# The Role of Inflammatory and Oxidative Stress Mechanisms in the Pathogenesis of Parkinson's Disease: Focus on Astrocytes

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**Abstract**  Neuroinflammation plays a key role in the patho-genesis of Parkinson's disease (PD). Epidemiologic, animal, human, and therapeutic studies support the role of oxidative stress and inflammatory cascade in initiation and progression of PD. In Parkinson's disease pathophysiology, activated glia affects neuronal injury and death through production of neurotoxic factors like glutamate, S100B, tumor necrosis factor alpha (TNF-$\alpha$), prostaglandins, and reactive oxygen and nitrogen species. As disease progresses, inflammatory secretions engage neighboring cells, including astrocytes and endothelial cells, resulting in a vicious cycle of autocrine and paracrine amplification of inflammation leading to neurodegeneration. The exact mechanism of these inflam-matory mediators in the disease progression is still poorly understood. In this review, we highlight and discuss the mech-anisms of oxidative stress and inflammatory mediators by which they contribute to the disease progression. Particularly, we focus on the altered role of astroglial cells that presumably initiate and execute dopaminergic neurodegeneration in PD. In conclusion, we focus on the molecular mechanism of neurodegeneration, which contributes to the basic understand-ing of the role of neuroinflammation in PD pathophysiology.

**Keywords**  Parkinson's disease · Inflammatory mediators · Oxidative stress

## Abbreviations

| | |
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| NGF | Nerve growth factor |
| GDNF | Glial cell line-derived neurotrophic factor |
| MANF | Mesencephalic astrocyte-derived neurotrophic factor |
| bFGF | Basic fibroblast growth factor |
| PD | Parkinson's disease |
| ROS | Reactive oxygen species |
| RNS | Reactive nitrogen species |
| TNF-$\alpha$ | Tumor necrosis factor-$\alpha$ |
| NF-$\kappa$B | Nuclear factor kappa-B |
| COX-2 | Cyclooxygenase-2 |
| GFAP | Glial fibrillary acidic protein |
| CHOP | C/EBP homologous protein 10 |
| iNOS | Inducible nitric oxide synthase |
| IL-1$\alpha$ | Interleukin-1$\alpha$ |
| IL-1$\beta$ | Interleukin-1$\beta$ |
| IL-6 | Interleukin-6 |
| P-p38 MAPK | Phosphorylated p38 mitogen-activated protein kinase |
| NO | Nitrite |

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## Introduction

Neuroinflammation results primarily from the presence of chronically activated glial cells (astrocytes and microglia) in the brain and is a common feature in the pathology of PD [1]. The role of reactive astrocytes and microglia is further em-phasized by the fact that neuroscientists initially spoke of "Reactive gliosis" instead of neuroinflammation in describing glial responses of the central nervous system (CNS) tissue to injury [2]. Reactive gliosis, is the cellular manifestation of neuroinflammation and characterized by formation of glial cell soma, and accumulation and activation of enlarged glial cells, notably microglia and astrocytes, appearing immediate-ly after injury [3]. Best considered as a local tissue response without any involvement of the peripheral immune system, neuroinflammation in PD is a complex process with multiple mediators, signaling pathways, and feedback loops. Further, various studies demonstrated beneficial effects of nonsteroidal anti-inflammatory drugs in treatment of CNS and other

neurodegenerative diseases, which supported the role of neuroinflammation in the progressive degeneration of neurons [4, 5]. However, neuroinflammation and oxidative stress are connected to each other, but still they play very distinct and independent roles in disease progression. Among the neuroinflammatory mediators, cytokines and prostaglandins play important roles in causation and progression of neurodegenerative diseases [6, 7]. Oxidative stress-induced mediators include reactive oxygen species (ROS) and reactive nitrogen species (RNS). In this review, we discuss the role of inflammatory and oxidative stress as evidenced by various studies in the causation and progression of PD pathogenesis [8]. Last but not least, we also describe and highlight the potential role of astrocytes in the causation of neurodegeneration in Parkinson's disease.

