Journal of
Alzheimer's Disease & Parkinsonism

Sadek et al., J Alzheimers Dis Parkinsonism 2014, 4:3
DOI: 10.4172/2161-0460.1000148

Review Article Open Access

The Inflammatory Cytokines in the Pathogenesis of Parkinson's Disease

Hanaa L Sadek, Sayedah F Almohari, and Waleed M Renno*

Department of Anatomy, Faculty of Medicine, Kuwait University, Kuwait

***Corresponding author:** Waleed M Renno, Department of Anatomy, Faculty of Medicine, Kuwait University, 24923, Safat 13110, Kuwait, Tel: 00965 2463 6283; Fax: 00965 25319478; E-mail: wrenno@hsc.edu.kw

Received date: Feb 10, 2014; **Accepted date:** Apr 20, 2014; **Published date:** May 20, 2014

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopamine neurons in the substantia nigra pars compacta. Research and clinical data suggest that the etiology of PD is multifactorial. However, recent studies indicate that neuroinflammation and associated infiltration of inflammatory cells, chemokines and cytokines may play a critical role in the pathogenesis of PD. Cumulative evidences suggest that cytokines activation and neuroinflammation may have deleterious effects on the dopaminergic system and are key factors contributing to disease progression. The levels of proinflammatory cytokines in peripheral blood tend to be higher in PD patients. Studies of brains from PD patients and animal models have provided evidence for neuroinflammation, including activation of microglia, release of IFN-γ and TNF-α and infiltration of the midbrain by CD4 and CD8 lymphocytes. However, the influence of proinflammatory factors on the risk of PD remains unclear. In this review, we attempt to discuss the most recent publications on the role of inflammatory factors in PD. One hypothesis concerning the cause of degeneration of the nigrostriatal dopaminergic neurons is that PD is triggered by programmed cell death (apoptosis) due to increased levels of cytokines, apoptosis-related proteins and/or to decreased levels of neurotrophins such as brain-derived neurotrophic factor. Astrocytes stimulated by neuro-derived α-synuclein synthesize and release a number of proinflammatory cytokines and chemokines that in turn recruit and activate microglia. Thus, the effects of small amounts of neuronal α-synuclein protein can be amplified and sustained, thereby establishing an inflammatory microenvironment and further damaging neurons. This neuroprotection was shown to be associated with the anti-inflammatory properties of drugs that act as PPAR-γ agonists. In addition, these studies suggest that molecules that prevent inflammation and apoptosis may be useful in preventing or treating PD. In conclusion, protection of neurons against inflammation may help in slowing the neuronal degeneration in PD.

Keywords: Neuroinflammation; Apoptosis; Neurodegeneration; Degenerative diseases; TNF; Interleukins; Cytokines

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative illness of unclear pathogenesis affecting mainly the elderly. PD is the second most common neurodegenerative disease [1], only superseded by Alzheimer's disease. PD is characterized by the selective loss of the substantia nigra pars compacta dopaminergic (DA) neurons accompanied by the formation of intra cytoplasmic inclusions known as Lewy bodies that contain α- synuclein as well as by complex interactions between susceptible genes and various environmental risk factors [2]. Previously studies of brains from PD patients and animal models have provided evidence for neuroinflammation [3], including activation of microglia and infiltration of the midbrain by CD4 and CD8 lymphocytes [4].

