



# Neuroinflammation in Parkinson's Disease – Putative Pathomechanisms and Targets for Disease-Modification

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Parkinson's disease (PD) is a progressive and debilitating chronic disease that affects more than six million people worldwide, with rising prevalence. The hallmarks of PD are motor deficits, the spreading of pathological  $\alpha$ -synuclein clusters in the central nervous system, and neuroinflammatory processes. PD is treated symptomatically, as no causally-acting drug or procedure has been successfully established for clinical use. Various pathways contributing to dopaminergic neuron loss in PD have been investigated and described to interact with the innate and adaptive immune system. We discuss the possible contribution of interconnected pathways related to the immune response, focusing on the pathophysiology and neurodegeneration of PD. In addition, we provide an overview of clinical trials targeting neuroinflammation in PD.

**Keywords:** Parkinson's disease, neuroinflammation, T cells, microglia, neurodegeneration, animal models, inflammatory cascades

## 1 INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD) (1–4). Motor symptoms such as bradykinesia, rigidity, resting tremor, and postural instability (5, 6) are hallmarks of PD and essential for staging. PD patients also exhibit a wide variety of non-motor symptoms, ranging from anosmia, rapid eye movement (REM) sleep disorders, and constipation to severe psychiatric symptoms such as dementia (6). Some of these non-motor symptoms are observed long before motor counterparts occur and are therefore essential to early PD diagnosis (7). From the defined histological description, a staging model arose in which progression of PD symptoms can be matched with intracellular deposits of pathological  $\alpha$ -synuclein aggregates (p $\alpha$ SYN) or Lewy pathology (LP) of the corresponding brain areas (8–11). However, LP is also observed in the brains of older patients with no PD symptoms during their lifetime, indicating that LP is not specific as a standalone for PD diagnosis (10, 12). Moreover, it remains unclear why p $\alpha$ SYN occurs, why p $\alpha$ SYN spreads from cell to cell (10, 13–16), and how cell death is mediated by p $\alpha$ SYN (17). Since  $\alpha$ -synuclein ( $\alpha$ SYN) has been described as a critical mediator of inflammation and immune responses, and is released from inflamed neurons,  $\alpha$ SYN may trigger a self-amplifying proinflammatory response (18). Intriguingly, neuroinflammation has emerged as a key aspect in PD (19–22) – but the extent to which neuroinflammation contributes to the development and maintenance of PD is controversial. Hence, knowledge transfer from neuroinflammatory

diseases, where the concept of immune system-induced neuronal cell damage is established, could help to elucidate the still-obscure role of the immune system in PD.

Immunomodulatory therapies are established as effective treatments in 'classical' inflammatory neurological diseases, such as multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), or myasthenia gravis (MG) (23–27). Although the pathophysiology differs regarding the antigen in NMOSD and MG, common therapeutic strategies are implemented (28). In both entities, antibodies are pathophysiologically relevant and inhibition of the complement system has proven beneficial (29, 30). This supports the idea that similar inflammatory processes can be addressed across different neuroinflammatory diseases.

Various concepts have been tested as a causal treatment for PD, including vaccination against  $\alpha$ SYN (31, 32). However, none have yet proven successful and traditional treatment of PD is still symptomatic and largely based on dopaminergic medication (33–35). To determine the relevance of neuroinflammation in PD pathogenesis, large-scale clinical observational studies are essential to generate appropriate hypotheses, which can be subsequently tested in animal models. In our review, we discuss the evidence for neuroinflammation in PD and potential future targets. We further illustrate immunological pathways linked to neuroinflammation and dopaminergic neurodegeneration.

## 2 PATHOMECHANISMS OF NEUROINFLAMMATION IN PD PATIENTS

The pathophysiologic role of the immune system in PD is still enigmatic. Neuroinflammation was proposed by James Parkinson himself in the initial description of PD (1). There is also early literature discussing PD as an 'autoimmune disease' (36). Yet interest in the topic was only rekindled in 1988, when microglia activation was described in brain autopsies of PD and AD patients (21). Since then, evidence has accumulated that neuroinflammation is likely to play a critical role in PD (36–38). Significant elevation of inflammatory cytokines in the blood and cerebrospinal fluid (CSF) of PD patients has now been confirmed in a meta-analysis over 25 clinical studies (39). Increased expression of NLRP3 and caspase-1 genes in peripheral blood mononuclear cells (PBMC) and elevated protein levels of NLRP3, caspase-1, and IL-1B in the blood plasma were found to correlate with PD severity (40), further supporting the perception of PD as a chronic systemic inflammatory disease. Evidence suggests that both innate and adaptive immune responses are involved in PD progression (41–44).

### 2.1 Innate Immune Response

Microglia are permanently in contact with astrocytes, neurons, and endothelial cells, constantly monitoring surrounding tissue for an ongoing infection or trauma *via* thin processes (45). In response to injury or infection, resting microglia undergo morphological alterations, change their transcriptional activity, and present antigens *via* the major histocompatibility complexes (MHC)-I and -II (46–48). Unlike MHC-I, which is constitutively

expressed on all nucleated cells and platelets (49–52), MHC-II is specifically expressed on antigen-presenting cells such as microglia, astrocytes, monocytes, macrophages, dendritic cells, and granulocytes, and can be induced upon activation.

As brain-resident innate immune cells, microglia are typically the first responders to altered homeostasis within the CNS. Microglia activation increases the amount of nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF $\kappa$ B) and NLR family pyrin domain-containing 3 (NLRP3), with subsequent upregulation of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase and cytokines such as interleukin-1 beta (IL-1B) and tumor necrosis factor alpha (TNF) (53, 54). Phagocytic activity and MHC-II expression are also enhanced (55, 56). An increase in activated microglia has been observed in both PD patients and healthy older people, indicating that various triggers might induce a proinflammatory shift with age (21, 57). Compared to age-matched controls, PD patients exhibited significantly elevated levels of proinflammatory cytokines such as IL-1B, IL-6, and TNF in CSF and blood (39, 58). Furthermore, ( $^{11}$ C)(R)-PK11195)-based positron emission tomography (PET) has revealed a higher density of activated microglia in the midbrain and putamen of early PD patients (59, 60), which correlated with decreased activity of dopamine transporter ligands ( $^{11}$ C) CFT). Similar results were described in patients suffering from a REM sleep behavior disorder (60, 61). While the presence of chronic inflammatory processes in PD is now widely accepted, the underlying reason for neuroinflammation is still unclear. Due to its function as a damage-associated molecular pattern (DAMP) (53, 62, 63), p $\alpha$ SYN might trigger and maintain a proinflammatory shift of the immune system. In addition, DAMPs may be released from dying or damaged cells. Well-known DAMPs triggering an innate immune response upon interaction with pattern recognition receptors (PRRs) are IL-1 $\alpha$  or mitochondrial reactive oxygen species (mROS), which activate NLRP3. Consecutive NLRP3 activation leads to increased IL-1B synthesis as a trigger for further innate immune responses (64). Initial microglia activation in PD (21, 65) may therefore result from PRR-mediated responses to DAMPs.

