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Inflammation: Role in Parkinson's Disease and Target for Therapy

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<http://dx.doi.org/10.5772/63027>

Abstract

Evidence is now overwhelming that inflammation is a central process in the pathogenesis of progressive Parkinson's disease (PD). The hallmark of this neuroinflammation is the activation of microglial cells and the secondary role of adaptive immunity in both the familial and idiopathic forms of PD, leading to the loss of dopamine-producing cells within the Substantia nigra. This activation is characterized by the oxidative stress response, production of inflammatory mediators, recruitment and activation of immune effector cells which create a toxic environment for dopaminergic neurons, and in forming a continuous cycle of inflammatory responses that result in chronic neuroinflammation and progressive neurodegeneration. This chapter focuses on the different components of the inflammatory response that are involved in Dopamine-neurodegeneration, the evidence for inflammation in different forms of PD, and the role of inflammation in the various animal models of PD. Finally, we provide current evidence that targeting this inflammation with a number of anti-inflammatory therapies can be an effective way to halt the progression of chronic neuroinflammation-induced PD.

Keywords: Inflammation, Microglia, Cytokines, Therapeutics, Neurodegeneration

1. Introduction

Recently accumulated evidence suggests that neuroinflammation and chronic inflammation of the central nervous system (CNS) may play a critical role in the development of a number of neurodegenerative diseases. Particularly, in Parkinson's disease (PD), neuroinflammation has been proposed as a major contributing factor that plays a role in the initiation and progression of the dopaminergic neuronal loss that is the hallmark of the disease. Evidence to support neuroinflammation as the mode of pathogenesis for PD originates from postmortem studies

in patients and animal models. The proliferation and activation of microglial cells, as well as increased levels of pro-inflammatory mediators such as tumor necrosis factor (TNF)- α , interleukin (IL)-6, IL-1 β , nitric oxide (NO), and reactive oxygen species (ROS), are present in postmortem analysis of brains and in the cerebrospinal fluid (CSF) of PD patients [1]. These findings suggest that pro-inflammatory cytokines, specifically TNF- α , may be involved in neuronal cell death. Likewise, neuronal cell death can release mediators that activate microglial cells — thereby potentiating a vicious cyclical inflammatory-mediated neuronal cell death. PD is unique in that the clinical symptoms appear after a loss of approximately 70–80% of striatal nerve terminals and 50–60% of dopaminergic cells in the Substantia nigra pars compacta (SNpc), the region of the brain that is responsible for controlling movement [2, 3]. This recent scientific understanding is vital to developing potential early biomarkers and/or therapeutic strategies to help with better diagnosis and disease management. We discuss various components of neuroinflammation, focusing on the role of the innate and adaptive immune responses as they relate to PD. In addition, we briefly summarize the inflammatory pathology seen in the genetic and toxin-induced models of this disease, as well as discuss several anti-inflammatory therapies currently being used or tested as potential treatments for PD.

2. Innate immune response and PD

The innate immune response serves as the first line of defense to both infiltrating pathogens and/or endogenous insults. As such, it primarily functions to initiate an immediate and nonspecific response to any compound it deems unnecessary and/or a potential threat. Pathogen-associated molecular patterns (PAMPs) and/or endogenous damage-associated molecular patterns (DAMPs) can trigger an innate immune response. In the case of CNS, the innate immune system has several components: cells that mediate an immune response, such as microglia and astroglia, the complement system, and the physical obstruction imparted by the blood-brain barrier (BBB). For centuries, the CNS was thought to be immune privileged because the BBB did not allow various compounds to enter the CNS through the circulatory system. However, as we are beginning to appreciate the intricacy of the immune-nervous system interaction, the notion of immune privilege no longer holds [4].

In PD, the various components of the innate immune system are activated and the integrity of the BBB is compromised, allowing for the innate-mediated recruitment and activation of the adaptive arm of the immune system. While PD is not among other immune-dependent degenerative diseases, Parkinsonian symptoms have been shown to develop after infectious inflammatory diseases such as Epstein-Barr virus (EBV)-induced encephalitis. Likewise, many anti-inflammatory therapeutic agents have served protective functions in PD models [5]. As such, while the role of the immune system is not clear and/or extensively studied in the etiology of the disease, it is well established that the immune system is critical for the progression of the disease. Initial activation of the innate immune cells as well as the complement proteins may serve protective roles, but when these innate defense mechanisms become unregulated and maladaptive, it leads to disease progression. As immediate responders, cells of the innate immune system play an important role in initiating an inflammatory response against various nonspecific components of endogenous DAMPs and/or PAMPs. The innate cells, astrocytes

and microglia, play an active role in the pathological mechanism responsible for the progression of the disease.

2.1. Astrocytes

Astrocytes make up about 20–40% of the glial cell population in the CNS. Their functions include, but are not limited to, maintaining the integrity of the BBB, facilitating repair and scar formation, and maintaining the extracellular ion homeostasis. The expression of receptors that are critical for innate immunity such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domains, double-stranded RNA-dependent protein kinase, scavenger receptors, mannose-binding lectin receptor, and complement system components has implicated a role for astrocytes in innate immunity [6]. The role of astrocytes in PD is debatable and not well understood. Studies are inconclusive as to whether astrocytes have a neuroprotective effect and/or a neurotoxic effect in PD. However, astrogliosis, the activation of astrocytes, has been reported in some cases of PD as demonstrated by an increase in the glial fibrillary acid proteins (GFAP) [7, 8]. GFAP is an intermediate filament needed by astrocytes to synthesize cytoskeletal structures and is a well-established biomarker for astrogliosis [8]. Furthermore, activated astrocytes are reported in postmortem brains of PD patients; however, this activation is not confined to the SNpc and its function therefore still remains elusive [9]. In contrast, astrocyte activation is not only well documented in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) models of PD, but it has been reported to precede neuronal cell death [10–12]. In the MPTP model, astrogliosis and dopaminergic cell death are synchronized. In the 6-OHDA model, several laboratories demonstrate that astrogliosis occurs in a time-dependent manner, peaking at 4 days post injection and remaining in the brain for about a month. There are also studies that contradict the presence of astrogliosis post 6-OHDA injection [13]. Therefore, while astrocytes are an important cell type in the CNS, their role in inflammation and PD is not yet well established.

