroinflammatory response associated with chronic neurodegenerative diseases. The primary role of immune surveillance is performed by microglia, the monocyte-derived resident macrophages of the brain (1, 2). Expansion of this population can occur through recruitment of peripheral macrophages to the CNS as a result of increased permeability of the BBB following an initial physical or pathogenic events in the CNS. The mechanisms that regulate microglial activities in the brain are poorly understood. In recent years, a more thorough understanding of the functional link between microglial activation markers and specific cellular functions has evolved. Moderately activated microglia are believed to play a homeostatic role in the CNS by scavenging excess neurotoxins, and removing dying cells and cellular debris (see reviews by (32, 33)). Acute activation of microglia often results in secretion of neurotrophic factors such as glial-derived neurotrophic factor family ligands (GFLs) that limit tissue injury by protecting vulnerable neuronal populations and aiding in repair processes (1, 34). However, activated microglia can also overproduce prostaglandins, chemokines, cytokines, and reactive oxygen and nitrogen species (ROS and RNS) including nitric oxide (NO) which can have a deleterious effect on neuronal survival by enhancing oxidative stress and activating cell

death pathways (35). If glial activation persists for extended periods, a cycle of chronic neuroinflammation ensues and contributes to tissue damage. A deeper understanding of the mechanisms that regulate the balance of neuroprotective and neurotoxic microglial activities will be required to understand how dysregulation of this balance hastens the death of vulnerable neuronal populations such as DA neurons.

Astrocytes, another type of glial cell in the CNS, regulate the permeability of the BBB (1, 34). Specifically, the cellular processes of astrocytes are functionally coupled to neurons, oligodendrocytes, and other astrocytes. This tight coupling enables astrocytes to regulate the homeostatic environment (including regulation of the excitatory neurotransmitter glutamate) to insure proper functioning of the neuronal network. Disruption of this process (transiently or permanently) may occur during periods of chronic neuroinflammation because cytokines have important roles in reprogramming gene expression in glia (both microglia and astrocytes) during injury and recovery. The term reactive gliosis refers to the upregulation of glial fibrillary acidic protein (GFAP) in astrocytes and may be part of a response to acute injury or neurodegeneration that can lead to permanent scarring and tissue damage. Development of animal models in which particular proteins and pathways have been manipulated in astrocytes (including TNF, TGF β 1, IL-6, and IL1-receptor antagonist) have contributed to our understanding of the normal biology of astrocytes and support a role for astrocytes in neurological disorders (36-41) and have accelerated the development of astrocyte-targeted therapeutic approaches (42, 43) which will likely influence the clinical treatment of ALS.

3.2. Inflammatory mediators involved in neuroinflammation

Microglia and astrocytes secrete multi-functional immunoregulatory proteins called cytokines, most notably Tumor Necrosis Factor- α (TNF), the interleukin-1 (IL-1) and interleukin-6 (IL-6) families, interferon gamma (IFN γ), and Transforming Growth Factor beta (TGF- β), all of which act in context-dependent ways to modulate inflammatory processes and the permeability of the BBB (11, 44, 45). Cytokines can exert neuroprotective effects independent of their immunoregulatory properties and some of them (e.g. TNF) have been shown to modulate synaptic plasticity (46). However, under other conditions, cytokines as well as chemoattractant factors called chemokines promote apoptosis of neurons, oligodendrocytes, and astrocytes and cause damage to myelinated axons. The outcome of cytokine action in the brain depends on the dynamics, cellular source, degree of compartmentalization of cytokine release, the pathophysiological context, and the presence of co-expressed factors. A wide range of neurodegenerative CNS disorders including MS, AD, PD, HD, ALS, tauopathies, and age-related macular degeneration (ARMD) are often associated with chronic neuroinflammation and elevated levels of several cytokines (9, 27, 28, 47). While there is no evidence to support a role for any cytokine in the direct triggering of any of these neurodegenerative conditions,

cytokine-driven neuroinflammation and neurotoxicity may modify disease progression in a number of these disorders.

