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Neuroinflammation in Parkinson's Disease and its Treatment Opportunities

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Parkinson's disease (PD) is a complex, chronic, and progressive neurodegenerative disease that is characterized by irreversible dopaminergic neuronal loss in the substantia nigra. Alpha-synuclein is normally a synaptic protein that plays a key role in PD due to pathological accumulation as oligomers or fibrils. Clustered alpha-synuclein binds to the Toll-like receptors and activates the microglia, which initiates a process that continues with pro-inflammatory cytokine production and secretion. Pro-inflammatory cytokine overproduction and secretion induce cell death and accelerate PD progression. Microglia are found in a resting state in physiological conditions. Microglia became activated by stimulating Toll-like receptors on it under pathological conditions, such as alpha-synuclein aggregation, environmental toxins, or oxidative stress. The interaction between Toll-like receptors and its downstream pathway triggers an activation series, leads to nuclear factor-kappa B activation, initiates the inflammasome formation, and increases cytokine levels. This consecutive inflammatory process leads to dopaminergic cell damage and cell death. Microglia become overactive in response to chronic inflammation, which is observed in PD and causes excessive cytotoxic factor production, such as reactive oxidase, nitric oxide, and tumor necrosis factor-alpha. This inflammatory process contributes to the exacerbation of pathology by triggering neuronal damage or death. Current treatments, such as dopaminergic agonists, anticholinergics, or monoamine oxidase inhibitors alleviate PD symptoms, but they can not stop the disease progression. Finding a radical treatment option or stopping the progression is essential when considering that PD is the second most reported neurodegenerative disorder. Many cytokines are released during inflammation, and they can start the phagocytic process, which caused the degradation of infected cells along with healthy ones. Therefore, targeting the pathological mechanisms, such as microglial activation, mitochondrial dysfunction, and oxidative stress, that should be involved in the treatment program is important. Neuroinflammation is one of the key factors involved in PD pathogenesis as well as alpha-synuclein accumulation, synaptic dysfunction, or dopaminergic neuronal loss, especially in the substantia nigra. Therefore, evaluating the therapeutic efficiency of the mechanisms is important, such as microglial activation and nuclear factor-kappa B pathway or inflammasome formation inhibition, and cytokine release interruption against neuroinflammation may create new treatment possibilities for PD. This study examined the pathological relation between PD and neuroinflammation, and targeting neuroinflammation as an opportunity for PD treatments, such as Toll-like receptor antagonists, NOD-like receptor family pyrin domain containing-3 inflammasome inhibitors, cytokine inhibitors, peroxisome proliferator-activated receptor-γ agonists, reactive oxygen species inhibitors, and nonsteroidal anti-inflammatory drugs.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting approximately 1-2% of the human population over 65 years of age, with a prevalence rising to approximately 4% over 85 years old.[1] The main pathological feature of PD is the dopaminergic neuronal loss in the substantia nigra (SN).[2,3] Tremor, rigidity, bradykinesia, and postural instability are common motor symptoms of PD. Additionally, non-motor symptoms, such as sleep disturbances, autonomic dysfunction, psychological distress, and cognitive impairment, have been reported in patients with PD.[4] Non-motor symptoms, such as hyposmia, constipation, depression, and rapid eye movement sleep behavior disorder, are common in PD, which may precede classical motor symptoms in most cases.[3,5]

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The underlying PD mechanisms remained unclear. However, several pathologies were involved in neurodegeneration, such as alpha-synuclein (α-syn) overexpression, excitotoxicity, mitochondrial dysfunction, oxidative stress, and neuroinflammation. Existing treatments provide only symptomatic relief because the main reasons for PD are not fully understood and many different mechanisms are involved. Therefore, neuroinflammation studies have recently gained attention in PD.

Inflammation is a reaction of living tissues to injury but should be distinct as acute and chronic inflammation, which could be protective or harmful, respectively. Neuroinflammation is a physiological response to exogenous and endogenous attacks targeting the central nervous system (CNS). An acute response represents a protective response, but excessive inflammatory responses are detrimental to the CNS.[6] Generally, chronic neuroinflammation is closely associated with neuronal damage and death through many biological mechanisms, such as high oxidative stress, astrocytes, microglial activation, and cytokine release, which are also common features of PD.[7,8] Beyond these, targeting neuroinflammation as a treatment approach using nonsteroidal anti-inflammatory drugs (NSAID), microRNAs, and peroxisome proliferator-activated receptor (PPAR)-γ agonists showed beneficial effects by inhibiting Toll-like receptors (TLR), decreasing nuclear factor-kappa B (NF-kB) expression, and preventing microglial activation, thereby inhibiting prostaglandin synthesis and α-syn accumulation and interrupting apoptosis in PD pathology.[9-11] By implication, widespread and sustained neuroinflammation is an important component of PD pathogenesis.

COMPONENTS OF NEUROINFLAMMATION IN PARKINSON'S DISEASE

Neuroinflammation is a component of several neurological disorders, as well as PD. Immune cells of the CNS, such as the microglia and astrocytes, regulate the inflammation by releasing factors, including interleukins (IL), tumor necrosis factor-α (TNF-α), NF-κB, inducible NO synthase (iNOS) together with NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, and reactive oxygen species (ROS) formation. The release of these factors causes an inflammatory response, which is toxic to the neurons. Therefore, excessive and irregular microglial activation plays an important role in PD pathology causing the release of pro-inflammatory cytokines, IL, and ROS, activation of apoptosis, and loss of dopaminergic neurons.[12-17]

Microglia

Microglia comprise approximately 10% of the total brain cell population.[18] In addition to homeostatic functions, these cells are the front line of the defensive immune system. Microglia density shows variety compared to the brain region with the highest concentration in the hippocampus, olfactory bulb, basal ganglia, and SN to a lesser extent in the putamen, transentorhinal, cingulate, and temporal cortices.[13,18]