2.2. Microglia

In contrast to astrocytes, consistent microglial activation and the accompanying inflammatory response have been reported in both patient and animal models of PD. As the resident CNS macrophage, microglia cells are responsible for scavenging the CNS milieu for potential infiltrating pathogens and/or endogenous insults. Consequently, the phagocytic, cytotoxic, and antigen-presenting capabilities of these cells enable them to protect the CNS from various insults. Activated microglia targets infiltrating pathogens and damaged cells by releasing toxic ROS, free radicals, and phagocytosis. Evidence of microglial activation and its role in PD pathogenesis is indisputable. Knott et al. [9] and others [14] have reported activated amoeboid-shaped microglia in postmortem brain of PD patients. These activated microglia cells are densely located and confined to the SNpc with a limited presence in the vasculature of the caudate and putamen regions. Additionally, in determining the role of microglia in PD pathogenesis, our results as well as those from other groups [15–17] have shown that in various PD models, microglial cells are needed for the pathogenesis of PD. For example, we have shown that high doses of the β_2 -adrenergic receptor agonist salmeterol can induce dopami-

nergic cell toxicity. However, microglial cells are indispensable in the $\beta 2$ -AR-mediated toxicity, as high-dose salmeterol has no effect on neuron-only cultures [15]. In PD, the expression of ROS, free radicals, and the enzymes responsible for the production of these species such as NADPH oxidase (NOX or PHOX), induced nitric oxide synthase (iNOS), and myeloperoxidase (MPO) are elevated in the SNpc. These reactive species can activate microglial cells, and these activated microglia release pro-inflammatory cytokines TNF- α , IL-1 β , and IL-6 to recruit additional lymphocytes in the process of inflammation. Additionally, these cytokines can cause cytotoxicity in a direct, receptor-mediated manner, and/or in an indirect manner by inducing the further production of ROS and pro-inflammatory cytokines [18]. For example, dopaminergic cells express receptors for TNF- α , which, upon binding the TNF- α ligand, can cause cell death through Fas ligand-mediated apoptosis, and Tumor Necrosis Factor Receptor (TNFR) knockout is protective in the MPTP model of PD [19]. Indirectly, TNF- α can also activate additional microglia to release ROS and a variety of pro-inflammatory cytokines. This leads to a cyclical pathway whereby activation of a few cells can amplify the initial insult to a greater magnitude. This process has been termed reactive microgliosis and is now a leading working model for understanding and targeting neuroinflammation in PD [20].

3. Adaptive immune response and PD

Adaptive immune response is a highly specific response to injurious agents mediated by B- and T-lymphocytes, which is characterized by the humoral and cell-mediated response, respectively. These cells are activated by specific antigens and directly induce toxicity and cell death to the antigen-expressing cell. It is important to note that the adaptive immune cells require an antigen-presenting cell to prime the B- and/or T-cell to recognize a specific antigen. In PD, innate immune activation leads to an increased BBB permeability, allowing for the infiltration of peripheral T-cells and B-cells [21]. These infiltrating cells are activated by active microglia expressing MHC 1/II through presentation of endocytosed peptides to the respective cells. Evidence to suggest the involvement of adaptive immune system is that single-nucleotide polymorphism (SNP) in the MHC Class II predisposes individuals to PD, implying the role of both the innate and adaptive immune response in PD pathogenesis. Recent genome-wide association studies (GWAS) have highlighted alleles HLA-DRA (for Class I) and HLA-DRB5 (for Class II) as risk factors for PD [22]. Furthermore, MHC Class I proteins are typically used by CD8 T-cells and require $\beta 2$ -microglobulin, a protein required for the structural stability of MHC Class I, and in PD, the expression of $\beta 2$ -microglobulin is found to be increased on microglial cells [21]. Additionally, an increase in the number of cytotoxic CD8 and CD4 T-cells infiltrating into the SNpc of PD patients is accompanied by a decrease in the cytotoxicity-suppressing capacity of regulatory T-cells (T_{reg}) [23, 24]. Therefore, it suggests that toxicity of these effector T-cells is not properly regulated and can exacerbate neuronal cell death in the SN. With regard to B-cells, antibodies (Ab) to dopaminergic neurons have been found in the CSF of a proportion of the PD patients, thus implicating the involvement of the peripheral humoral arm of the adaptive immune response [25, 26]. Furthermore, immunization, which uses B-cells to generate antibodies against an antigen, with bovine mesencephalic homoge-

nates [27] and hybrid dopaminergic cell line homogenates [25], can cause selective DA neuron damage in a microglia-dependent manner. The adaptive immune system has a delayed contribution to the pathology of PD but, nevertheless, is important to understand in order to develop therapies that can mitigate and counter the pathology induced by this system.

4. Neuroinflammation and overlapping vulnerability of Substantia nigra (SN) neurons

The oxidative stress hypothesis focuses on the role that reactive oxygen and nitrogen species play in the neurodegeneration seen in PD. Reviews by Fahn and Cohen [28] as well as by Zigmond and Burke [29] discuss four characteristics of SNpc dopaminergic neurons that support the oxidative stress hypothesis as one of the major mechanisms responsible for the pathology of PD. However, understanding these characteristics can help explain the chronic, self-perpetuating inflammatory pathology that is responsible for disease progression in PD. While inflammation involves activated immune cells and the release of a multitude of pro-inflammatory cytokines, the cycle does require a start point. The etiology of PD is unknown as is what gives rise to the chronic inflammatory pathogenesis seen in PD. Two different explanations of the chronic etiology of PD suggest that neuronal cell death leading to activated immune cells and the resulting uncontrolled inflammation further exacerbates cell death, or that activated immune cells cause cell death which results in the activation of additional immune cells resulting in a vicious cycle of immune cell-mediated inflammation and neuronal death. The characteristics of SNpc dopaminergic cells make them vulnerable to ROS, subsets of which are important pro-inflammatory cytokines. First, dopamine degradation occurs by oxidative deamination, resulting in the production of H_2O_2 that then react with iron present in the neurons to form reactive radicals. Second, superoxides and free radicals are by-products of the reaction between dopamine and the readily available oxygen to form reactive quinones. Third, the SNpc particularly rich in iron and hence the neurons found therein are more vulnerable to cell death via oxidative stress. Fourth, the SNpc neurons contain neuromelanin, which is formed by the auto-oxidation of DA, and the by-product of this reaction is ROS. These characteristics make SNpc neurons particularly sensitive to a cyclical process of oxidative stress contributing to inflammation that that leads to furthermore neuronal damage.

5. Genetic causes of PD and neuroinflammation

Although PD is typically a sporadic disease, approximately 10% of PD cases have been linked to several specific genes. These genes are α -synuclein, Parkin, UCH-L1 (ubiquitin C-terminal hydrolase L1), PINK1 (PTEN-induced kinase 1, NB for mitochondrial function), DJ-1, LRRK2 (leucine rich repeat kinase2), Pael-R, and glucocerebrosidase [21, 30, 31]. These genes and their products have a role in the degradation of α -synuclein and/or in the control of the oxidative milieu. Mutations in genes encoding α -synuclein, Parkin, and/or UCH-L1 result in the

accumulation of misfolded α -synuclein protein and are accompanied by neuronal cell death [21]. Additionally, a pathological feature of PD is the Lewy body cytoplasmic inclusion bodies, which primarily consist of α -synuclein, tau, ubiquitin, and Parkin. These genes were identified in familial PD, as risk factors for sporadic PD, and further verified by a GWAS. Therefore, understanding the role of these genes and their products in mediating inflammation can help not only in developing more holistic model(s) of PD but also for therapy development.

