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NEUROINFLAMMATION MODIFYING APPROACHES IN PARKINSON'S DISEASE

PARKİNSON HASTALIĞINDA NÖROİNFLAMASYONU MODİFİYE EDİCİ YAKLAŞIMLAR

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Abstract

Parkinson's disease is a chronic and slowly progressing neurodegenerative disease characterized by the degeneration of dopaminergic neurons in the substantia nigra. Currently, the treatment strategies of Parkinson's disease can only alleviate motor symptoms but not prevent from neurodegeneration. In recent years, among the treatment approaches for the pathophysiology of the disease, there is a rapid increase in publications related to drug and/or drug candidates targeting neuroinflammatory mechanisms in the disease. In this review, we summarize the neuroinflammatory mechanisms and treatment approaches that modify neuroinflammation in Parkinson's disease and present the recent preclinical and clinical data on possible drug candidates. The interactions between neuroinflammation and degeneration in dopaminergic neurons must first be elucidated in order to develop novel drug candidates targeting neuroinflammatory mechanisms in Parkinson's disease.

Keywords: neuroinflammation, parkinson's disease, new drug candidates

Özet

Parkinson hastalığı, substansiya nigradaki dopaminerjik nöronların dejenerasyonu ile karakterize, yavaş ilerleyen kronik bir hastalıktır. Günümüzde Parkinson hastalığında uygulanan tedaviler yalnızca motor semptomları hafifletebilmekte, ancak nörodejenerasyonu önleyememektedir. Son yıllarda, hastalığın patofizyolojisine yönelik tedavi yaklaşımları arasında, hastalığın nöroinflamatuvar mekanizmalarını hedefleyen ilaç ve/veya ilaç adaylarına ilişkin yayınların hızla arttığı görülmektedir. Bu derlemede, Parkinson hastalığının nöroinflamatuvar mekanizmaları ve hastalıkta nöroinflamasyonu modifiye edici yaklaşımlar özetlenip olası ilaç adayları hakkında güncel veriler sunulmuştur. Parkinson hastalığında nöroinflamatuvar mekanizmaları hedef alan ilaç adaylarının geliştirilmesinde, öncelikle nöroinflamasyon ve dopaminerjik nöronlarda oluşan dejenerasyon arasındaki etkileşimlerin aydınlatılması gerekmektedir.

Anahtar Kelime: *nöroinflamasyon, parkinson hastalığı, yeni ilaç adayları*

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1. Introduction

Parkinson's disease (PD), is a slowly progressing neurodegenerative disease (von Euler Chelpin & Vorup-Jensen, 2017) with the worldwide prevalence of 6.3-10 million and the incidence of 17/100,000, but it is estimated that this rate is much higher with the undiagnosed cases (Twelves, Perkins, & Counsell, 2003). The management strategies for PD are focused on two targets: improving symptom control and prevention of neurodegeneration (Mhyre, Boyd, Hamill, & Maguire-Zeiss, 2012). Therapies that increase the reduced dopaminergic neurotransmission provide a better quality of life, however, none of these drugs are neuroprotective or disease-modifying. For that reason, research on PD, especially in the last two decades, has focused on slowing the progression of the disease or preventing neurodegeneration. Although the neurodegeneration mechanisms in PD are not fully understood, mounting evidence postulated that neuroinflammatory mechanisms may contribute to the progressive degeneration of dopaminergic neurons that occurs in PD (Barcia, Fernandez Barreiro, Poza, & Herrero, 2003). In this review, we discuss how neuroinflammation affects neurodegeneration in PD, and possible neuroprotective strategies related with inflammation.

2. Components of neuroinflammation in PD

Although it has not been clarified when starts or how occurs neuroinflammation in PD (Hunot & Hirsch, 2003), dysregulation of immune responses could be particularly relevant with neurodegeneration (Tiwari & Pal, 2017). Since the inflammatory responses may trigger the disease progression and play important role in the degeneration of dopaminergic neurons, inflammatory processes are suggested as novel targets for PD.

2.1. Immun Cells in neuroinflammation

There are many studies that clarify the mechanisms of immun cells in PD pathophsiology. Activation of pro-inflammatory pathways through immun cells causes damage on dopaminergic neurons. Experimental data indicate that microglial activation, infiltration of T lymphocyte, increase of pro-inflammatory cytokines lead neurodegeneration and progress disease pathology (Kaur, Gill, Bansal, & Deshmukh, 2017).

2.1.1 Microglia in neuroinflammation in PD

Glia, resident brain cells, are known to mediate the inflammatory process in parenchyma and have role in neurodegenerative diseases such as PD (Barcia et al., 2003). For example, microglia, protecting the central nervous system (CNS) in physiological conditions, are pathologically activated in PD and involved in inflammation and phagocytosis (Gonzalez-Burgos, Fernandez-Moriano, & Gomez-Serranillos, 2015; McGeer & McGeer, 2004). Furthermore, wide range of free radicals and possible neurotoxins are produced by this activated microglia (McGeer & McGeer, 2004). Activated microglia is able to show either pro-inflammatory or anti-inflammatory features depending on their phenotypic activation. (Rydbirk et al., 2017). While classical activated microglia (M1) is related to production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, reactive oxygen species (ROS) and nitric oxide (NO), and is also related to the activation of inducible nitric oxide synthase (iNOS) and nuclear factor kappa B (NF-κB) signaling pathway; the alternative activated phenotype takes roles in anti-inflammatory pathways, tissue repair, extracellular matrix reconstruction and debris clearance (Shan et al., 2017).

The neurotoxic effects of M1 phenotype microglia was shown both in vitro (Gao et al., 2002; Le et al., 2001) and in vivo models of PD (Cicchetti et al., 2002; Sherer, Betarbet, Kim, & Greenamyre, 2003). Activated microglia (M1) was found both in PD patients (Gerhard et al., 2006), and in substantia nigra (SN) and striatum in animal models of PD (Marinova-Mutafchieva et al., 2009; Vazquez-Claverie et al., 2009).