4. EVIDENCE FOR OXIDATIVE STRESS AND INFLAMMATION IN EXPERIMENTAL MODELS OF PARKINSON'S DISEASE

Extensive evidence exists to indicate that genetic and environmental factors contribute to the development of sporadic PD (48). Despite a great deal of effort, none of the animal models available today faithfully reproduces all the features and outcome of the disease process that occurs in humans (reviewed in (49). Nevertheless, it should be noted that the majority of experimental models of PD display features of inflammation (25, 50-63). The best characterized of these are the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), N-methyl(R)salsolinol, rotenone, and paraquat neurotoxin models (64-69). The MPTP and 6-OHDA neurotoxin models are both accompanied by a robust glial reaction. Studies with non-human primates exposed to MPTP indicate that the cycle of neuroinflammation triggered by these neurotoxins persists long after the initial insult abates and may contribute to the progressive degeneration of the nigrostriatal pathway (6, 7, 13, 70, 71). We posit that the higher sensitivity of nigral DA neurons to injury induced by neuroinflammatory mediators may be secondary to reduction of endogenous anti-oxidant capacity (i.e. glutathione depletion) (72) some of which may be mediated by TNF (73). Findings obtained from histopathologic, genetic, and pharmacologic studies in animals implicate a role for cytokine-driven inflammation and neurotoxicity in MPTP-, 6-OHDA oxidative neurotoxin-, and bacteriotoxin-induced loss of nigral DA neurons. Rapid increases in cytokine levels are detectable in rodent midbrain substantia nigra (SN) within hours of *in vivo* administration of 6-OHDA (74) or MPTP (75-77). Although it is likely that each neurotoxin triggers different initial cascades of events, it is almost certain they both involve oxidative stress as the critical mechanism that elicits DA neuron death. Nitric oxide (NO), generated by activated microglia also contributes to DA neuron death through mechanisms that involve mediation of excitotoxicity, activation of PARP-1 (poly-ADP ribose polymerase), DNA damage, activation of caspase-dependent and independent cell death, and/or nitrosylation of proteins including alpha-synuclein and parkin (78).

Bacteriotoxin-induced inflammatory models of PD consisting of single intranigral delivery of lipopolysaccharide (LPS) (50, 51, 79), chronic low-dose infusion of LPS into SNpc of rats (80), or intrauterine exposure to LPS (65) all induce microglia activation as well as delayed, chronic, and progressive loss of DA neurons in the adult SNpc or in the offspring, respectively. The role of activated microglia and neuroinflammation in degeneration of the nigrostriatal pathway has also been demonstrated in the weaver mouse, which harbors a mutation in the G-protein inwardly rectifying potassium channel Girk2 (63). Together, these experimental models of PD lend further support for a role of neuroinflammation in the degeneration of the nigrostriatal pathway.

5. EVIDENCE IMPLICATING TNF IN NIGROSTRIATAL PATHWAY NEURODEGENERATION

The levels of several cytokines, including TNF, IL1 β , and IFN γ are significantly increased in the SNpc of PD patients compared to normal controls (81), particularly in the area of maximal destruction where the vulnerable melanin-containing dopamine-producing neurons reside. Several key findings implicate TNF as a critical mediator of DA neuron loss in PD and in experimental models of PD. A single nucleotide polymorphism in the TNF promoter that drives transcriptional activity was found to be over-represented in a cohort of early onset PD patients (20). In experimental models of PD, significantly elevated levels of TNF mRNA and protein can be detected in the rodent midbrain substantia nigra within hours of *in vivo* administration of two neurotoxins widely used to model parkinsonism in rodents, 6-OHDA (74) and MPTP (Rousselet *et al.*, 2002; Sriram *et al.*, 2002; Ferger *et al.*, 2004). Consistent with a role of TNF in contributing to dopaminergic neuron death in chronic parkinsonism, plasma TNF levels were shown to remain elevated in MPTP-treated non-human primates one year after administration of the neurotoxin (82). Mice deficient in TNF or both TNF receptors have been reported to have reduced sensitivity to MPTP-induced neurotoxicity (Sriram *et al.*, 2002; Ferger *et al.*, 2004) and altered dopamine metabolism (76). Additional evidence that inflammation, and possibly TNF, are involved in nigral DA neuron degeneration comes from two recently developed endotoxin models of PD. In the first model chronic low dose LPS infusion into SNpc of rats results in delayed, selective and progressive loss of nigral DA neurons (80). In the second model exposure of pregnant rats to LPS and thus, *in utero* exposure of embryos to the endotoxin, caused a loss of DA neurons in postnatal brains (83). Most importantly, chronic infusion of dominant negative TNF inhibitor proteins into SNpc of adult rats protected nigral DA neurons from LPS and 6-OHDA induced degeneration (84). Given that TNF receptors are expressed in nigrostriatal dopamine neurons (85, 86) and that these neurons are selectively vulnerable to TNF-induced toxicity (Aloe and Fiore, 1997; Ling *et al.*, 1998; McGuire *et al.*, 2001; Gayle *et al.*, 2002; Carvey *et al.*, 2005), the early genetic studies and the more recent chronic inflammation models of PD strongly implicate TNF-dependent mechanisms and downstream targets in neurotoxin- and endotoxin-induced loss of nigral DA neurons *in vivo*. In relation to human disease, these observations suggest that high TNF levels in the midbrain may increase susceptibility for PD in humans. In summary, these pre-clinical studies have validated TNF as an important neurotoxic mediator in nigrostriatal pathway degeneration and provide strong rationale for targeting this cytokine as new drug development and delivery efforts are undertaken to halt progression of PD.

