Neuroinflammation in Parkinson’s disease: a target for neuroprotection?

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Parkinson’s disease is characterised by a slow and progressive degeneration of dopaminergic neurons in the substantia nigra. Despite intensive research, the cause of the neuronal loss in Parkinson’s disease is poorly understood. Neuroinflammatory mechanisms might contribute to the cascade of events leading to neuronal degeneration. In this Review, we describe the evidence for neuroinflammatory processes from post-mortem and in vivo studies in Parkinson’s disease. We further identify the cellular and molecular events associated with neuroinflammation that are involved in the degeneration of dopaminergic neurons in animal models of the disease. Overall, available data support the importance of non-cell-autonomous pathological mechanisms in Parkinson’s disease, which are mostly mediated by activated glial and peripheral immune cells. This cellular response to neurodegeneration triggers deleterious events (eg, oxidative stress and cytokine-receptor-mediated apoptosis), which might eventually lead to dopaminergic cell death and hence disease progression. Finally, we highlight possible therapeutic strategies (including immunomodulatory drugs and therapeutic immunisation) aimed at downregulating these inflammatory processes that might be important to slow the progression of Parkinson’s disease.

Introduction

Parkinson’s disease is the second most common neurodegenerative disorder after Alzheimer’s disease. It is characterised by a slow and progressive degeneration of dopaminergic neurons in the substantia nigra. Yet, other dopaminergic neurons are also affected, although to a lesser extent.¹ This loss of dopaminergic neurons causes most of the motor symptoms of Parkinson’s disease, which can be alleviated by restoring neurotransmission with the dopamine precursor levodopa or with dopaminergic agonists. Nevertheless, patients with Parkinson’s disease also have levodopa-resistant symptoms, suggesting that non-dopaminergic systems are affected as well.² For example, non-dopaminergic neurons, including norepinephrinergic neurons in the locus coeruleus, cholinergic neurons in the basal forebrain and the brainstem, and serotonergic neurons in the raphe nuclei, are also affected by the pathological process. Even neurons outside the CNS, such as those in the olfactory bulb or mesenteric system, degenerate in Parkinson’s disease. In addition to the neuronal loss, this disorder is pathologically characterised by the presence of proteinaceous inclusions, such as Lewy bodies or Lewy neurites. These inclusions seem to emerge following an ascending gradient that originates within the lower brainstem, expands to the basal ganglia, and ends in the cerebral cortex.³

Despite intensive research, the cause of neuronal loss in Parkinson’s disease and the role of these protein inclusions are not fully understood. However, several molecular and cellular changes that might be involved in neuronal degeneration have been identified, including abnormal protein handling, oxidative stress, mitochondrial dysfunction, excitotoxicity, and apoptotic processes. Neuroinflammatory mechanisms probably also contribute to the cascade of events leading to neuronal degeneration. These mechanisms comprise microglial activation, astrogliosis, and lymphocytic infiltration (figure 1). However, it must be emphasised that these changes are unlikely to be specific for Parkinson’s disease, because neuroinflammatory processes contribute to several neurodegenerative disorders, such as Alzheimer’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and progressive supranuclear palsy.⁴ This does not imply that neuroinflammation is merely a consequence of neuronal degeneration, as several lines of evidence suggest that it might be involved in the progression of neuronal degeneration by producing deleterious proinflammatory molecules. In this Review, we describe the evidence for neuroinflammatory processes in Parkinson’s disease, and the cellular and molecular events associated with neuroinflammation involved in the degeneration of dopaminergic neurons in animal models. Finally, we highlight possible therapeutic targets associated with inflammation that might help to slow down the progression of this neurodegenerative disease.

Studies in humans

Post-mortem studies

Data from post-mortem studies provided the first evidence for neuroinflammatory processes in Parkinson’s disease. In 1988, McGeer and co-workers⁵ reported the presence of activated microglial cells within the substantia nigra of patients with Parkinson’s disease at post-mortem. These cells were identified by their immunoreactivity to human leucocyte antigen DR (HLA-DR), a cell-surface receptor belonging to the MHC class II. This seminal finding was confirmed by other investigators using additional markers, such as HLA-DP, HLA-DQ, HLA-DR (CR3/43), CD68 (EBM11, a low-density lipoprotein-binding glycoprotein, equivalent to macroslain in mice), and ferritin.⁶ Although Mirza and colleagues⁷ did not find microglial activation in the putamen, Bertrand and co-workers⁸ reported mild microglial activation in the locus coeruleus.
The astrocytic reaction is another well known neuropathological characteristic of the substantia nigra in Parkinson’s disease. By use of gliofibrillary acidic protein (GFAP) or glutathione peroxidase as astrocytic markers, Damier and colleagues showed that astrocytes are heterogeneously distributed within the mesencephalon in healthy individuals. The density of astrocytes is low in the substantia nigra pars compacta, which is severely affected in Parkinson’s disease, whereas the density is high in the ventral tegmental area and the catecholaminergic cell group A8, areas that are less affected in Parkinson’s disease. Therefore, vulnerable neurons in patients with Parkinson’s disease might have few surrounding astroglial cells, which detoxify oxygen free radicals by glutathione peroxidase in healthy individuals, and this limited astroglial environment might be a susceptibility factor for the disorder. A 30% increase in the density of astroglial cells in the substantia nigra of patients at post-mortem was detected by quantitative analysis. Although the role of these astroglial cells in the pathological process is unknown, they might contribute to neuroprotective mechanisms by detoxifying oxygen free radicals or secreting neurotrophic factors such as glial-cell-line-derived neurotrophic factor (GDNF). However, Mirza and colleagues did not detect an astroglial reaction by immunolabelling for GFAP in the substantia nigra or the putamen of patients with Parkinson’s disease. More recently, it has been suggested that not all astrocytes express GFAP at a concentration that is detectable, and that cyastatin C and connexin 43 might in fact label astrocytes that are negative for GFAP. Therefore, immunolabelling for GFAP might identify only a subset of astrocytes that might or might not be protective. Further post-mortem studies are needed to analyse the roles of these different populations of astrocytes in Parkinson’s disease.