There is a question about what are the determinants of the M1/M2 microglia phenotyping in PD. For example, mis-folded alpha-synuclein (α-syn) and environmental toxins are known to induce the activation of M1 microglia in animal models of PD (Wang, Liu, & Zhou, 2015). Mis-folded aggregated α-syn but not monomeric form was found to inhibit microglial phagocytosis, which is essential to degradation of infectious agents and senescent cells, thereby may have role in inducing secondary immun response and exacarbating neuroinflammation. The different effects of monomeric and aggregated α-syn on phagocytosis may arised from their localization in cells (Park, Paik, Jou, & Park, 2008). Activated microglia (M1) was shown to be gathered around α-syn-positive aggregates in certain regions of the PD brain (Yamada, McGeer, & McGeer, 1992). It is now known that microglia is able to detect oligomeric α-syn through Toll-like receptors, pattern recognition receptors. For example, interlock of α-syn with Toll-like receptors leads to the translocation of NF-kB and expression of pro-inflammatory cytokines (von Euler Chelpin & Vorup-Jensen, 2017). Persistent exposure to these microglia-derived pro-inflammatory cytokines is harmful for dopaminergic neurons. For example, chronic expression of low levels of TNF-α in the SN caused time-dependent neurodegeneration, motor symptoms and microglia/macrophage activation in rats (De Lella Ezcurra, Chertoff, Ferrari, Graciarena, & Pitossi, 2010). Similarly chronic systemic expression of IL-1 also aggravated neurodegeneration and microglial activation in the SN in 6-hydroxydopamine (6-OHDA) models of PD (Pott Godoy, Tarelli, Ferrari, Sarchi, & Pitossi, 2008). Consistent with this data, increased levels of inflammatory cytokines, IL-1β, IL-6 and TNF-α, were detected in the basal ganglia, striatum and cerebrospinal fluid of PD patients (Hunot & Hirsch, 2003; McGeer & McGeer, 2004; Rydbirk et al., 2017). Qin and colleagues have recently been drawn a conclusion from a meta-analysis that concentrations of IL-6, TNF-a, IL-1β, C-reactive protein, IL-10, RANTES (regulated on activation, normal T-expressed, and presumably secreted), and IL-2 were significantly higher in patients with PD compared with healthy controls (Qin, Zhang, Cao, Loh, & Cheng, 2016).

2.1.2. Astrocytes in neuroinflammation in PD

Like microglia, astrocytes which have many functions on structural and metabolic support and neuronal synaptic transmission also react to the inflammatory stimulations by producing pro-inflammatory cytokines (Booth, Hirst, & Wade-Martins, 2017; Tzeng, Hsiao, & Mak, 2005; Wang et al., 2015). When a brain injury occurs, astrocytes are involved in a process called astrogliosis in which they are reactivated in response to tissue damage and develops glial scar to prevent axonal regeneration (Yu, Wang, Katagiri, & Geller, 2012). The astrogliosis in the PD brain imply the role of astrocytes in the immune mechanism in this disease (Yamada, Kawamata, Walker, & McGeer, 1992). Astrocytic responses arise from activated microglia-derived pro-inflammatory mediators and then these immunosignals are further intensified by them, therefore astrocytic responses are relatively slower than microglial activation (Wang et al., 2015). Specific overexpression of PD-related A53T mutant α-syn in astrocytes were found to lead widespread astrogliosis and microglial activation leading to dopaminergic neuron and motor neuron loss in mice (Gu et al., 2010). Recently, the striatal debris following by dopaminergic neurodegeneration has been observed within surrounding astrocytes after the dopaminergic denervation of rat striatum with 6-OHDA, impyling that if astrocytes work correctly before the onset of PD, the mentioned transautophagy should be enough to metabolize all dopaminergic debris. If not, the activation of microglia could be required to complete the cleaning of dopaminergic debris, and this would probably accelerate the onset and progression of PD (Morales, Sanchez, Rodriguez-Sabate, & Rodriguez, 2017).

Dopamine receptors on astrocytes are known to be involved in inflammatory process as well. Astrocytic dopamine D2 receptor modulates immune cell response by way of αB-crystallin, a neuroinflammation suppressor, thereby decrease the pro-inflammatory cytokines released by astrocytes (Shao et al., 2013). Dopamine D2 receptor also inhibits the production of angiotensinogen, decreases the angiotensin type-1 receptors expression and increases the angiotensin type-2 receptors expression in brain. This inhibition of brain renin angiotensin system, a key component of neuroinflammation, occurs via downregulation of the angiotensin-II derived from astrocyte, and via regulation of microglial angiotensin receptors (Dominguez-Meijide, Rodriguez-Perez, Diaz-Ruiz, Guerra, & Labandeira-Garcia, 2017). However, decrease of dopamine D2 receptor binding sites with age may lead reduction of astrocytic dopamine D2 receptor signal and therefore may progress the neurodegeneration (Antonini & Leenders, 1993). Interestingly, Elgueta et al., showed lack of dopamine D3 receptor in astrocytes provide beneficial astrogliosis with anti-inflammatory consequences on microglia by using a dopamine D3 receptor-selective antagonist, PG01037, which improved the locomotor activity and decreased the dopaminergic neuron loss in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mice model of PD (Elgueta et al., 2017). The neuroprotection that is observed with pramipexole, dopamine D3 receptor agonist, in MPTP mice model of PD may be conflicting (Joyce, Woolsey, Ryoo, Borwege, & Hagner, 2004), however, Elgueta et al., indicated in their paper that pramipexole prevent the 1-methyl-4-phenylpyridinium (MPP+) to enter the cell by downregulation of dopamin transporter, a cation transporter for MPP+, thereby make the cell less susceptible to neurodegeneration (Elgueta et al., 2017).

Besides dopamine receptors, alpha-7 nicotinic acetylcholine receptors (α7-nAChRs) expressed in astrocytes are also a therapeutic approach for PD management since the neuroprotective effects of nicotine are attributed to activation of α7-nAChRs (Jurado-Coronel et al., 2016). Similarly, nicotine was shown to prevent H2O2-induced astrocyte apoptosis and glial cell-derived neurotrophic factor downregulation in MPTP model of PD probably via stabilizing mitochondrial membrane potential and Bax/Bcl-2 balance, inhibited activity of cleaved caspase-9 activity through α7-nAChR activation (Y. Liu et al., 2015). Recently, Liu and collegues have also reported that Wnt/β-catenin signaling which comprises important mediator proteins of cell-to-cell communication and intracellular signaling related to CNS development, is a key component of α7-nAChRs-mediated neuroprotection in PD (Y. Liu et al., 2017).