Microglial cells secrete neurotrophic factors, remove toxic substances, and participate in neuronal repair, remodeling, and synaptic pruning.[19] Under physiological conditions, microglial activation regulates brain development by the programmed neural cell elimination and increases neuronal survival through the release of trophic and anti-inflammatory factors.[13] However, overactive microglia can cause significant and highly deleterious neurotoxic effects by excessive release of cytotoxic factors, such as superoxide, NO, and TNF-α.[13,14,20,21] Overexpression of α-syn or duplications in the *SNCA* gene in PD triggers the toxic α-syn fibril accumulation, which is the main component of Lewy bodies and neurites.[2] Lewy bodies and neurites are toxic and cause a dopaminergic neuronal loss in PD.[22] Beyond that, α-syn pathology can activate the microglia by stimulating the TLR on the microglial surface and initiating the inflammatory response. Inflammatory response promotes the release of pro-inflammatory cytokines and activates the NF-KB signaling pathway, which leads to further inflammatory response exacerbation.[23]

α-syn is an endogenous protein that is mainly found at the presynaptic terminal with an unknown physiological function. Evidence from various in vitro and in vivo studies in pathological conditions has shown that α-syn misfolding or aggregation is an important pathogenic factor of PD.[3,24] Extracellular α-syn oligomers induced the immune receptors located on the microglial surface, including TLR-2, upregulates NF-kB and p38, a protein that is a member of the mitogen-activated protein kinase (MAPK) signaling pathway, by inducing TLR-2 signal.[7,25] TLR 1/2 receptor activation by α-syn increases the IL-1 receptor-associated kinase (IRAK) complex activity, and stimulated IRAK activates TNF receptor-associated factor 6 (TRAF6).[26] These sequential events leading to the release of inhibitory kappa kinases (IKKs), which mediate the degradation of inhibitory kappa B alpha (IκB-α). Hence, pro-inflammatory cytokines are produced through MAPK and nuclear translocation of NF-κB, c-Jun N-terminal kinase (JNK), and p38 activation.[26] Pro-inflammatory cytokine production and secretion following phagocytosis of α-syn fibrils induce cell death and accelerate PD progression.[25,27] Additionally, the interaction between α-syn fibrils, TLR, and NF-kB increases NLRP3 upregulation.[25] NF-kB pathway activation by TLRs or cytokines increases the NLRP3 expression by pro-IL (pro-IL)-1β and pro-IL-18, which leads to NLRP3 inflammasome activation. Activated NLRP3 convert procaspase-1 to active caspase-1.[12,28] Then caspase-1 activates pro-IL-1β and pro-IL-18 to IL-1β and IL-18, which take a part in neuroinflammation.[12,28,29] Additionally, caspase-1 is involved in "pyroptosis," which is the process of an inflammatory form of cell death.[28]

Damaged dopaminergic neurons cause secretion of matrix metalloproteinase 3 (MMP3), which is a proteinase that degrades the extracellular matrix, α-syn, and neuromelanin that activates the microglia. Overactivated microglia induce ROS production and release pro-inflammatory cytokines, which cause dopaminergic neuronal death.[30] This self-consuming process propagates PD progression.

Astrocytes

Astrocytes are the most abundant glial cell type in the CNS. One of the cytoplasmic extensions is connected to the neuron and the

other to the blood vessels, thereby establishing a connection and ensuring the exchange of substances. Astrocytes metabolically support neurons by providing lactate for mitochondrial respiration, participating in tissue repair, and secreting trophic factors that are necessary for neuronal survival and synaptogenesis.[31] It also plays a role in regulating the blood-brain barrier (BBB) permeability, cerebral blood flow protection, and ion homeostasis.[31,32]

Evidence of astrogliopathy in the SN and striatum was found in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD.[33] Losing their normal functions, such as supplying nutrition for neurons and synaptic function regulation, secretion of IL-1α, complement component 1q (C1q) and TNF-α, reactive astrocytes secrete neurotoxic factors that cause the death of neurons and oligodendrocytes. On the contrary, astrocytes upregulate many neurotrophic factors, which are considered neuroprotective.[31,32]

Reactive astrocytes are common in PD.[2,31] α-syn positive inclusions are seen not only in neurons but also in astrocytes in postmortem brain tissue of patients with PD.[2] Neuronal α-syn clusters were transmitted to neighboring astrocytes and formed pathological inclusion bodies.[34] An increased α-syn in astrocytes leads to accelerated pro-inflammatory cytokines production (such as IL-6 and TNF-α) mediated by TLR4 and increases intercellular adhesion molecule 1 (ICAM1) and ROS expression, thereby worsening the pathology.[35,36]

Leukotrienes

Leukotrienes (LTs) are a family of lipid mediators derived from arachidonic acid via the 5-lipoxygenase (5-LOX) enzyme. After synthesizing LT from free arachidonic acid to LTA4 by the 5-LOX enzyme, it is metabolized to LTB4, C4, D4, and E4. LTC4, D4, and E4 are collectively referred to as cysteinyl leukotrienes (CysLT) because they contain an additional cysteinyl group and mainly activate two receptors, CysLT1R and CysLT2R. LTs play important roles in inflammatory responses, such as leukocyte chemotaxis, vascular permeability, and proliferation.[37] Both CysLT1R and CysLT2R activation is limited in the brain under physiological conditions. However, CysLT1R and CysLT2R levels increase in various diseases, such as Alzheimer's disease (AD) and PD.[38,39] The binding of CysLTs to microglial CysLT1R increased inflammatory response by NF-κB-mediated MAPK pathway upregulation, which ultimately results in increased release of cytokines, such as IL-1β and TNF-α.[39]

THERAPEUTIC MODULATORS OF NEUROINFLAMMATION IN PARKINSON'S DISEASE

Neuroinflammation is one part of PD pathogenesis.[7] However, whether it is the cause or result of the disease next to neurodegeneration remained uncertain. Therefore, neuroinflammation modulation could be effective in stopping or partially interrupting PD progression. Inflammation has been studied in many in vivo and in vitro PD models.[20,40-45] Some of the most commonly used PD animal models are neurotoxin models, such as MPTP or 6-hydroxydopamine (6-OHDA) administration, pesticides injections, such as rotenone and paraquat, genetic models and α-syn overexpression models via viral vectors or preformed fibril injection. Cell culture models are also important tools to study PD. The most commonly used cell lines are SH-SY5Y derivative of neuroblastoma, PC12 cell, which can easily differentiate into neuronal-like cells, primary DAergic cultures, and human induced pluripotent stem cells (iPSC) technology or BV2 microglial cell line, which is especially useful to study inflammatory responses.