5.1. LRRK2

Leucine-rich repeat kinase 2 (LRRK2) is an enzyme that is commonly expressed on multiple immune cells such as B-cells, monocytes, dendritic cells, and microglia [32]. Mutations in LRRK2 are associated with autosomal dominant form of PD with high resemblance to the idiopathic PD phenotype and other inflammatory-mediated diseases as Crohn's disease [33] with a high predisposition to leprosy infection [34]. LRRK2 is a member of the receptor-interacting protein kinase (RIPK) family. The RIPK family has important roles in immunity as well as regulating of cell death [35]. Furthermore, TLRs are an important activator of microglial cells. In the TLR-signaling pathway, LRRK2 is phosphorylated [36], and Kim et al. [37] as well as other groups [38] have reported a decrease in NF- κ B-mediated transcription, specifically of TNF- α , post LRRK2 phosphorylation. NF- κ B is a major transcription factor for many of the pro-inflammatory cytokines that are reported to play a role in the pathogenesis of PD, such as TNF- α , IL-1 β , and IL-6; LRRK2 modulation of NF- κ B will have important cellular effects on the inflammatory state of the activated microglial cells. Furthermore, a mutation in LRRK2, specifically R1442G, is reported to alter the phenotype of activated microglial cells to produce higher amounts of inflammatory cytokines with a decrease in the production of anti-inflammatory cytokines [39]. Gillardon et al. [39] tested the neurotoxicity of these microglial cells on cortical neurons by exposing neurons to conditioned medium from LPS-activated microglial cells, compared to conditioned medium from LPS-activated wild-type (WT) microglia, conditioned media from LPS-activated LRRK2 mutant significantly increased cell death. In addition, Kim et al. [37] have shown that LRRK2 deficiency mitigates LPS-mediated increase in the mRNA of iNOS, TNF- α , IL-1 β , and IL-6. By itself, overexpression of the mutant LRRK2 *in vivo* and *in vitro* causes neurotoxicity [40]. These data support a role for LRRK2 in regulating the inflammatory response of microglial cells and the resulting effect on neuronal viability.

5.2. Parkin

Parkin is an important component of the multi-protein E3 ubiquitin ligase complex that is responsible for the ubiquitin-proteasome-mediated degradation of α -synuclein in the brain. Mutations resulting in loss of function of Parkin are responsible for autosomal recessive form of juvenile PD [41]. Parkin not only regulates mitochondrial health but also is involved in the regulation of the NF- κ B signaling pathway [42]. Parkin ubiquitinates damaged mitochondria and subjects it to mitophagy and clearance from the cell [43]. Similarly, activated Parkin catalyzes ubiquitination of the I κ B kinase (IKK) subunit IKK γ , resulting in the downstream activation of NF- κ B [42, 44]. In this NF- κ B signaling pathway, TNF-receptor-associated

factor-6 (TRAF6) also plays a role in regulating IKK activity. Loss-of-function mutation in Parkin increases the expression of TRAF6 [45], thereby activating transforming growth factor-1 (TAK1) that activates IKK and ultimately NF- κ B and its associated transcriptional activity [44]. With regard to Parkin and mitochondria, while mitophagy and PD have not yet been linked, damaged mitochondria are a source of ROS that can activate microglial cells through TLR-PAMP/DAMP pathways [30].

5.3. α -Synuclein

α -synuclein is an 18-kDa protein found in high concentrations in the CNS compared to other areas. While the function of α -synuclein is unclear, it is thought to be important for the release of neurotransmitters and vesicle trafficking [46, 47]. Mutations in the *SCNA*, gene coding for α -synuclein, is implicated in inherited forms of PD. Similarly, α -synuclein aggregation is a critical component of Lewy bodies in both sporadic and genetic PD. With regards to inflammation, α -synuclein is thought to activate microglial cells through the nonspecific DAMP-TLR2/4 pathway [48,49]. An emerging link between gut microbiota and peripheral inflammation and PD is of interest to note. A study by Forsyth and colleagues [50] reported increased gut permeability and *Escherichia coli* (*E. coli*), a Gram negative bacterium, staining in early onset PD patients. The implication of this study is that *E. coli*-dependent inflammatory processes resulted in an increased iNOS that then nitrosylated α -synuclein. WT, mutant, aggregated forms of α -synuclein can all trigger microglial activation by acting as a TLR-ligand. Conditioned media from dopaminergic cell line SH-SY5Y that either overexpressed WT or A53T mutant α -synuclein activated BV-2 microglial cell line, with the conditioned media from the neurons overexpressing mutant α -synuclein caused a more robust increase in TNF- α , IL-1 α , and IL-1 β [51]. More importantly, mutant and aggregated fibrils of α -synuclein are reported to have cell-to-cell transmission capacity, thereby causing neuronal toxicity in a prion-like mechanism as well [52]. Moreover, nitrated α -synuclein can activate peripheral immune activation, especially T-cells and initiate the involvement of the adaptive immune response. Lastly, Tran and colleagues [53] have recently reported that antibodies to α -synuclein can offer a promising protective effect by inhibiting the entry of α -synuclein fibrils into neurons and causing neuronal death.

5.4. PINK1

PINK1 is a mitochondrial serine/threonine protein kinase implicated in providing cellular protection against mitochondrial-associated oxidative stress. As such, it is reported to regulate stressed mitochondria by enabling the binding of Parkin to stressed mitochondria and inducing autophagy. The role of PINK1 in inflammation is somewhat unclear; as evidence suggests that in PINK1 null animals injected with LPS, IL-1 β , IL-12, and TNF- α are increased [54]. However, in PINK1-deficient embryonic fibroblasts, there is no increase in pro-inflammatory cytokine production post LPS injection because of decreased NF- κ B activity [54, 55]. As such, experiments aimed at understanding the role of PINK1 in inflammation should be investigated in microglial cells which are known to propagate the inflammatory response in PD.

5.5. DJ-1

DJ-1, or Parkinson's disease Protein 7, inhibits the aggregation of α -synuclein, thereby acting as an oxidative stress sensor. PINK1 and DJ-1 deletion causes disruption of other genes involved in mitogen-associated protein kinase (MAPK)/NF- κ B signaling pathway and thereby alters the innate immune response of the microglia and other inflammatory cascades [6]. MAPKs are signaling proteins that mediate various intracellular signals in response to external stimuli. Several important MAPKs play an essential role in the integrity of the cell as well as modulating inflammation such as p38, C-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinases (ERKs). In astrocytes, DJ-1 loss of function primes astrocyte to release increased pro-inflammatory cytokines post LPS challenge [56]. This response was mediated through p38 and JNK, thereby DJ-1 may have a pivotal role in regulating TLR4-MAPK signaling and downstream transcriptional responses [57]. LPS-mediated activation of macrophages increases DJ-1 expression [58], which is aligned with the associated TLR/MAPK-mediated signaling in microglial cells challenged with LPS.