The diagnosis of PD is based on motor symptoms such as tremor, rigidity bradykinesia, and postural instability associated with the striatal dopaminergic deficit that is associated with neurodegenerative processes in the substantia nigra (SN). Non-motor signs such as dementia and memory loss are most frequent symptoms affecting PD patients result from the deterioration in the adult neurogenesis in the hippocampus. Approximately 20% of patients with PD report a family history of the disease and monogenic forms of PD are relatively rare [5]. Genetics and heredity are known to influence the incidence of PD. PD is believed to result from a complex interaction between multiple genetic and environmental factors, nevertheless rare monogenic forms of the disease do exist. Although hereditary PD is extremely rare, the study of such families has provided important insights into the pathogenesis of PD. Genetic mutations in six genes (SNCA, LRRK2, PRKN, DJ1, PINK1, and ATP13A2) have conclusively been shown to cause familial Parkinsonism [6]. In addition, common variation in three genes (MAPT, LRRK2, and SNCA) and loss-of-function mutations in the glucocerebrosidase (GBA gene) have been well-validated as susceptibility factors for PD [7,8]. Although Parkinson's disease (PD) has been classically defined as a motor disorder, a range of non-motor symptoms (NMS) including cognitive, mood, autonomic and sleep disturbances develop with the passage of time. Many NMS including pain, fatigue, bladder dysfunction, cognitive decline and delusion had been described by classic authors (James Parkinson, Charcot, Gowers, Oppenheim and Wilson). In this review, we have gathered the classic literature of NMS in PD [9]. Bradykinesia, rigidity, resting tremor, and postural instability are some of the motor symptoms. Non-motor symptoms affecting autonomic, affective, and cognitive functions are seen frequently early in the course of the disease. These symptoms include autonomic dysfunction, pain, sleep disturbances, and depression; however, their impact on quality of PD patients" life has been relatively neglected [10]. A study done by O'Sullivan et al. [10] suggested that non-motor symptoms (NMS) are increasingly recognized as a significant cause of morbidity in later stages of Parkinson's disease. The presenting complaints of 433 cases of pathologically-proven PD archived at the Queen Square Brain Bank for Neurological Diseases were identified from the clinical case notes.

Twenty-one percent of patients with PD presented with NMS of which the most frequent were pain (15%), urinary dysfunction (3.9%), anxiety, or depression (2.5%) [10].

Patients with Parkinson's disease (PD) have a higher risk for the development of dementia. The prevalence of dementia in PD ranges from 10 to 30%. So, PD with dementia may represent the second most common cause of dementia after Alzheimer's disease (AD) [11]. Cognitive impairment of a lesser severity is also common in patients with PD without dementia, designated as mild cognitive impairment (MCI) of PD, or PD-MCI. Patients with PD-MCI have an increased risk of developing dementia, compared with those without MCI [12]. A pooled analytic study on 1346 PD subjects showed that a total of 25.8% of subjects was classified as having MCI. Memory impairment was most common (13.3%; 11.6–15.3), followed by visuospatial (11.0%; 9.4–13.0) and attention/executive ability impairment (10.1%; 8.6–11.9). The cognitive profiles were categorized as follows: 11.3% (9.7–13.1) non-amnestic single-domain MCI, 8.9% (7.0–9.9) amnestic single-domain, 4.8% (3.8–6.1) amnestic multiple-domain, and 1.3% (0.9–2.1) non-amnestic multiple-domain MCI. The occurrence of MCI was associated with older age at assessment and disease onset, male gender, depression, more severe motor symptoms, and advanced disease stage [12].

Pathology/Histopathology and CSF Biomarkers of PD

Parkinson disease is considered a multisystem disease, affecting the central nervous system diffusely rather than single circuits within the basal ganglia. Initial pathological studies have associated PD almost solely with the degeneration of dopaminergic neurons of the substantia nigra (SN) pars compacta projecting into the striatum. These neurons are tightly associated with the prototypical motor features of the disease such as hypokinesia, rigidity, tremor, and postural instability [13]. However, Braak et al. [13] proposed a model for the progressive nature of the disease starting within brainstem nuclei and the olfactory bulb (OB) that continues with a stepwise affection of midbrain, mesocortical, and finally cortical regions. Interestingly, neuropathological alterations in affected brain regions correlate with the onset of clinical features other than the cardinal motor symptoms. These non-motor features are present at early premotor stages of the disease and include olfactory dysfunction, cardiac sympathetic denervation and constipation, REM sleep disorder, depression, and anxiety.

Histopathologically, the disease is characterized by formation and accumulation of intracytoplasmic inclusions known as Lewy bodies, containing α- synuclein. These inclusions mostly accumulate in the striatum, hippocampus, and neocortex, affecting the neurogenesis due to diminished survival of neuronal precursor cells (NPCs) in neurogenic regions [14]. Furthermore, the endolysosomal pathway appears to be involved in α-synuclein degradation and, thus, may be relevant to PD pathogenesis. This hypothesis is further strengthened by the association between PD and mutations in the gene encoding for the lysosomal hydrolase glucocerebrosidase [15].