## Some Important Aspects of the Parkinson's Disease Pathophysiology

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's dementia [9]. Parkinson's disease is a common neurodegenerative disorder of unknown cause which cardinal clinical features include tremor, stiffness, slowness of movement, and postural instability [10]. Although the etiology of idiopathic Parkinson's disease is unknown, this neurodegenerative disease is characterized by the degeneration of dopamine (DA)-producing neurons. The origin or central cause of this neuronal degeneration is unknown and may involve several molecular and cellular cascade of events, including oxidative stress, inflammation, accumulation of altered proteins, excitotoxicity, proapoptotic mechanisms, and mitochondrial dysfunction [11, 12]. It has recently been suggested that a glial reaction and inflammatory processes also participate in the cascade of events leading to neuronal degeneration [12–14]. First, an astroglial reaction was generally described at neuropathological examination in the substantia nigra (SN) of patients with PD and has been confirmed quantitatively using glial fibrillary acidic protein (GFAP) immunostaining [15]. An increased number of activated microglial cells has consistently been reported in PD [16]. The role played by these glial cells is not fully understood and still under debate [11, 13, 17]. Activated microglial cells may have a deleterious effect on DA neurons. Microglial cells represent resident brain macrophage cells and can be transformed into activated immunocompetent antigen-presenting cells during the pathological process [11]. Further, it has been reported that, in PD, there is an increased density of glial cells expressing proinflammatory cytokines including tumor necrosis factor alpha (TNF-$\alpha$) and interleukin-1$\beta$ [18]. Aside from increased levels of cytokines such as TNF-$\alpha$, several investigators have also reported interleukins in the brain parenchyma or cerebrospinal fluid of PD patients

[18, 19]. In addition to astrocytes and microglial, other cells may also participate in the neuroinflammatory processes in PD [20]. One may, thus, speculate that after a primary insult of environmental or genetic origin, the glial reaction may maintain the degeneration of DA neurons. However, this question, and more generally the role of inflammation in the pathogenesis of PD, cannot be addressed by postmortem studies alone [20]. Therefore, epidemiological and genetic studies also suggest a role of inflammatory processes in susceptibility to Parkinson's disease [21]. Data from an epidemiological study regarding the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the risk of PD emphasize the role of inflammation [4, 22]. Interestingly, participants who reported regular use of nonaspirin, nonsteroidal anti-inflammatory drugs at the beginning of the study had a significantly lower risk of PD than nonregular users during the follow-up [22]. However, a majority of data from clinical studies and from experimental models show the potential use of NSAIDs in the treatment of Parkinson's disease, but there are also few exceptional studies that contradict with the use of NSAIDs [23, 24].

## The Evidences of Inflammation in Various Animal Models of PD

It is important to note that major cell types involved in the process of neuroinflammation-associated neurodegeneration are the microglia and astroglia [13]. In some parts, other types of cells can also participate in the initiation and progression of neuroinflammation-associated neurodegeneration [13, 25]. It is now further evident that various models of PD that ultimately result in the dopaminergic neurodegeneration involved the neuroinflammation and activation of resident glial cells. Almost a decade ago, intranigral delivery of lipopolysaccharide (LPS) was first shown to induce an inflammatory reaction that activated microglia and induced selective and irreversible damage to nigral dopaminergic (DA) neurons [26–28]. A study from a transgenic animal model of TNF-$\alpha$ expression has showed a significant loss in tyrosine hydroxylase activity and grooming behavior [29]. This study strongly supported the notion that DA neurons are intrinsically more susceptible to inflammatory stimuli. In recent years, two additional bacteriotoxin-induced inflammatory models of PD consisting of chronic low-dose LPS infusion into substantia nigra pars compacta (SNpc) of rats or intrauterine exposure to LPS were reported and shown to induce delayed, chronic, and progressive loss of DA neurons in the adult SNpc or in the offspring, respectively [30, 31]. Together, these inflammogen models of PD lend further support for a role of toxin-induced inflammation in the degeneration of the nigrostriatal pathway. Several exogenous compounds that inhibit specific protein complexes along the mitochondrial electron transport chain and cause DA neurotoxicity have been used to generate

animal models of PD and all of them have a robust associated glial reaction [11, 32]. The best characterized models include 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), $N$-methyl(R) salsolinol, rotenone, and paraquat [33, 34]. The enzyme monoamine oxidase B is present in astrocytes and microglia, where it converts MPTP into $MPP^+$ [1-methyl-4-phenyl-pyridinium], a free radical oxidant that is taken up by DA transporters in neurons [35]. MPP+ enters the mitochondria, where it inhibits complex I function, thereby disrupting the first step in the electron transport chain required to sustain oxidative phosphorylation and triggering a circular cascade of oxidative stress that culminates in activation of the mitochondrial cell death machinery [36]. Although each neurotoxin may trigger different initial cascades of events, they all consistently involve oxidative stress as the critical mechanism that elicits the death of DA neurons [12]. Thus, general antioxidants are being intensely investigated for their ability to offer DA neuroprotection in experimental models of PD [37]. Evidence that the cycle of neuroinflammation triggered by exogenous neurotoxins persists long after the initial insult and may contribute to the progressive degeneration. Loss of DA neurons in MPTP models is associated with a glial response that peaks prior to the death of neurons [38]. MPTP is capable of inducing massive and prolonged microglia activation after single exposure in mice, monkeys, and humans [3]. Consistent with a critical role of the glial reaction in MPTP-mediated nigral neurotoxicity, anti-inflammatory drugs such as pioglitazone (a PPARγ agonist) and minocycline (a immunosuppressive and anti-inflammatory tetracycline derivative) have been shown to provide clinical benefit in MPTP-intoxicated mice. Numerous other anti-inflammatory compounds are under intense investigation as potential neuroprotective agents in experimental models of PD (Fig. 1). The neurotoxin of choice for inducing