Lymphocytes might also participate in the inflammatory reaction in the brains of patients with Parkinson’s disease. McGeer and co-workers reported the presence of cytotoxic T lymphocytes (CD8+) in the substantia nigra from one patient with Parkinson’s disease. In a recent immunohistochemical analysis of several leucocyte markers in the substantia nigra of patients with Parkinson’s disease, Brochard and co-workers reported that, although no B cells or natural killer cells were detectable, there were higher densities of CD8+ and CD4+ T cells in the brains of patients with Parkinson’s disease than in healthy individuals. These cells were in close contact with blood vessels (suggesting migration from the bloodstream) and near to melanised dopaminergic neurons (suggesting an interaction between the lymphocytes and the dopaminergic neurons). The CD8+ and CD4+ T cells were not detected in the red nucleus—an area not affected in Parkinson’s disease—suggesting that this infiltration is highly selective for the lesioned brain areas. These data indicate that some peripheral cells can enter the brain parenchyma during the neurodegenerative process; therefore, changes in blood–brain barrier function might occur in the brains of patients with Parkinson’s disease. Furthermore, Faucheux and colleagues reported an increased density of endothelial cells in the substantia nigra of patients with Parkinson’s disease, and Farkas and co-workers reported pathological changes in the microanatomy of capillaries in the brains of patients with Parkinson’s disease or Alzheimer’s disease. The origin of the changes in brain capillaries is unknown. Reactive species released by activated microglia probably stimulate angiogenesis: whether these molecules could also induce damage to brain capillaries to enable peripheral cells such as lymphocytes to enter the brain warrants further investigation. However, in animal models, lymphocyte infiltration is not a result of blood–brain barrier opening.

In humans, the disease is characterised by profound remodelling of the cellular interactions between brain parenchyma and blood circulation. Further studies are needed to better understand the functional consequences of these changes.

The presence of neuroinflammatory processes at post-mortem has also been confirmed on a molecular basis. Mogi and co-workers reported an increase in concentrations of TNFa, β2-microglobulin, epidermal growth factor (EGF), transforming growth factor α (TGFA), TGFB1, and interleukins 1β, 6, and 2 in the striatum of patients with Parkinson’s disease. TNFa, interleukin 1β, and interferon γ were also detected in the brain parenchyma, suggesting that the inflammatory process is highly selective for the lesioned brain areas. These data indicate that some peripheral cells can enter the brain parenchyma during the neurodegenerative process; therefore, changes in blood–brain barrier function might occur in the brains of patients with Parkinson’s disease. Furthermore, Faucheux and colleagues reported an increased density of endothelial cells in the substantia nigra of patients with Parkinson’s disease, and Farkas and co-workers reported pathological changes in the microanatomy of capillaries in the brains of patients with Parkinson’s disease or Alzheimer’s disease. The origin of the changes in brain capillaries is unknown. Reactive species released by activated microglia probably stimulate angiogenesis: whether these molecules could also induce damage to brain capillaries to enable peripheral cells such as lymphocytes to enter the brain warrants further investigation. However, in animal models, lymphocyte infiltration is not a result of blood–brain barrier opening.

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Panel 1: Evidence for neuroinflammatory processes in the brains of patients with Parkinson’s disease at post-mortem

Substantia nigra
- Microglia HLA-DP, HLA-DQ, HLA-DR (CR3/43), ferritin
- Astrocytes: glial fibrillary acidic protein, glutathione peroxidase
- Tumour necrosis factor α
- Microglia HLA-DP, HLA-DQ, HLA-DR (CR3/43), CD68 (EBM11)
- Interleukin 1β, interferon γ, tumour necrosis factor, CD23
- Inducible nitric oxide synthase, cyclo-oxygenase
- Inducible nitric oxide synthase
- Interferon γ

Striatum
- Tumour necrosis factor
- β2-microglobulin
- Interleukin 1β, interleukin 6, epidermal growth factor, transforming growth factor α
- Transforming growth factor β1
- Interleukin 2
- Interferon γ

Locus coeruleus
- Microglia mild staining

Panel 2: Evidence for neuroinflammatory processes in Parkinson’s disease

**Serum**
- Increase in interleukin 2 concentration
- Increase in TNFα and interleukin 6 concentrations
- Increase in RANTES concentration
- Presence of antibodies against synthetic product of dopamine-oxidised protein

**Cerebrospinal fluid**
- Increase in TNFα concentration
- Increase in interleukin 1β and interleukin 6 concentrations

**Cerebrospinal fluid and serum**
- Increase in γδ+ T-cell number
- Increase in interleukin 6 concentration
- Increase in osteopontin (family of integrins)

**PET scan**
- ¹¹C-(R)-PK-11195 binding

In summary, both cellular and molecular studies of human brain tissue at post-mortem indicate that there are neuroinflammatory processes in the affected brain regions of patients with Parkinson’s disease (panel 1). However, these studies do not help to determine whether such changes are involved in the pathological process or are merely a consequence of neuronal degeneration. In vivo studies in patients with Parkinson’s disease, however, provide more information.

**In vivo studies in patients**

Studies of biological fluids (serum or cerebrospinal fluid) also support a role for neuroinflammatory processes in Parkinson’s disease. Expression of interleukin 2, TNFα, interleukin 6, and RANTES is increased in the serum of patients with this neurodegenerative disease. Antibodies that recognise various components of dopaminergic neurons, including products of proteins oxidised by dopamine, have also been found in the serum of patients with Parkinson’s disease. However, the presence of such antibodies has been detected only in some patients with this disorder and even the data from these patients are disputed. A decreased amount of CD4+ and CD45RA+ T-cells (indicative of naive lymphocytes) and an increased amount of CD4+ and CD45RO+ T-cells (indicative of activated T cells) have been reported in the serum of patients with Parkinson’s disease, suggesting peripheral activation of lymphocytes. Increased numbers of regulatory T cells have also been reported in sera from patients by use of CD25 or FOXP3 as a marker, although Baba and co-workers found decreased counts of these cells and a low ratio of CD4+ to CD8+ lymphocytes, mainly due to a low count of CD4+ cells and a high count of CD8+ cells. Similarly, the ratio of interferon-γ-positive T cells to interleukin-4-positive T cells was increased, suggesting a phenotypic shift to a proinflammatory phenotype of T-helper-1/T-cytotoxic-1 cells. Additionally, an increased number of circulating CD4+ bright CD8+ dull lymphocytes has been detected in the serum of patients. The counts of these lymphocytes increase after a viral infection, suggesting that viral infections might contribute to the pathogenesis of the disease. Such a hypothesis is of great interest, in line with the origin of postencephalitic parkinsonism seen at the beginning of the 20th century. Whether viral effects indirectly. Proinflammatory cytokines, such as TNFα, interleukin 1β, and interferon γ, can induce the expression of the inducible form of nitric oxide synthase (iNOS) or cyclo-oxygenase 2 (COX2)—enzymes that produce toxic reactive species. In support of this finding, Hunot and colleagues reported a CD23-mediated increase in iNOS in the substantia nigra of patients with Parkinson’s disease. Other enzymes involved in neuroinflammatory processes mediated by oxidative stress, such as NADPH oxidase, COX2, and myeloperoxidase (MPO), also have increased concentrations in Parkinson’s disease.