Mitochondrial dysfunction in the dopaminergic neurons of idiopathic and familial PD is well known although the underlying mechanisms are not clear [16]. The most direct evidence for disrupted mitochondrial metabolism has come from studies using autopsy tissues and other tissue samples and from in vitro cell cultures derived from human patients with PD [2]. Moreover, mitochondrial abnormalities have been reported in Parkin-defect mouse and fruit fly models of PD [17]. For instance, Lewy body formation, oxidative damage and decreased mitochondrial complex I activity are consistent pathological findings in PD [18]. Impaired mitochondrial function leads to increased oxidative stress (OS) and OS has a significant pathogenic role in the selective loss of DA neurons in human patients and experimental models for PD. OS or reactive oxygen species (ROS) not only implicit direct cellular damages but also activate signaling pathways leading to cell death [19]. Mao et al. [20] reported that the oxidative stress and mitochondrial dysfunction may be involved in the pathogenesis and progression of multiple sclerosis. They stated that Mito Q, a mitochondrial-targeted antioxidant, has a neuroprotective role in several mitochondrial and neurodegenerative disease such as PD.

To assess the discriminating power of multiple cerebrospinal fluid (CSF) biomarkers for PD, Parnetti et al. [21] had measured several proteins playing an important role in the disease pathogenesis. The activities of total and oligomeric α-synuclein, β-glucocerebrosidase and other lysosomal enzymes, together with phosphorylated tau, were thus assessed in CSF of 71 PD patients and compared to 45 neurological controls. They have found that the levels of total α-synuclein were significantly reduced in PD compared to increased levels of α-synuclein oligomers, with a higher oligomeric/total α-synuclein ratio in PD patients. A combination of β-glucocerebrosidase activity, oligomeric/total α-synuclein ratio, and age gave the best performance in discriminating PD from neurological controls. These results demonstrated the possibility of detecting lysosomal dysfunction in CSF and further support the need to combine different biomarkers for improving the diagnostic accuracy of PD [21]. Likewise, Kang et al. [22] observed a significant correlation between CSF levels of tau proteins and α-synuclein, but not β-amyloid 1-42 (Aβ1-42), and lower concentration of CSF biomarkers (total tau [T-tau], tau phosphorylated at threonine 181 [P-tau181])compared with healthy controls, in a cohort of entirely untreated patients with PD. They found a significant correlation of the levels of α-synuclein with the levels of T-tau and P-tau181. Thus, measuring CSF Aβ1-42, T-tau, P-tau181, and α-synuclein has prognostic and diagnostic potential in early-stage PD. In this regard, intense multidisciplinary research has provided detailed knowledge of the molecular pathogenesis of neurodegenerative diseases with Lewy bodies. Amyloid-β (Aβ42), total-tau (t-tau), phosphorylated tau (p-tau) and α-synuclein (α-Syn) pathology-associated biomarkers have been extensively studied in the CSF. These biomarkers and their combination showed good diagnostic accuracy for Alzheimer dementia and dementia with Lewy bodies [23].

In addition to the key biomarkers (amyloid β or Aβ, tau and α-synuclein), neurotrophins such as cocaine- and amphetamine-regulated transcript (CART) have also drawn an attention due to their expressions and functions. To prediction or early diagnosis of dementia, the role of specific and sensitive CSF biomarkers seems to be crucial in a routine clinical setting [23].

Inflammatory response appears to be involved in the pathological process of the PD. Prospective clinical studies with several non-steroidal anti-inflammatory drugs (NSAIDs) showed that ibuprofen decreases the risk of PD. Swiatkiewicz et al. [1] have examined the effect of ibuprofen on dopaminergic neuron injury in the mouse model of PD. This study showed that the neuroprotective effect of Ibuprofen against MPTP-induced injury in the striatum may be associated with decreased dopamine turnover and cyclooxygenase inhibition resulting in the reduction of the reactive oxygen species formation [1].

In PD, there is a deficiency in the neurotransmitter dopamine at the nerve terminals in the striatum, as a result of degeneration of the nigrostriatal dopamine (DA) neurons in the substantia nigra pars compacta [24]. Camicioli et al. [11] reported hippocampal atrophy in patients with Parkinsonism and Alzheimer disease when compared with normal controls using MRI [11]. Likewise, Bruck et al. [25] also showed significant atrophy in the hippocampus as well as the prefrontal cortex in twenty non-medicated non-demented Parkinson disease patients compared to twenty-two controls using MRI. Impaired memory was associated to hippocampal atrophy, whereas sustained attention was associated to prefrontal atrophy [25].