**Fig. 1** All chemical-induced models of PD produce inflammation. A diagrammatic representation of inflammatory mechanisms involved in PD models. All chemically induced models of PD produce inflammation in the brain and astroglial activation. Activated astroglia produces toxic inflammatory mediators that contribute to PD neurodegeneration [110]

nigrostriatal degeneration in rats is the neurotoxic dopamine analog 6-hydroxydopamine (6-OHDA) and several studies support the importance of glial activity and inflammatory mediators in the neurodegenerative activity of this DA neurotoxin. 6-OHDA can be injected directly into the SN, forebrain bundle, or the striatal terminals, where it induces a retrograde degeneration and leads to the apoptotic death of DA neuron cell bodies in the SNpc [39]. The microglial activation and delayed loss of DA neurons induced by direct administration of 6-OHDA into the SN of mice can be blocked by the potent anti-inflammatory tetracycline derivative minocycline. Similarly, the cyclooxygenase-2 (COX-2) inhibitor celecoxib attenuated microglia activation induced by intrastriatal 6-OHDA administration and the delayed and progressive phase of DA neuron loss [40]. Although 6-OHDA-lesioned rats have been demonstrated to have increased levels of cytokines, in particular TNF, in both SN and striatum, the identity of the inflammatory mechanisms that mediate 6-OHDA-induced DA neurodegeneration has not been clearly established [41]. However, pharmacologic evidence implicates TNF-dependent events in death of DA neurons. Specifically, chronic pharmacological inhibition of soluble TNF signaling for 2 weeks with a dominant negative TNF inhibitor attenuated 6-OHDA-induced DA neuron loss detected at 3 weeks postlesion by approximately 50 % [41].

## Role of Mediators of Inflammation in the PD Pathogenesis

Evidence implicating cytokines in nigrostriatal pathway degeneration and from postmortem analyses indicated that the levels of several cytokines including TNF-α and interleukin 1-beta (IL-1β) are significantly elevated in the area of substantia nigra [42]. In the same area, maximal destruction of vulnerable melanin-containing dopamine-producing neurons occurs in PD patients [43–45]. In a research report, it has been evident that the serum concentrations of some cytokines are upregulated in the PD patients compared to the healthy individuals [19]. Among the cytokines, more importantly, are TNF and IL-1β and the downstream signaling pathways activated by them may represent common pathways on which divergent stimuli converge to elicit death of vulnerable neuronal populations through mechanisms that include mitochondrial toxicity (as described for TNF below) and caspase-dependent apoptosis or other forms of programmed cell death [46]. In addition to these, IL-1α and IL-6 are also involved in the pathophysiology of PD and play a very important role in dopaminergic neurodegeneration by the modulation of either glial or neuronal cell functions [47, 48].

Strong evidence implicates TNF-α as an early and late player in the pathophysiology of PD [49]. TNF-α signals through one of two receptors. Tnfrsf1a (formerly TNFR1) is
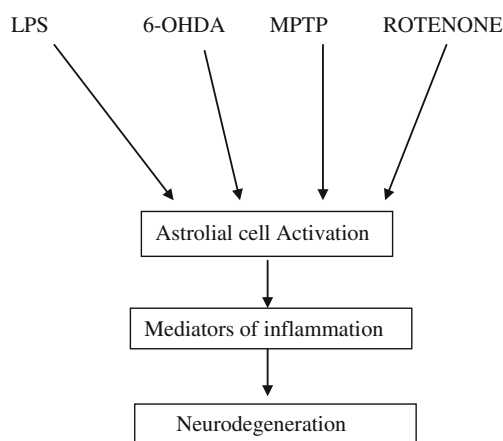
expressed in many cell types including nigrostriatal DA neurons [42, 50]. Tnfrsf1b (formerly TNFR2) is expressed primarily by cells of the immune system including microglia, but its expression has also been reported in heart and endothelial cells as well as dopaminergic, cortical, and hippocampus neurons [51, 52]. Moreover, mice lacking TNF-α receptors are generally resistant towards dopaminergic neurodegeneration [53, 54]. Levels of TNF in the healthy adult brain are generally very low and produced primarily by neurons [52]. In contrast, high levels of TNF and soluble Tnfrsf1a have been detected in CSF and in the SN of postmortem brains of PD patients [44]. SN dopaminergic neurons are extremely sensitive to TNF [49, 51]. In addition, TNF can activate the abundant numbers of microglia in the midbrain, potentiating inflammatory responses that lead to autoamplification of ROS, NO, and superoxide radicals to form highly oxidizing peroxynitrite species [55]. TNF-dependent microglia activation in the SN creates an environment of oxidative stress through activation of NADPH oxidase that further hastens oxidative damage of DA neurons [52, 56, 57]. Lastly, single-nucleotide polymorphisms (SNPs) in the promoter of the TNF gene have been studied in 1patients with sporadic PD [58]. Collectively, findings obtained from histopathologic, genetic, and pharmacologic studies strongly implicate a role for TNF-dependent mechanisms and downstream targets in neurotoxin- and bacteriotoxin-induced loss of nigral DA neurons and suggest that high TNF levels in the midbrain may increase susceptibility for Parkinson's disease in humans [59]. After an initial toxic insult, a self-perpetuating cycle of microglia activation would contribute to persistently elevated levels of toxic mediators in the nigral environment. Under either of these scenarios and independent of trigger that elicits its production, we hypothesize TNF action in the high oxidant environment of the SN is likely to result in (1) depletion of endogenous antioxidant capacity in vulnerable DA neurons, (2) potentiation of microglial production of ROS via NADPH oxidase-dependent pathways, and (3) activation of cell death pathways in oxidative stressed neurons (Fig. 2).