In addition to DAMPs, pathogen-associated molecular patterns such as viral RNA or the bacterial cell wall component lipopolysaccharide (LPS) may also maintain neuroinflammation. While a correlation between viral infection and PD has not strictly been established, preceding infections might still modulate the risk for developing PD (66). For example, there is evidence for toxin-related PD, which implies that toxins released by infectious agents might also be responsible for some cases of 'sporadic' PD. Other toxins such as the pesticide rotenone have neurotoxic and neuroinflammatory effects that may kill dopaminergic cells and thereby cause PD in people exposed to higher concentrations (67).

Possible links between PD and infection have become even more topical with the still-ongoing worldwide COVID-19 pandemic. While there is very little consolidated knowledge regarding possible interactions between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and PD, there are some interesting observations on pathogenic coronaviruses and neuroinflammation or, more specifically,

PD. Antibodies against coronavirus antigens have been found in the CSF of PD patients (68). In addition, intranasal infection of hACE2 transgenic mice with SARS-CoV-1 caused severe CNS infections that spread from the olfactory bulb to the basal ganglia and midbrain within approximately four days (69). Considering that COVID-19 patients often experience anosmia, SARS-CoV-2 is also likely to reach the CNS *via* the olfactory bulb. Disconcertingly, *in vitro* assays have shown that the nucleocapsid(N)-protein of SARS-CoV-2 accelerates p $\alpha$ Syn-aggregation by a factor of 10 (70). Thus, it is concerning that COVID-19-related inflammation may trigger or accelerate PD in patients at risk. Yet to date, there are only a few case studies describing the development of PD after SARS-CoV-2 infection (71, 72). Whether infection with SARS-CoV-2 impacts the development of PD remains to be explored.

## 2.2 Adaptive Immune Response in PD: T Cells Friends and Foes

Neuroinflammation in PD is not confined to the innate immune system; it also involves adaptive immune responses. Several findings indicate that various T cell subpopulations may contribute to PD pathophysiology (73).

Neuroinflammation within the substantia nigra (SN) is well-described in PD. Significant infiltration of both CD4<sup>+</sup> and CD8<sup>+</sup> T cells into the SN of PD patients has been described (42), particularly elevated levels of CD8<sup>+</sup> T cells (74, 75). It is possible that CD8<sup>+</sup> T cells have an important role in early PD, even before p $\alpha$ SYN can be detected in the SN, as relevant infiltration into the SN has been observed in very early PD that subsides with disease progression (74). Altered counts of CD4<sup>+</sup> T cell populations in the blood of PD patients have also been reported, but remain controversial. Many studies describe a decrease in the overall CD4<sup>+</sup> T cell population in PD patients (44, 76–78). However, both elevated (76) and reduced T<sub>reg</sub> cell counts (79) were found in the blood of PD patients, although the studies used a relatively non-specific marker (CD4<sup>+</sup>CD25<sup>+</sup>) to identify T<sub>reg</sub> cells. Increased numbers of CD4<sup>+</sup>FoxP3<sup>+</sup> T<sub>reg</sub> have been observed in the blood of PD (aged 46–80 years) and AD (62–82 years)

patients and healthy older people (51–87 years) compared to healthy young controls (23–40 years) (80). An increase in T<sub>reg</sub> cell activity with age was also seen, which was significantly more pronounced in PD and AD patients compared to young controls (80). In contrast, decreased levels of CD4<sup>+</sup>CD25<sup>high</sup>CD127<sup>low</sup> T<sub>reg</sub> cells (44, 81) and reduced suppressive activity of T<sub>reg</sub> cells has also been found in PD patients (77). Furthermore, peripherally-reduced T<sub>reg</sub> cells and increased Th1 cell counts were found to correlate with the severity of motor dysfunction (assessed by Unified Parkinson's Disease Rating Scale III [UPDRS III]) (44, 81). In addition, decreased Th2 cell numbers and a relative increase in Th1 cells were seen in PD patients (44). Despite these discrepancies, most studies highlight an increased peripheral immune response in PD, with a reduced amount of T<sub>reg</sub> cells (CD4<sup>+</sup>CD25<sup>high</sup>CD127<sup>low</sup>) (44, 81) (Table 1).

This population and activity shifts of T cells, along with an increase in HLA-DR positive antigen-presenting microglia in PD patients (82), support the idea that CD4<sup>+</sup> T cells might contribute to neurodegeneration in PD. Studies on the role of Th17 cells in PD have generally confirmed this concept. Addition of IL-17 to autologous cocultures between T cells and pluripotent stem cells (iPSC)-derived mid brain neurons (MBN) from PD patients also induced NF $\kappa$ B-dependent cell death. iPSC-derived MBN from PD patients further showed higher expression of IL-17 receptors, together with enhanced susceptibility towards death induction by recombinant IL-17 or autologous Th17 cells (73). Interestingly, Th17 cells are increased in PD patients, which is consistent with the results of previous studies (81, 83, 84). However, one study in PD patients reported a decrease in the Th17 cell count, along with unchanged levels of IL-17 (44). Based on these studies, Th17 cells and IL-17 are likely to favor the progression of PD, but their distinct role remains unresolved (85, 86). Consequently, a comparison of different analytical approaches might be needed to rule out possible methodological issues.

In addition to flow cytometric analyses, gene expression analyses and genome-wide association studies that investigate alterations in immune response pathways are playing an

**TABLE 1** | Overview of human and animal studies on T cells with special regard to T<sub>reg</sub> cells.

Publication	derived from	origin	Major finding (referring to PD)	T <sub>reg</sub> identification (total amount)
(42), 2009	brain tissue	human, mouse	sign. infiltration of CD4 <sup>+</sup> and CD8 <sup>+</sup> T cells in the SN	-
(74), 2020	brain tissue	human	sign. infiltration of CD8 <sup>+</sup> T cells in early stages of PD	-
(75), 2022	brain tissue, spleen	human (brain), mouse (brain, spleen, lymph nodes)	sign. infiltration of CD8 <sup>+</sup> T cells in the SN of humans and of CD4 <sup>+</sup> and CD8 <sup>+</sup> T cells in the SN of AAV1/2-A53T- $\alpha$ Syn mice	-
(76), 2001	mesenteric lymph nodes	rat	no changes (6-OHDA); increase of CD4 <sup>+</sup> CD25 <sup>+</sup> T cells (MPTP)	CD4 <sup>+</sup> CD25 <sup>+</sup>
(44), 2018	blood	human	decrease of CD4 <sup>+</sup> T cells, Decrease of Th2, Th17 and T <sub>reg</sub> cells	CD4 <sup>+</sup> CD25 <sup>high</sup> CD127 <sup>low</sup>
(76), 2001	blood	human	total CD4 <sup>+</sup> T cells decreased, CD4 <sup>+</sup> CD25 <sup>+</sup> T cells increased	CD4 <sup>+</sup> CD25 <sup>+</sup>
(77), 2012	blood	human	total CD4 <sup>+</sup> T cells decreased. suppressive activity of T <sub>reg</sub> impaired	CD4 <sup>+</sup> CD25 <sup>high</sup> CD127 <sup>low</sup>
(79), 2005	blood	human	decrease of T <sub>reg</sub>	CD4 <sup>+</sup> CD25 <sup>+</sup>
(80), 2007	blood	human	no change of CD4 <sup>+</sup> CD25 <sup>+</sup> T cells but increase in CD4 <sup>+</sup> FoxP3 <sup>+</sup> T cells	CD4 <sup>+</sup> CD25 <sup>high</sup> CD4 <sup>+</sup> FoxP3 <sup>+</sup>
(81), 2015	blood	human	decrease of CD4 <sup>+</sup> , T <sub>reg</sub> T cells Increase of Th1, Th2, Th17 T cells	CD4 <sup>+</sup> CD25 <sup>high</sup> CD127 <sup>low</sup>