The generation and maturation of adult neural stem and progenitor cells are impaired in neurodegenerative disease models, in particular PD [26]. Paus et al. [26] investigated the impact of a gene called (Lrrk2), by knocking out that gene from rats and then studying the neuronal proliferation, survival, density and maturation. The results of this study showed a significant difference in expression profile of maturation markers in newly surviving generated cells [26]. Furthermore, the Wingless-type MMTV integration site (Wnt) signaling cascade has emerged as an essential system regulating multiple processes in developing of adult brain [27]. Wnts are highly conserved family of lipid-modified glycoproteins that work as morphogens to activate several signaling pathways. Wnt signaling regulates various cellular functions and cell systems, including the development and maintenance of midbrain dopaminergic (mDA) neurons. Recent reports show that appropriate levels of Wnt signaling are essential to improving the quantity and quality of stem cell- or reprogrammed cell-derived mDA neurons to be used in drug discovery and cell replacement therapy for PD [27,28].

Novikova et al. [29] studied the early signs of neuronal apoptosis in the substantia nigra pars compacta in the progressive neurodegenerative mouse MTPT/ Probenecid model of Parkinson's disease. Using TUNNEL essay and immuno histochemistry, the study showed that the apoptosis is an early sign of SNpc neuron degeneration in a chronic, progressive model of PD. Apoptotic DNA fragmentation, nuclear condensation, vesicular degranulation, and neuro cytoplasmic dissolution specifically in the SNpc as early signs of neurodegeneration preceding the detection of inclusion bodies buildup and motor impairment. This study suggests that primary neuronal apoptosis may be responsible at least in part for the cell loss during the slow induction of dopaminergic neurodegeneration in the chronic MPD. Therefore, molecules that block apoptotic process might be potentially useful for preventing further neuronal loss and functional deterioration in neurodegenerative diseases [29].

As stated earlier, PD is characterized by Lewy bodies accumulation in between the neurons, degeneration of dopaminergic neurons, and also activation of microglial cells in the substantia nigra and other brain regions. As a response to inflammation, microglial activation may enhance apoptosis of strange aggregations. Microglial activation can lead to harmful effects by releasing lots of pro-inflammatory cytokines that can deteriorate the disease condition. One hypothesis regarding the cause of the degeneration of nigrostriatal DA neurons is that PD is caused by microglial activation due to increased levels of cytokines [30]. Cytokines produced in the brain freely diffuse and pass the blood brain barrier into the peripheral blood supply. The activated microglia in PD was seen in several brain regions, such as the hippocampus and cerebral cortex, in addition to the nigrostriatal region [31]. In addition, oxidative stress can play a role in the neuroinflammation and protein aggregation due to the action of reactive oxygen species (ROS) in the course of the disease. Many studies were done on using anti-inflammatory drugs, as well as anti-oxidant drugs, to reduce and prevent PD [32].

Based on gene expression profiling study done by Lee et al. [33], a working model for the α-synuclein mediated neuroinflammation process was proposed. Neurons under stress release increased amounts of α-synuclein into the extracellular space that induce inflammatory responses from neighboring glia. Microglia, the major immune cells in the CNS, can be directly activated by α-synuclein. In addition, microglia activation can be attained indirectly by activation of astrocytes. Astrocytes, upon stimulation by neuron derived α-synuclein, synthesize and release a number of pro-inflammatory cytokines and chemokines that in turn recruit and activate microglia. Therefore, through eliciting the production of inflammatory factors in astrocytes, the effects of small amounts of α-synuclein protein released from neurons can be amplified and sustained, thereby establishing an inflammatory microenvironment and further damaging neurons. On the other hand, some factors released from α-synuclein stimulated astrocytes have neuroprotective functions. Thus, astrocytes may act as a key modulator, sensing the levels of α-synuclein proteins released from neurons; in some conditions, establishing a neuroprotective milieu, but in other conditions, causing full-blown inflammation. Studying the role of astrocytes in α-synuclein-mediated neuroinflammation would likely shed critical insight into the mechanisms of neuron-glia and glia-glia interactions in a parenchymal inflammatory microenvironment in brains of PD and other related neurodegenerative diseases [34].