It is already known that IL-1β significantly affects dopaminergic neuronal functions in many ways [45]. There is also conflicting data regarding the role of IL-1β in dopaminergic neuron survival, but due to its high concentrations in cerebrospinal fluid (CSF) and postmortem brains of PD patients, it has been implicated in the pathophysiology of the disease [9]. IL-1β has been shown to increase the intracellular calcium through IL-1β receptor in C6 rat astrocytes [60]. Moreover, IL-1β regulates C/EBP, homologous protein 10 (CHOP) transcriptional activity that, in turn, regulates a number of genes involved in the pathogenesis of PD [61]. In addition to TNF-α and IL-1β, other cytokines like IL1-α and IL6 are also predominantly involved in the process of neuroinflammation-mediated dopaminergic neurodegeneration. However, much less is known about the role of IL-1α and IL-6 in the pathogenesis of PD. One important role of IL-1α and IL-6 is that they promote the growth of neuronal terminal in the mouse [62]. Further, IL-6 and IL-6 receptor have also been involved in the regulation of VCAM-1 gene expression that is a major gene responsible for the astrocyte function [63]. Therefore, targeted inhibition of the glial reaction and inflammatory processes triggered by various stimuli may represent an attractive therapeutic approach to slow down or delay progression of PD.

If the initial trigger that triggers microglial activation is not resolved (as in the case of a genetic mutation or a prolonged or repeated environmental exposure), a loop of neuroinflammation is likely to ensue and contribute to neuronal dysfunction and eventual death of vulnerable neuronal populations [64]. In support of this idea, experimental, clinical, and epidemiological studies indicate that activation of resident microglial populations may be occurring in parallel with the neuronal dysfunction underlying the disease process in certain neurodegenerative diseases. The two common ways by which neuroinflammation induces oxidative stress are via production of high levels of ROS by activated glia such as microglia and astrocytes and via arachidonic acid signaling through the activation of cyclooxygenase and lipoxigenase (LOX) pathways [65–67]. The brain expresses both COX-1 and COX-2; COX-1 is the key cyclooxygenase enzyme in microglia that is upregulated during inflammatory responses, whereas COX-2 levels are dynamically regulated by proinflammatory mediators under physiological conditions [40, 65, 68]. In addition, COX-2 has been shown to catalyze oxidation of cytosolic DA and its expression is upregulated in neurons and astrocytes in response to CNS injury [69, 70]. Consistent with these evidences, examination of brain samples from humans or mice exposed to MPTP confirms the presence of elevated COX-2 levels and extensive DA quinone formation as well as formation of protein-bound 5-cysteinyl-DA adducts [71, 72]. COX-2 ablation or pharmacological inhibition protects against MPTP- and 6-OHDA-induced nigral DA neuron loss [73]. ProstaglandinE-2 (PGE2), produced by COX-2, can induce an intraneuronal