Drugs were used in either animal or cell culture models and the study results, which are mentioned in this review, were summarized in Tables 1 and 2, respectively. Therefore, only the key findings were presented in the text.

Non-steroidal anti-inflammatory drugs

The use of NSAIDs has been an important research topic as neuroprotective agents and continues to be an area of interest due to the role of inflammation in PD pathogenesis. Several studies showed that the use of NSAIDs has a therapeutical effect against PD by inhibiting cyclooxygenase (COX) enzyme, as well as cytokine release, which leads to an anti-inflammatory effect dose-dependently.[9,45,46] Conversely, some studies, especially with aspirin and acetaminophen, show no protective effect against neuroinflammation in PD.[46,47] The findings showed that NSAIDs doses should be carefully evaluated in clinical studies.

Ibuprofen is widely known as an anti-inflammatory agent that reduces prostaglandin synthesis by inhibiting COX activity. In a study, MPTP was injected into the mice's brain together with ibuprofen administration. MPTP caused dopaminergic denervation, while ibuprofen reduces the inflammation through COX inhibition, prevents the dopaminergic decrease, and provides partial protection against MPTP toxicity by reducing COX-induced ROS generation.[45]

Indomethacin is an indole acetic acid derivative of NSAIDs and is a most potent COX inhibitor and shows >50% selectivity to the COX-1 enzyme. In a study, pretreatment with indomethacin before the MPTP revealed reduction in microglia and lymphocyte infiltration to SN and dopaminergic neurons protection against MPTP toxicity.[48] However, indomethacin treatment 24 h after MPTP administration or higher doses of indomethacin, such as 2.5 mg/kg, did not show any protective effect.[48]

Celecoxib is another NSAID that selectively inhibits COX-2 and is used in rheumatoid arthritis and osteoarthritis treatment due to its COX-2 enzyme selectivity, which lowers the risk of gastropathy and gastrointestinal bleeding. A study pretreated animals with celecoxib in before 6-OHDA administration, which leads to a decreased microglial activation but without any protective effect on dopaminergic neurons against 6-OHDA toxicity at 12 days. Surprisingly, celecoxib shows some protective effects on the dopaminergic neurons at 21 days.[44] In conclusion, selective COX-2 inhibition by celecoxib may result in reduced dopaminergic degeneration through microglial activation inhibition in a time-dependent manner. Another study tested the effects of celecoxib, indomethacin, and ibuprofen on neurodegeneration in 6-OHDA induced PC12 cells. The results showed no cytotoxic effects between the drugs, and they all inhibited 6-OHDA toxicity together with ROS synthesis in a time and dose-dependent manner.

TABLE 1. Animal Studies of Parkinson's Disease Regarding Neuroinflammation and Drug Treatments Result

Drugs	Treatment duration	Animal	MPTP	6-OHDA	Others	Behavioral tests	Dopaminergic loss	Inflammatory reactions	Alpha-synuclein	Ref
Ibuprofen (10, 30, or 50 mg/kg) 1 h before MPTP injection	Daily for 7 days	Male C57Bl mice	MPTP (10 mg/kg i.p.) four injections at 1 h intervals				**MPTP injection** decreased TH expression by 90% on day 7 and 85% on day 21 **After Ibuprofen** decreased TH expression 21% on day 7 and 26% on day 21		Ibuprofen (50 mg/kg) decreased the α-syn	(45)
Indomethacin (1 and 2.5 mg/kg) 1 day before MPTP injection	Every second day for a week	Male C57Bl/10 mice	MPTP (10 mg/kg i.p.) four injections at 1 h intervals				**MPTP injection** decreased TH expression by 51% on day 3 and 59% on day 7 **After indomethacin** decreased the TH expression 27% and 19% (1 mg/kg) on day 7	**MPTP injection** Reactive microglia increase 2.5 times on day 3 and 2 times on day 7 **After indomethacin** Decreased the microglial activation on day 3 but not on day 7		(48)
Celecoxib (20 mg/kg/day) 1 h before the 6-OHDA injection	At 14 and 21 days	Sprague-Dawley (SD) rats		3.0 µg/µl free base 6-OHDA into 3 locations in the right striatum			**6-OHDA injection** 40% TH+-cell loss at day 12 65% TH+-cell loss at day 21 **After celecoxib** >50% TH+-cell	**After celecoxib** decreased the microglial activation more effectively on day 12		(44)
Alpha-lipoic acid (ALA) (50 mg/kg/day i.p.) 2 h before MPTP	For 14 days	Male C57BL/6 mice	MPTP (30 mg/kg/day i.p.) for 5 consecutive days			**Motor function assessment; MPTP injection** caused impairment in footprint test **ALA injection** improved it (step length of 4.44 vs. 5.13) Suspension time (MPTP of 4.2 vs. ALA of 7.4)		**MPTP injection** increased the NF-κB level increased iNOS gene expression **ALA injection** decreased the microglial activation decreased the NF-κB level decreased iNOS gene expression		(51)