6. Inflammation and PD models

There are several models of PD, both toxin based and gene based, used to study disease progression and/or therapeutic development. In many of these models, inflammatory mechanisms are reported to play roles in the pathogenesis and manifestation of the disease in various animal models. In the remainder of this chapter, we will focus on characterizing the inflammatory response seen in the various models.

6.1 Toxin-based models

6.1.1. MPTP

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a dopaminergic neurotoxin selective for the dopaminergic cells of the SNpc. It is a lipophilic compound capable of crossing the BBB, and once it has crossed the BBB, it is oxidized to MPP⁺ by MAO-B. MPP⁺ interrupts the mitochondrial complex I of the electron transport chain (ETC) and results in cell death and release of ROS [23]. The MPTP model is a widely used model to develop animal models of the disease, as PD progression post MPTP administration is similar in both humans and monkeys [59]. In the MPTP model, microglial activation accompanied with an increased endothelial expression of adhesion molecules on the BBB to enable infiltration of T-cells is reported [21]. Additionally, there are an increased number of activated microglial cells which are amoeboid in shape representative of activated cells [23]. Astroglial cells are activated late in the disease, and their role is unclear. Infiltrated CD8 and CD4 T-cells have lymphocyte function-associated antigen-1 (LFA-1), a protein expressed for recruitment and these infiltrated T-cells are primarily located in the SNpc and striatum. Furthermore, an increased expression of MHC I and MHC II and microglial iNOS expression are observed [23]. In conjunction

with anti-inflammatory therapies, minocycline, a potent inhibitor of microglial activation and iNOS knockout mice, is protective against MPTP-induced neuronal cell death.

6.1.2. 6-OHDA

Oxidopamine, commonly known as 6-hydroxydopamine (6-OHDA), is another dopaminergic neurotoxin capable of inducing PD symptomatology in animal models. In the 6-OHDA model, inflammatory pathology is propagated by activated microglial cells which occurs 1–3 days post intranigral injection of 6-OHDA and DA neuronal loss occurring 1 week post injection [23]. As part of the inflammatory milieu, there is an increase in TNF- α , a pro-inflammatory cytokine capable of inducing cell death through TNFR.

6.1.3. LPS/rotenone

Lipopolysaccharide (LPS) is an endotoxin derived from Gram negative bacteria and another widely used toxin to induce PD in animal models. The LPS model is different from MPTP and the 6-OHDA toxin-based models, as LPS will activate microglial cells through the TLR2/4 receptors. Activated microglial will upregulate NO, superoxide, TNF- α , and IL-1 β production and release [60]. These pro-inflammatory mediators can cause neuronal cell death. In animal models, intranigral injection of LPS induces microglial activation prior to neuronal loss [32]. Rotenone is another lipophilic herbicide that disrupts the mitochondrial complex 1 causing cell death and associated upregulation in ROS. In the rotenone animal models of PD, fibrillary cytoplasmic inclusions equivalent of Lewy bodies is found in the SNpc. In addition, rotenone injection in neuronal-only culture does not cause DA cell death, but in a mixed neuronal-microglial culture, DA neuron cell death is observed. This suggests that rotenone requires microglial cells for its toxicity [23, 61]. Lastly, inhibition of superoxide is protective against rotenone-induced DA neuron degeneration. These two models suggest that while the etiology of disease is unknown, microglial cells are indispensable for the progression of disease and the resulting neuronal degeneration is seen in PD.

6.2. Gene-based models

6.2.1. α -synuclein

Genetic model of PD is very rare and not all as consistent and reproducible as the toxin-based models. While many genes are implicated in the PD etiology, α -synuclein is the most widely used gene-based model so far [62]. The α -synuclein models include a transgenic knockout and overexpression of mutant or WT α -synuclein [63]. Viral vectors expressing human α -synuclein injected into adult brains have also been used to increase α -synuclein in the respective brain regions. α -synuclein models have been developed in monkeys, rats, mice, and in flies. Bae et al. [63] as well as Watson et al. [64] reported astroglia and microglia activation accompanied with increased mRNA transcripts of TNF- α and several TLRs (1, 4, and 8) in SNpc [65]. α -synuclein can act as a DAMP and activate microglia via TLRs, thereby suggesting a primed microglial sensitivity. In the knockout transgenic models of α -synuclein, little neuronal loss and behavioral changes are reported. In addition, transgenic null mice can offer a degree of

protection against MPTP intoxication and cell death [66, 67]. In contrast, viral overexpression models of α -synuclein in brain of adult animals show DA neurotoxicity accompanied by the activation of both the innate and adaptive immune response [68]. Learning from these models includes and further verifies a gain of function of α -synuclein as ablation of α -synuclein features no neuropathological changes [62]. Furthermore, in a recent study, Van der Perren et al. [69] reported the immunophilin ligand FK506 in a rAAV2/7 α -synuclein overexpression rat model to have anti-inflammatory therapeutic potential. Specifically, the group [69] reported a decrease in the infiltration of CD4+ and CD8+ T cells as well as in the number of activated microglial cells. This further supports neuroinflammation as a key to the progression of the disease and efficacy for therapeutic development.

6.2.2. *LRRK2*

LRRK2 mutations are implicated in an autosomal dominant form of PD with similar phenotypic expression as idiopathic PD. To study the role of LRRK2 in PD pathogenesis, LRRK2 knockout animals were developed. Several groups [70,71] report no DA degeneration in LRRK2 deficient rat and mice models. Lee et al. [72] developed herpes simplex virus (HSV) amplicon-based mouse model of LRRK2 dopaminergic neurotoxicity. Overexpression of the LRRK2 G2019S resulted in significant loss of tyrosine hydroxylase (TH+) neurons. Thereby these data suggest that knockout of LRRK2 may provide neuroprotection, and similarly, Lee et al. [72] used LRRK2 inhibitors and found that it protected the overexpressed LRRK2 mice from developing PD [72]. Most notably, the mechanism of protection seems to be dependent on the activation and proliferation of microglial cells [70], implicating LRRK2 in the inflammatory etiology for PD. Therefore, it appears LRRK2 is critical in PD pathology and plays a significant role in regulating cellular inflammation, thereby supporting the notion that neuroinflammation is critical to PD pathogenesis.