increasing role in PD research. Expression quantitative trait loci (eQTLs) are obtained by analyzing the genome and transcriptome of patients with correlating alleles and the expression level of transcripts. Based on CD4<sup>+</sup> T cells and monocytes from a multi-ethnic cohort of 461 healthy individuals, susceptibility alleles for MS, rheumatoid arthritis, type 1 diabetes, and PD were found to be overrepresented in CD4<sup>+</sup> T cells, while disease- and trait-associated cis-eQTLs associated with AD and PD were primarily overrepresented in monocytes (87). Further evidence for the relevance of the immune system in PD pathogenesis comes from the association of PD with an immune haplotype, including the DRB5\*01 and DRB1\*15:01 alleles, and from a non-coding polymorphism in the region that might increase MHC-II expression (88). Finally, a very recent study stratified PD patients by their T cell responsiveness to  $\alpha$ -SYN as a proxy for an ongoing inflammatory autoimmune response (89). Gene expression analysis in peripheral memory T cells then revealed a clear PD-specific gene signature with transcriptomic markers for inflammation, oxidative stress, phosphorylation, autophagy of mitochondria, cholesterol metabolism, and chemokine signaling via CX3CR1, CCR5, and CCR1.

### 2.3 Adaptive Immune Response in PD: B Cells and Humoral Immunity

While T cells are the more prevalent adaptive immune cells in CSF (90), B and T cell immunity are closely intertwined (91). Although immunohistochemical analyses have found B cell-rich tertiary lymphoid structures in most brains from patients with MS, but not in the two PD patients investigated (92), there is ample evidence for the involvement of B cells, antibodies, and humoral immune effector mechanisms in PD (93–95). In a postmortem study of 13 patients with idiopathic PD and three with genetic PD (compared with 12 controls), all PD patients showed IgG (mostly IgG1) but no IgM binding to dopaminergic neurons, while Lewy bodies were strongly immunolabelled with IgG (94). Nearby activated microglia expressed the high-affinity activating IgG receptor Fc $\gamma$ RI, which implies a significant role for antibody-dependent cell-mediated cytotoxicity. The inhibitory IgG receptor Fc $\gamma$ R2 was absent in all cases. Subsequent studies on B cell-related adaptive immune responses in PD support the involvement of B cells and humoral immune effector mechanisms (96–98). Remarkably, some patient sera also contained antibodies capable of neutralizing p $\alpha$ SYN ‘seeding’ (forming of  $\alpha$ SYN aggregates) *in vitro* (99). Elevated levels of serum antibodies against  $\alpha$ SYN have also been reported in a comparison of sera from PD patients with AD patients and controls (100). Of note, B cell numbers were found to be reduced in PD patients (96, 101), along with an increase in IgA levels (102) that correlated with non-motor symptoms (96). Moreover, cytokine expression of B cells was altered in PD (96). Cytokine-dependent interactions between B cells and Th1 and Th17 cells (103) imply that B cells may also modulate proinflammatory Th17 cells in PD patients (73). In addition, there are relevant interactions between the humoral immune response and the complement system, as described in a comprehensive review (104).

Given the paucity of studies focusing on the distinct function of B cells in PD or other neurodegenerative diseases (103, 105), a more profound understanding of B cell function might reveal new opportunities for disease modification. Again, the targeted transfer of knowledge from ‘classical’ neuroinflammatory disease would be useful (103).

### 2.4 Anti-Inflammatory Disease Modification

Since proinflammatory changes have been consistently observed in PD, several studies analyzed whether suppressing inflammation might modify the disease course of PD. A population-based, case-control study found that patients receiving immunosuppressive therapy had a decreased risk of developing PD (106). Interestingly, the greatest risk reduction was conveyed by drugs affecting T cells such as the inosine monophosphate dehydrogenase inhibitors, azathioprine and mycophenolat mofetil (106), while a protective effect was revealed for corticosteroids. However, this finding might be biased by smoking behavior. Smoking is described as a possible protective factor for PD, and smokers frequently need corticosteroids due to pulmonary maladies (106, 107). Moreover, cigarette smoke induces chronic inflammation, which results in immune cell exhaustion and generally attenuates the function of many immune responses (108). Therefore, smoking can be considered an immune-inhibitory activity (109, 110). The potential effectiveness of anti-inflammatory treatment is further exemplified by a lowered risk for developing PD in patients receiving immunosuppressive therapy (111).

Accordingly, patients with inflammatory bowel disease (IBD) receiving an anti-TNF treatment had a 78% reduction in the incidence of PD compared to IBD patients who did not receive this therapy (112). However, the lack of direct comparison between the incidence of PD in treated IBD patients compared with non-IBD patients (112) means that the ability of anti-TNF treatment to reduce PD incidence in non-IBD patients remains unanswered. Other research has indicated that severity of IBD is inversely associated with the risk of developing PD (-15%) (113). However, although patients suffering from severe IBD are more likely to receive anti-inflammatory drugs, immune-modulatory treatment was not directly assessed. Accordingly, further studies are necessary to verify a positive or negative correlation between PD and anti-inflammatory treatment, both for IBD and for non-IBD patients.

One of the most frequently used anti-inflammatory drugs is ibuprofen, a reversible cyclooxygenase-2 (COX-2) inhibitor and non-steroidal anti-inflammatory drug (NSAID) (114). Intriguingly, ibuprofen users showed a lower risk for PD, whereas no protective effect could be demonstrated for acetylsalicylic acid (ASA) (114). In a prospective study of subjects without PD who were assessed at baseline for NSAID intake, 0.2% developed PD during a 6-year follow-up (115). A significant dose-response relationship between ibuprofen intake (tablets/week) and reduced PD risk was found. Again, this effect was not observed for ASA, other NSAIDs (e.g., indomethacin), or acetaminophen. Although all NSAIDs and ASA are known to inhibit COX-2, only ibuprofen was shown to have some impact on PD prevention. Pre-clinical findings from *in vitro* models

indicate that ibuprofen prevents oxidative damage induced by LPS injection and better protects dopaminergic neurons against glutamate neurotoxicity than ASA (116, 117). The neuroprotective effects of ibuprofen have been confirmed in studies that considered confounder variables of PD, such as age, smoking, and caffeine intake (115, 118). However, the putative neuroprotective effect of ibuprofen in PD remains controversial; other research focusing on all NSAIDs rather than on ibuprofen alone found that NSAIDs had no neuroprotective effects (107). In this context, it is noteworthy that ibuprofen is known to reduce inflammation *via* inhibition of COX-2, but also *via* modulation of the angiotensin pathway by shifting the ACE/ACE-2 (angiotensin converting enzyme) receptor ratio towards ACE-2 (119, 120) (discussed in detail in Section 4.2).