TNF=tumour necrosis factor.
infections of other origins, such as the influenza virus, are involved in the development of Parkinson’s disease, either as causative or susceptibility factors, needs to be analysed.

Proinflammatory changes have also been reported in the cerebrospinal fluid of patients with Parkinson’s disease. TNFα, interleukin 1β, interleukin 6, and osteopontin (a member of the integrins family) are present in samples from patients. Additionally, PET scan analysis with PK-11195 (a ligand of the peripheral binding site of benzodiazepine indicative of microglial activation) as a marker also indicates neuroinflammatory processes in Parkinson’s disease. Binding of PK-11195 is increased in the pons, basal ganglia, and frontal and temporal cortical regions but the specific resolution of the technique prevents direct analysis of the microglial reaction in the substantia nigra. Furthermore, Gerhard and colleagues longitudinally followed eight patients with Parkinson’s disease over 2 years and found no changes in binding of PK-11195 with disease progression. Therefore, PET scan analysis of the microglial reaction probably cannot be used to monitor disease progression.

In summary, these findings indicate that inflammatory changes are detectable during the course of the disease before the death of the patients and are associated with the progression of the disease (panel 2). However, these data do not support direct involvement of neuroinflammation in the pathological process: data in support of such a hypothesis are provided by risk factor studies.

Risk factor studies
Evidence from three types of studies—blood sample, genetic, and epidemiological analysis—indicate that neuroinflammatory processes can be risk factors for Parkinson’s disease (panel 3). In a blood-sample study, men with high plasma concentrations of interleukin 6 had increased risk of Parkinson’s disease; however, because of the limited number of participants analysed, these findings need further confirmation.

Several genetic studies have analysed the relation between a given polymorphism in neuroinflammation-associated genes and the risk of Parkinson’s disease (panel 3). For the TNFα polymorphism at position 308, individuals heterozygous for alleles 1 and 2 were more common in the group of patients with this disorder than in the group of healthy individuals. However, in the same study, the frequency of the B2 haplotype of the TNFα receptor 1 polymorphism at positions –609 and +36 was decreased in patients with Parkinson’s disease. The CC genotype of T1030C site in TNFα promoter increases risk of Parkinson’s disease.

Panel 3: Evidence for a role for neuroinflammatory processes in the development and progression of Parkinson’s disease

Serum analyses
- Men with high plasma concentration of interleukin 6 have increased risk of PD

Genetic analyses
- Heterozygous TNFα polymorphism at position 308 increase risk of PD
- B2 haplotype frequency of TNFα receptor 1 at positions –609 and +36 decrease risk of PD
- CC genotype of T1030C site in TNFα promoter increases risk of PD
- Allele 122 of interferon γ is less common in early-onset than in late-onset PD
- Interleukin 1β T-genotype at position –511 is increased in PD whereas interleukin 1α T-genotype at position –889 is not
- Interleukin 1β polymorphism *1/*1 and *1/*2 increase risk of PD
- Interleukin 1α and interleukin 1 receptor antagonist genotypes are not associated with PD
- Interleukin 1α –889 polymorphism is not changed in PD but T position –511 in IL1β is more common
- Interleukin 1α –889 polymorphism is not associated with risk of PD
- Risk of PD with homozygous variant of IL1β at position –511 or of TNFα at position –308 increased by two times; risk of PD for carriers of both homozygous variants increased by three times
- Increased frequency of GG phenotype of interleukin 6 at position –174 in PD
- CD14 T allele at position –260 of the promoter of the CD14 monocyte receptor gene is increased in women with PD

Epidemiological studies
- Decreased risk of PD in people who take non-aspirin non-steroidal anti-inflammatory drugs
- Decreased risk of PD in people who take two or more tablets of aspirin
- Decreased risk of PD for people who take ibuprofen but not other non-steroidal anti-inflammatory drugs or paracetamol
- Decreased risk of PD in men who take non-aspirin non-steroidal anti-inflammatory drugs, but not in women
- No change in risk of PD for people who take non-steroidal anti-inflammatory drugs

PD=Parkinson’s disease. TNF= tumour necrosis factor.
alleles of genes associated with neuroinflammation do not directly affect the risk of Parkinson’s disease, such as allele 122 of interferon γ, but might affect its clinical progression.39 Allele 122 is less common in cases of early-onset Parkinson’s disease than in late-onset disease. Therefore, polymorphisms in neuroinflammation-associated genes might be involved in susceptibility to the unknown agent causing the disease. However, most of these studies had few participants and their results need to be confirmed in larger studies. Furthermore, the importance of these polymorphisms associated with inflammation is unknown. On the one hand, these polymorphisms might affect the basal level of the inflammatory status of the patient or their response to inflammatory stimuli and thus decrease or increase the effect of inflammation on cell death. On the other hand, these polymorphisms might affect the response to anti-inflammatory drugs given to patients for reasons not related to Parkinson’s disease. If such drugs have a neuroprotective effect, these polymorphisms might indirectly affect the progression of the disease.

Epidemiological studies also support a role of neuroinflammatory processes in the progression of Parkinson’s disease. Results from one of the first epidemiological studies of Parkinson’s disease indicated in a prospective analysis that the risk of this disorder was lower in people who regularly took non-aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) than in people who did not take these drugs.33 The risk of Parkinson’s disease was also decreased in individuals who took two or more tablets of aspirin, although statistical significance was not reached for this result. The same investigators later reported a decreased risk of Parkinson’s disease for people who took ibuprofen, which was not seen in people who took other NSAIDs or paracetamol.41 Two other groups of investigators only partly confirmed these results. Hernan and colleagues41 reported that non-aspirin NSAIDs decreased the risk of Parkinson’s disease in men but not in women. Bower and co-workers41 found a trend towards reduced risk in people who took non-aspirin NSAIDs and steroidal anti-inflammatory drugs. By contrast, Ton and co-workers44 found no change in the risk of Parkinson’s disease for people who took NSAIDs. Therefore, larger studies are needed. In most studies, NSAIDs were analysed without any clear subdivision of the drugs by their exact pharmacological target. Because of the complexity of the molecular changes associated with neuroinflammatory processes, more careful analyses of possible links between the use of specific anti-inflammatory drugs and the risk of Parkinson’s disease are needed.