toxic effect directly on DA neurons [70]. Prostaglandins of the J2 series also induce oxidative stress by causing a decrease in glutathione and glutathione peroxidase activity, a decrease in mitochondrial membrane potential, and overproduction of protein-bound lipid peroxidation products including acrolein and 4-hydroxy-2-nonenal (HNE) [74]. These effects suggest that prostaglandins of the J2 series are either a source of markedly increased ROS generation or modulators of ROS sensitivity. The high density of microglia in midbrain relative to other parts of the brain coupled with expression of major histocompatability complex-1 (MHC1) and beta2-microglobulin in SN, DA neurons may promote microglial-derived oxidative stress in this region of the brain by facilitating presentation of misfolded, aggregated, or oxidized proteins or protein fragments to microglia, thereby
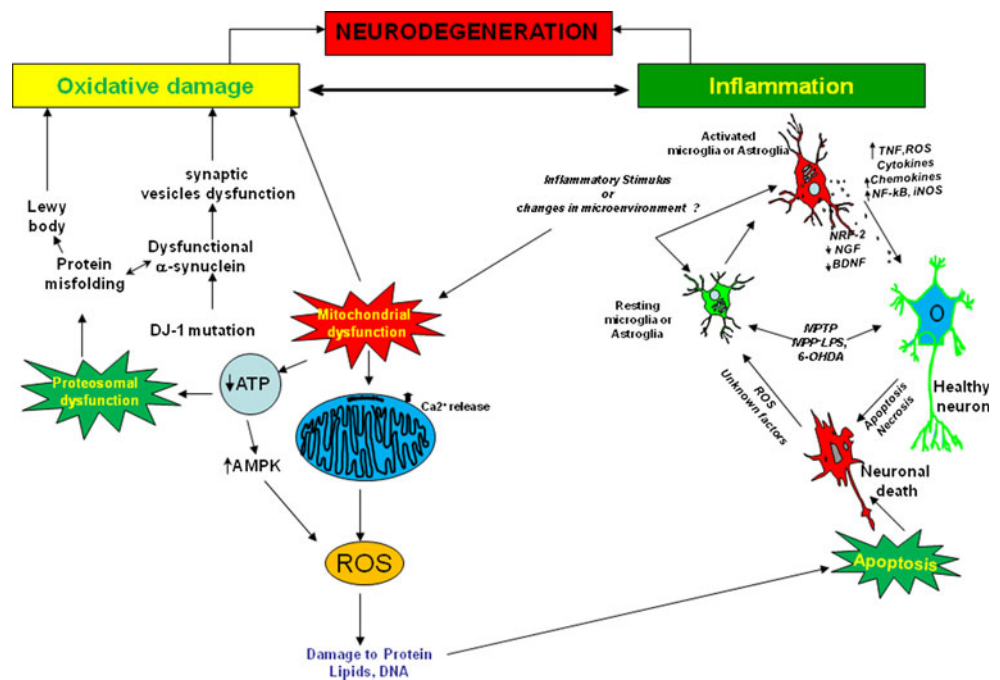
enhancing their phagocytic activity against DA neurons [75–77]. Collectively, all of the above conditions of the mid-brain microenvironment may act in concert to confer increased susceptibility to the dopamine-producing neurons to inflammatory stimuli [78]. The existence of inflammatory processes in PD is supported by evidences of activated microglia, accumulation of cytokines, nuclear factor kappa B (NF-κB) pathway activation, and oxidative damage to proteins in the CSF of live patients as well as in postmortem brain samples of Parkinson's diseases and most experimental models of PD [19, 44, 79].

Even if neuroinflammation does not occur in the early stages of DA neuron dysfunction, the release of chemoattractants by the dying DA neurons would be expected to lead to greater infiltration of the region by activated microglia coming to remove neuronal debris and may be a contributing factor in progression of disease as the respiratory bursts associated with phagocytic activities would further enhance oxidative stress for the remaining population of DA neurons. 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. Specifically, a large prospective study of hospital workers indicated that the incidence of idiopathic Parkinson's disease in chronic users of over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) that scavenge free oxygen radicals and inhibit cyclooxygenase activity was 46 % lower than that of age-matched nonusers. Inhibitions of COX-mediated DA oxidation 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 [4, 73]. 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 [73]. Results of these studies are less surprising in light of the fact that it is well-documented that certain neuron–glia interactions can lead to neuronal death [80]. Mechanistically, these PD risk-lowering effects of NSAIDs strongly suggest that neuroinflammatory processes contribute to DA neuron loss and development of PD in humans [13]. Although the protective effect of NSAIDs are likely to be primarily mediated by COX inhibition, multiple mechanisms, including the Rho kinase pathway, cannot be ruled out at this time in mediating the beneficial effects of NSAIDs [4].