Drugs such as  $\beta$ -agonists and  $\beta$ -antagonists have been shown to affect the incidence of PD in opposing directions, with  $\beta$ -agonists seeming to be somewhat protective (121, 122). However, further evidence is needed to confirm whether  $\beta$ -agonists might act directly on immune cells and are thus capable of modulating PD-related inflammation (122). It should be noted that  $\beta$ -agonists are often used in patients suffering from chronic obstructive pulmonary disease, a common consequence of frequent smoking. The fact that smoking was reported to lower the incidence of PD in one study represents an epidemiological bias (121).

Given that observational studies have yielded controversial data regarding the neuroprotective effects of different drugs and immunomodulators (123–128), randomized, controlled trials are needed to better decipher which drugs have distinct neuroprotective effects in PD.

## 2.5 Current Clinical Trials for Anti-Inflammatory Disease Modification in PD

Current clinical trials on anti-inflammatory therapy in PD focus on the treatment of glucose metabolism, improvement of oxidative stress, and regulation of gut microbiota.

### 2.5.1 Regulation of Glucose Metabolism

Impaired insulin signaling resulting in altered energy balance and impaired cell repair mechanisms has been observed in PD patients (129–131). Glucagon-like peptide-1 (GLP-1) is a growth factor and insulin-stimulating hormone that can activate the same effector molecules as insulin, and its receptor (GLP1R) is expressed in neurons. In addition to the known effects of GLP1R on blood sugar regulation and stimulation of the hypothalamus to regulate appetite, studies have shown that GLP1R agonists have neuroprotective effects in different animal models of PD. One agonist, exendin-4, can enhance cognitive function (132) and attenuate neurodegeneration in 6-hydroxydopamin (6-OHDA) rats (133). In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice, the newer GLP-1 mimetics liraglutide and lixisenatide can improve motor impairment and reduce dopaminergic cell loss in the SN (134, 135). In a human A53T  $\alpha$ SYN (hA53T- $\alpha$ SYN) transgenic mouse model, a long-acting GLP1R agonist reduced behavioral deficits and neurodegeneration (136). It is noteworthy that activation of GLP1R can inhibit the production of proinflammatory cytokines in microglia, such as TNF and IL-1B

(137, 138). The neuroprotective effect of semaglutide treatment is currently under investigation (139).

### 2.5.2 Regulation of Gut Microbiota

The gastrointestinal (GI) tract and CNS have complex mutual interactions (140) that are affected by the intestinal flora (141–143). Therefore, a healthy and stable intestinal flora is important for immunity, homeostatic balance of barrier integrity, and metabolism (144). Interestingly, changes in the intestinal flora may alter nerve development and even cause neurodegenerative disorders (145). Conversely, traumatic brain injury may lead to impaired intestinal barrier function (146, 147). GI dysfunction in PD patients, particularly constipation, is commonly known to be one of the initial symptoms that precedes motor impairment (148). Changes in intestinal microbial flora can alter the barrier function and permeability of the gut and subsequently influence the immune system (140, 149), and have been linked to PD (149). It is noteworthy that p $\alpha$ SYN can be found in the enteric nervous system (150).

A speculative hypothesis is that the methylation status of the SNCA gene might be influenced by the gut microbiome. It is accepted that duplications and triplications of the SNCA gene confer a higher risk of developing PD (151, 152). Decreased methylation of the SNCA gene, which would lead to increased transcription, could likewise affect  $\alpha$ SYN expression and influence the risk of PD (153). Postulating a potential role of the gut microbiota as an epigenetic factor for DNA methylation, an ongoing clinical study is investigating the composition of the GI bacteria in the stool of PD patients and healthy controls by extracting total bacterial DNA from the samples (154).

### 2.5.3 Regulation of Oxidative Stress

Oxidative stress in the brain plays a key role in the development of PD (155, 156), and results from an imbalance between reactive oxygen species (ROS) and the ability to scavenge reactive intermediates (157). ROS, which include superoxide, nitric oxide, hydroxyl radical, hydrogen peroxide, and peroxynitrite, can be generated from various sources including the electron transport chain or activated immune cells. Interestingly, increased oxidative stress seems to be target-specific and, in the case of PD, related to LP and the p $\alpha$ SYN contained in Lewy bodies, where p $\alpha$ SYN nitration (an oxidation marker) was found to be elevated (158–160). Furthermore, the SN of early PD patients has been found to contain reduced amounts of the antioxidant glutathione (GSH), which correlated with PD severity (159).

Increasing the availability of reduced GSH N-acetylcysteine (NAC) can potentially reduce the damage to neurons caused by oxidative stress. In a current clinical trial, NAC is being used to protect PD patients from oxidative damage (161). Aside from NAC, other supplements with antioxidative properties are under investigation. In the CNS, vitamin B<sub>3</sub> (niacin) is considered a key mediator of neuronal development and survival (162). Niacin is a cofactor of nicotinamide adenine dinucleotide and NADPH, which are necessary for the scavenging of oxidants and needed for GSH regeneration (157). Niacin can improve the integrity of mitochondria and hence the energy supply of neurons. By enhancing antioxidant defense

mechanisms, niacin can protect the normal structure and function of neurons exposed to oxidative stress, thereby delaying the progression of PD (163). Furthermore, niacin binds to the G-protein-coupled hydroxycarboxylic acid receptor 2, which is upregulated in a proinflammatory environment and which may downregulate inflammation (164–166). Since PD patients are known to have low levels of niacin due to mitochondrial malfunctioning, supplementation of niacin could be beneficial (166). A clinical trial is evaluating the effectiveness of niacin or niacinamide supplementation on inflammation and severity of PD symptoms (167).

### 3 ANIMAL MODELS AND THEIR CONTRIBUTION TOWARDS UNDERSTANDING PD PATHOMECHANISMS

Animal models play an important role in understanding PD pathophysiology, including neuroinflammatory processes. Next to the 6-OHDA model (168), one of the most often used PD models is induced by MPTP delivery (169), which persists extensively in the SN and results in PD symptoms with inhalation and cutaneous contact (169). Immune responses in the various MPTP models used are, however, quite different.