7. Anti-inflammatory therapies in PD

While evidence strongly suggests that inflammation plays a major role in the etiology of a number of different forms of PD, emerging evidence also demonstrates that therapies used to lessen inflammation, including those directed against immune cells or inflammatory mediators, can play a positive role in halting the degeneration of DA neurons in several models of PD. Many studies suggest that inflammatory mediators such as $\text{TNF}\alpha$, PGE_2 , NO, free radicals, and other immune mediators play a role in the pathogenesis of PD and degeneration of dopamine-producing neurons, and that the use of specific reagents that target these mediators, inhibition of cellular signaling mechanisms that regulate the production of these mediators, or the use of neurotrophic factors that help protect against the neurotoxicity induced by these mediators hold significant promise as therapeutic treatments for PD. In addition, epidemiological and observational studies already suggest that use of anti-inflammatory drugs lower the risk of developing PD [73].

Observations which demonstrate that inflammation in SNpc plays a role in PD led many investigators to initially study the potential use of steroidal and nonsteroidal anti-inflammatory drugs for the treatment of PD. Steroidal anti-inflammatory drugs (SAIDs) such as dexamethasone showed neuroprotective effects and LPS-induced neurotoxicity in Substantia nigra [74]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used as analgesics and anti-pyretics to suppress the adverse effects of inflammation. NSAIDs as a group normally reduce the production of prostaglandins by inhibiting cyclooxygenase (COX, an enzyme that catalyzes specific prostaglandin synthesis) and also reduce the synthesis of nitric oxide. In addition, it has been found that a subset of NSAIDs called as selective A β 42 lowering agents (SALAs) reduces the risk of Alzheimer dementia (AD) [75] and consequently may be effective in PD as well. Neuroprotective effects of ibuprofen have been studied in PD pathogenesis, and these studies show that it can protect dopaminergic neurons against glutamate toxicity *in vitro* [76, 77]. It is interesting to note that some neurologic drugs used to treat PD have been found to result in changes to immune system. One such drug, amantadine (Symmetrel, Endo Pharmac LPS induced mice and mesencephalic culture 6-OHDA induced euticals) which functions as an antagonist of the NMDA-type glutamate receptor leading to increased dopamine release and dopamine reuptake, also increases the CD4:CD8 ratio [78] and enhances IL-2 levels in PD patients. In contrast, L-DOPA monotherapy does not show similar effects [79]. In the next sections, we discuss the effectiveness of a number of anti-inflammatory treatments in preventing dopaminergic cell death in animal models of PD (section summarized in **Table 1**).

Therapy	Compounds	Study design	Outcomes	Reference
SAIDs and NSAIDs	Dexamethasone	Intra-nigral injection of LPS in rats	↑ TH activity in striatum.	[73]
	Ibuprofen	Primary mesencephalic culture from rats treated with ibuprofen	↑ dopamine uptake, protected neurons against excitotoxicity.	[76]
	Amantadine	Peripheral blood mononuclear cells from idiopathic PD patients	↑ CD3 ⁺ CD4 ⁺ cells, improves T-cell mediated immunity.	[77]
Antibiotics	Rifampicin	LPS induced BV2 microglia	↓ in NFκB activation, ↓ expression of iNOS, COX2, TNF-α, IL-1β ↓ production of NO, PGE ₂ .	[81]
		MPP induced PC12 cells	↓ MPP induced neuronal death, ↓ expression of α-syn multimer.	[83]
	Ceftriaxone	PC12 cells exposed to neurotoxin 6-OHDA	Binds with α-syn and blocks its polymerization <i>in vitro</i>	[85]
		6-OHDA induced PD rat model	↑ GLT-1 expression, reduces striatal TH loss.	[86]

Therapy	Compounds	Study design	Outcomes	Reference
	D-cycloserine	MPTP induced PD rat model	Improved behavioral deficits restored IL-2 level ↓microglial activation.	[87]
	Rapamycin	In PC12 cells and MPTP induced mouse model	↓neuronal death, regulate Akt phosphorylation at Thr308.	[89]
	Minocycline	In MPTP induced mouse model, primary mesencephalic culture	↓expression of iNOS, caspase-1, inhibited NO induced neurotoxicity, ↓phosphorylation of p38.	[90]
		In differentiated LUHMES cells induced by reactive oxygen species	Specific scavenger of peroxynitrite, ↓microglia activation.	[91]
Neuropeptides	PACAP	MPP ⁺ induced SHSY-5Y neuroblastoma	↓cell death, ↑cAMP	[98]
		Oxygen and glucose deprived BV2 microglia	↓TRL4, MyD88, NFκB ↓production of pro-inflammatory cytokines	[95]
		MPTP induced mice	↑TH expression, ↓caspase-3, IL-6, TNF-α	[98]
	VIP	LPS induced mice and mesencephalic culture 6-OHDA induced	↓pro-inflammatory cytokine, ↓NO	[99]
Polyphenols	Pinocembrin	6-OHDA SHSY-5Y	↓apoptosis, ↓ROS	[101]
	Naringenin	6-OHDA induced mice and SHSY-5Y	↑Nrf2. ↑neuroprotection, ↓ROS	[102]
	Flavonoids from <i>Selaginella</i> extract	Rotenone induced Drosophila PD model	↑anti-oxidant enzyme activity, ↓oxidative stress	[103, 104]
	Curcumin	6-OHDA induced SHSY-5Y	↓p-p38, ↓caspase-3	[105]
	Baicalein	MPTP induced mice and primary rat astrocytes	↓NFκB nuclear translocation, ↓microglia and astrocyte activation, ↓COX2, ↓phosphorylation of JNK and ERK	[106]
	Theaflavin	MPTP with probenecid induced mice	↑TH expression, ↓caspase-3,8,9, ↓COX2, IL-1β, TNF-α, IL-6	[109]
	Resveratrol	MPTP induced mice	↑TH protein and mRNA, ↑SOCS-1, ↓TNF-α, IL-1β, IL-6, ↓TNF-αR1, IL-1βR1, IL-Rα	[110]