6. LINKING PROTEINOPATHIES TO NEURODEGENERATION VIA CHRONIC NEUROINFLAMMATION

It is well-known that neurodegenerative diseases are characterized by the loss of specific neuronal

populations often by intracytoplasmic as well as extracellular accumulation of fibrillary materials. Formation of intracellular inclusion bodies may result from mutations that give rise to abnormal protein processing, aberrant protein-protein interactions or protein misfolding, and/or dysregulation of the autophagic-lysosomal pathway and/or the ubiquitin-proteasome system (UPS) (87-89). These conditions, often referred to as 'proteinopathies,' play a central role in the neuronal dysfunction present in the early stages of many neurodegenerative diseases (90-93). An attractive model by which a number of divergent molecular or cellular events (e.g., mutations, oxidation, protein misfolding, truncation, or aggregation) may all contribute to death of neurons is through persistent activation of resident microglial populations in specific brain regions. If resident microglia are unable to eliminate the initiating trigger (e.g., proteinopathy caused by a mutation), they may become chronically activated and microglial-derived oxidative stress may contribute to progressive neuronal dysfunction. One important prediction of this model is that if neuroinflammation in fact contributes to degeneration of vulnerable dopaminergic populations in SNpc, then timely use of specific anti-inflammatory drugs should afford neuroprotection and may limit the progression of proteinopathy-related disease and development of motor symptoms resulting from the death of these neurons. Although neuroprotection has been achieved with a number of different drugs and compounds in experimental models of PD, human clinical trials with the same or similar approaches have had limited success in the management of patients with PD (reviewed in (94). The failure could be in part due to problems pertaining to the patient populations chosen for the studies, ineffectual timing of treatment, and/or the dosing regimens. Therefore, further investigation into the potential long-term neuroprotective benefits of anti-inflammatory drugs in patients with early stage PD should be undertaken before dismissing the possibility that anti-inflammatory approaches are unlikely to modify the course of the disease.

7. ANTI-INFLAMMATORY DRUGS AND PARKINSON'S DISEASE

An overwhelming number of animal studies now indicate that chronic elevation of certain cytokines in the CNS can contribute to progressive degeneration of nigral dopamine-producing neurons and raise the interesting possibility that environmental triggers initiate cytokine-driven neuroinflammation and contribute to the development of PD in humans. Empirical observations that nigral DA neuron death is strongly linked to oxidative stress have given rise to mechanism-based interventions aimed at neuroprotection of the nigrostriatal pathway. Specifically, general synthetic anti-oxidants as well as natural products with anti-oxidant properties (including green tea, omega oils, curcumin, and various varieties of berries) are being intensely investigated for their ability to provide DA neuroprotection in experimental models of PD and in the clinic (95-99). NSAIDs scavenge free oxygen radicals and inhibit cyclo-oxygenase (COX) enzymes and in particular COX-2 which participates in oxidation of dopamine. In pre-clinical studies, chronic infusion of anti-

inflammatory compounds, including COX-2-selective NSAIDs (100) and dominant negative-TNF inhibitors (84), affords neuroprotective effects to nigral DA neurons and attenuates progressive degeneration in rodent models of PD. In humans, epidemiological studies reveal that chronic use of over-the-counter NSAIDs lowers incidence of PD in human populations by as much as 46% (101, 102). Although a number of additional NSAID target(s) have been identified in addition to cyclo-oxygenases, such as Rho kinase (103), these recent findings strongly suggest that neuroinflammatory processes contribute to dopamine neuron loss and development of PD in humans. In concert with findings derived from experimental models, the results of these epidemiological studies raise the possibility that anti-inflammatory therapy may be effective in delaying or preventing onset of PD through a variety of mechanisms and should be explored further in clinical trials (reviewed in (104).