#### 3.1 Innate Immune Responses in Animal Models for PD

Toxins such as MPTP, rotenone, and 6-OHDA act as DAMPs and initiate a strong innate immune response with microglia activation and subsequent neurodegeneration in the SN (170–172). This immune response resembles the microglia activation found in human brain autopsies (21, 173). In the 6-OHDA model, neurodegeneration is accompanied by a gradual repolarization of microglia from an anti-inflammatory M2 to a pro-inflammatory M1 phenotype (174). Cytokine production by M1 cells is intracellularly initiated by NF $\kappa$ B (53, 175, 176), which in turn induces interleukin and procaspase-1 transcription. Together with the inflammasome NLRP3, caspase-1 activates IL-1 $\beta$ . Moreover, other proinflammatory proteins such as iNOS and TNF are also released from M1 cells (53, 175, 176) and contribute to neurodegeneration in PD (177). Consequently, inhibition of NF $\kappa$ B protects MPTP mice from neurodegeneration (178). M2 macrophages, in contrast, contribute to neuroprotection and release neurotrophic factors (176) (**Figure 1**). Since TLR-4 knock-out reduced the number of MHC-II<sup>+</sup> microglial cells and partially protected MPTP-treated mice from dopaminergic degeneration in the SN, MPTP triggers also neuroinflammation *via* TLR-4 (179). However, the canonical ligand for TLR-4 is LPS, which is commonly found on cell walls of gram-negative bacteria (180). In LPS-driven models, LPS is either systemically administered or focally injected into the SN (181). Since microglia activation after delivery of LPS or another of the aforementioned toxins results in the same downward cascades, all of these models lend themselves to studying innate immune responses (181–183). However, in mice lacking the mitophagy inducers PINK and Parkin, LPS triggers the

release of mitochondria-derived vesicles (184, 185). This can prime CD8<sup>+</sup> T cell responses against mitochondrial antigens (184, 185). External stressors such as LPS can thus also induce adaptive immune responses, in particular in transgenic models with impaired mitochondrial functions.

For MPTP, but not 6-OHDA, a Lewy body-like pathology has been found in non-human primates (186). An even more prominent Lewy body-like histopathology was observed in viral vector-based models overexpressing human mutations of  $\alpha$ SYN (e.g., A53T) (187). Furthermore, viral vector-based models demonstrate a similar innate immune response, as seen in toxin-based models. p $\alpha$ SYN, which is believed to enter the cell *via* TLR-2 to unleash its toxic potential (53, 188, 189), thus apparently acts like a DAMP (190). Interestingly, orthotopic injection of an  $\alpha$ SYN-encoding AAV into the SN only induced neurodegeneration in the presence of Fc gamma receptors (191), which implies an antibody-dependent activation of the complement cascade and/or antibody-dependent cellular cytotoxicity that may be mediated by microglia, for example (192). However, unlike astrocytes, microglia do not directly contribute to a proinflammatory environment after exposure to p $\alpha$ SYN (193). Nevertheless, progressive neurodegeneration can be induced by microglia-specific overexpression of p $\alpha$ SYN in the absence of p $\alpha$ SYN in dopaminergic cells (194). The critical role of CD4<sup>+</sup> T cells was confirmed by showing that virus-based  $\alpha$ SYN-overexpression can only induce microglia activation and neurodegeneration when MHC-II is present (195). Therefore, viral vector-based models require a complex interplay between different types of immune cells, which may also best reflect observations made in human PD.

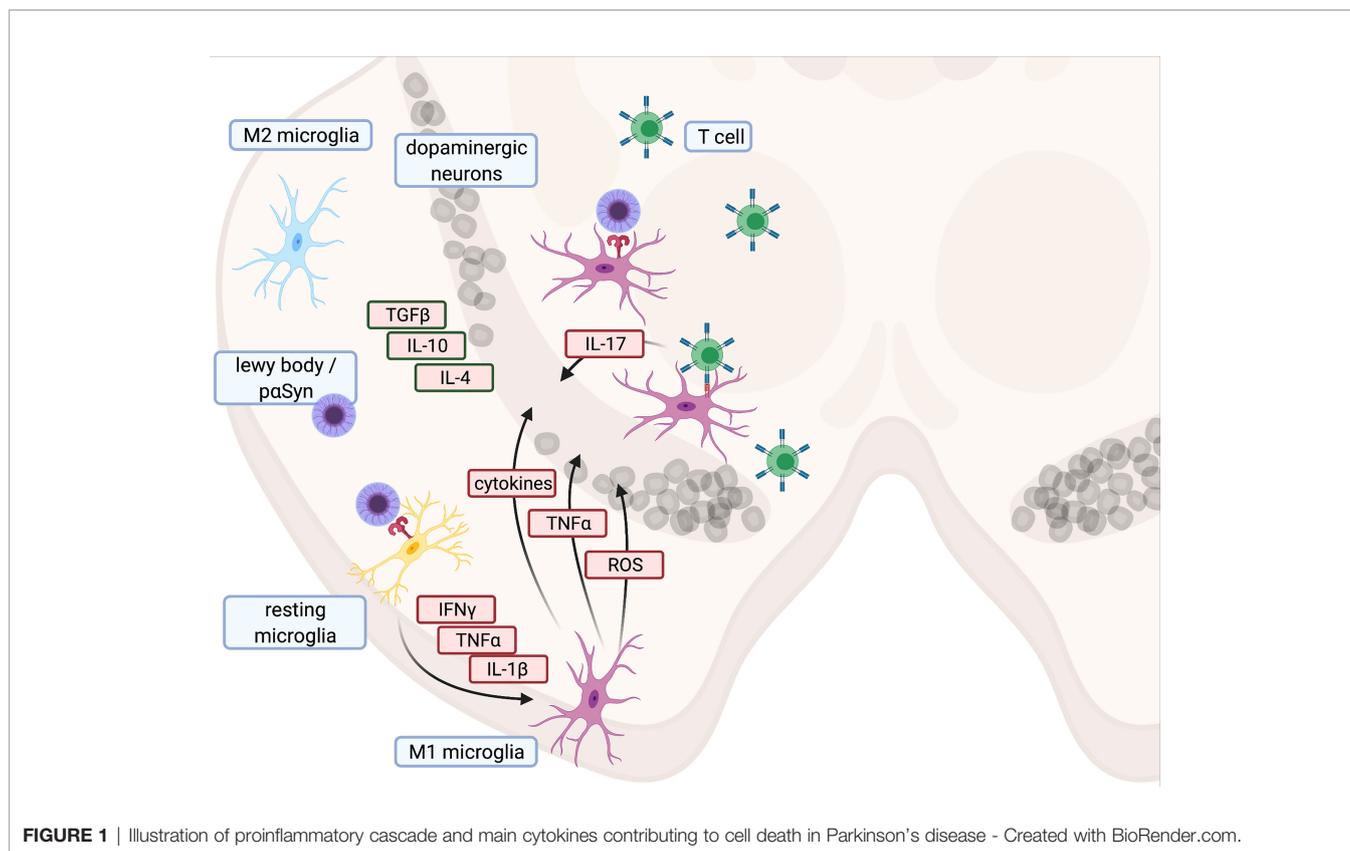
Since animal research in PD has focused mostly on alterations within the CNS, our understanding of peripheral innate and adaptive immune processes in PD pathology is still limited. Recent studies have provided evidence that increased gut permeability and gut microbiota are likely to contribute to PD development (149, 196). This has resulted in PD becoming more and more accepted as a systemic disease (197). For instance, overexpression of human TNF (hTNF) in a mouse model leads to microglia activation in various regions of the brain (198, 199), while immunomodulation with infliximab could attenuate microglia activation (199). Since infliximab cannot penetrate the blood-brain barrier, this finding indicates that effective treatment of neuroinflammation could be achieved by modulating peripheral immune mechanisms.