**Animal models**

Both the cellular and molecular changes seen in the brains of patients with Parkinson’s disease have been reproduced in several animal models. The blockade of these changes in animals has provided strong evidence to suggest that neuroinflammatory processes are involved in the death of dopaminergic neurons. In this section we discuss the cellular changes and describe the molecular pathways involved in the neuroinflammatory processes in various animal models of Parkinson’s disease.

**Cells involved in neuroinflammation**

A glial reaction involving astrocytes and microglial cells and lymphocytic infiltration has been described in several animal models of Parkinson’s disease. Such models include intracerebral 6-hydroxydopamine injection and peripheral injection of complex I inhibitors such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), rotenone, and annonacin. Activated microglial cells have been identified in the brains of rats with unilateral lesions of the nigrostriatal pathway caused by both intrastriatal and medial forebrain bundle injection of 6-hydroxydopamine.45–46 However, data from this model must be treated with caution because 6-hydroxydopamine is injected intracerebrally, leading to a transient rupture of the blood–brain barrier and possible involvement of peripheral immunological factors. Peripheral injections of complex I inhibitors avoid this complication. Microglial activation has also been reported after subchronic injection of MPTP in mice and monkeys.47,48–50 However, this activation seems to vary with the method of exposure to MPTP because, whereas this event was constantly seen after acute MPTP injection in mice, it is more difficult to detect after subchronic injection.47 Nevertheless, we detected microglial activation after a subchronic MPTP injection method (unpublished data). Microglial activation was also seen after osmotic infusion of complex 1 inhibitors in rats.51,52 Microglial activation has also been reported in mice that overexpress α synuclein.4 Therefore, microglial activation is a common feature of animal models in which parkinsonism is induced by neurotoxins or manipulations of genes involved in inherited forms of the disease. Furthermore, the direct role of this microglial activation in the events leading to neuronal degeneration is supported by animal studies showing that the microglial activation precedes neuronal degeneration (figure 2)116 and that inhibition of this event prevents neuronal degeneration.75 Furthermore, injection of lipopolysaccharide, a gram-negative bacteriotoxin that activates microglial cells, can selectively kill dopaminergic neurons in animals after intranigral injection54 or systemic injection.7 Ling and co-workers55 reported that injection of lipopolysaccharide into gravid female rats led to offspring with fewer dopaminergic neurons, a high proportion of which were abnormal, and a lower TNFα concentrations in the striatum than in controls. These animals were also more susceptible to subsequent exposure to parkinsonian toxins such as 6-hydroxydopamine than were controls.

Further studies in animal models support the idea that microglial activation can increase neuronal degeneration in Parkinson’s disease. In mice and dopaminergic neuronal cultures (derived from mice with wild-type and...
mutant A53T α-synuclein in a murine α-synuclein-null background) that were exposed to lipopolysaccharide, neuroinflammation was associated with dopaminergic neuronal death and accumulation of insoluble cytoplasmic inclusions of α-synuclein in nigral neurons, which was not the case for α-synuclein-null mice.79 Nitrated or oxidised α-synuclein was detected in these cytoplasmatic inclusions and abatement of microglia-derived nitric oxide and superoxide provided substantial neuroprotection. Furthermore, chronic peripheral inflammation caused by repeated peripheral exposure to lipopolysaccharide increased vulnerability to inflammation-induced degeneration in mice negative for Park2 or Rgs10 (regulator of G-protein signalling 10), whereas the genetic deficiency was insufficient to induce nigral degeneration.80,81 Neuramelanin, a pigment present in some monoaminergic neurons in primates, can also activate microglia in cell cultures by inducing release of nitric oxide, interleukin 6, and TNFα.82 Microglia activation and degeneration of dopamine neurons were seen after neuramelinan was injected into the substantia nigra of rats.83 These models are particularly relevant to Parkinson’s disease because they mimic the cellular conditions of the substantia nigra in patients, in whom extraneuronal neuramelanin is present with activated microglia and degenerating dopamine neurons. Altogether, the evidence on microglial activation from animal models, whether chronic or acute, supports its involvement in dopamine cell loss.

An astroglial reaction has been reported in the substantia nigra and striatum of rats exposed to 6-hydroxydopamine84,85 and mice exposed to MPTP.86 Although there is already a notable microglial reaction 2 days after exposure to MPTP, the astroglial reaction peaks 5 days after MPTP injection and is less transient than the microglial reaction (figure 2).87 The astroglial and microglial reactions also differ in terms of cell proliferation. Whereas newborn microglial cells were identified by BrdU labelling in mice and monkeys exposed to MPTP, no such staining was seen in astrocytes positive for GFAP.13,87 The microglial reaction involves both an increased amount of microglial cells and a morphological change of microglial cells, whereas the astrocytosis is only associated with a phenotypical change (increased expression of GFAP and morphological changes of the astrocytes). So far, the role of astrocytes in parkinsonian syndromes is poorly understood but the astroglial reaction is unlikely to participate directly in the initiation of cell death because it takes place late in the degenerative process. To clarify the contribution of astrocytes in Parkinson’s disease, selective blockade of the astroglial reaction is awaited.

Cells of the peripheral immune system are also likely to play a part in neurodegeneration as seen from animal models. Kurkowska-Jastrzebska and colleagues88 reported an infiltration of T lymphocytes in the brains of mice exposed to MPTP. Recently, we found high amounts of infiltration from CD8+ T-cytotoxic and CD4+ T-helper cells into the nigrostriatal system after MPTP injection in mice.89 Because no B lymphocytes were detected after MPTP exposure, cell infiltration must be selective for T cells. Furthermore, the infiltration was also selective for the nigrostriatal pathway and was not found in brain regions in which neurons do not degenerate. There was T-cell transmigration 2 days after MPTP injection, which increased continuously for up to 7 days and stopped by 21 days. Therefore, brain infiltration of T cells happened after microglial activation but preceded astrogliosis (figure 2). Furthermore, no intracerebral clonal expansion of T cells was detected, suggesting a continuous extravasation process together with long-term survival in the brain parenchyma. Adoptive transfer strategies showed that CD4+ T-helper cells, but not CD8+ T-cytotoxic cells, were deleterious to dopaminergic neurons, suggesting that the adaptive immune system might contribute to neuronal degeneration in the MPTP mouse model. The mechanisms involved in such cell-specific and region-specific T-cell recruitment are still unknown but might involve early microglial cell activation and innate neuroinflammatory processes that could modify the local microenvironment. The contribution of T cells to the degeneration of dopaminergic neurons supports findings from a recent study that show that nitrated α-synuclein immunity accelerates degeneration of nigral dopaminergic neurons.90

These data from animal models indicate that the mechanism of cell death in the nigrostriatal pathway...
Involves non-neuronal cells. An analysis of the molecular factors involved in this altered cellular interaction might enable the identification of targets to reduce microglial activation and lymphocytic infiltration, and thereby reduce neuronal degeneration.