TABLE 1. Continued

Drugs	Treatment duration	Animal	MPTP	6-OHDA	Others	Behavioral tests	Dopaminergic loss	Inflammatory reactions	Alpha-synuclein	Ref
MicroRNA-7 (miR-7) (stereotaxically)		wild type and A53T$^{tg/tg}$ mice	MPTP (20 mg/kg s.c.) probenecid (250 mg/kg i.p.) 1 h interval every 3.5 days over 5 weeks				α-syn and MPTP injection caused TH+-cell loss **miR-7 injection** protected TH+-cells	**miR-7 injection** inhibits microglial activation, suppresses NLRP3 inflammasome activation		(10)
MicroRNA-7 (miR-7) (stereotaxically)		Male C57BL/6 J mice			α-syn PFF AAV-miR-7 AAV-miR-7-NT were injected stereotaxically	α-syn PFF impaired nesting behavior (38%) and motor deficits on rotarod test (42%) 6 months later **miR-7 injection** improved performance (5%-nesting, 14%-rotarod)	α-syn PFF reduced ipsilateral striatal dopaminergic terminals (63%) **miR-7 injection** protect the striatal dopaminergic terminals (43% protection)	α-syn PFF increased the reactive microglia in the striatum (12 times ipsilateral, 6 times contralateral) **miR-7 injection** reduced inflammatory cells in striatum (70% ipsilateral, 54%contralateral)	α-syn PFF pS129-α-syn immunoreactive neurons in ipsilateral striatum and SN of control mice **miR-7 injection** prevent seeding ipsilateral and contralateral striata	(55)
MicroRNA-30e (20 nmol/L) (stereotaxically)	stereotaxically by catheter for 7 consecutive days	Male C57BL/6 J mice	MPTP (20 mg/kg/day i.p.) at 1, 7, and 14 days			**MPTP injection** significantly decreased motor functions (in rotarod, pole, traction, and beam-crossing task tests) **miR-30e injection** improves the motor functions	**MPTP injection** decreased TH+-cell in SN **miR-30e injection** protect the TH+-cells	**MPTP injection** increased the inflammatory mediators (TNF-α, COX-2, and iNOS) **miR-30e injection** suppressed the mediators suppressed NLRP3 inflammasome activation in SN	**MPTP injection** caused α-syn expression **miR-30e injection** decreased α-syn expression	(43)
Fingolimod (0.5 mg/kg i.p.)	7 days before 6-OHDA	C57BL/6 mice		6-OHDA 6 µg (in 2 µl of normal saline with 0.02% ascorbic acid) 2 sites of right striatum		**6-OHDA injection** Contralateral rotations with 6-OHDA **Fingolimod injection** reduced the asymmetrical rotations	**6-OHDA injection** reduced the TH+-cell **Fingolimod injection** protected TH+-cells	**6-OHDA injection** induced astrogliosis and microgliosis in SN and striatum **Fingolimod injection** decreased the astrogliosis and microgliosis		(16)

TABLE 1. Continued

Drugs	Treatment duration	Animal	MPTP	6-OHDA	Others	Behavioral tests	Dopaminergic loss	Inflammatory reactions	Alpha-synuclein	Ref
Fingolimod (1 mg/kg) (orally)	14 days	C57BL/6 mice	MPTP (30 mg/kg i.p) for 5 days			**MPTP injection** caused motor deficits (Pole test, beam test) **Fingolimod administration** returned the control values	**MPTP injection** reduced the TH+-cell **Fingolimod administration** protected TH+-cells	**MPTP injection** induced astrogliosis and microgliosis in SN and striatum **Fingolimod administration** decreased the astrogliosis and microgliosis		(63)
Resveratrol (10, 20, or 40 mg/kg) (gavage)	once daily for ten weeks	Sprague–Dawley (SD) rats		6-OHDA (5 µg in 2 µl/site) 2 sites of the right striatum		**6-OHDA injection** ipsilateral rotations **Resveratrol administration** reduced the rotation		**6-OHDA injection** increased COX-2 and TNF-α mRNA level **Resveratrol administration** decreased the elevations		(66)
Montelukast (10, 20 and 40 mg/kg/day i.p.)		C57BL/6 mice		6-OHDA (5 µg/µl) into the right striatum		**6-OHDA injection** abnormal locomotor behavior after 6-OHDA and **Montelukast** treatment	**6-OHDA injection** caused TH+-cell loss at 7 days (44%) **Montelukast injection** protected the TH+-cell (20%) (40 mg/kg)	**6-OHDA injection** increased microglial activation **Montelukast injection** inhibited the activation		(41)
Exendin (10 µg/kg i.p.) 30 min prior to MPTP		C57BL/6 mice	MPTP (20 mg/kg i.p) four injection at 2 h intervals				**MPTP injection** caused TH+-cell loss (58%) in SN **Exendin injection** protected the TH+-cells (83% viable) in SN	**MPTP injection** increased microglial activation, increase TNF-α and IL-1β in SN and Striatum increased MMP-3 **Exendin injection** inhibited the activation of microglia, TNF-α and IL-1β attenuated the increase of MMP-3		(42)

TABLE 1. Continued

Drugs	Treatment duration	Animal	MPTP	6-OHDA	Others	Behavioral tests	Dopaminergic loss	Inflammatory reactions	Alpha-synuclein	Ref
Tiagabine (5 mg/kg i.p.) 1h before LPS or MPTP		C57BL/6 mice	MPTP (18 mg/kg i.p) four injection at 2h intervals		0.5 µl LPS into SN stereotaxically injected	**MPTP injection** reduced motor performances (rotarod) **Tiagabine injection** did not affect the rod performances	**MPTP injection** decreased dopamine and DOPAC concentration, 66% TH+-fibers in the striatum **Tiagabine injection** protected TH + -fiber (up to 75%), decreased striatal 5-HT and 5-HIAA	**MPTP injection** increased microglial activation **Tiagabine injection** reduced microglial activation (MPTP and LPS-induced) suppress LPS-induced NF-κB signaling		(71)
Nilotinib (25 mg/kg) (gavage)	For 7 days before LPS injection	C57BL/6 mice			LPS (0.5 mg/ml) micro-injection to ventral midbrain			**LPS injection** increased the microglial activation **Nilotinib administration** reduced microglial activation, COX-2, and IL-1β		(74)
Pioglitazone 20 mg/(kg day) (orally)	Starting 4 days before the first MPTP injection and one more week	C57BL/6 mice	MPTP (30 mg/kg i.p) two and five injections at 24 h intervals				**MPTP injection** caused TH+-cell loss (50%) in SN, a decrease in dopamine and DOPAC **Piaglitazone administration** completely protected the TH+-cells, partial prevention of dopamine decreased in striatum	**MPTP injection** increased microglial activation, iNOS, and astrocytes **Piaglitazone administration** decreased the activation, reduced İNOS and astrocytes		(20)