#### 3.2 Adaptive Immune System in Animal Models for PD

Several animal models support the hypothesis that the adaptive immune response in PD is mainly T cell driven, whereas the role of B cells remains enigmatic (41, 42, 73, 75, 88, 200). Nevertheless, the mechanisms of T cells vary across different animal models (42, 201).

##### 3.2.1 MPTP Model

Variations in frequency and dosage of MPTP injections in mice result in different PD models with diverse disease kinetics. The subacute MPTP model is generated by administering MPTP once daily over five consecutive days, whereas an acute model is



induced by delivering MPTP every two hours for four times in only one day (202). For the acute model, it is important to note that in contrast to humans, the initial immune response decreases significantly within 30 days, and MPTP-injected mice may recover over time (203). Moreover, p $\alpha$ SYN is not found in this model *per se*. However, if the adaptive immune response in the acute model is maintained by peripherally administering cytokines such as RANTES (Regulated on Activation, Normal T cell Expressed and Secreted) and eotaxin twice a week, the inflammation is sustained and p $\alpha$ SYN accumulates in the SN of the rodents (203). In this model, p $\alpha$ SYN formation is linked to a sustained proinflammatory environment.

CD4<sup>+</sup> and CD8<sup>+</sup> T cell infiltration in the SN of acute MPTP mice supports the idea that T cells contribute to neurodegeneration in this PD model (42). CD4<sup>+</sup> or recombinant activating gene 1 (RAG1)-deficient mice, which lack mature lymphocytes, show attenuated neurodegeneration upon treatment with MPTP. In contrast, neurodegeneration is unrestrained in CD8<sup>+</sup> T cell-deficient mice (42). Blockade of RANTES and eotaxin in the MPTP mouse and non-human primate model reduces microglia activation, CD4<sup>+</sup> and CD8<sup>+</sup> T cell infiltration, and neurodegeneration (204, 205). Continuous T cell trafficking and induction of p $\alpha$ SYN in the SN of MPTP mice is also driven by supplementation of RANTES and/or eotaxin, but not by TNF and IL-1B (203). Furthermore, MPTP-treated mice show altered and dysfunctional CD4<sup>+</sup>CD25<sup>+</sup> T<sub>reg</sub> cells. Administration of

natural T<sub>reg</sub> cells leads to attenuation of SN degeneration (206). As Th17 cells appear to contribute to nigrostriatal degeneration (206, 207), the beneficial effect of T<sub>reg</sub> may be due to their ability to inhibit TH17 cells. However, while mechanistic insights from the aforementioned studies are based on the acute MPTP model, CD4<sup>+</sup> T cell infiltration occurs earlier in the subacute model (208). Given the differences between the models, the choice of the most appropriate model may determine the outcome (209).

### 3.2.2 6-OHDA Model

This model is generated by injecting 6-OHDA either directly into the SN, the medial forebrain bundle, or the striatum (168, 210, 211). The initial cytotoxic effect of 6-OHDA is known to be mediated *via* oxidative stress (212) and impaired mitochondrial function (213). Data on the role of the adaptive immune response in the 6-OHDA model are still scarce. But it is known that 6-OHDA administration leads to infiltration of CD4<sup>+</sup> and T<sub>reg</sub> cells in the CNS (76, 174). In contrast to MPTP, 6-OHDA must only be administered once to induce continuous neuroinflammation and neurodegeneration (174, 201). Apart from neuroinflammation, 6-OHDA-treated rats also show decreased circulating T<sub>reg</sub> cells, indicating that this model can reflect aspects of human PD (174). However, while CD4<sup>-/-</sup> or Rag1<sup>-/-</sup> knock-out mice injected with MPTP were partly protected from severe neurodegeneration (42), 6-OHDA-treated Rag1<sup>-/-</sup> mice showed even more pronounced neurodegeneration in the SN than

immune-competent mice (201) or rats (214). Accordingly, the adaptive immune system is mostly neuroprotective in the 6-OHDA rodent model. Thus, toxin-based models provide contradictory data on the role of the adaptive immune system. Based on the epidemiological data linking PD and adaptive immune responses in humans, these models do not seem to adequately recapitulate the pathomechanisms underlying the human disease.

### 3.2.3 Viral Vector and Preformed Fibrils Models

Creating a model that shows a large overlap with the human phenotype and pathophysiology is the main objective when generating new animal models. Regarding chronic disease progression, mild-to-moderate nigrostriatal degeneration, Lewy-like pathology, and neuroinflammation, the AAV1/2-A53T- $\alpha$ SYN model resembles human PD much more closely than conventional toxin-induced models (75, 187, 215). Recently, CD4<sup>+</sup> and CD8<sup>+</sup> cells infiltrating the SN were found in the AAV1/2-A53T- $\alpha$ SYN model (75). Ten weeks after AAV1/2-A53T- $\alpha$ SYN injection, CD4<sup>+</sup> and CD8<sup>+</sup> cells in the spleen were also activated. Moreover, RAG deficiency protected dopaminergic SN neurons, indicating that CD4<sup>+</sup> and CD8<sup>+</sup> crucially contribute to neurodegeneration in this model (75). This reflects findings made in PD patients, thereby demonstrating a higher immune-related face validity of the AAV1/2-A53T- $\alpha$ SYN mouse model compared to the toxin-induced MPTP and 6-OHDA models. Comparable results, including gradual dopaminergic cell loss and CD3<sup>+</sup> infiltration in the SN, were also achieved by viral vector-based application of human  $\alpha$ SYN in the SN of mice (216, 217) or by directly injecting preformed  $\alpha$ SYN fibrils ( $\alpha$ SYN-PFF) into the striatum of mice (62). The immune response triggered by the presence of p $\alpha$ SYN is thus conserved and comparable between different models. This is in line with the recently revealed role of  $\alpha$ SYN as a critical mediator of inflammatory and immune responses (18).

Aside from PD models with direct injection of p $\alpha$ SYN or  $\alpha$ SYN-PFF into the brain, there are also models based on peripheral injection of  $\alpha$ SYN-PFF. Intriguingly, spread of p $\alpha$ SYN from the periphery to the brain is observed, accompanied by motor deficits (218, 219). However, in a more recent study where strong involvement of the adaptive immune response in the brain was confirmed, further inflammatory stress by LPS was required to achieve spreading of p $\alpha$ SYN into the brain (220). Accordingly, ongoing neuroinflammation contributes to the progression and maintenance of PD (197, 221–225).