2.1.3. T cells in neuroinflammation in PD

T lymphocytes may both initiate and propagate PD pathogenesis (Kannarkat, Boss, & Tansey, 2013). Infiltration of T cells into the SN was shown in both PD patients (McGeer, Itagaki, Akiyama, & McGeer, 1988) and animal models of the disease (Brochard et al., 2009; Sanchez-Guajardo, Febbraro, Kirik, & Romero-Ramos, 2010). Studies with immunodeficient mouse strains in MPTP model of PD showed significant decrease in dopaminergic neurodegeneration, suggesting that T-cells are not only relevant, but are also required for neurodegeneration in PD (Brochard et al., 2009). In PD, a lower ratio of CD4+ (helper T-cell):CD8+ T (killer T-cell) lymphocytes was reported resulting from a decreased percentage of CD4+ T lymphocytes and increased percentage of CD8+ T lymphocytes (Cao, Li, & Shen, 2011). Brochard et al., also showed that involvement of CD4+ T-cells is essential for promoting the neurodegeneration whereas CD8+ T-cell deficiency is negligible (Brochard et al., 2009). CD4+ T-cells normally have role in memory consolidation, hippocampal long-term potentiation and neurogenesis. Upon neuroinflammation which is started with microglial activation, peripheral T-cells infiltrate the CNS parenchyma in where they can not infiltrate under normal physiological conditions (Gonzalez, Elgueta, Montoya, & Pacheco, 2014). Pathogenic CD4+ T-cells also induce microglial activation and thereby promote neurodegeneration in PD (Gonzalez et al., 2014). A recent study showed that dopamine D3 receptor deficient mice were resistant to MPTP toxicity, however, when the animals were transfected with wild type CD4+ T-cells, they became susceptible to neurotoxin (Gonzalez et al., 2013). Conversely, some type of T-cells, such as regulatory T cells and Type 2 T helper cells, may provide microglial activation toward M2-like anti-inflammatory phenotype, which releases neurotrophic factors, and thereby provide neuroprotection (Gonzalez et al., 2014;

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Reynolds et al., 2010). Interestingly, carbidopa that blocks conversion of levodopa to dopamine outside of CNS, was found to strongly inhibit the T cell responses and T cell mediated autoimmunity in two different inflammatory animal models. Authors implying that if the reason of PD pathology is infiltration of activated/memory T cells to CNS, suppression of these T cells by carbidopa may be beneficial for PD patients, however, they may also have greater risk for infection because of immunosupression (Zhu et al., 2017).

2.2. Eicosanoids and nitric oxide in neuroinflammation

Various eicosanoids are found in CNS in neurons, astrocytes, cerebral vascular endothelial cells and in cerebrospinal fluid. They have roles in acute inflammatory responses as well as regulate cell signaling and gene transcription, therefore may take part in neurodegeneration (Phillis, Horrocks, & Farooqui, 2006). Besides, since the upregulation of nitric oxide synthase (NOS) was found in parkinsonians and the inducible form is located in several CNS cells (Knott, Stern, & Wilkin, 2000), these topics gain attention in neuroinflammation strategies in PD.

2.2.1. Eicosanoids in neuroinflammation

It is known that arachidonic acid is mainly derived from astrocytes in the brain and the neuronal arachidonic acid suppyling is provided by them (Tang, 2014). In physiological conditions, arachidonic acid metabolites (prostaglandins, leukotrienes, epoxyeicosatrienoic products) involved in synaptic function, cerebral blood flow regulation, apoptosis, angiogenesis, and gene expression. However, in PD, their activities increase as well as the function of astrocytes impairs, and these arachidonic acid metabolites take part in platelet aggregation, leukocyte chemotaxis, oxidative stress and release of pro-inflammatory cytokines that lead to neuroinflammation (Phillis et al., 2006; Tang, 2014).

Prostanoids, local regulators of neuroinflammation, are produced by cyclooxygenase (COX) pathway and widely generated by activated glial cells (Tzeng et al., 2005). There are two isoforms of COX enzyme as COX-1, localized in microglial cells, and COX-2, mainly expressed in neurons (Hunot & Hirsch, 2003; Teismann & Ferger, 2001). Inducible COX-2 encourages inflammation by way of production of prostaglandins, free radicals and excitotoxicity by enhancing of glutamate release (Teismann, Vila, et al., 2003). Contrary, Aids and collegues established that inhibiting COX-2 may worsen the inflammatory response induced by lipopolysaccharide (LPS) (Aid, Langenbach, & Bosetti, 2008). It is thought to be because of anti-inflammatory properties of COX-2 through production of cyclopentanone prostaglandins, however, these products are known to trigger apoptosis in neurons (Bartels & Leenders, 2010). Consistent with this information, Teissman et al. showed that inhibition and ablation of COX-2 significantly reduce the damaging effects of MPTP on dopaminergic neurons (Teismann, Vila, et al., 2003).

Furthermore, Zhang et al. determined that 5-lipoxygenase (LOX) is involved in rotenone-induced injury in PC12 cells, and zileuton, 5-LOX inhibitor, may diminish rotenone-induced 5-LOX activation and cell damage (Zhang et al., 2011). Similarly, Kang and collegues found that 5-LOX was overexpressed in astrocytes after the MPTP injury in mice, and MK-886, a specific inhibitor of 5-LOX activating protein, preserved the integrity of dopaminergic neurons in vitro following MPP+ treatment (K. H. Kang, Liou, Hour, Liou, & Fu, 2013). In addition to the COX and LOX pathways, the role of Epoxygenase (EPOX) in the pathogenesis of PD was also investigated. Dopamine metabolism in PD may be declined by the epoxygenation of arachidonic acid and free radical production (Thompson, Capdevila, & Strobel, 2000). Cytochrome P450 (CYP450) EPOXs that catalyze arachidonic acid conversion to biologically active compounds by a reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidative reaction, were found in brain tissues. Despite the fact that the levels of numerous CYP450 enzymes in brain are low, they are expressed comparatively high levels in astrocytes (Phillis et al., 2006).