TABLE 1. Continued

Drugs	Treatment duration	Animal	MPTP	6-OHDA	Others	Behavioral tests	Dopaminergic loss	Inflammatory reactions	Alpha-synuclein	Ref
Rosiglitazone (10 mg/kg i.p.)	between four to five week	C57BL/6 mice	MPTP (25 mg/kg i.p.) probenecid (100 mg/kg i.p.) 7 or 10 injections twice a week				**MPTP injection** caused TH+-cell loss (15% viable) in SN and reduced the dopamine and DOPAC level (75%-52%) **Rosiglitazone injection** protected the TH+-cells (30% viable) in SN and increased the levels	**MPTP injection** increased microglial activation increased the TNF-α in active microglia (35%) **Rosiglitazone injection** decreased the activation decreased the TNF-α activation (7%)		(21)
Cordycepin 10 mg/kg and 20 mg/kg 1h after MPTP		Sprague–Dawley rats	MPTP (20 mg/kg i.p.) four injections at 2 h intervals			**MPTP injection** caused motor dysfunction (increase pole climbing and time in grasping test, lower stay on rod at rotarod test) **Cordycepin administration** alleviated motor function (decreased pole climbing and time in grasping test, longer stay on rod at rotarod test)	**MPTP injection** caused TH+-cell loss (65%) **Cordycepin administration** increased the TH+-cells 1.46-fold and 2.15-fold	**MPTP injection** increased microglial activation (3.3 fold) increased the TNF-α (5.1 fold), IL-1β(4.5 fold), IL-6 (3.1 fold) increased the TLR2 (3.1 fold), TLR4 (1.7 fold), and NF-κB proteins increased the ROS activity, decreased SOD activity **Cordycepin administration** alleviated the activation (36%–57%) attenuated changes in TNF-α (5.1 fold), IL-1β (4.5-fold), IL-6 (3.1 fold) attenuated ROS and SOD activity attenuated TLR2, TLR4, and NF-κB proteins levels		(14)

TABLE 1. Continued

Drugs	Treatment duration	Animal	MPTP	6-OHDA	Others	Behavioral tests	Dopaminergic loss	Inflammatory reactions	Alpha-synuclein	Ref
Calycosin (15 and 30 mg/kg/day i.p.)	for 7 days	mice	MPTP (20 mg/kg i.p.) four injections at 2 h intervals				**MPTP injection** caused TH+-cells loss **Calycosin injection** protected the TH + -cells dose-dependently	**MPTP injection** increased microglial activation increased TNF-1β, IL-1β, and IL-6 mRNA expressions activated MAPK signaling activated TLR/NF-κB **Calycosin injection** decreased the microglial activation inhibited the TNF-1β, IL-1β, and IL-6 mRNA expressions suppressed the MAPK signaling restored the TLR/NF-κB TLR/NF-κB level		(81)

α-syn: alpha-synuclein, COX: cyclooxygenase, DOPAC: 3,4-Dihydroxyphenylacetic acid, h: hour, 5-HT: serotonin, 5-HIAA: 5-hydroxy indole acetic acid, IL: interleukin, iNOS: inducible nitric oxide synthase, i.p: intraperitoneally, LPS: lipopolysaccharides, MAPK: mitogen-activated protein kinase, MiR: microRNA, MPTP:1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, NF-KB: nuclear factor-kappa B, NLRP3: NLR family pyrin domain containing 3, 6-OHDA: 6-hydroxydopamine, PFF: preform fibril, ROS: reactive oxygen species, s.c: subcutaneously, SN: substantia nigra, SOD: superoxide dismutase, TH: tyrosine hydroxylase, TLR: Toll-like receptor, TNF: tumor necrosis factor.

The mechanism was speculated that this inhibition is most probably by FκB and stress-activated protein kinases (SAPK)/JNK pathways that play a role in cell survival, proliferation, and apoptosis.[49]

In conclusion, studies showed the beneficial effects of NSAIDs on neuroinflammation in PD could be a dose and time-dependent manner but none stop the disease progression.[45,47-50]

Alpha-lipoic Acid

Alpha-lipoic acid (ALA) is a water- and oil-soluble, powerful antioxidant that is found in the mitochondria. The mitochondria are important for energy metabolism, and ALA interacts with mitochondrial enzymes. Therefore, ALA is also important for anabolic and catabolic reactions. ALA can freely cross the BBB and show anti-inflammatory effects.[51,52]

A study revealed that ALA pretreatment for 14 days reduced the microglial activation in SN, inhibited the release of inflammatory factors, and improved the motor function in the MPTP mice model of PD.[51] The use of ALA in PD as an anti-inflammatory remained very up to date. More studies are necessary before considering ALA as a therapeutic option although the results of behavior tests and modulation of inflammatory factors look promising in this toxin model of PD.

microRNAs

MicroRNA-7 (MiR-7) is a conserved gene that is known to regulate synaptic plasticity and neuronal differentiation in the CNS. MiR-7 is the first miRNA identified to regulate α-syn levels by directly downregulating the α-syn expression after binding to the *SNCA* gene.[53] Additionally, the *MiR-7* gene level was decreased in the SN of patients with PD, indicating that the MiR-7 level might play a role in the α-syn accumulation and dopaminergic neuronal loss.[54]

A study revealed that MiR-7 protected the dopaminergic neurons and attenuated the neuroinflammation against exogenous α-syn preformed fibril toxicity in a mice model of PD.[55] Another study examined the effect of altered MiR-7 and anti-MiR-7 on endogenous NLRP3 expression in BV2 cells and revealed that α-syn activated the NLRP3 inflammasome and MiR-7 transfection