### 3.2.4 Conclusion for the Role of the Immune System in PD Animal Models

These animal models provide substantial support for the hypothesis that the immune system participates in the neurodegeneration observed in PD. However, for investigating adaptive immunity, choosing the right animal model is key. Central and peripheral immune responses must both be considered. Finally, since the overall role of the immune response in PD animal models is still understudied, interactions between p $\alpha$ SYN, microglia, astrocytes, the adaptive immune system, and peripheral inflammation need to be explored.

## 4 SIGNALING CASCADES RELATED TO PD AND NEUROINFLAMMATION AS POSSIBLE THERAPEUTIC TARGETS

Pathophysiology of PD is manifold and includes several well-investigated pathways, while others may still be unknown. There are several important signaling pathways related to inflammation and neurodegeneration.

### 4.1 COX-2 and Disease Modification With NSAIDs

ASA is a standard drug for secondary prophylaxis of ischemic stroke and a potent non-competitive inhibitor of COX-2. Since COX-2 is expressed in many cell types, including platelets and microglia, it is involved in many physiological processes. Intriguingly, the protective role of COX-2 inhibitors on neuroprotection remains controversial. An early administration of high ASA doses showed a neuroprotective effect in MPTP mice, while other COX-2 inhibitors including ibuprofen did not (226). In contrast, the protective effect of ASA in PD patients is comparatively low, while ibuprofen is associated with decreased disease risk compared to other NSAIDs (114, 115). Furthermore, some studies have shown that NSAID intake has no effect on PD development, but instead correlates with an increased risk for PD (107, 227). It is important to note that none of these studies compared equivalent dosages. In MPTP mice, however, COX-2 is upregulated and known to be involved in the oxidation of dopamine, forming dopamine quinone (DAQ) (202). Interestingly, COX-2-deficient mice are protected against induction of PD, which was not explained by reduced inflammation but by prevention of DAQ formation (202, 228, 229). DAQ conjugates with GSH to form GSHDAQ. After conversion to 5cysDAQ, GSHDAQ inhibits mitochondrial complex I. In turn, this leads to decreased degradation of ROS and increased DAQ levels. Subsequently, this vicious circle results in microglia and astrocyte activation and a shift towards a proinflammatory state (175), accompanied by exhaustion of the pentose-phosphate pathway (PPP). However, there are multiple pathways that result in upregulation of COX-2 in brain neurons, including increased N-methyl-D-Aspartate (NMDA) receptor-dependent activity (230), cerebral ischemia, seizures, and diseases such as AD or PD (231). Another important function of COX-1 and COX-2 is the further processing of arachidonic acid. COX-1 induction leads to a substantial increase in thromboxane A<sub>2</sub> (TXA<sub>2</sub>) in human endothelial cells, while induction of COX-2 by IL-1B leads to a minor increase in TXA<sub>2</sub> but a substantial induction of the proinflammatory proteins prostacyclin (PGI<sub>2</sub>) and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) (232).

PGI<sub>2</sub> and PGE<sub>2</sub> are physiologically involved in body temperature regulation. PGI<sub>2</sub> and TXA<sub>2</sub> have important roles in the maintenance of vascular homeostasis and can mainly be described as agonist and antagonist (233). Among the different PGE<sub>2</sub> receptors (EP1-4), EP2 contributes to neurodegeneration in the presence of p $\alpha$ SYN in PD (234). EP2-deficient microglia from mice showed increased clearance of p $\alpha$ SYN on brain slices from Lewy-body patients. Furthermore, EP2<sup>-/-</sup> MPTP mice were spared from neurodegeneration in the SN (234). However, this

mechanism only seems to apply for neurotoxicity associated with chronic inflammatory processes. In acute pathological processes such as brain ischemia or NMDA-induced toxicity, EP2 activation exerts protein kinase A-dependent protective effects (231). Interestingly, EP2 is also neuroprotective in the 6-OHDA primary cell culture (235). The cause of this dichotomous action of EP2 is not yet understood (231).

Beside possible neuroprotective effects, COX-2 inhibitors increase intestinal permeability that correlates with their potency to inhibit COX-2, thus ultimately leading to local inflammatory side effects (236, 237). Furthermore, since increased intestinal permeability is discussed as an important pathological axis of PD development, prolonged treatment of PD with potent NSAIDs is not advisable, which could explain the controversial results (149, 196).

## 4.2 Oxidative Stress, PPP, and Renin-Angiotensin System

### 4.2.1 Oxidative Stress and PPP

Under steady-state conditions, ROS are maintained in a stable range and participate in the regulation of cell growth, differentiation, apoptosis signals, and enzyme activity by modulating the production of ceramide, kinase regulatory proteins, and activation of transcription factor NF $\kappa$ B (238, 239). Oxidative stress is a potent and highly conserved defense mechanism against intruders such as bacteria or fungi (240). By stimulating the production of inflammatory factors, ROS play an essential role in pathogen clearance (238). Free radical scavengers such as GSH act as a counterpart to ROS and protect cells from excessive oxidative stress. Maintaining the reduced state of GSH by oxidation of NADPH is therefore important for tissue homeostasis. Under pathological conditions, such as in PD, the level of ROS outpaces the compensatory mechanisms. ROS are located upstream of many inflammatory signaling pathways, upregulate the expression of other inflammatory factors, interfere with signaling pathways that regulate growth factors, and often alter signal transduction. High levels of ROS can be generated (241–244) by M1 microglia, but also the renin-angiotensin system (RAS) or NADPH-oxidase and its homologues, the so-called NOX enzymes (240). High ROS concentrations may cause apoptosis, structural damage, and cell death (159). ROS can therefore directly exert neurotoxicity and amplify neurotoxic inflammatory responses (157, 159). Understanding the role of pathways such as the PPP, which expurgate excessive amounts of ROS, might be crucial for finding an effective treatment against PD. The PPP connects glucose metabolism with NADPH production and nucleotide precursor synthesis. In this pathway, glucose-6-phosphate (G6P) is metabolized to produce NADPH and ribose-5-phosphate. In nearly all cells, the main task of PPP is to provide ribose-5-phosphate. In neurons, however, its main task is to provide NADPH to eliminate ROS (245). The definite role of PPP in PD remains still uncertain (245), even though there is increasing evidence that PD is associated with disorders of glucose metabolism (246–248).

The rate-limiting enzyme of the oxidative part of the PPP is G6P dehydrogenase (G6PD), which catalyzes the reaction

between G6P and NADP<sup>+</sup>. Through consumption of NADPH, oxidative stress leads to the accumulation of large amounts of NADP<sup>+</sup> and subsequently to the activation of G6PD due to the increased concentration of oxidants (249). In MPTP mice, neurodegeneration was shown to correlate with NADPH oxidase upregulation (242). Moreover, G6PD expression was positively associated with microglial activation and dopaminergic neurodegeneration (245), indicating that oxidative stress is closely linked to neurodegeneration.

Another important protein related to oxidative stress is GSH, an important antioxidant in brain neurons. The level of GSH in cultured cells is directly related to the production of NADPH by PPP (250). Increased ROS and decreased GSH levels have been described in many PD models and patients (155, 251–254).