From a neuropathological standpoint, microglial activation is indicative of an active, ongoing process of cell death [81]. While the presence of activated microglia in PD is consistent with the fact that PD is a progressive condition, their demonstration in postmortem samples from MPTP-intoxicated individuals who came to autopsy several decades after being exposed to the toxin challenges the notion that MPTP produces a 'hit-and-run' kind of damage [5]. Conversely, this important observation suggests that a single acute insult to the SNpc by MPTP could set in motion a self-sustained cascade of events with long-lasting deleterious effects [82]. Looking at mice injected with MPTP and killed at different time points thereafter, it appears that the time course of reactive astrocyte formation parallels that of dopaminergic structure destruction in both the striatum and the SNpc, and that GFAP expression remains upregulated even after the main wave of neuronal death has passed [78, 83]. This is supported by the demonstration that blockade of MPP$^+$ uptake into dopaminergic neurons completely

prevents not only SNpc dopaminergic neuronal death but also GFAP upregulation [78]. Remarkably, activation of microglial cells, which is also quite strong in the MPTP mouse model, occurs much earlier than that of astrocytes and, more importantly, reaches a maximum before the peak of dopaminergic neurodegeneration [13].

## The Role of Oxidative Stress in the PD Pathophysiology

At the cellular level, a significant body of evidences supported the "oxidative stress hypothesis" for initiation of nigral dopamine-producing neuronal loss [12, 84, 85]. Oxidative stress generate when there is an intracellular accumulation of reactive oxygen and nitrogen species (ROS/RNS) due to reduced endogenous antioxidant capacity and/or overproduction of ROS within the cell [12, 86]. Clearly, all aerobic organisms are susceptible towards oxidative stress because ROS (primarily superoxide and hydrogen peroxide) are produced by mitochondria during respiration [87, 88]. In fact, the brain is considered to be abnormally sensitive to oxidative damage, in part, because oxygen consumption by the brain constitutes 20 % of the total oxygen consumption in the body, and the brain is enriched in the more easily peroxidizable fatty acids while its antioxidant defenses (such as catalase, superoxide dismutase, glutathione, and glutathione peroxidase) are relatively sparse [86, 89]. It is very important that the SN appears to be among the most vulnerable regions primarily because it operates under a prooxidative state relative to other parts of the brain even in healthy individuals [90]. Specifically, the substantia nigra has a high metabolic rate combined with a high content of oxidizable species that include DA, DA-derived ROS, neuromelanin, polyunsaturated fatty acids, iron, and a low content of antioxidants (glutathione in particular), all of which render this brain region highly vulnerable to the effects of peroxynitrite and sulfite [86]. In summary, evidence of enhanced oxidative stress in the brains of PD patients includes increased oxidation of lipids, DNA, and proteins and has been documented in a large number of studies [91]. Further, in support of oxidative stress, extensive evidence also supports the involvement of impaired mitochondrial function in PD [92].

Mitochondria generate ROS as by-products of molecular oxygen consumption in the electron transport chain. Mitochondrial dysfunction of complex I of the respiratory transport chain has been reported from PD brain, particularly in the substantia nigra. A defect in complex I function would likely increase production of superoxide anion and free radical production by impairing electron flow from NADH to ubiquinone, building up oxidative stress through subsequent superoxide dismutase. Mutations in somatic mitochondrial DNA have been reported in PD brain and also in the aging brain. These findings are important because the mitochondrial DNA encodes components of the respiratory transport chain complexes, and such mutations may impair efficient electron flow from NADH to molecular oxygen. Oxidative phosphorylation in the substantia nigra has been shown to become increasingly impaired as a function of age. Clinically, untreated PD patients display decreased mitochondrial activity of complexes I and I/III [93]. It has been proposed that DA neurons may have an intrinsic sensitivity to complex I defects or agents that compromise its function on the basis of studies that demonstrate selective toxicity of the pesticide rotenone for DA neurons despite the fact that rotenone inhibits mitochondrial complex I throughout the brain [93]. Homozygous mutations linked to familial PD affect the activity of its kinase domain that has high homology to that of Ca2+/calmodulin-dependent serine/threonine kinases and prevent its ability to preserve mitochondrial membrane potential in conditions known to compromise mitochondrial integrity [93–95]. Among the mediators of neuroinflammation, NO contributes to DA neuron death through mechanisms that, while not completely understood, are likely to 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 α-synuclein and Parkin [86]. Mitochondria are not only sources of ROS but have also been shown to be subcellular targets of cytokines such as TNF that promote overproduction of ROS in mitochondria [96]. Glutathione is the only antioxidant in the cell available to metabolize hydrogen peroxide and a small fraction of the total cellular GSH pool is sequestered in mitochondria (mGSH) by the action of a carrier that transports it from the cytosol to the mitochondrial matrix [97]. Other evidence consistent with an important role of mitochondrial function in the etiology of PD includes the observation that inhibition of the mitochondrial respiratory complex I after exposure to the neurotoxin MPTP gives rise to PD-like pathologies in humans, non-human primates, mice, and rats [93, 98, 99].