Molecular pathways involved in neuroinflammation

Innate immune response associated with gliosis, in particular microglial cell activation, is an important neuropathological feature of Parkinson’s disease in humans and in animal models of the disease. Because of the myeloid origin of microglia, the fact that these immune cells of the brain use effector functions that are similar to those used by peripheral monocytes and macrophages to respond to and fight pathogens is not surprising. After appropriate activation, microglial cells are capable of antimicrobial activity as well as cell toxicity through the production and release of toxic oxygen-derived and nitrogen-derived products, which are generated in a process known as the respiratory or oxidative burst. This toxic mechanism for phagocytic cells relies on the regulated induction of several enzymatic systems, among which NADPH oxidase (NOX or Phox), iNOS, and MPO bring about the production of toxic amounts of superoxide ($\text{O}_2^-$) and nitric oxide (NO) free radicals, and hypochlorous acid (HOCl, derived from hydrogen peroxide and chloride anion), respectively. The expression of these biocatalytic systems within the substantia nigra is substantially increased in both patients with Parkinson’s disease at post-mortem and animal models of the disease. Each of these catalysts is instrumental in various in vitro and in vivo experimental conditions, recapitulating Parkinson’s disease-associated dopaminergic neurodegeneration.

On the basis of these studies, a hypothetical scenario for a cell-death mechanism can be suggested (figure 3). Although poorly reactive, NO and $\text{O}_2^-$ free radicals can combine to form the highly reactive nitrogen species peroxynitrite (ONOO$^-$), which can cause oxidative damage in various proteins, such as tyrosine hydroxylase and $\alpha$ synuclein. Peroxynitrite-dependent nitratative modification of tyrosine hydroxylase is associated with decreased enzymatic activity, whereas that of $\alpha$ synuclein potentiates its aggregation. However, NO and $\text{O}_2^-$ free radicals might follow distinct pathways. Iron content within the substantia nigra pars compacta is increased in patients with Parkinson’s disease and in animal models of the disease. Therefore, a substantial amount of highly reactive hydroxyl radical free radicals (OH) might be produced through a superoxide-driven Fenton’s reaction between hydrogen peroxide and the free ferrous iron catalyst, thereby further increasing the pool of toxic reactive species. Non-reactive nitrates (NO$^-$), the main end product of the free radical NO and whose concentration is increased in parkinsonism, can be oxidised by MPO into reactive NO$^-$ free radicals, which can, in turn, also contribute to protein nitrosylation. MPO probably contributes to generating damaging reactive nitrates; this enzyme is particularly implicated in the production of the non-radical oxidant HOCl, which can damage macromolecules directly (by amine conversion into chloramines, phenol, and unsaturated bond chlorination) or indirectly (by OH free-radical fuelling). Overall, a toxic oxidative environment can be created by activated glial cells close to dopaminergic neurons, which most probably accounts for most of the deleterious role of the inflammatory reaction in parkinsonian syndromes. The finding that MPO is mostly expressed by reactive astrocytes in both Parkinson’s disease and MPTP mouse tissue suggests that this glial cell population, usually associated with protective and repair properties, can contribute to the elaboration of the deleterious inflammatory network to some extent.

COX2, a key enzyme that causes prostaglandin synthesis during inflammation and is a direct target of NSAIDs such as aspirin and ibuprofen, is another important inflammatory component potentially involved in neurodegeneration in Parkinson’s disease. Genetic or
pharmacological inactivation of COX2, but not of COX1, is associated with neuroprotection in mice and rats exposed to MPTP and in rats exposed to 6-hydroxydopamine.104–107

Unlike COX1, the expression of COX2 is inducible, particularly under inflammatory circumstances, and can be abundant in macrophages and other cell types, including neuronal and glial cells in the CNS. The finding that increased COX2 expression associated with parkinsonism is limited to dopaminergic neurons suggests that this at-risk neuronal population might participate directly in the inflammatory processes and, consequently, in their own degeneration.108,109 However, although still disputed,110 COX2 cytotoxicity in Parkinson’s disease does not seem to derive from the inflammatory properties of prostanoids but rather from oxidative damage mechanisms through the formation of reactive oxygen species generated during the peroxidase catalysis of prostaglandin G2 to prostaglandin H2.111 Therefore, inflammatory-associated oxidative stress can participate in dopaminergic cell death both in a cell-autonomous and a non-cell-autonomous way (figure 3). As for the regulatory mechanisms of COX2 induction in dopaminergic neurons, activation of the c-Jun N-terminal kinase (JNK) signalling pathway is crucial.109,110 Genetic or pharmacological inhibition of the JNK transduction pathway can be as efficient as COX2 ablation in protecting dopaminergic neurons against degeneration in rodent models.109,110,111

Inflammatory cytokines are also important mediators of harmful inflammation. Among them, TNFα, interleukin 1β, and interferon γ have had much attention with regard to neuroinflammatory processes in Parkinson’s disease. In principle, two mechanisms could account for their neurotoxicity: either a direct mechanism through receptor binding on dopaminergic neurons or an indirect mechanism through glial-cell activation and expression of inflammatory factors. As proposed for TNFα, these proinflammatory cytokines might directly activate cell-surface receptors expressed on dopaminergic neurons that are coupled with a proapoptotic cell death pathway (figure 4). However, there are conflicting results from animal models depending on whether TNFα or its receptors were targeted. In a chronic MPTP mouse model, Ferger and colleagues112 found that genetic ablation of TNFα was associated with decreased MPTP-induced striatal terminal damage, but did not affect nigral dopaminergic cell degeneration. Targeted deletion of either Tnfr1 or Tnfr2 (also known as Tnfrsf1a and Tnfrsf1b) did not have a similar effect,113 in agreement with findings from another study in which single and double TNFα receptor knockout mice were investigated using a more acute paradigm of MPTP intoxication.114 By contrast, Sriram and co-workers115,116 reported that mice lacking both TNF receptor 1 and receptor 2 had attenuated striatal damage after a single injection of a low dose of MPTP. However, only short-term effects were assessed, and dopaminergic cell loss in the substantia nigra has not been investigated. Although the developmental compensatory mechanisms that could circumvent the genetic defect in TNFα or TNFα receptors cannot be ruled out, discrepancies in results are probably due to different extents of MPTP lesioning and survival time. More straightforward evidence for a role for TNFα has been recently provided in the 6-hydroxydopamine model in rats, in which intranigral infusion of TNFα inhibitors or lentivirus-encoding dominant-negative TNFα attenuated dopaminergic neurodegeneration.117,118