PD Animal Models

Although many toxins and neurological insults that damage the basal ganglia and/or the substantia nigra result in neurological disorders, which include parkinsonian features, one toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), appears to target relatively specifically those neurons that are involved in Parkinson's disease [35]. MPTP has been widely used to develop animal models for testing new therapies in the human disease. MPTP is lipid-soluble, readily penetrates the blood-brain barrier and enters the brain cells. Because it is amphiphilic, it is captured into acidic organelles, mostly lysosomes of astrocytes. MPTP itself does not appear to be toxic, but its oxidized product, 1-methyl-4-phenylpyridinium (MPP+) is toxic. Astrocytes and serotonergic neurons contain MAO-B, which converts MPTP to MPP+. The toxic oxidation product reaches the extracellular fluid and then is transported by the dopamine transporter into dopamine nerve terminals. Inhibition of either MAO-B or the dopamine transporter protects against MPTP-generated MPP+ toxicity [35].

6-Hydroxydopamine (6-OHDA) is another substance that is also used by researchers to induce Parkinsonism in animals [36]. 6-OHDA is a hydroxylated analogue of the natural neurotransmitter dopamine. Inside neurons, 6-OHDA accumulates in the cytosol and induces cell death without apoptotic characteristics. Electron-microscopic studies have provided evidence for the ability of 6-OHDA to destroy adrenergic nerve terminals after systemic injection. It has been reported that 6-OHDA-induced neuron degeneration involves the processing of hydrogen peroxidase and hydroxyl radicals in the presence of iron. Furthermore, it has been shown that 6-OHDA treatment reduces striatal glutathione (GSH) and superoxide dismutase (SOD) enzyme activity [37].

Inflammatory Cytokines and PD

Cytokines are pleiotropic factors, promote signals such as interleukins and interferons that either lead to cell death or exert neuroprotective effects [24]. They are regulators of a wide range of host responses to infection, immune responses, inflammation, and trauma. Some cytokines are proinflammatory factors that initiate an inflammatory response necessary to recruit granulocytes, and later on, lymphocytes, to fight disease. Some of the cytokines are anti-inflammatory and serve to reduce inflammation and promote healing once the injury, infection, or foreign body has been destroyed [38].

The pathogenesis of the neuronal degeneration in PD is unknown and may involve many molecular and cellular events, including oxidative stress, accumulation of altered proteins, excitotoxicity, proapoptotic mechanisms and mitochondrial dysfunction. One hypothesis concerning the cause of degeneration of the nigrostriatal dopaminergic neurons is that PD is caused by programmed cell death (apoptosis) due to increased levels of cytokines apoptosis-related proteins and/or to decreased levels of neurotrophins such as brain-derived neurotrophic factor (BDNF) [3]. A study done by Brodacki et al. [39], examined serum levels of interleukin (IL)-2, IL-10, IL-6, IL-4, TNFα, INF-ϒ in 7 patients with atypical parkinsonism (AP), 31 idiopathic PD (iPD) patients, 17 idiopathic PD with cardiovascular risk factor (iPD-CVRF) patients, and 20 age-matched controls (healthy, non-parkinsonian patients). The leukocyte levels were significantly higher in AP and both iPD and iPD-CVRF patients as compared to control. All cytokines were detectable in the serum obtained from the control and Parkinsonism patients. The concentrations of IL-2, IL-4, IL-10, IL-6, TNF-α, and INF-ϒ were significantly higher in all parkinsonian patients as compared to control subjects. The greatest elevations of serum IL-2, IL-4, IL-6, TNFα, and INF-ϒ concentrations were found in AP patients as compared to the iPD and iPD-CVRF patients [39]. These results show that the pro-inflammatory and anti-inflammatory factors are higher in PD patients suggesting that there is a strong relationship between systemic inflammation and immune responses and PD. The accumulation and aggregation of α-synuclein and hyper phosphorylation of the tau protein may be responsible for enhanced cytokine levels in Atypical Parkinsonism patients, probably by activating neighboring microglia to produce Nitrogen Oxide and hydrogen peroxide [40].

A recent study using MPTP mouse model examined the expression of interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6 and their receptors (IL-1RI, TNF-αRI, IL-6Rα) in the substantia nigra and caudate-putamen (CP) regions [41]. This study revealed a significant increase in IL-1β, TNF-α and IL-6 mRNA expression levels in both the substantia nigra and caudate-putamen in MPTP-treated animals compared to controls. In addition, both mRNA and protein levels of IL-1RI, TNF-αRI and IL-6Rα were significantly enhanced in the substantia nigra of MPTP-treated mice. In contrast, no significant differences were seen in the caudate-putamen between treated and untreated mice. These results suggested a role of both pro-inflammatory cytokines and their receptors in the pathogenesis of PD [41].