Arachidonic acid pathway was found to be upregulated in the caudate-putamen and frontal cortex of unilaterally 6-OHDA lesioned rats. Furthermore, reported microglial activation both in SN and striatum bring to mind that neuroinflammation may be together with upregulated arachidonic acid metabolic enzymes (Lee, Bazinet, Rapoport, & Bhattacharjee, 2010). Additionally, in LPS-induced acute neuroinflammation rat model of PD, the level of arachidonic acid metabolic enzymes was increased (Rosenberger et al., 2004). These increasing effects are thought to be possibly mediated by the effect of microglial-derived cytokines on the NF-κB transcription factor of mentioned enzymes (Lee et al., 2010). Arachidonic acid is also known to take part in the regulation of synaptic transmission. Interestingly, the capability of arachidonic acid to excite the formation of soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) complex and exocytosis was shown to be regulated by α-synuclein, both in vitro and in vivo. α-synuclein acts by sequestering arachidonic acid and thus blocks the activation of SNAREs (Darios et al., 2010). Taken all this clue together, many non-steroidal anti-inflammatory drugs (NSAIDs) have been investigated to find a protective effect on neurodegenerative diseases. Epidemiological studies show conflicting data regarding the neuropretective effect of NSAIDs whereas animal studies provide beneficial activities.

2.2.2. Nitric oxide in neuroinflammation

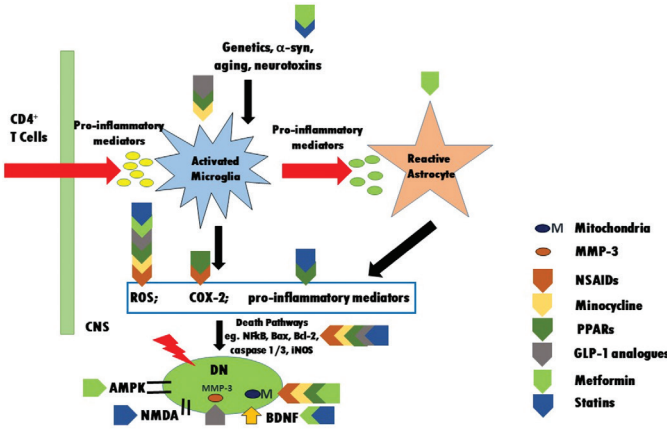
A calcium-independent readily inducible form of NO, iNOS, is detected in several types of cells including astrocytes, microglia, macrophages, and neutrophils and is upregulated consecutive exposure to TNF-a, interferon-γ, and IL-1 (Knott et al., 2000). Liberator et al., showed that iNOS provoked dopaminergic neurodegeneration in the MPTP-induced PD (Liberatore et al., 1999). In another study with LPS, Gayle et al., indicated that iNOS inhibiton did not affect LPS toxicity, however, LPS-induced levels of both TNF-α and IL-1β were increased. Therefore, it has

been suggested that neuroinflammatory provocation that cause raised cytokine levels may induce dopaminergic cell loss in a NO-independent manner and contribute to PD pathogenesis (Gayle et al., 2002). Similar findings were confirmed in 6-OHDA model of PD by Barthwal et al. (Barthwal, Srivastava, & Dikshit, 2001). Lopez and collegues reported that MPTP increased iNOS activity in SN and striatum in mice whereas potently decreased the complex I activity and mitochondrial bioenergetics. Since the presence or absence of neuronal NOS did not modify mitochondrial respiration status and the absence of iNOS did not affect the activity of the complex I in MPTP-treated mice, it was suggested that iNOS-dependent elevated NO is a major pathological hallmark of neuroinflammation in PD, but it does not contribute to mitochondrial impairment (Lopez et al., 2017). Additionally, in 6-OHDA lesioned rats, levodopa (L-DOPA) combined with 7-nitroindazole, an inhibitor of neuronal NOS, prevent animals to be dyskinetic by downregulation of inflammatory cascade involving NO. Therefore, NOS inhibitors may be a therapeutic strategy for preventing neuroinflammatory and glial components of dyskinesia in PD (Bortolanza et al., 2015).

3. Pharmacological approaches targeting neuroinflammation in PD

Possible neuroinflammatory mechanisms and drug candidates targeting these mechanisms in Parkinson's disease are summarized in Figure 1.

Figure 1. Drug candidates targeting neuroinflammatory mechanisms in Parkinson's disease



It should be noted that the indicated mechanisms targeted by the drug groups may not be applied to all drugs in the mentioned drug groups. Please check the text for detailed information.

AMPK: Adenosine monophosphate-activated protein kinase; BDNF: Brain-derived neurotrophic factor; CD4 + T: Helper T-cell; CNS: Central nervous system; COX: Cyclooxygenase; DN: Dopmainergic neuron; GLP-1: Glucagon-like peptide-1; iNOS: Inducible nitric oxide synthase; MMP-3: Matrix metalloproteinase-3; NF-κB: Nuclear factor kappa B; NMDAR: N-methyl-D-aspartate Receptor; NO: Nitric oxide; NSAIDs: Non-steroidal anti-inflammatory drugs; PPARs: Peroxisome proliferator-activated receptors; ROS: Reactive oxygen species; α-syn: Alpha-synuclein

3.1. Non-steroidal anti inflammatory drugs

Although it is not certain whether neuroinflammation plays a role as primary or secondary in the pathogenesis of PD and the neuroinflammatory pathways accelerate or delay the degenerative process, anti-inflammatory drugs are being used as potential disease modifying agents for the management of PD (AlDakheel, Kalia, & Lang, 2014). NSAIDs share pharmacological properties with steroidal anti-inflammatory drugs. Both of them inhibit eicosanoid production, however, NSAIDs mostly prevent COX activity whereas steroidal anti-inflammatory drugs inhibit phospholipase A2, thereby decrease the amount of arachidonic-acid derived prostaglandins (Hirsch & Hunot, 2009). The neuroprotective effect of NSAIDs was demonstrated experimentally in various animal models of PD and these beneficial effects were reported to be mediated through the decreasing NF-κB inhibition, ROS, and NO protection as well as COX inhibition (Esposito et al., 2007).