TABLE 2. Cell Culture Model of Parkinson's disease regarding neuroinflammation and Drug Treatments Result

Drugs	Cell culture	MPTP	6-OHDA	Others	ROS inhibition	Apoptosis	Inflammatory reactions	Ref
Celecoxib (2.5–50 μM), Indomethacin (2.5–100 μM) Ibuprofen (2.5–100 μM) for 24 h	PC12 cell		200 μM of 6-OHDA for 24 h		2.5 and 5 μM indomethacin and ibuprofen suppress ROS generation	**6-OHDA administration** 32% apoptotic cell **Celecoxib, Indomethacin, Ibuprofen administration** (2.5 and 5 μM) decrease the apoptotic cell		(49)
MiR-7	SH-SY5Y cell line	MPTP-induced neurotoxicity				Tunel-positive neuron **MPTP administration** increased **miR-7 administration** decreased Caspase 3 activity **MPTP administration** increased **miR-7 administration** decreased it		(57)
MiR-7	BV-2 microglial cells			WT α-Syn human or A53T α-Syn human for 24 h incubation	**α-Syn administration** increases ROS accumulation		**α-Syn administration** activates NLRP3 inflammasome **miR-7 administration** inhibits the NLRP3 inflammasome formation	(10)
MicroRNA-30e	BV-2 microglial cells						**miR-30e administration** mimic dose-dependently decreased NLRP3 mRNA expression (5, 10, 20, and 40 nmol/L)	(43)
Fingolimod (0.5, 1, 2, and 4 μM)	SH-SY5Y cell line	100 μM 6-OHDA				**6-OHDA administration** increased the apoptotic cells **Fingolimod administration** (2 and 4 μM) decreased the apoptotic cells		(16)
Resveratrol 1–50 μM	BV2 microglia cells			Transferred to an anaerobic chamber, then de-oxygenated			**Hypoxia** caused the microglial activation **Resveratrol administration** (25 μM) reduced the activation attenuated the TNF-α mRNA level, suppressed NF-κB activation, increased the IL-10	(67)
Montelukast (0.01 μM)	BV2 microglia cells			Rotenone 3 nM			**Rotenone administration** increase IL-1β, TNF-α, actives 5-LOX, induced CysLT1R expression **Montelukast administration** decrease IL-1β, TNF-α, and inhibits 5-LOX	(69)

TABLE 2. Continued

Drugs	Cell culture	MPTP	6-OHDA	Others	ROS inhibition	Apoptosis	Inflammatory reactions	Ref
Nilotinib	BV-2 microglial cells			LPS 100 ng/mL		**LPS administration** increased the apoptotic markers in dopaminergic neurons	**LPS administration** increase iNOS, COX-2, IL-1β, and TNF-α expression **Nilotinib administration** suppress the expressions, attenuate in a dose-dependent manner, inhibited NF-κB signaling	(74)
Cordycepin 10 μg/ml	BV-2 microglial cells			LPS 5 μg/ml			**LPS administration** increase TNF-α (8 fold), IL-1β (6.5 fold), IL-6 (5.2 fold), and ROS (1.2 fold) expression, decreased SOD by 58% increased TLR2 (3.5 fold), TLR4 (3.1 fold), and nuclear NF-κB (3.6 fold) **Cordycepin administration** suppressed these changes attenuated TLR2, TLR4, and nuclear NF-κB level	(14)
Cordycepin (1, 2.5, 5, or 7.5 μg/ml) 1h before LPS	BV-2 microglial cells			LPS (0.5 μg/ml)	**LPS administration** increased the NO production **Cordycepin administration** Prevented in a dose-dependent manner		LPS administration induced PGE2 expression iNOS and COX-2 expression increased TNF-α and IL-1β, nuclear accumulations of NF-κB **Cordycepin administration** (7.5 μg/ml) suppressed the PGE2 suppressed the iNOS and slightly COX-2 in a dose-dependent manner decreased the TNF-α and IL-1β prevented the accumulation of NF-κB	(79)
Calycosin	BV-2 microglial cells			LPS (100 ng/ml)			**LPS administration** increased the mRNA expressions of TNF-1β, IL-1β, and IL-6 activated MAPK signaling activated TLR/NF-κB **Calycosin administration** inhibited the expressions suppressed the MAPK signaling, restored the TLR/NF-κB level	(81)

α-syn: alpha-synuclein, COX: cyclooxygenase, CysLT1R: cysteinyl leukotrienes receptor 1, IL: interleukin, iNOS: inducible nitric oxide synthase, 5-LOX: 5-lipoxygenase, LPS: lipopolysaccharides, MAPK: mitogen-activated protein kinase, MiR: microRNA, MPTP:1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, NF-KB: nuclear factor-kappa B, NLRP3: NLR family pyrin domain containing 3, 6-OHDA: 6-hydroxydopamine, PGE2: prostaglandin E2, ROS: reactive oxygen species, TLR: Toll-like receptor, TNF: tumor necrosis factor.

significantly reduced NLRP3 protein levels, which was reversed after anti-MiR-7 transfection by NLRP3 expression upregulation.[10] Another study of animal and cell culture models showed that MiR-7 downregulated the p65, which is a protein that is a member of NF-κB, and increase the Glut3 expression, thereby supporting the glycolysis to supply energy to cells and preventing apoptosis.[56] Additionally, MiR-7 suppressed Bax and SIRT2 expression, which are apoptotic cell markers, and attenuates the dopaminergic neuronal loss by preventing apoptosis.[57]

MicroRNA-30e (MiR-30e) affects the NLRP3 gene expression. NLRP3 inflammasome activation was inhibited after MiR-30e treatment, and Caspase-1 expression, as well as IL-18 and IL-1β secretions, were decreased in the SN of MPTP mice.[43]