Particularly, here, it is important to know that astroglial-mediated inflammatory and oxidative stress mechanism may be more important than the microglia or neurons, since they are the more abundant cell type in the brain and extensively involved in the nourishment of neurons. A small change in the surrounding astroglial cells may effectively cause neuronal cell death compared to any other type of the cells in the brain. In addition to the multiple factors such as cytokines and fatty acid metabolites produced from activated astroglia cells, ROS and nitrite may be the key mediator of glia-facilitated MPTP neurotoxicity. Dopaminergic neurons in the nigra are known to be particularly vulnerable to oxidative stress, presumably due to their lower antioxidant capacity, increased accumulation of ion and oxidation-prone dopamine (DA), and possible defects in mitochondria. In addition to oxidative and nitrative stresses, $Ca^{2++}$ ion release in astrocytes is an important event and involved in the regulation of

a number of mechanisms including release of S100B and other neurotoxins. However, earlier studies have reported alteration in the calcium ion homeostasis in PD, but the state of intracellular $Ca^{++}$ ion level in astrocytes in response to MPTP and melatonin was not demonstrated (Fig. 2).

## Astrocytes Play an Important and Distinct Role in the Initiation and Progression of Parkinson's Disease

Astrocytes play direct, important, active, and critical roles in mediating neuronal survival and function in Parkinson's disease (Fig. 3). [100]. This role of astrocytes is well accepted in the progression of amyotrophic lateral sclerosis (ALS), in which the removal of glutamate from the extracellular space by astrocytes confers neuroprotection, whereas astrocytic release of soluble, potentially toxic molecules promotes

neurodegeneration [101]. In recent years, this context-dependent dual role of astrocytes has also been documented in experimental models of PD [100]. Astrocytes, in particular, are more susceptible and recognize various signals from activated microglia in forms of soluble chemokines and cytokines and function differentially [13]. Particularly, here, it is important to know that astroglial-mediated inflammatory and oxidative stress mechanism may be more important than the microglia or neurons, since they are the more abundant cell type in the brain and extensively involved in the nourishment of the neurons [102]. A small change in the surrounding astroglial cells may effectively cause neuronal cell death compared to any other type of cells in the brain. More recently, we have demonstrated a distinct role of astrocyte-mediated oxidative stress and inflammation in the models of PD [102].

The neuroprotective and neurodegenerative functions of astrocytes depend largely on the molecules that they release
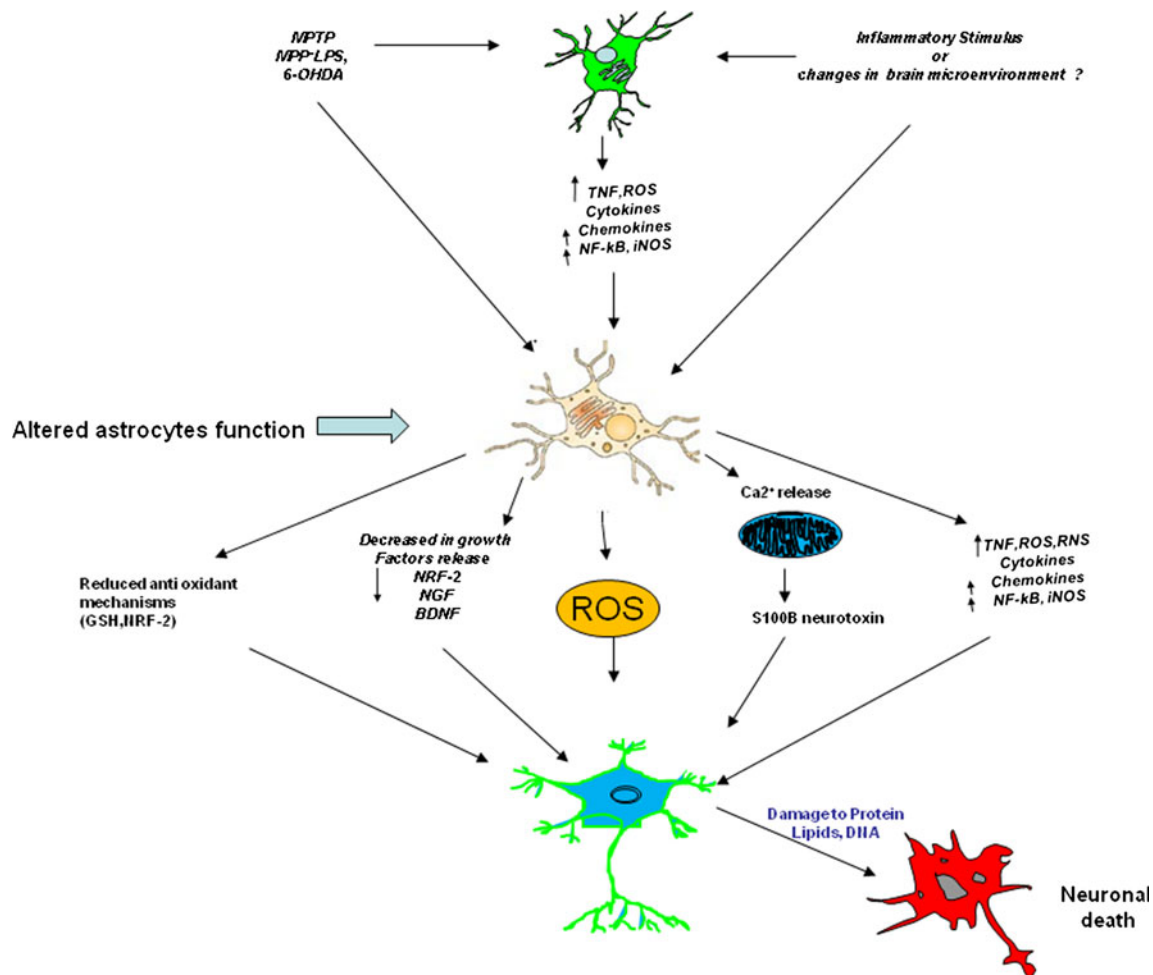