Grili et al., revealed for the first time that acetylsalicylic acid and salicylic acid but not indomethacin are neuroprotective against glutamate-induced neurotoxicity in vitro. This was because of inhibition of NF-κB, the shared mechanism for only acetylsalicylic acid and salicylic acid (Grilli, Pizzi, Memo, & Spano, 1996). Ferger et al., later demonstrated that the neuroprotective effect of salicylic acid in MPTP mouse model of PD was dedicated to its ROS scavenger activity rather than COX inhibition (Ferger, Teismann, Earl, Kuschinsky, & Oertel, 1999). Similarly, in an in vivo microdialysis study, aspirin showed neuroprotective effects with ROS scavenging activity but not COX-2 inhibition in MPTP or 6-OHDA-induced models of PD (Di Matteo et al., 2006). Teismann and Ferger are the who took a new approach to COX-2 inhibition on PD. They proposed that COX-2 inhibiton protects dopaminergic neurons in MPTP mice model of PD by blocking of the production of oxidant species, not by diminishing neuroinflammation (Teismann, Tieu, et al., 2003). Contrary to previous work of Teismann et al., in which rofecoxib given before MPTP provided apparent neuroprotection (Teismann, Tieu, et al., 2003); in Przybyłkowski et al., study, rofecoxib did not provide neuroprotection when administered after MPTP intoxication in mice (Przybylkowski et al., 2004). These data reveals that the timing of COX-2 inhibition is important to gain neuroprotection. However, COX-2 inhibition may not be detrimental to neurons after injury because of the production of cyclopentenone prostaglandins originated from prostaglandin D2, which are involved in regeneration process (Przybylkowski et al., 2004).

Maharaj et al., claimed the mitochondria as a new molecular target of NSAIDs. In their study, acetylsalicylic acid and acetaminophen impeded the inhibition of the electron transport chain and complex I activity and of superoxide anion production by MPP+. These findings

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suppose that mentioned NSAIDs protect mitohondria and block the generation of superoxide anion as well as scavenge hydroxyl radicals (Maharaj, Maharaj, & Daya, 2006). Besides these beneficial results, there are some unfavourable findings. For instance, PC12 cells incubated with indomethacin, ibuprofen, ketoprofen, or diclofenac but not acetylsalicylic acid and NS-398, a COX-2 selective inhibitor, showed boosted cell death induced by MPP+ (Morioka, Kumagai, Morita, Kitayama, & Dohi, 2004). The authors assumed that increased intracellular accumulation of MPP+ is the potential mechanism of cell death since these drugs suppress multidrug resistance proteins and thereby abolish the MPP+ efflux (Morioka et al., 2004).

Although NSAIDs have been shown to be successful in experimental models of PD, they have not yet been formally tested in PD and there is no started or ongoing clinical trial on this topic. Only epidemiological studies provide an insight to the relation between the use of NSAIDs and the risk of PD. In a recent meta-analysis of Gagne and Power, nonaspirin NSAIDs have been associated with reduced risk of PD (Gagne & Power, 2010). In addition, epidemiological studies in which the long-term use of NSAIDs, especially ibuprofen, reduces the risk of PD by 21%, support the therapeutic potential of these drugs in PD (Wang et al., 2015). However, there are some converse reports found that any NSAIDs or aspirin had no effect on the risk of developing PD. Although the use of non-aspirin NSAIDs have been shown to reduce the risk of PD by 13%, this was not statistically significant (Rees et al., 2011).

3.2. Minocycline

Minocycline is a second-generation semi-synthetic derivative of tetracycline. Since its high lipophilicity, it crosses the blood-brain barrier easily, and is also an inhibitor of the caspase-1/3 and iNOS which are important for apoptotic cell death (Thomas & Le, 2004; Wang et al., 2015). Minocycline was shown to protect nigrostriatal dopaminergic neurons by inhibiting microglial activation in MPTP (Wu et al., 2002) and 6-OHDA-induced PD models in mice (He, Appel, & Le, 2001) and in LPS-induced PD model in rats (Tomas-Camardiel et al., 2004). In a study with MPTP and maneb-paraquat mice models of PD, which are induce mitochondrial dysfunction and microglial activation, minocycline restored the altered expression of some mitochondrial proteins involved in neurodegeneration process especially in maneb-paraquat mice models of PD (Dixit et al., 2013). That results show that minocycline is not able to repair the inhibition of complex I by MPTP and the diminished manganese-dependent superoxide dismutase level, but its reduction of microglial activation represents the anti-inflammatory property of minocycline against maneb-paraquat-induced neurodegeneration (Dixit et al., 2013).

In addition to these beneficial effects, minocycline was also shown to increase dopaminergic neuronal cell death and to induce worsening in behavioral tests in a non-human primate model of PD (Diguet et al., 2004). This difference is thought to depend on the animals used in the experiment, on the dose, duration and route of administration of the drug used (Diguet et al., 2004). Furthermore, minocycline failed to protect of rat cerebellar granular cells' degeneration induced by malotone which causes mitochondrial dysfunction, ROS production and subsequent glutathione depletion. Malotone does not affect the mRNA expression of caspase-3, -8, and -9 as well as iNOS but it decreases the mRNA of the antiapoptotic Bcl-2 protein, however, minocycline did not abolish this reduction (Fernandez-Gomez et al., 2005). Therefore, the neuroprotection of minocycline in different models of neurodegeneration may thought to be model-selective (Fernandez-Gomez et al., 2005).

Data from 18-month phase II trial (NCT00063193) of creatine (10 g/d) and minocycline (200 mg/d) with PD participants within 5 years of diagnosis and not yet requiring symptomatic therapy revealed that creatine and minocycline did not change the response to symptomatic treatment nor increase adverse events. According to this small study, creatine and minocyline seem safe alone or in combination with antiparkinsonian agents. However, it should be noted that the tolerability of minocyline is decreased and since the sample size of the study is small, the idea that safety concerns may not show up with larger sample, and longer duration of study could not be deduced from this trial (N. N.-P. Investigators, 2008).

3.3. Peroxisome proliferator-activated receptor agonists

Peroxisome proliferator-activated receptors (PPARs) are ligand-induced nuclear hormone receptors found highestly adipose tissue and immune cells, thus have functions in glucose and lipid metabolism, and inflammation. The expression of them in basal ganglia regions as well as in neurons and in microglia in the CNS makes these receptors important in neurodegenerative diseases (Carta et al., 2011). PPARs are promising therapeutic target for neurodegenerative diseases since they involve in the step back of major pathogenetic mechanisms underlie these diseases such as mitochondrial and proteasomal dysfunction, oxidative stress, and neuroinflammation (Agarwal, Yadav, & Chaturvedi, 2017). Many different studies that determine the effect of PPARs on neuroprotection thus far are made.