Fas ligand, a cell-surface molecule of the TNFα family expressed mainly in activated T cells, can activate the Fas receptor and induce apoptosis in cells that express Fas. Fas expression is increased in patients with Parkinson’s disease and in mice exposed to MPTP.119,120 The detrimental consequence of Fas–Fas ligand pathway activation in parkinsonism has recently been established by several investigators. In addition to the finding that mice deficient in Fas were more resistant to MPTP exposure than wild-
type controls, we showed that leucocyte expression of Fas ligand was necessary for infiltrated CD4+ T-cell-induced injury to dopaminergic neurons in mice given MPTP. Whether the Fas–Fas ligand pathway inflicts direct toxicity on dopaminergic neurons or proceeds indirectly by stimulating the production of glial-derived inflammatory factors is still uncertain (figure 4). However, activation of death-associated signalling pathways possibly linked to Fas and TNF receptor 1 within dopaminergic neurons has been reported. These pathways are the JNK, NFκB, and p38 MAP kinase pathways. Although two of these transduction pathways (JNK and p38) seem to have a crucial role in MPTP-induced degeneration of dopaminergic neurons, there are conflicting results about the involvement of NFκB. Despite strong in vivo evidence for a role of JNK in neurodegeneration in rodent models of Parkinson’s disease, inhibition of this pathway with a semisynthetic inhibitor of the mixed-lineage kinase (MLK) family, CEP-1347, was ineffective in modifying disease outcomes in patients who were newly diagnosed with Parkinson’s disease (Parkinson Research Examination of CEP1348 Trial; PRECEPT). Although a reassessment of the preclinical experimental data that provided the scientific rationale for the trial might be needed, limitations of the preclinical experimental data that provided the scientific rationale for the trial might be needed, limitations include uncertainties about whether efficient inhibition of the MLK family in dopaminergic neurons has been achieved and whether the progression of signs of Parkinson’s disease is directly associated with dopamine neuron loss. Finally, modulating only one cell-death pathway might not be sufficient when, for example, additional signals such as the pro-survival Akt pathway are needed for long-term neuronal survival.

Another mechanism of neurotoxicity might be triggered by Fas ligation on astrocytes, which could cause an inflammatory response by inducing expression of several cytokines and chemokines, including interleukin 6, interleukin 8, and CCL2/MCP1. Although interleukin 6 is associated with neuroprotective mechanisms in models of Parkinson’s disease, the role of interleukin 8 and CCL2 in dopaminergic cell death is still unclear. Proinflammatory cytokines might also exert their neurotoxicity indirectly through their regulatory activities on glial cells. For example, interferon-γ-null mice challenged with MPTP show a decrease in microglial cell activation and subsequent dopaminergic cell loss in comparison with injected wild-type controls. However, this protective effect seems to be dependent on the MPTP protocol because we were unable to confirm this result with a lower cumulative dose of neurotoxin.

The overall inflammatory network in different neurodegenerative situations (ie, acute or chronic) can vary both in intensity and in its cytokine signature, which might explain why inactivation of a single cytokine might not always prevent inflammation-driven dopaminergic cell death. Chronic expression of interleukin 1β within the substantia nigra induces a microglial cell reaction, an inflammatory cell infiltrate, and progressive dopaminergic degeneration in rats. Transgenic mice expressing a dominant-negative mutant of caspase 1 (interleukin 1β converting enzyme), an enzyme involved in mediating the inflammatory response, have decreased susceptibility to MPTP toxicity. Although caspase 1 might be involved in dopaminergic cell death through its role in the caspase-dependent apoptotic cascade, a more indirect mechanism might be involved (ie, through the processing and export of active interleukin 1β, which in turn would mediate inflammatory-dependent and glial-dependent mechanisms of cell death). Recently, Koprich and co-workers showed that giving an interleukin-1 receptor antagonist to parkinsonian rats exposed to 6-hydroxydopamine decreased the intensity of the dopaminergic lesion, probably through the downregulated expression of TNFα and interferon γ. Therefore, proinflammatory cytokines are essential not only for glial cell activation but also for regulating secretion of inflammatory mediators in a positive feedback manner. These inflammatory factors can be linked to the previously described oxidative mechanisms because these mediators are potent regulators of the respiratory burst machinery within macrophage and microglial cells. Interferon γ and TNFα are strong inducers of inducible nitric oxide synthase and NADPH oxidase in macrophage and microglial cells and, supporting this, we have shown that CD23-dependent iNOS expression in human glial cells is strongly potentiated by the combined action of interferon γ, TNFα, and interleukin 1β. Additionally, we have reported that nitric oxide production under these experimental conditions further increases the production of TNFα by astrocytes, thereby inducing a continual cycle of glial-dependent injury to neurons (figure 4). In the 6-hydroxydopamine rat model, interleukin 1β exacerbated dopaminergic neuron death, partly through iNOS-dependent production of nitric oxide.

**Therapeutic developments and future directions**

The extensive, and still growing, body of evidence discussed above indicates that neuroinflammatory processes are probably involved in the pathophysiology of Parkinson’s disease. However, the origin and role of these neuroinflammatory changes need to be established. Neuroinflammation might be a simple consequence of neuronal changes or degeneration. Alternatively, neuro-inflammatory processes might be a main cause of the disease. The role of an autoimmune reaction in Parkinson’s disease is highly debated and the studies that show the presence of antibodies against nigral neurons are controversial. However, involvement of a viral cause that could stimulate neuroinflammatory processes cannot be excluded, and postencephalitic parkinsonism, which developed early in the 20th century, supports such a hypothesis.