In recent years, a number of innovative anti-inflammatory approaches tested in pre-clinical studies and shown to be neuroprotective of DA neurons have advanced to clinical trials. The selective inducible Nitric Oxide Synthase (iNOS) inhibitors S-methylisothiourea and L-N(G)-nitroarginine were shown to exert neuroprotective effects on DA neurons in rats treated with LPS (105-108), suggesting that free radical scavengers or iNOS inhibitors may have potential therapeutic effects in PD. At the time of this writing, minocycline, a tetracycline derivative which readily crosses the BBB and is well-tolerated in humans, was under evaluation in Phase III clinical trials to determine if it could beneficially alter long-term progression of PD and other neurodegenerative diseases (109). Furthermore, 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 against the damage caused by MPTP in the nigrostriatal pathway 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 Glial Derived Neurotrophic Factor (GDNF) (110, 111). The glucocorticoid dexamethasone, often used in treatment of brain tumors, was shown to rescue DA neurons from MPTP (112) and intranigral LPS (79); but because of side-effects associated with chronic use (e.g., weight gain, myopathy, decreased bone density, etc.), steroids are not likely to be suitable for long-term use in humans the management of neurodegenerative disease. Similarly, clinical trials in PD patients using short-term administration of immunophilin ligands (which lack immunosuppressive properties) have also had limited success in the treatment of PD (113). In brief, a re-examination of the available classes of anti-inflammatory agents may be justified to identify other compounds that can cross the BBB for potential therapeutic use in neurodegenerative diseases. Alternatively, novel modes of therapeutic delivery for introduction of promising anti-inflammatory compounds that cannot readily cross the BBB will need to be developed, including viral vector-based delivery of anti-inflammatory genes or peptides. Time will tell if successful development and timely use of

any of these anti-inflammatory approaches can modify the progressive course of this disease and provide therapeutic benefit in the early stages of PD.

8. CONCLUSIONS

Over the last decade, the concept of the brain as an immune-privileged organ has been rejected in light of unequivocal evidence that the permeability of the blood-brain barrier can be regulated under normal conditions and may become dysregulated in chronic and acute neurodegenerative conditions. Reactive astrocytes, activated microglial cells, and overproduction of inflammatory mediators orchestrate neuroinflammatory responses that either promote or compromise neuronal survival depending on duration and context. Collectively, whether cytokine action has beneficial or harmful outcomes in the brain depends on the dynamics, the cellular source, the degree of compartmentalization of cytokine release, the pathophysiological context, and the presence of co-expressed factors. In general, acute inflammatory responses during trauma to the CNS involve neuroprotective actions of microglia aimed at limiting injury and enhancing neuronal repair. When inflammation becomes chronic however, microglial activities create an environment that often enhances oxidative stress in neurons, contributes to neuronal dysfunction, and hastens neurodegeneration. While there is no evidence to support a role for any specific inflammatory mediator in the etiology of any neurodegenerative disease, it is clear that cytokines in the brain and/or cerebrospinal fluid become chronically elevated in a wide range of CNS disorders, including MS, AD, PD, HD, and ALS and the evidence is strong that they modify (i.e. accelerate) disease progression. Nigral DA neurons may be uniquely vulnerable to neuroinflammatory insults that enhance oxidative stress. Over the last decade, a great wealth of new information has emerged to suggest that inflammation-derived oxidative stress and cytokine-dependent neurotoxicity may contribute to nigrostriatal pathway degeneration and increase the risk for development of idiopathic PD in humans. Most compelling however, is the strong epidemiological data indicating that chronic use of NSAIDs lowers risk for development of sporadic PD in humans. Although the relevant molecular target of NSAID action has not been clearly identified, these exciting observations warrant further basic science investigations to identify the mechanisms conferring neuroprotective effects as well as clinical research to determine if use of anti-inflammatory approaches represents a viable strategy for future development of antiparkinsonian drugs that can delay or halt the progressive degeneration of nigral DA neurons that gives rise to the disabling clinical symptoms of PD.

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