Pioglitazone is a PPAR-γ agonist that developed for the treatment of type II diabetes mellitus. It is known to increase the oxygen utilization, mitochondrial DNA contents and enhances mitochondrial biogenesis (Agarwal et al., 2017). Pioglitazone was shown to be neuroprotective by favour of anti-inflammatory actions in MPTP rat and rhesus monkey models and in rotenone rat model of PD (Barbiero et al., 2014; Swanson et al., 2011; Ulusoy et al., 2011). Recently, pioglitazone has been tested to identify the effects on neuroinflammation, cell proliferation, and hippocampal neurogenesis in the 6-OHDA model of PD (Bonato, Bassani, Milani, Vital, & de Oliveira, 2018). On the contrary to previous reports, pioglitazone had no effect on intranigral 6-OHDA infusions-induced dopamine cell loss in the SN or ventral tegmental area in rats as similar in the work of Laloux et al. (Laloux, Petrault, Lecointe, Devos, & Bordet, 2012). In a new mouse model of PD in which mitochondrial complex IV is defected and simulates the

late stages of the disease, chronic pioglitazone treatment improved motor phenotypes eventhough there is no enhancement in mitochondrial functions nor the increase of dopaminergic neurons (Pinto et al., 2016). In a 44-week, phase II, multicentre, double-blind, randomised trial of pioglitazone (NCT01280123), early-diagnosed 210 Parkinson's patients who have an ongoing treatment with 1 mg/day rasagiline or 10 mg/day selegiline were randomly selected (1:1:1) to pioglitazone (15 or 45 mg/day) or placebo. After the evaluating Unified Parkinson's Disease Rating Scale (UPDRS) scores, it was found that pioglitazone at these doses seemed not effective to modify the disease progression and further and larger trials of pioglitazone in Parkinson's patients were not recommended (N. E. T. i. P. D. F.-Z. Investigators, 2015). In this context, Simon and collegues analyzed peripheral biomarkers of inflammation and oxidative DNA damage and found that pioglitazone did not significantly change the biomarker levels. Therefore, it is more rational to focus on other agents that have more potential to modify the disease (Simon et al., 2015).

In a study with rosiglitazone, another PPAR-γ agonist, it was shown that mitochondrial dysfunction and increase the production of free radical and autophagy by the complex I inhibitor rotenone were reversed by pre-treatment of rosiglitazone in human differentiated SHSY-5Y cells and PINK1 knockdown cells, (Corona, de Souza, & Duchen, 2014). In mice model of PD, induced by MPTP/probenecid, rosiglitazone treatment reversed PPAR-γ overexpression which have already seen in microglia without affecting tyrosine hydroxylase+ neurons. Furthermore, rosiglitazone was found to inhibit the highly activated morphology of microglia and revert the increased levels of TNF-α. Therefore, it seems that microglia and neuroinflammation are the key factors that thiazolidinediones-induced neuroprotection is focused on in PD (Carta et al., 2011). Besides the pioglitazone and rosiglitazone, a novel thiobarbituric-like compound MDG548 which is a non-thiazolidinedione compound acting as a functional PPAR-γ agonist with higher and selective affinity as compared to thiazolidinediones, have been shown to be neuroprotective both in vitro and in MPTP-treated mice. These neuroprotective effects are believed to underlie the reduction of neuroinflammation by MDG548 (Lecca et al., 2015). Although there are several experimental PPAR-γ agonists that were found neuroprotective by different mechanisms such as reducing p38 mitogen-activated protein kinase, NF-kB activation, COX-2 expression, ROS production and by anti-inflammatory properties, any clinical trial have not yet been started to confirm these mentioned effects in humans (for further detail (Agarwal et al., 2017)).

3.4. GLP-1 analogues

Since PD has been found to be related with a higher incidence rate in type II diabetes mellitus patients, it is assumed that there are several common pathological mechanisms shared by two diseases such as insulin dysregulation. Therefore, it reveals the importance of the homeostasis of gut-brain axis for the health of both central and peripheral nervous system (D. S. Kim et al., 2017). Glucagon-like peptide-1 (GLP-1) is one of the endogen incretin hormones that regulates the insulin release. The effects of GLP-1 is mediated by the G-protein coupled GLP-1 receptor which increases intracellular cyclic adenosine monophosphate then activates protein kinase A and phosphoinositide 3-kinase that lead to phosphorylation of several downstream signaling pathways. These receptors are mostly found in pancreas and periphery, however, are also expressed in CNS, particularly in the frontal cortex, hypothalamus, thalamus, hippocampus, cerebellum and SN (D. Athauda & Foltynie, 2017). In brain, they involve in neurogenesis, anti-inflammation, synaptic plasticity, inhibiting apoptosis and enhancing mitochondrial function (D. S. Kim et al., 2017).

Exenatide, a synthetic derivative of exendin (EX-4), is an agonist of the GLP-1 hormone which has important roles in insulin and glucose homeostasis (Aviles-Olmos et al., 2013). EX-4 which readily crosses the blood brain barrier is currently used in type-II diabetes, therefore the clinical efficacy of it in PD patients should be immediately assessed (Harkavyi et al., 2008). EX-4 was shown to induce neurite development, support neuronal differentiation, and protect neuronal cells from degeneration through neurotrophic effects, by inhibiting microglial activation and matrix metalloproteinase-3 expression both in vitro and in vivo (Harkavyi et al., 2008; S. Kim, Moon, & Park, 2009; Li et al., 2009; Perry, Haughey, Mattson, Egan, & Greig, 2002; Perry, Lahiri, et al., 2002). In a PD rat model inducing by noradrenergic lesions with N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine and dopaminergic lesions with 6-OHDA, early EX-4 treatment provided behavioural improvement and repait dopamine and noradrenaline levels as well as tyrosine hydroxylase+ cell counts (Rampersaud et al., 2012). Additionally, the finding that EX-4 potentiated the effects of L-DOPA in leisoned rats with 6-OHDA and reducted the levodopa-induced dyskinesias indicates that lower doses of L-DOPA might be required in the clinic with the co-administraion of EX-4 and less side-effects might occur (Abuirmeileh et al., 2012). Data from a small, open-label, randomised controlled trial (NCT01174810) with 48 PD patients revealed that exenatide which is given 10ug twice a day for 12 months followed by a 12-month wash-out period provided several advantages on both motor and non-motor measures on the Movement Disorder Society-UPDRS scale and on the Mattis Dementia Rating scale (Aviles-Olmos et al., 2014). Based on this study, in a recently announced a single-centre, randomised, double-blind, placebo-controlled clinical trial (NCT01971242) in PD patients on a treatment regimen already, who were given exenatide (2 mg/week, sc) or placebo for 48 weeks followed by a 12-week wash-out period, significant improvement of motor symptoms has been detected by using Movement Disorder Society-UPDRS motor subscale (Dilan Athauda et al.).