Fig. 3 Astrocytes play an important role in the neuronal death in PD. Here, we want to stress that altered astrocyte functions may be an important mechanism in the initiation and progression of dopaminergic neurons. Microglia and other microenvironment in the brain can assist in trigging astrocyte function that generates a massive quality of neurotoxic factors and lack of growth factors to the neurons causing, ultimately, dopaminergic neuronal demise. Figure shows that astrocytes functions are altered in the parkinson's disease pathophysiology. As described in the top portion of the figure, chemically induced models of PD shows increase in the production of inflammatory meditators from microglia. These inflammatory mediaters alone or in conjugation of other agents may trigger altered astrocytes functions leading to neurodegeneration

into and uptake from the extracellular space, also sometimes described as the microenvironment that astrocytes and neurons commonly share [100]. For example, it is well documented that astrocytes can release and supply neurons with neurotrophic factors such as nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and mesencephalic astrocyte-derived neurotrophic factor (MANF), neurotrophin-3, and basic fibroblast growth factor (bFGF) as well as metabolic substrates such as lactate and the antioxidant glutathione for the survival and proper functioning of neurons [100, 103]. Astrocytes also confer neuroprotection by siphoning away excess extracellular excitotoxic agents such as glutamate, potassium, and calcium. On the other hand, when astrocytes undergo a state of gliosis in response to neuronal injury or toxic insults, together with microglia, they release cytokines and chemokines that are deleterious to neurons. In addition to the multiple factors such as fatty acid metabolites, cytokines produced from activated astroglial cells, reactive oxygen species (ROS), and nitrite may be the key mediator of glia-facilitated MPTP neurotoxicity [104]. In addition to oxidative and nitrative stresses, $Ca^{2++}$ ion release in astrocytes is an important event and is involved in the regulation of a number of mechanisms including release of S100B and other neurotoxins [105] (Fig. 3).

In addition to these functions, there have been some more advances in the recent understanding of astroglial role in the pathogenesis of Parkinson's disease. In a recent study, it has been confirmed that astroglial-derived GDNF is a potent inhibitor of microglial activation, suggesting an important and regulatory role of astroglial cells [103]. Another recent study based on the genomic analysis of the astroglia shows that there are two different kinds of reactive astrogliosis that means there may be more that one kind of phenotypes existing in pathogenesis [106]. A study that provides a direct role of astrocytes in neuroinflammation-associated pathophysiology in Parkinson's disease has also been recently confirmed [107]. Interestingly, it has been shown that interferon regulatory factor 3 inhibits astrocyte inflammatory gene expression through suppression of the proinflammatory miR-155 and miR-155, exploring newer targets to reduce astrocyte-specific neuroinflammation [108]. More recently, it has been shown that cobalt(II) beta-ketoaminato complexes can be novel inhibitors of astrocyte-specific neuroinflammation [109]. Importantly, it has been demonstrated that alteration in Parkinson-associated gene DJ-1 mutation is directly linked to astrocyte neuroinflammation [110].

## Conclusion

In conclusion, in this review, we have tried to give a perspective on the wide variety of interactions between inflammatory mediators with etiology of Parkinson's disease.

Inflammatory and oxidative stress mechanisms are likely to play an important role in the neurodegenerative pathogenesis of PD. Defects in mitochondrial functions, suggested by the presence of mutations in mitochondrial DNA and impaired respiratory transport chain function in PD brain further provides connection to redox metabolism to PD. Understanding the role of, particularly, astrocytes in PD pathology may lead to development of mechanism-based therapeutics and improved pharmacotherapy for PD.

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