Therapy	Compounds	Study design	Outcomes	Reference
Anti-inflammatory Cytokines	IL-10	Rotenone or MPP ⁺ induce primary rat astrocytes/microglia, mesencephalic culture, BV2	↓NO, ROS, MPO, ↓iNOS, COX2, TNF-α, IL-1β mRNA, ↓phagocytic activity	[111]
		LPS induced mesencephalic culture	↓TNF-α, NO, ↓extracellular superoxide, inhibit PHOX activity	[112]
		Hu-IL-10 gene transfer in 6-OHDA induced rats.	↑TH-positive neurons, ↓ glial activation	[113]
	TGF-β	Retrograde model of PD induced with 6-OHDA and treated with TGF-β alone and in combination with GDNF.	Reduce dopamine receptor hypersensitivity, ↑TH-positive neurons, induce synaptogenesis	[114]
		LPS and MPTP induced mice	↓ROS, ↓PHOX p47 ^{phox} activity, ↓LPS activated phosphorylation of ERK and p47 ^{phox}	[116]
Insulin therapy	Pioglitazone	MPTP induced mice	↓microglial activation, ↓GFAP positive cells in SN, ↑ IκBα, ↓NFκB activation	[121]
	GLP-1 receptor agonist: Exenatide	LPS induced rat microglial cells	↓NO, iNOS, TNF-α, IL-1β, IL-6, ↓phosphorylation of p38.	[119]
		MPTP mice and 6-OHDA induced mesencephalic culture	↓neurotoxicity, improve motor functions, ↑TH-positive cells, ↑cAMP ↓TNF-α, superoxide, NO	[122]
Beta2-adrenergic receptor agonists	Salmeterol	LPS and MPTP induced mice	↓phosphorylation of MAPK, p65 NFκB.	[16]
Morphinan compounds	L-morphine	LPS and MPP ⁺ induced rat mesencephalic culture	↓PHOX activity, ↓pro-inflammatory cytokines, ↓ERK phosphorylation.	[127]
	Sinomenine	LPS and MPP ⁺ induced rat mesencephalic culture	↓TNF-α, PGE ₂ , ROS ↓PHOX activity.	[128]
	3-HM	Rat mesencephalic culture stimulated with LPS	↓NO, TNF-α, PGE ₂ , ROS ↓microglia activation	[129]
		LPS and MPTP models	↑expression of neurotrophic factors ↑acetylation of histone H3 ↓reactive microgliosis ↓ROS	[130]
Therapy against NFκB	NBD	MPTP induced mice	↓NFκB activation, ↓iNOS, ↓TNF-α, IL-1β ↓CD11b, ↓neuronal death	[132]

Therapy	Compounds	Study design	Outcomes	Reference
Anti-oxidants	Compound A (IKK inhibitor)	LPS induced rats and mesencephalic culture	↓neurotoxicity, ↓TNF- α , IL-1 β , ↓NO, iNOS, ↓IKK β phosphorylation and NF κ B activation	[133]
	DPI (NADPH oxidase inhibitor)	LPS induced midbrain neuron-glia culture	↓phosphorylation of ERK, p38, JNK, ↓ROS, ↓superoxide	[135]
		LPS induced rats and mesencephalic culture	↓neurotoxicity ↓NOX2 activation.	[136]
	Coenzyme Q10	MPTP model	↓ROS, ↓TNF- α , NO ↓ERK phosphorylation, ↓PHOX activity	[137]
	NAC	MPTP model	↓ROS, ↓free radicals production, ↓neurotoxicity	[140]
	Edaravone	Intravenous infusion of NAC in PD patients MPP ⁺ induced PC12 cells	↑glutathione level in blood	[142]
			↓oxidative stress, ↓ROS ↑Heme-oxygenase-1 expression	[142]

Table 1. Neuroprotective effects of anti-inflammatory therapies.

7.1. Antibiotics in neuroprotection in PD

Antibiotics are routinely used to kill or inhibit the growth of microorganisms at low concentrations. In addition to their antimicrobial activity, antibiotics can either directly or indirectly regulate the expression of many inflammatory gene transcripts [80], and a number of antibiotics such as tetracycline and β -lactams have been shown to have significant anti-inflammatory properties [81]. Antibiotics now appear to have protective effects against neurodegeneration and the neuroinflammatory process [82]. These properties of antibiotics make them suitable for the development of effective therapies against neurodegenerative diseases such as PD. Rifampicin, a macrocyclic antibiotic, upregulates Ab clearance in brain, and it is also neuroprotective in other chronic neurodegenerative diseases and cerebral ischemia [83]. Pretreatment with Rifampicin increases cell viability and reduces α -synuclein expression and its aggregation. Moreover, in MPP⁺-induced PC12 cells, Rifampicin prevents the formation of α -synuclein oligomer [84]. It can also block the release of pro-inflammatory cytokines such as NO, PGE₂ TNF- α , and IL-1 β from LPS-stimulated BV-2 microglial cells [85]. Similarly, β -lactam also has protective role against neurodegeneration and can cross BBB. β -lactam antibiotic ceftriaxone has demonstrated neuroprotective activity as well as high binding affinity with α -synuclein and can block its *in vitro* polymerization [86]. Ceftriaxone also increases the expression of glutamate transporter-1 (GLT-1) which enhances glutamate uptake and therefore reduces excitotoxicity in 6-OHDA model of PD [87]. D-cycloserine (DCS), an antibiotic prescribed for Mycobacterium tuberculosis, also acts as an NMDA receptor antagonist that prevents excitotoxicity damage induced by MPTP [88] and inhibits the

production of MMP3 and MMP9 in LPS stimulate microglial cells. In addition, Rapamycin was able to prevent mitochondrial dysfunction in PINK1/Parkin *Drosophila* mutants [89]. Furthermore, it enhances the expression of neuronal survival promoting kinase Akt, antioxidant enzymes and anti-apoptotic markers [90]. Similarly, Minocycline has shown neuroprotective effects in PD models [91]. Minocycline suppresses α -synuclein aggregation and its toxicity [92], as well as microglial activation of p38 the MAPK signaling pathway resulting in the suppression of pro-inflammatory mediator release [93]. These results support the potential of antibiotics as neuroprotective and therapeutic agents in PD.

7.2. The role of anti-inflammatory compounds in neuroinflammation and PD

Neurotrophic factors are essential for neural growth and development, and these factors normally signal through Trk receptors. Adenosine and pituitary adenylate cyclase-activating peptide (PACAP) act as ligands and induces activation of Trk receptors through adenosine (A_{2A}) receptor and PAC1 receptors, respectively [94]. Recent studies reported the antioxidant and anti-inflammatory properties of PACAP [95, 96]. It can inhibit the release of several pro-inflammatory mediators from LPS-activated microglial cells by inhibiting the transcriptional activity of NF- κ B [97], as well as the production of several chemokines like MIP-1 α , -1 β , MCP-1, and RANTES [98]. A synthetic analog of PACAP showed neuroprotection in MPP⁺-induced SHSY-5Y cells and MPTP-injected mice. It restored the expression of tyrosine hydroxylase in Substantia nigra and modulated the inflammatory response [99]. Another peptide, called vasoactive intestinal peptide (VIP), can also inhibit the expression of pro-inflammatory cytokines from LPS-activated cultured microglia [100]. These studies suggest these peptides can serve as promising molecules for the development of anti-inflammatory and neuroprotective drugs in the treatment of PD.