Fingolimod

Fingolimod (FTY720) is the first oral medication approved to treat relapsing-remitting multiple sclerosis. Fingolimod is a sphingosine-1 phosphate (S1P) receptor modulator. S1P has several roles in the CNS that modulate growth and cell survival, synaptic transmission, and memory formation together with inflammatory responses by playing a role in lymphocyte upregulation.[58,59] FTY720 reduces T and B lymphocyte infiltration into the CNS by causing the S1P receptor downregulation expressed in lymphocytes.[60]

FTY720 was observed to have neuroprotective effects in other neurological disorders, such as PD, AD, Huntington's disease, Rett syndrome, and ischemia experimentally, in addition to multiple sclerosis (MS).[16,40,61,62] FTY720 was observed to ameliorate motor deterioration and reduce the loss of dopaminergic neurons due to its neuroprotective effect on the 6-OHDA animal model of PD.[16] Further, fingolimod pretreatment before MPTP toxicity showed a protective effect similar to previous studies and reduced microgliosis and astrogliosis.[63]

Resveratrol

Resveratrol is an effective component of plants, such as red grapes, giant kiwi rhizome, and peanuts, with many pharmacological effects, such as anti-tumor, anti-apoptosis, anti-inflammatory, and neuroprotective.[64] Resveratrol can reduce the pro-inflammatory cytokine and enzyme expression. Several studies reported the resveratrol's beneficial effects on neuroinflammation by regulating NF-κB pathways, as well as a review of the phytochemicals that emphasize the role of resveratrol used in different neurological disorders.[65-68] which leads researchers to assess its beneficial effect in PD.

A study investigated the neuroprotective effects of resveratrol on 6-OHDA-injected mice.[66] Resveratrol was chronically administered in different doses after 6-OHDA injections. Results showed that resveratrol treatment improved motor function and reduced the TNF-α and COX-2 mRNA expression in the SN caused by 6-OHDA toxicity.[66] Additionally, resveratrol increases IL-10 concentration and exerts an anti-inflammatory effect by decreasing NF-κB and TNF-α levels in the hypoxia-injured BV cell culture model.[67]

Montelukast

Montelukast is a potent and selective CysLT1R antagonist that is currently used as adjuvant therapy for patients with asthma. Montelukast was considered a therapeutic opportunity for neuroinflammation due to its effect on leukotrienes.

An in vitro cell culture study revealed that montelukast reduced the release of TNF-α and IL-1β after low-dose rotenone-induced microglial activation in cell culture.[69] A 6-OHDA-induced PD mouse model study showed that intraperitoneally (i.p.) injected montelukast in different doses protects dopaminergic neurons against microglial activation and reduces the production of neurotoxic cytokines, such as TNF-α and IL-1β.[39,41] Montelukast shows some beneficial effects as an anti-inflammatory agent in vitro that can alleviate diseases, such as PD, but its neuroprotective effects against the nigrostriatal dopaminergic system in vivo remained lacking.

Exendin

Exendin is a more potent and stable analog of glucagon-like peptide-1 (GLP-1) that selectively binds to the GLP-1 receptor. GLP-1 is an endogenous peptide hormone of 30 amino acids that is synthesized from proglucagon-derived peptides in intestinal endocrine L cells, small groups of neurons in the brain stem, and the hypothalamus. Exendin can pass through BBB, show neuroprotective effects, and improve cognitive function. Exendin increases GLP-1 receptor expression in the hippocampus, which plays a role in neuronal plasticity and neuroprotection.[70] Thus, exendin thought to be an effective treatment for PD.

A study, wherein exendin was intraperitoneally administered to determine the neuroprotective effects on the MPTP mouse model of PD, revealed that exendin prevents microglial activation by significantly attenuating the MMP-3 upregulation, suppressing the pro-inflammatory cytokine expression, and protecting against dopaminergic neuronal loss.[42]

Tiagabine

Tiagabine is a Food and Drug Administration (FDA)-approved anti-convulsive drug that inhibits the GABA transporter 1 (GAT 1). The precise mechanism of action of tiagabine in epilepsy and panic disorders is not fully understood, but its pharmacological effects are related to GAT 1 blockage and subsequent increase in GABAergic transmission.

A study examined the neuroprotective effects of tiagabine pretreatment in MPTP-induced PD mice and revealed a reduced microglial activation in both striatum and SN 9 days after tiagabine + MPTP injection, which alleviates the nigrostriatal dopaminergic neurodegeneration.[71] Further, tiagabine pretreatment did not block microglial activation induced by MPTP in GAT 1 knockout mice. Neither muscimol nor baclofen suppressed the microglial activation as much as tiagabine.[71] Another experiment was designed to determine whether tiagabine, muscimol, and baclofen

could prevent microglial activation induced by lipopolysaccharides (LPS) in BV-2 microglia cell culture.[71] Tiagabine inhibits LPS-induced microglial activation and protects against dopaminergic neuronal loss in SN, as well as muscimol and baclofen in vivo, by suppressing the NF-κB signaling activation.[71] Besides, baclofen and muscimol show a protective effect only against LPS toxicity and not MPTP, but tiagabine attenuated MPTP and LPS-induced dopaminergic toxicity, inhibited in vivo microglial activation, and improved motor behavior in PD mice.[71] The results suggest tiagabine as a new therapeutic approach for PD and other inflammation-related neurodegenerative diseases.

Nilotinib

Nilotinib (AMN107) is a non-Abelson receptor tyrosine kinase (Abl) inhibitor that is approved by the FDA for chronic myeloid leukemia. Abl is a tyrosine kinase that is distributed both in the nucleus and cytosol and involved in a variety of functions, including apoptosis.[72] Abl levels are elevated in the nigrostriatal region of patients with PD and Abl inhibition increases the survival of dopaminergic neurons.[73]

A study examined the effects of nilotinib on the neuroinflammatory response in LPS-induction in BV2 cells and LPS injection into mouse brains and revealed that pro-inflammatory mediators, including COX-2, iNOS, IL-1β, IL-6, and TNF-α, and the mRNA levels of pro-inflammatory factors were significantly reduced by NF-κB signaling pathway inhibition, and dopaminergic neuronal loss was decreased.[74]

Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) Agonists

PPAR-γ agonists belong to the nuclear receptor superfamily and are expressed in neurons, microglia, macrophages, astrocytes, and oligodendrocytes. PPAR-γ agonists regulate lipid and carbohydrate metabolism and effects insulin sensitivity.[75] Additionally, PPAR-γ agonists take part in reducing inflammation and free radical formation, and increasing microglial phagocytosis.[11] Therefore, PPAR-γ agonists may be effective in the neuroinflammation process of common neurodegenerative diseases, such as PD.