Besides the exenatide, liraglutide and lixisenatide are newer GLP-1 mimetics with longer half-life. They are shown to be neuroprotective in MPTP mouse model of PD by improving motor impairment and by reserving tyrosine hydroxylase levels in the SN and basal ganglia and by preventing apoptosis (W. Liu et al., 2015). However, liraglutide, long-acting GLP-1 receptor agonist, had no

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neurprotective effects in 6-OHDA-injured rats (Hansen et al., 2016). It seems that there are conflicting results with the data from another recent study of Badawi et al. In their study, sitagliptin, a dipeptidyl peptidase-4 inhibitor, which inactivates GLP-1, and liraglutide, GLP-1 mimetic, inhibited the inflammatory-apoptotic degenerative process induced by rotenone in rats. These GLP-1 agonists improved motor functions, reversed nigral neuronal loss and increase striatal dopamine, nigral cell-derived neurotrophic factor and tyrosine hydroxylase+ cells besides the decrease of pro-apoptotic protein Bax and increase of anti-apoptotic protein Bcl-2 (Badawi, Abd El Fattah, Zaki, & El Sayed, 2017). Saxagliptin, another the the dipeptidyl peptidase-4 inhibitor showed neuroprotective effects in Alzheimer's disease, therefore it was assumed as a promising agent for PD treatment. In rotenone rat model of PD, saxagliptin significantly enhanced motor behaviour and protect tyrosine hydroxylase immunoreactivity in SN via antioxidant, anti-inflammatory, antiapoptotic, neuroprotective and neurorestorative mechanisms (Nassar, Al-Shorbagy, Arab, & Abdallah, 2015). There is an ongoing, single center, double-blind, placebo-controlled Phase II clinical trial with 57 idiopathic PD patients on safety and efficacy of liraglutide in PD (NCT02953665). Any different clinical study on other mentioned analogues have not been started yet.

3.5. Metformin

Metformin is an orally active biguanide that commonly used in type II diabetes mellitus and is known to have anti-inflammatory properties through the activation of adenosine monophosphate-activated protein kinase (AMPK), which is an essential cellular nutrient and energy sensor that is activated with collapsing energy supply. When activated, AMPK triggers catabolic processes and stops the energy-consuming steps, thereby, it may support energy conservation and restoration (Hang, Thundyil, & Lim, 2015; Ismaiel et al., 2016). It is known that in PD, the activation of AMPK may lead to both improve or provoke neurodegeneration (Choi, Park, & Jeong, 2010). There are many conflicting results that one shows that AMPK activation may avoid neuronal cell loss in vitro/in vivo models of PD with MPP+/MPTP (Choi et al., 2010) while the other one shows that AMPK mediates the atrophy of dopaminergic neurons in 6-OHDA mice model of PD and that metformin steps up the neurodegeneration in those mice (T. W. Kim et al., 2013). Interestingly, a cohort study in 2012 (n=800,000) showed that the incidence of PD was almost twice as high as in the Taiwanese population with type II diabetes mellitus, and that this risk increased with the use of sulfonylureas and decreased with the use of metformin as co-therapy, implying the beneficial effect of AMPK activation by metformin in PD (Wahlqvist et al., 2012). However, a recent retrospective cohort study has been claimed that long-term metformin exposure in patients with type II diabetes mellitus may cause to the development of neurodegenerative diseases such as dementia and PD (Kuan, Huang, Lin, Hu, & Kao, 2017). Additionally, the longer exposure and the higher dosage of metformin lead to the higher risk of the dementia and PD (Kuan et al., 2017). Escalation of intracellular and extracellular β-amyloid peptides through increasing both β-amyloid precursor protein expression and transcriptional upregulation of beta-secretase; metabolic stress and threby dendritic spine loss in hippocampal cells through metformin-induced AMPK activation; and vitamin B12 deficiency, a vital risk factor for Alzheimer's disease and PD, through the disruption of absorption and changes in intestinal motility by metformin might be the mechanisms underlying these results (Kuan et al., 2017).

In MPTP-induced mice models of PD, metformin was shown to be neuroprotective by means of reducing oxidative stress, increasing brain-derived neurotrophic factor levels, diminishing the activation of astroglia, decreasing α-synuclein phosphorylation via by phosphatase 2A, a phosphatase related to α-synuclein dephosphorylation and by activating cell survival signal pathways (Katila et al., 2017; Patil, Jain, Ghumatkar, Tambe, & Sathaye, 2014). In human cell models, overexpression of the regulator protein of energy metabolism and mitochondrial biogenesis, TNF receptor associated protein 1, found to be neuroprotective and TNF receptor associated protein 1 mutation was associated with PD because of poor control of energy metabolism. Fitzgeral et al., revealed that metformin improves mitochondrial function against TNF receptor associated protein 1 mutation-associated changes in PD (Fitzgerald et al., 2017). However, a recent study has been suggested that although metformin reduces microglial activation at both cellular and molecular levels and serves as anti-inflammatory agent, it fails to protect dopaminergic neurons, even worsens MPTP-induced dopaminergic damage (Ismaiel et al., 2016). The discrepancy of the results is attributed to different doses of both metformin and neurotoxin used in experiments. For instance, Patil et al., (Patil et al., 2014) used metformin in a dose more than three-fold higher than Ismaiel et al., while they used MPTP in lower dose, which probably cause slow onset of the MPTP damage. It is also known that MPTP and metformin compete for the same transporter (organic cation transporter 1) to cross the blood-brain barrier, therefore relatively high concentrations of metformin would replace with MPTP on the transporter, leading to avoid harmful effects of MPP+ on the dopaminergic neurons. The delayed onset of MPTP-induced PD is also an issue that might allow metformin to provide neuroprotection (Ismaiel et al., 2016). Further experimental and clinical trials are required to provide more accurate information about metformin protection in neurodegenerative diseases.