7.2.1. Neuroprotective and anti-inflammatory role of polyphenols

Several traditional medicinal plants and herbs are rich in polyphenol, and their neuroprotective effects have been studied extensively. These compounds have neuroprotective properties against oxidative stress, neuroinflammation, mitochondrial dysfunction, and protein fibrillization. Kong et al. reported that polyphenols reduce the intracellular level of ROS in DA neurons [101]. Recently, it has been found that pretreatment with flavonoids such as pino-cembrin [102] and naringenin [103] reduces the formation of ROS, in 6-OHDA-challenged human neuroblastoma SHSY-5Y cells. This effect was due to an increase in Nrf2 protein level and by activating ARE pathway genes. In addition, flavonoids from *Selaginella* species have the ability to increase the expression and activity of anti-oxidative enzymes endogenously [104], and the aqueous extract of *Selaginella* suppresses rotenone induced neurotoxicity, attenuated locomotor dysfunction, oxidative stress, and mitochondrial dysfunction in *Drosophila melanogaster* [105]. Polyphenols may also target MAPK pathways and apoptosis, since phosphorylation of MAPK and expression of cleaved caspase 3 were reduced in 6-OHDA induced SHSY-5Y cells by curcumin [106]. Similarly, the phosphorylation of NF- κ B, JNK, and ERK was inhibited by flavone baicalein in MPP⁺-induced primary astrocytes and indicated its implication in the treatment of PD [107]. Several other polyphenols have been shown to reduce

the expression of pro-inflammatory cytokine such as IL-1 β , TNF- α , and IL-6 [108, 109]. Furthermore, theaflavin treatment in MPTP mice model of PD increases the expression of anti-inflammatory cytokines such as IL-4 and IL-10 by the modulation of the suppressor of cytokine signaling 1 (SOCS1). Oral administration of resveratrol in MPTP mouse model upregulated the expression of SOCS1 in striatum and Substantia nigra and suppresses the production of pro-inflammatory cytokines [110] and also improved cell survival in rotenone-induced primary mesencephalic culture. Resveratrol also diminished the level of MPO (MPO; an enzyme produces hypochlorous acid and tyrosyl radical during microglial respiratory burst) and ROS in MPP⁺-induced BV2 microglia cells [111, 112]. Many polyphenol compounds have been studied to test their neuroprotective and anti-inflammatory properties, but further research will be needed to understand the signaling mechanism of how these compounds act to offset neuroinflammation.

7.2.2. Anti-inflammatory cytokine therapies in PD

The use of anti-inflammatory cytokine serves as a potent approach for the development of anti-parkinsonian drugs. Two major anti-inflammatory cytokines, IL-10 and transforming growth factor beta 1 (TGF β 1), produced by T_{reg} cells, have been studied in PD models. Pre- and posttreatment of rat mesencephalic neuron glia culture with IL-10 showed neuroprotective effects against LPS-induced neurotoxicity by inhibiting the production of TNF- α , nitric oxide, and extracellular superoxide [113]. Gene delivery of human IL-10 by using adeno-associated viral type-2 (AAV2) in 6-OHDA rat model of PD also showed neuroprotection by suppressing the 6-OHDA-induced loss of TH-positive neurons [114]. Similarly, TGF β 1 also shows protective effects against neurotoxicity. TGF β 1 in combination with GDNF reduces progressive cell death and enhances the expression of TH in surviving nigral neurons in retrograde model of Parkinsonism in rats [115]. It has also been shown that TGF β 1 protects from neuronal death induced by glutamate excitotoxicity [116]. The neuroprotective effect of TGF β 1 is primarily due to its ability to inhibit the production of ROS from microglia during activation. Additionally, after LPS activation, ERK phosphorylation and subsequent serine phosphorylation on p47^{phox} were significantly inhibited by pretreatment with TGF β 1 [117]. Recently, it also has been reported that overexpression of fractalkine (CX3CL1) reduces neuronal loss in 6-OHDA model of PD and suppresses α -synuclein-mediated neurodegeneration [118]. The use of these anti-inflammatory mediators therapeutically to suppress represents a new therapeutic avenue for the treatment of PD.

7.2.3. Regulatory T-cell therapy

T_{reg} cells have the capability to mitigate inflammation and serve as an attractive therapeutic target. T_{reg} cell therapy can be used for neuroprotection in PD as these cells also utilize immunosuppressive mechanisms including the production of anti-inflammatory cytokines. The neuroprotective effects of bee venom is associated with the deactivation of microglia and suppression of CD4⁺ T cell infiltration, and it also increases the proportion of CD4⁺, CD25⁺ and Foxp3⁺ T_{reg} cells in MPTP mouse model of PD. Several studies have been shown that T_{reg} cell responses inhibit microglial activation and enhance neuronal survival in MPTP mouse model

of PD [24, 119]. In addition, another type of T_{reg} cell, Th2 cells also inhibit microglial activation by the production of IL-4 and IL-10 against MPTP-induced neurotoxicity. What signals suppress the T_{reg} cell functions and how to improve anti-inflammatory activity are yet to be determined.

7.2.4. *Insulin as potent therapeutic agent for treatment in PD*

Insulin is the enzyme most responsible for lowering the blood glucose, but it has also been found to have potent anti-inflammatory effects. Insulin signaling regulates a number of cellular processes such as neurotransmission, vesicle trafficking cell survival, and inflammatory mediator production. Recent evidence has shown that insulin signaling is impaired in Alzheimer and, to some degree to, Parkinson's patients. Preclinical studies suggest that the application of insulin or long-lasting analogs of incretin peptides in transgenic animal model of PD, and AD reduces neurodegeneration and neuronal and synaptic functionality [120, 121]. Pioglitazone is generally prescribed for type 2 diabetes mellitus and reduces insulin resistance and acts on peroxisome proliferator-activated receptor γ (PPAR γ) receptors. It also functions to reduce microglial activation and induction of iNOS positive cells by enhancing inhibitory protein kappa B (IkB α) and inhibition of NF-kB subunit p65 in MPTP mouse model of PD [122]. In LPS model of PD, Pioglitazone showed neuroprotection by inhibiting microglia-mediated oxidative stress [120]. Another anti-diabetic agent, GLP-1 (glucagon-like peptide), is a hormone which maintains homeostasis between insulin and glucose. Exenatide is a synthetic agonist for the GLP-1 receptor and shows significant promise as neuroprotective in PD animal models [123]. These studies describe the potent impact of insulin or anti-diabetic treatments as possible anti-inflammatory neuroprotective therapies for PD.