Ciesielka et al. [42] examined the relationship between age and gender on cytokine's expressions in MPTP PD mice model. They assessed striatal tyrosine hydroxylase (TH) protein concentrations by using western blot and cytokine (TNFα, IFNγ, IL-1β, IL-6 and TGFβ1) mRNA levels (RT-PCR) in young and aged male and female mice after 6 h, 1, 3, 7, 14, 21 days following MPTP intoxication. Western blot analysis showed that males showed a greater reduction in striatal TH versus females at early time points. Additionally, in contrast to the aged mice, in young males and females, the TH concentration gradually increased between day 7 and day 21 after intoxication. The increase in TNFα, IL-1β and IFNγ after intoxication was faster in both young and aged males than females. In males (both ages), they observed an increase in TGFβ1 at the early time points. In contrast, in females (both ages) TGFβ1 was high at later time points [42].

Tumor necrosis factor (TNF)-α, a pro-inflammatory cytokine, has been implicated in both neuronal death and survival in PD. Many studies on human or mice brain showed an elevation of this cytokine after exposure to Parkinsonism. A recent study was done by Chertoffe et al. [43] compared the effect of TNF-α elevation in two groups of adult mice with two different high and low chronic expressions to TNF-α. The nigrostriatal neurodegeneration was mediated by intrastriatal (6-hydroxydopamine) administration. The results showed a neuroprotective effect on the nigrostriatal neurons after chronic low expression, whereas the chronic high up-regulating TNF-α had a slow and progressive neurodegenerative effect in the SN on the animal model of PD mediated by the chronic expression of a particular cytokine. So they concluded that the TNF-α levels and the duration of expression are relevant for the final effect of TNF-α cytokine on the SN. Regardless, this protective property of low TNF-α expression should encourage the design of anti-TNF-α treatments specifically targeting the toxic effects of TNF [43].

Another study by Ezcurra et al. [44] showed the effect of over expression of TNF-α to adult mouse SN. To achieve chronic over expression of TNF-α in the SN, they injected an adenovector expressing a recombinant mouse TNF-α (AdTNFα) directly into the SN. As a control, they used the same dose of an adenoviral vector expressing β-galactosidase (Adβgal). In order to determine whether over expression of TNF-α had a neurodegenerative effect, they quantified the number of dopaminergic, tyrosine hydroxylase (TH)-positive neurons remaining in the SN at different time points after the injection of AdTNFα and Adβgal. The number of TH-positive cells was reduced in animals expressing TNF-α compared to control animals and this difference increased as the number of days increased. This study also demonstrated motor impairment, leukocyte infiltration and increase in the number of activated microglia/macrophages after chronic expression to TNF-α [44].

Interleukin-1 beta (IL-1β) also known as catabolin, is a cytokine protein that in humans is encoded by the IL-1β gene and is produced by activated macrophages as a proprotein. A study done on an animal model of PD using 6-OHDA revealed the effect of neuroinflammation on PD, and in particular the IL-1β [36]. In this study, one group of rats underwent a surgery to inject the SN with 6-OHDA which induces PD either with or without injection of lipopolysaccharide (LPS) that induces neuroinflammation. The results showed a significant difference in the number of neurons in the group of neuroinflammation. They also reported microglial activation following injection of 6-OHDA and LPS. IL-1β was high after injection of LPS. These data suggest that mild inflammation caused by LPS increased the vulnerability of midbrain DA neurons to PD like degeneration in vivo, and identified the specific changes in cytokine brain tissue levels associated with the increased risk of degeneration. In contrast, systemic treatment of IL-1 receptor antagonist provided direct evidence that the inflammation induced neuronal vulnerability can be counteracted. These data give new intuitions into how low-grade inflammation may initiate the onset of PD and other

neurodegenerative diseases and the specific therapeutic opportunities to limit such pathogenesis [36].