Neuroinflammation in Parkinson’s disease is a consequence of a primary neuronal alteration due to various causes in the different subtypes of the disease,
and it might perpetuate the neurodegenerative process. In support of a role of the microglial reaction in the propagation of neuronal loss, Langston and co-workers\textsuperscript{122} reported activated microglial cells in the substantia nigra of three individuals who developed a parkinsonian syndrome after exposure to MPTP and who died several years after the onset of the disease when MPTP was no longer present in the body. Similar results were obtained in MPTP-injected monkeys, in which persistent microglial activation was detected years after the toxin injection.\textsuperscript{48–70} Therefore, MPTP initiates a self-perpetuating neurodegenerative process in which microglial cells might be involved.

Whatever the origin of the neuroinflammatory processes in Parkinson’s disease, therapeutic intervention aimed at prevention or downregulation of these immune-associated mechanisms could be of great use to stop disease progression or even halt the pathological process. With the available knowledge of the cellular and molecular network implicated in the immune-associated damage to dopaminergic neurons, several immunotherapeutic approaches are possible, some of which have already been applied or tested in other neurological disorders, including multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer’s disease.

**NSAIDs and COX2 inhibitors**

NSAIDs are commonly used as analgesics and antipyretics during inflammatory episodes. Although these drugs work via distinct mechanisms, they share pharmacological properties with steroid anti-inflammatory drugs (such as cortisone), including inhibition of eicosanoid production. Whereas steroid anti-inflammatory drugs inhibit phospholipase A\textsubscript{2}, thereby decreasing the amount of arachidonic-acid-derived prostaglandins, NSAIDs mostly prevent COX activity, resulting also in a decrease in prostaglandin concentrations. As well as their inhibitory effect on COX activity, NSAIDs are also potent reactive oxygen species and reactive nitrite species scavengers\textsuperscript{133} and some (eg, ibuprofen and indomethacin) can activate the anti-inflammatory peroxisome proliferator-activated receptor γ (PPARγ) pathway.\textsuperscript{144}

Because experimental and epidemiological evidence supports the protective role of NSAIDs and of COX2 inhibition in Parkinson’s disease, the hypothesis that the therapeutic use of such drugs could successfully provide neuroprotection against dopaminergic cell death is tempting. Although NSAIDs and COX2 inhibitors have not been tested in Parkinson’s disease, much can be learned from other neurodegenerative disorders, in particular Alzheimer’s disease, for which there have been clinical trials. Overall, these studies have not shown any substantial positive effect of NSAID treatment on improvement of the patients’ clinical scores.\textsuperscript{150} It is an open debate as to whether such findings indicate that these drugs are ineffective in preventing inflammation-driven neuronal cell death or if the inflammation hypothesis is incorrect. Nonetheless, as indicated by epidemiological studies, NSAIDs or other anti-inflammatory drugs, might be beneficial as a preventive treatment rather than as a postsymptomatic cure. The finding that COX2 inhibition in mice exposed to MPTP had no neuroprotective effect when pharmacological treatment was started 1 day after injury\textsuperscript{152} supports this idea. Notwithstanding the therapeutic value of NSAID treatment in Parkinson’s disease, it is important to consider that their long-term use might be associated with adverse side-effects, particularly gastrointestinal lesions. To circumvent this problem, selective COX2 inhibitors have been developed to avoid NSAID-induced COX1 inactivation, which causes stomach injury in chronic treatment. Clinical trials in Alzheimer’s disease that used these compounds were stopped before final assessment because some drugs, including celecoxib, were associated with increased cardiovascular risks.\textsuperscript{137,138} Therefore, a final assessment of the therapeutic benefit that COX2 inhibitors could provide for Parkinson’s disease and other neurodegenerative disorders will have to await the development of new and safer drugs.

**Drugs regulating glial-associated innate immunity**

Strategies aimed at suppressing the activation of glial cells and their inflammatory properties by use of various drugs have been extensively tested in animal models.\textsuperscript{139} Use of drugs with a broad spectrum of action on inflammation would be more likely to protect dopaminergic neurons efficiently than more selectively targeted drugs. Among these compounds, agonists of PPARγ seem to be promising candidates for therapeutic use in Parkinson’s disease.\textsuperscript{140} Preclinical studies have shown that pioglitazone, a PPARγ agonist that crosses the blood–brain barrier, can partly prevent dopaminergic cell loss induced by MPTP in mice.\textsuperscript{86,141} However, there are concerns about whether pioglitazone is protective because of its inhibitory action on monoamine oxidase B, which biotransforms MPTP to its active neurotoxic metabolite MPP\textsuperscript{+} (1-methyl-4-phenylpyridinium).\textsuperscript{142} Nonetheless, in a model of inflammation-induced dopaminergic neurodegeneration by intrastriatal lipopolysaccharide in rats, pioglitazone is protective.\textsuperscript{80} In addition to the fact that pioglitazone is a drug approved by the US Food and Drug Administration, another major advantage of agonists of PPARγ is that these drugs have several mechanisms of action beyond their immunoregulatory properties. Plenty of evidence supports a role of agonism of this nuclear receptor in the regulation of mitochondrial bioenergetics, insulin signalling, glucose metabolism, and lactate production.\textsuperscript{149} The possibility that treatment with these compounds could simultaneously decrease the inflammatory burden and restore mitochondrial function and cellular metabolism within the affected dopaminergic neurons is a novel therapeutic perspective for Parkinson’s disease, in which mitochondrial dysfunction and disturbed metabolism are recognised as pathological...
mechanisms. Because preclinical testing of pioglitazone was successful and long-term use of agonists of PPARγ was safe (best exemplified in patients with diabetes144), we believe that clinical trials of such drugs should be encouraged in Parkinson’s disease.

The antibiotic minocycline is another immunoregulatory drug that has been extensively tested in preclinical studies. This semisynthetic tetracycline analogue is well known for its antimicrobial activity by protein synthesis inhibition. However, many studies have shown that minocycline has many other properties including anti-inflammatory and antiapoptotic actions.145 Minocycline provides neuroprotection in various experimental models of neurodegenerative disorders such as amyotrophic lateral sclerosis, Alzheimer’s disease, Huntington’s disease, and Parkinson’s disease.146 Although the original studies gave encouraging results in models of Parkinson’s disease,45,39,147 more recent investigations have raised some concerns about the use of minocycline as a treatment for this disorder. Depending on the dose and the route of administration, minocycline treatment in rodent and non-human primate models of Parkinson’s disease can exacerbate neurodegeneration.148-149 Despite uncertainty as to whether minocycline might be beneficial or detrimental in human beings, a randomised, double-blind, futility, 12-month, phase II trial of minocycline and creatine in patients newly diagnosed with Parkinson’s disease has been conducted. The trial showed that neither drug should be considered futile,149 encouraging future phase III trials to determine whether these drugs could change long-term progression of Parkinson’s disease.