7.2.5. *Use of β -adrenergic receptor agonists as an anti-inflammatory agent in the treatment of PD*

Beta2-adrenergic receptors (β 2AR) are seven transmembrane G-protein-coupled receptors found on numerous cell types, including inflammatory cells and neurons. β 2AR agonists are FDA approved for the treatment of chronic obstructive pulmonary disorders (COPD), and their use as treatment for neurodegenerative diseases such as PD represents a new and potentially very productive therapeutic approach. In the CNS, microglia expresses high levels of β 2AR, and it has been demonstrated that long-acting β 2AR agonists such as salmeterol (Advair, GlaxoSK) protect against DA neuronal death from microglia-mediated neuroinflammation [16]. In addition to inhibiting the production of inflammatory mediators and oxidative stress responses by microglial cells, several *in vivo* studies also reported neuroprotective roles of long-acting β 2AR agonists by inducing neurotrophic growth factors and astrocyte activation [124, 125]. Long-acting agonist such as salmeterol showed neuroprotective effects by pretreatment in LPS-stimulated long-term mouse model and also by the treatment with salmeterol after MPTP injection. Low dose of salmeterol treatment in these models suppressed the NF-kB activation and its nuclear translocation. Similarly, it also reduces phosphorylation of MAPK such as ERK1/2, p38, and JNK [126]. Furthermore, it has been shown that low dose of salmeterol also inhibits TGF-beta-activated kinase 1 (TAK1), which is a common upstream regulatory molecule for MAPK and NF-kB activation, and involves in

various inflammatory signaling pathways [127]. This suggests the anti-inflammatory effects of salmeterol by reducing phosphorylation of MAPK and NF- κ B activation via inhibition of TAK1. The activation of β 2AR stimulates MAPK signaling also via β -arrestin-dependent and G-protein-independent mechanism [126]. Overall, these agonists can inhibit inflammatory response and have potential to regulate inflammation in chronic inflammatory disorders of CNS. These results suggest that β 2AR agonists can be developed as anti-inflammatory therapy to subside the progressive loss of dopaminergic neurons in PD patients.

7.2.6. Use of morphinan-related anti-inflammatory compounds in PD

Several morphinan analogs such as naloxone, dextromethorphan, or naltrexone have been described as anti-inflammatory and neuroprotective. Morphine isomers (L-morphine and its D stereoisomer) can inhibit microglial activation and LPS- or MPP⁺-induced neurotoxicity in rat primary mesencephalic cultures. Furthermore, it also suggests that morphinan compounds bind to the catalytic subunit of PHOX and inhibits its activity leading to the reduced production of superoxide and other pro-inflammatory cytokines [128]. Similar results were observed with sinomenine, a dextrorotatory isomer of morphine and protective effects of sinomenine mediated through the inhibition of microglial PHOX activity [129]. Similarly, 3-hydroxymorphinan (3-HM), a metabolite of dextromethorphan, recently emerged as a potent therapeutic agent for the treatment of PD. These compounds show neuroprotection by two different pathways; one through a neurotrophic effect mediated by astrocytes and another by their anti-inflammatory effect mediated by the suppression of microglial activation. When the 3-HM compound was studied for its mechanistic effects *in vivo*, it was found that it attenuated the depletion of striatal levels of dopamine and showed neuroprotection against LPS- and MPTP-elicited neurotoxicity [130]. These effects were observed even when drug was administered post MPTP injections [131]. Collectively, these findings offer a different yet highly potent new therapeutic direction for the treatment of neuroinflammation in PD.

7.2.7. Pro-inflammatory transcription factor, NF- κ B as a therapeutic target in PD

Nuclear transcription factor NF- κ B plays an important role in inflammation. It regulates the expression of various genes involved in immune function and cell survival. NF- κ B activation has been reported in Substantia nigra of PD patients and in animal models of PD. The inhibition of NF- κ B activation can suppress oxidative stress and production of pro-inflammatory cytokines and chemokines in microglia [132]. Ghosh et al. [133] reported that intraperitoneal injection of NBD (NF- κ B essential modifier-binding domain) peptide reduces nigral activation of NF- κ B, inhibits microglial activation in Substantia nigra, and improves motor function in MPTP mouse model of PD. Selective inhibitors against IKK- β also reduce microglial n and neuronal death in SNpc in MPTP-intoxicated PD mice [133] and in LPS-induced neurodegeneration by inhibiting NF- κ B activation and decreasing the production of pro-inflammatory cytokines. It also suppresses the activity of microglial NADPH oxidase and reduces the production of ROS [134]. These reports suggest the suppression of NF- κ B signaling pathway in microglia is neuroprotective and represent NF- κ B as a strong potential target for anti-inflammatory therapy in the treatment of PD.

7.2.8. *Antioxidants as neuroprotective agents in PD*

Oxidative stress and generation of free radicals have been reported to be a major effector of neuronal death seen in neurodegeneration in PD. This can also be linked to other processes such as nitric oxide toxicity, excitotoxicity, mitochondrial dysfunction, and inflammation. Oxidative stress impairs cell viability by damaging lipid, proteins, and nucleic acids [135]. The development of therapies against oxidative stress and free radicals may be beneficial in PD by inhibiting the onset of apoptotic cell death and degeneration of nigrostriatal dopaminergic neurons. The neurotoxin MPTP inhibits the mitochondrial electron transport chain and suppresses the activity of mitochondrial complex I and eventually elevates oxidative stress within DA neurons. MPTP also increases the production of free radicals and ROS by microglial cells, ultimately leading to the death of dopamine producing neurons. It has been found that mice lacking the NADPH oxidase complex do not exhibit DA neurotoxicity from MPTP- or LPS-induced neurodegeneration, and that the administration of NADPH oxidase inhibitor DPI can prevent DA neurotoxicity [136, 137]. Several other antioxidants have been investigated in the treatment of PD, and it has been found that coenzyme Q10 is a potent antioxidant and electron acceptor for mitochondrial complex I and II, can enhance activity of complex I, and reduce oxidative stress [138]. Clinical trial with randomized, parallel group, placebo controls, and double-blind with multiple doses of CoQ10 (300, 600, or 1200 mg/day) in 80 early PD patients showed that CoQ10 is well tolerated at doses up to 1200 mg/day, less disability was developed in PD subjects, and symptomatic relief was higher in subjects receiving the highest dose [139]. In contrast, a recent phase III, randomized, double-blind, placebo-controlled clinical trial concluded that CoQ10 is safe and well tolerated but showed no evidence of clinical benefits [140]. Another antioxidant and a pro-drug of amino acid cysteine called N-acetyl-cysteine (NAC) also showed neuroprotective effects. Preclinical data suggest NAC is neuroprotective and can reduce oxidative stress and ROS accumulation. Recently, a clinical trial with NAC intravenous infusion concludes that NAC enhances the level of glutathione (a potent antioxidant) in blood and brain in PD patients [141]. Similarly, Edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one) is a neuroprotective antioxidant, generally prescribed for recovery of acute brain ischemia and cerebral infraction [142]. It showed neuroprotective effects in MPP-induced PC12 cells by reducing oxidative stress and enhancing expression heme oxygenase-1 expression (a cellular stress response protein) [143], but clinical trials are yet to be done.

8. Conclusion

Inflammation plays an important role in the etiology of a number of different forms of PD, and anti-inflammatory drugs hold much promise as a therapeutic treatment for patients with mild and moderate forms of PD. The continued evaluation of these drugs, including their efficacy, target, and mechanism of action, hold much promise for the future treatment of PD.

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