3.6. Statins

It is known that the statins, which are 5-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors and are a class of lipid-lowering medications, also have anti-inflammatory effects by reducing the TNF-α, NO and superoxide produced by microglia and by scavenging free radicals (AlDakheel et al., 2014). A small, retrospective case-control study (Huang et al., 2007) which claimed that lower low-density lipoprotein-cholesterol may be associated with higher incidence of PD and that statins decreased the risk of PD was further confirmed by a

large, prospective, population-based cohort study (de Lau, Koudstaal, Hofman, & Breteler, 2006). This result was assumed to be because either a role of low-density lipoprotein-cholesterol in disease pathogenesis or increased levels of coenzyme Q10 which inversely correlates with serum cholesterol and is a potent antioxidant as well (de Lau, Stricker, & Breteler, 2007). The data from US Veterans Affairs database, simvastatin was found to be related with a significant decrease of both dementia and PD incident whereas atorvastatin was associated with a modest reduction with only a trend towards significance and was insignificant when other comorbid diseases are included, and lovastatin was not associated with any reduction (Wolozin et al., 2007). In a retrospective study with statins (pravastatin, simvastatin, atorvastatin, fluvastatin and rosuvastatin) although UPDRS progression was similar, the required L-DOPA-equivalent daily dose over two years was significantly lower in the statin used (+24 mg) group than in controls, probably because statins activate the PPAR-α, that controls inflammation, apoptosis and oxidative stress (Mutez et al., 2009).

There were still conflicting results between statin use and PD risk. For instance, in a new meta-analyses of Bai et al. it has been reported that the use of statin is associated with reduced the risk of PD (Bai et al., 2016). However, more recently, Bykov and collegues have claimed that statins provide a neuroprotective effect if there is no adjustment for cholesterol, otherwise, no protection has been observed (Bykov, Yoshida, Weisskopf, & Gagne, 2017). In a retrospective case-control analysis (n= 2322) of Liu and collegues, the use of lipophilic statins was associated with higher risk of PD. In addition, the statin-PD association was strongest in the initial use of statins (< 2.5 years) suggesting that statins may have a facilitating effect in PD. Most data that obtained different epidemiological studies not factored hyperlipidemia as a confound. It drew attention that the protective effects of statins ceased when hyperlipidemia considered (G. Liu et al., 2017).

Besides the mentioned clinical data, preclinical evidence is also reflected the role of statins in neuroprotection. For example, in MPTP mice model of PD simvastatin weakened nigral activation of NF-kB, prevented nigral expression of pro-inflammatory substances, and overcomed nigral activation (Ghosh et al., 2009). However, in another study with MPTP, simvastatin prevented the neurotoxicity that is induced by LPS but not by MPTP in vivo. This data confirms that simvastatin may exert neuroprotective effects by anti-inflammatory properties since LPS is an inflammatory model of PD whereas MPTP directly kills the neurons (Santiago, Hernandez-Romero, Machado, & Cano, 2009). In another LPS model of PD, simvastatin was found to promoted neuronal repair and regeneration and inhibited oxidative stress via decreasing expression of iNOS and increasing brain-derived neurotrophic factor (Tan et al., 2016). In 6-OHDA models of PD, simvastatin provided neuroprotection partly via N-methyl-D-aspartate receptor (NMDAR) mediated anti-inflammatory mechanisms as reducing pro-inflammatory cytokines (Yan, Sun, Huang, Fu, & Du, 2014; Yan et al., 2011). This NMDAR-modulatory effect have also been concerned as a new approach to alleviate anxiety-like activity in PD, because it anxiolytic-like activity in behavioral tests (Yan et al., 2011). In the same model atorvastatin as well as simvastatin restored locomotor activity, rota-rod performence, oxidative defense and mitochondrial complex function, also decreased the inflammatory cytokine levels as compared to naive animals (Kumar, Sharma, Gupta, Kalonia, & Mishra, 2012).

Lovastatin, pravastatin as well as simvastatin was shown to reduce the aggregated α-syn levels in vitro. This was followed by a redistribution of α-syn in caveolar fractions, a decrease in oxidized α-syn, and enhancement of neurite outgrowth. Conversely, α-syn aggregation was increased and neurite outgrowth was decreased when the media was supplied with cholesterol (Bar-On et al., 2008). In two different transgenic mice models of PD, that neuronally overexpress human α-syn, lovastatin caused a significant reduction of neuronal α-syn aggregates. Lovastatin, which itself can cross blood brain barrier, is an antioxidant as well, and oxidative stress produces nitrative radicals that might modify α-syn post-transcriptionally, however further studies should be performed to be sure the exact mechanism of this protection (Koob et al., 2010). Recently, in vitro model of rotenone-induced toxicity showed that rosuvastatin increased the levels of mechanistic target of rapamycin-independent/upstream autophagy markers, including Beclin-1 and AMPK which are suppressed by rotenone, thereby provide neuroprotection by enhancing autophagy, that may be a new therapeutic strategy for the managament of PD (S. Y. Kang et al., 2017).

A phase II study (NCT02787590) which is named PD STAT (Simvastatin as a Neuroprotective Treatment for Moderate Parkinson's Disease) investigating the neuroprotective effect of simvastatin in moderate PD started in 2016. Randomly allocated participants will take simvastatin (orally) for 24 months and the results of questionnaires and motor tests will be compared with control group in which participants will take placebo. Estimated completion time of the study is 2020. Another phase II, single-center, randomized, double-blind, placebo-controlled, parallel-group study with losuvastatin in early stage PD patients is now ongoing (NCT03242499). Participants will randomize to a 48-week double-blind treatment period of lovastatin 80mg/day or placebo. Movement Disorder Society-UPDRS total scores, the timing and the dose of added anti-parkinsonism medication during the treatment period, the changes of 18F-dihydroxyphenylalanine positron emission tomography (18F-DOPA PET) uptake and Mini-Mental State Examination scores, and global impression scale of patients will be compared.

4. Conclusion

A growing body of evidence suggest that the cure of PD would be possible with the prevention of degeneration of dopaminergic neurons in SN. Although there are many drug targets and/or candidates in preclinical studies, currently there are no approved drugs as neuroprotective. Animal models of the disease and some clinical trials show that neuroinflammation is potential key

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component of the disease initiatiton or/and progression. Here, we summarized the neuroinflammation modifying approaches and related mechanisms in PD. While some positive results have been obtained from clinical studies conducted with a large number of drug candidates with different mechanisms of action, it is not always possible to translate from the well-recieved experimental data into the phase studies. Further efforts are required to identify the whole contribution of neuroinflammation components in PD and should pave the way for rational drug targeting.

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