Other strategies aimed at preventing microglial cell activation that use more specific targeting compounds have recently emerged and would merit further assessment in preclinical settings. For example, in vitro and in vivo microglial cell activation can be substantially inhibited through activation of cell-surface α7 nicotinic acetylcholine receptors.150-152 Of note, cigarette smoking is associated with a lower incidence of Parkinson’s disease.153,154 Because nicotine is the main biologically active compound of tobacco, speculation that this alkaloid mediates most of the protective effect in everyday smokers is tempting. In support of this hypothesis, both cigarette smoke and nicotine itself have protective effects on MPTP-induced nigrostriatal pathway injury in mice and monkeys.155-158 Although the neuroprotective effect of nicotine is not limited to anti-inflammatory mechanisms,159 these studies suggest that α7 receptor agonists, such as quinuclidines160 or PHA-79829,161 might be of interest to target microglia-associated immunity in Parkinson’s disease.

Another potentially useful molecular target to prevent microglial cell reaction is the purinergic P2X, ionotropic receptor, which mediates the mobilisation of intracellular calcium ions.162 This receptor has a crucial role in the inflammatory response of microglial cells, and its modulation by, for example, the oxidised ATP antagonist, attenuates lipopolysaccharide-mediated microglial activation and neuronal damage in the inflamed brain.163 Although, P2X, receptor inhibition has not been tested in animal models of Parkinson’s disease, a recent report showed that this blockade was neuroprotective in an animal model of Alzheimer’s disease.164

Active or passive immunisation

Besides the role of glial-associated innate immunity in dopaminergic cell death, an adaptive immune response mediated by T cells might also be involved in neurodegeneration. Therefore, manipulating the adaptive immune system could be a successful strategy for neuroprotection. Antigen-based immunointervention has emerged as a possible way to redirect the harmful T-cell response into an anti-inflammatory and protective immune reaction.165 The therapeutic value of such an approach has been successfully tested in preclinical experiments in mice exposed to MPTP by use of glatiramer acetate (copolymer 1 or copaxone, a synthetic random amino acid polymer composed of glutamine, lysine, alanine, and tyrosine) as an immunisation-based antigen.166-168 Glatiramer acetate–specific T cells given to animals exposed to MPTP by adoptive transfer can reach the injured brain areas and suppress activation of microglial cells; furthermore, these T cells can stimulate the synthesis of GDNF from astrocytes, thereby conferring neuroprotection against MPTP-induced dopaminergic neuronal death.169 The T-cell subsets involved in this positive outcome are characteristic of a CD4+ CD25+ regulatory T-cell population, known to produce high amounts of the anti-inflammatory cytokine interleukin 10 and TGFβ.170 The therapeutic potential of interleukin 10 has recently been reported in the 6-hydroxydopamine model in rats, in which long-term expression of human interleukin 10 in the CNS by adeno-associated type 2 vector-delivering gene transfer substantially decreased dopaminergic cell death.171 Whether active immunisation of oral or systemic glatiramer acetate, or other antigens that can induce suppressor T cells to release inhibitory cytokines, could confer similar benefits in Parkinson’s disease needs to be assessed. Nonetheless, glatiramer acetate treatment not only showed remarkable safety and tolerability in controlled clinical trials but also significantly decreased disability in patients with multiple sclerosis.172-174 Additionally, immune deviation by vaccination against major molecular constituents of the nervous system, such as myelin oligodendrocyte glycoprotein (MOG), or treatment with complete Freund’s adjuvant can modulate the extent of MPTP-induced nigrostriatal injury in mice and supports a rationale for the use of such vaccination strategies.175,176 Active vaccination with human α synuclein in a familial Parkinson’s disease mouse model characterised by the accumulation of aggregates of a synuclein provides some benefit in terms of pathological outcomes.177 Importantly, however, as previously shown in Alzheimer’s disease,178 the route and mode of antigen delivery are key determinants in the
development of active immunity or immunological tolerance. Consequently, the outcome of vaccination can be either beneficial or detrimental, as, for example, when active vaccination results in meningoencephalitis.53 Therefore, there is still much to learn about immune changes associated with Parkinson’s disease to develop efficient and safe vaccination-based immunotherapeutics.

Conclusions

Since microglial cell activation was first characterised in the brains of patients with parkinsonian symptoms 20 years ago,5 there has been great interest and developments in the study of neuroinflammation in Parkinson’s disease. As can be seen from the data reviewed here, neuroinflammation is now recognised as an important pathophysiological feature of this neurodegenerative disorder. However, despite the progress made so far, one question remains: are immune-associated mechanisms the main cause of the progressive loss of dopaminergic neurons? Although much evidence from preclinical studies in animal models suggests a deleterious role of immune-associated mechanisms in parkinsonism, the ultimate goal of translating our basic understanding of the neuroinflammatory network into therapeutic interventions remains distant. One main reason for such scepticism about the role of neuroinflammation is the overall inability of available animal models to predict accurately the outcomes of trials that test neuroprotection in human beings. As recently reviewed by Dragunow,179 many factors could explain the failure of translation from animal models to human beings in the clinic. Until animal models that closely mimic the neurodegenerative process of Parkinson’s disease are available and until biomarkers that correctly indicate both neuronal dysfunction and inflammation of the CNS are developed, more vigorous investigation into immune-associated changes will provide important clues for the development of more effective neuroprotective drugs. In the meantime, futility studies aimed at assessing the potential use of both putative anti-inflammatory and more generally neuroprotective drugs are needed, not only to guide the scientific community and avoid useless and expensive large-scale trials, but also to provide hope for patients with Parkinson’s disease and their families.179

Contributors

Both authors searched papers for this Review. ECH drafted the paper, wrote the sections on neuroinflammatory processes in patients with Parkinson’s disease and the cells involved in neuroinflammation in animal models, and prepared the panels. SH wrote the sections on the molecular pathways involved in neuroinflammation in animal models and the therapeutic developments and future directions. SH developed the figures and wrote the legends. Both authors reviewed and discussed the whole paper.

Conflicts of interest

We have no conflicts of interest.

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Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms “Parkinson’s disease”, “inflammation”, “cytokine”, “glial cell”, “microglia”, “astrocyte”, “lymphocyte”, “MPTP”, and “6-hydroxydopamine” between January, 1988, and January, 2009. Further papers were identified from the references cited in those articles. Only papers published in English were reviewed. The final reference list was generated from papers that were relevant to the topics covered in this Review.


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