Pioglitazone is a thiazolidinedione derivative and is a very selective PPAR-γ agonist that is approved for diabetes mellitus treatment. Pioglitazone was considered for investigation as a therapeutic candidate for neurodegenerative disorders due to the anti-inflammatory effect of PPAR-γ agonists.

A study created a mouse model of MPTP-induced PD to investigate the effect of pioglitazone and revealed that pioglitazone pretreatment protects the dopaminergic neurons from cell death and reduced the microglial activation through PPAR-γ activation, IκB-α expression induction, and NF-kB activation inhibition.[20]

Rosiglitazone is another thiazolidinedione derivative and a selective agonist of PPAR-γ. A study investigated the effects of rosiglitazone in the progressive MPTP model of PD. Rosiglitazone was chronically given after microglial activation due to MPTP treatment, revealing that rosiglitazone administration decreased the PPAR-γ overexpression and reduced TNF-α expression but did not adequately stop dopaminergic neuronal loss.[21]

In conclusion, PPAR-γ agonist treatment could be a treatment opportunity to mediate the inflammation in PD and slow down the disease progression but is inadequate for stopping it.

Cordycepin

Cordycepin is obtained from a fungus called *Cordycepin militaris* and has anti-inflammatory, antioxidant, and anti-cancer properties.[76] Cordycepin increases the IL-10 expression on human cancer cell lines and inhibits the pro-inflammatory and inflammatory cytokine secretion.[77] Additionally, cordycepin shows neuroprotective effects by attenuating oxidative damage, thereby increasing the cleaning of free radicals and suppressing neuronal cell death.[15,76,78]

A study with the MPTP rat model showed that cordycepin pretreatment attenuated the MPTP toxicity, motor impairment, inflammation, and oxidative stress, as well as activated the microglia and regulated the TNF-α, IL-1β, and IL-6 in cell culture.[14] This effect of cordycepin is based on the inhibition of TLR-2 and TLR-4 upregulation through the TLR/NF-kB signaling pathway suppression.[14] They also revealed an increased ROS activity and a decreased superoxide dismutase (SOD) activity due to MPTP toxicity, which was alleviated by cordycepin.[14] Cordycepin affects not only inflammatory factors but also ROS and oxidative stress generation that are part of the PD pathology.

Potential anti-inflammatory properties of NO and prostaglandin E2 (PGE2) production of cordycepin were studied in an LPS-stimulated BV2 rat microglia cell culture model,[79] which revealed that PGE2 and NO levels were decreased after cordycepin pretreatment.[79] LPS-induced NO, TNF-α, and IL-1β release were significantly reduced and prevented the microglia-induced cytotoxicity by inactivating NF-kB through inhibition of IkB-α degradation when the effects of cordycepin on inflammatory cytokines are examined in cell culture.[79]

Calycosin

Calycosin is an isoflavone phytoestrogen that is isolated from *Astragalus membranaceus*. Calycosin has anti-cancer, anti-virus, antioxidant, and anti-inflammatory effects.[80]

Calycosin treatment for a week improves motor behavior, suppresses the loss of dopaminergic neurons, inhibits the microglial cell activation, partially inhibits the mRNA expression of TNF-α, IL-1β, and IL-6, and suppresses TLR/NF-kB activation in a dose-dependent manner in MPTP-induced PD mice model.[81]

In conclusion, widespread and chronic neuroinflammation in the CNS is one of the key factors in PD pathogenesis. Clustered α-syn, oxidative stress, mitochondrial dysfunction, and microglia-mediated neuroinflammation play a fundamental role in the onset and progression of PD. Various factors, such as TLR, NLRP3 inflammasome, and leukotrienes, which have an effective role in neuroinflammation, seem to be activated in PD. Therefore,

targeting these pathways may be an effective strategy for PD treatment.

The main goal of PD treatment is to develop a drug that slows or stops the underlying neurodegeneration process. However, current treatments are inadequate to eradicate or limit the disease progression, and they only help in symptom improvement. Therefore, drugs with the potential to reduce neuroinflammation, in an animal or cell culture model, were examined in this review for future therapeutic opportunities.

Targeting microglia, cytokine receptors, and astrocytes, or using microRNAs to inhibit NLRP3 inflammasome shows promising results in moderating the inflammatory symptoms, which is just one piece of the puzzle, thereby not providing a radical solution. NSAIDs, which are safely used for years against inflammation in many diseases, may have the potential to reduce neuroinflammation but with a risk for PD. microRNAs are useful and successful tools to target the α-syn. Fingolimod, resveratrol, montelukast, tiagabine, and cordycepin were successful to improve motor performances. Exendin, PPAR agonists, and calycosin were successful to protect dopaminergic neurons against neurotoxins. Additionally, they all showed a significant effect on inflammatory pathway modulation but were limited in stopping the disease progression.

Conversely, the agents that are used in inflammation modulation are non-specific inflammatory system inhibitors, and they need to be used in higher doses to be effective. Hence, they can cause various side effects and toxicity in physiological conditions. Besides, the findings were obtained only from cell culture or animal models. Instead of evaluating the entire disease pathology, some studies focused on motor functions, some on dopaminergic neuronal loss, some on oxidative stress, and some on the regulation of inflammatory factors and the involved pathways. Therefore, comprehensive examination of different mechanisms of these agents in more in vivo studies, direct targeting and dose adjustment studies, and clinical trials are needed in the future before they can be used in patients.

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