In a nested case-control study performed by Chen et al. [45], high plasma IL-6 concentration was prospectively associated with an increased risk of developing PD. The blood was collected on average four years before disease diagnosis from 18,018 men who provided blood samples constituted the base group for the study. Eighty four incident Parkinson's disease cases were identified according to a standardized procedure. For each case, two controls were selected randomly from men who did not report a diagnosis of Parkinson's disease. IL-6 has both proinflammatory and anti-inflammatory activities. In the CNS, it is expressed on specific neurons, astrocytes, and microglia and could be induced by both proinflammatory cytokines such as IL-b and TNF-α and, in the cases of glia, viral and bacterial pathogens such as lipopolysaccharide [45].

Anti- Inflammatory PPAR and PD

In the last few years, peroxisome proliferator-activated receptors (PPARs) have been identified as promising targets for inducing neuroprotection in neurological diseases [46]. The PPAR isoforms α, β, and γ are ligand-activated transcription factors that regulate cell functions such as lipid and glucose metabolism, cell growth, differentiation and inflammation. In particular, PPAR-γ agonists have attracted significant scientific interest as agents that can protect against inflammation, oxidative stress and apoptosis [47,48]. Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear hormone receptor that has been shown to have anti-inflammatory, and matrix metalloproteinase (MMP) inhibitor properties [49]. Many studies have shown the effect of PPAR agonists to prevent neurodegeneration of dopaminergic neurons in PD models using MMTP or 6-OHDA. One of those studies [50] compared the effects of the PPAR-γ agonist (pioglitazone) on motor activity and nigral dopaminergic neuron loss in MPTP-treated mice model and the bilateral 6-OHDA rat model. The results showed improvement in motor activity, in the MPTP mice but not the 6-OHDA animals, after Pioglitazone treatment. Pioglitazone drug partially protected dopaminergic neurons from the neurotoxic effects of MPTP but not from those of 6-OHDA [50]. Another study was done by Sadeghian et al. [49] looked at the effect of partial PPAR agonists on a 6-OHDA model of PD. The results showed that both pioglitazone and GW855266X (partial PPAR-γ agonist) protected against 6-OHDA induced loss of dopaminergic neurons in the substantia nigra and depletion of striatal dopamine. Moreover, the administration of 6-OHDA was associated with an increase in the microglial activation and in numbers of MMP-3 immunoreactive cells which were attenuated by pioglitazone and GW855266X. Full agonists showed no effect on the neuroprotection process [49].

A recent study by Lee et al. [51] investigated the effect of the PPAR-γ agonist (rosiglitazone) in an animal model injected with 6-OHDA. The results showed that intranigral 6-OHDA injection elicited a loss of tyrosine hydroxylase (TH) fibers and an up-regulation of glial fibrillary acidic protein (GFAP) expression and preceded the increase in cyclooxygenase (COX)-2 expressions in the striatum. However, application of the PPAR-γ agonist, rosiglitazone prevented the striatal TH fiber loss. The protective effects of rosiglitazone are most likely attributable to anti-inflammatory effects with increases in astrocyte function [51].

Conclusion

In summary, the present review indicates that the molecular pathogenesis of Parkinson's disease could be due to different pathophysiological reasons. Accumulation of aggregations of the α-synuclein protein between nerves is well recognized because that leads to PD. Motor symptoms including bradykinesia, rigidity and tremor, are a subsequent result of the loss of dopaminergic neurons within the substantia nigra. The non-motor symptoms such as dementia that is related highly to the onset of PD is known to be a result of hippocampal atrophy as seen in most PD patients. One hypothesis regarding the loss of dopaminergic neurons in the substantia nigra is increased apoptosis due to elevation of cytokines level in the brain. These cytokines such as IL-1β, il-6, TNF-α and IL-10 are all either proinflammatory or anti-inflammatory in nature. Many studies were done on animal models of PD using toxic materials such as MPTP and 6-OHDA to show the elevation of these cytokines after induction of Parkinsonism. These studies suggest an increase in the microglial activation after induction of PD. Furthermore, these investigations suggest that molecules that can prevent inflammation and apoptosis may be valuable drugs in preventing or treating Parkinson's disease. One of these drugs that are under discovery is the PPAR-γ agonists which have shown to be useful in shielding against dopaminergic neuronal degeneration in models of PD. This neuroprotection was attributed to the anti-inflammatory effects of drugs that act as PPAR-γ agonists. However, more studies are required to appreciate the role of the inflammatory pathway in pathophysiology and clinical application of the PD. In conclusion, protection of neurons against inflammation can help to minimize or slow the neuronal degeneration in many neurodegenerative diseases including Parkinson's disease.

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