Maintaining or adding NADPH in therapeutic dosages might help to overcome high levels of ROS, keep a stable level of GSH in the brain, and finally result in neuroprotection.

### 4.2.2 Renin-Angiotensin(-Aldosterone) System

The renin-angiotensin[aldosterone] system (RA[AS]) is well-known in the context of blood pressure regulation (255). Stimuli such as increased activity of kidney baroreceptors, low plasma sodium levels, and activation of  $\beta$ 1-receptors result in release of renin from the kidney into the blood circulation. Renin then cleaves liver-synthesized angiotensinogen into angiotensin I (AngI). Subsequently, AngI is cleaved *via* ACE to angiotensin II (AngII). Binding of AngII to the G-protein-coupled AngII receptor type 1 (AT<sub>1</sub>R) is essential for blood circulation. AT<sub>1</sub>Rs are commonly expressed in the vascular system, the heart, and the brain. Aside from binding to AT<sub>1</sub>R, AngII also induces release of aldosterone from the adrenal cortex (256). Drugs for the treatment of arterial hypertension therefore interfere with the RA[AS] by inhibiting renin, ACE, AT<sub>1</sub>R, or the aldosterone receptor (257). Investigations into the role of the RA[AS] in the brain, and more specifically in dopaminergic neurons, have deepened our understanding of neurodegeneration in PD. Different groups have demonstrated in both 6-OHDA and MPTP mice that neurodegeneration can be accelerated or decelerated through AT<sub>1</sub>R activation or blockade, respectively (243, 255, 258, 259). However, the RAS includes many complex crosslinks with pro- and anti-inflammatory endpoints (**Figure 2**). The main axis consists of core substrates including angiotensinogen, AngI/II, and renin. AngII mainly binds AT<sub>1</sub>R, but also the AngII receptor (AT<sub>2</sub>R), which initiates anti-inflammatory and anti-oxidative cascades (123, 260). This contrasts with AT<sub>1</sub>R, which initiates and maintains neuroinflammation and oxidative stress (260–262). AngII can be cleaved to AngIII by aminopeptidase-A, and further to AngIV and Ang3-7 by aminopeptidase N or carboxypeptidase P and prolyl-oligopeptidase, respectively. AngIII binds to AT<sub>1</sub>R and AT<sub>2</sub>R, whereas AngIV has a low affinity to AT<sub>1</sub>R and AT<sub>2</sub>R but a high affinity to the AngIV receptor (**Figure 2**). AngIV and analogues were shown to have a positive effect on synaptogenesis and improved clinical outcomes after stroke and subarachnoid hemorrhage by increasing cerebral blood flow (263–266).

The neurodegenerative effect mediated by AngII and the AngII-AT<sub>1</sub>R complex are mediated by an increased release of ROS *via* the

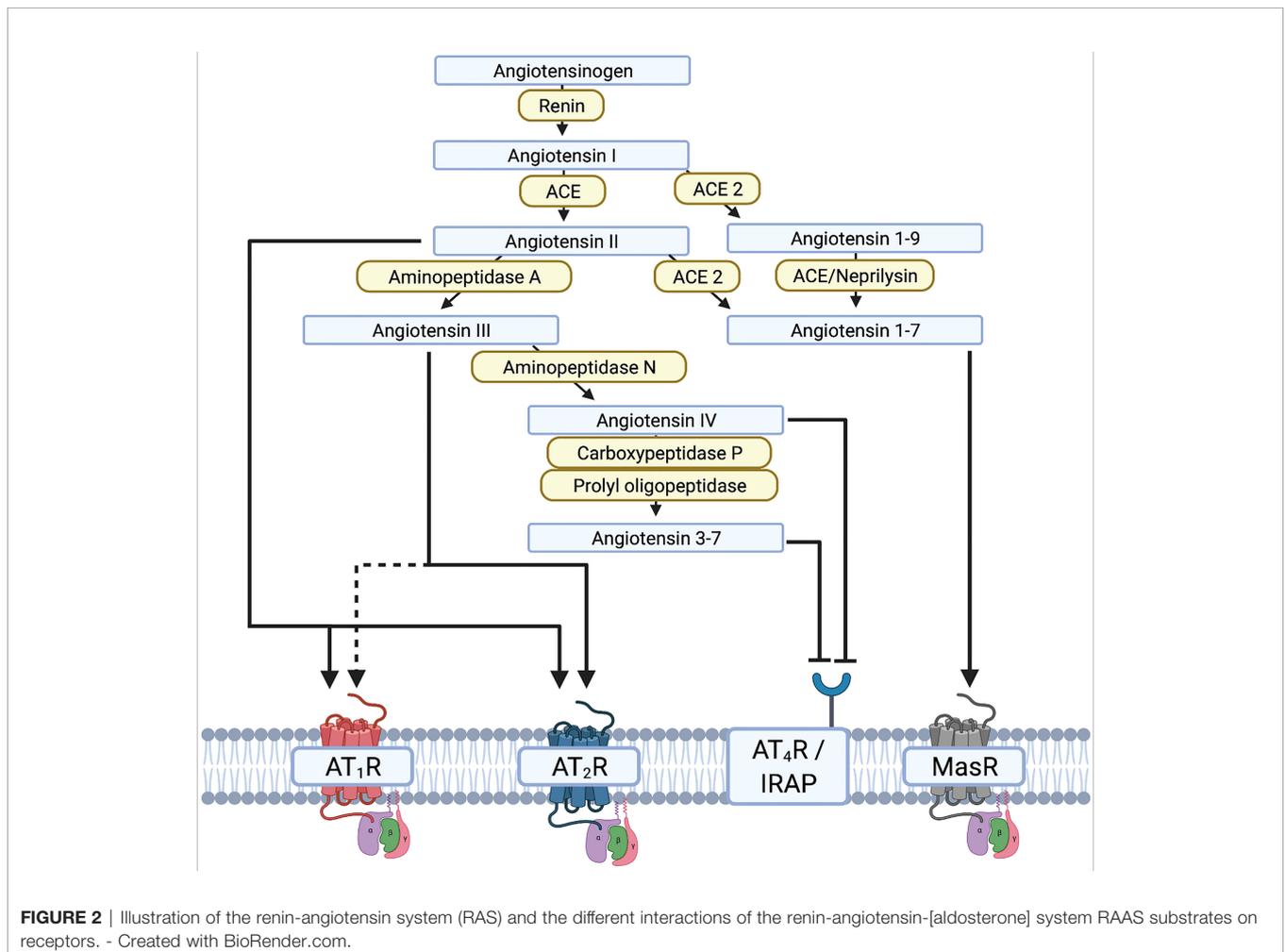
NADPH-oxidase complex in microglia and dopaminergic neurons, resulting in a vicious proinflammatory circle (123). The increased release of ROS is mediated by increased nuclear expression of AT<sub>1</sub>R and NOX in dopaminergic neurons of PD patients, resulting in oxidative DNA damage and cell loss (267). In contrast, the cytoplasmic and membrane expression of AT<sub>1</sub>R is reduced (267). Under normal conditions, the AT<sub>1</sub>R-NOX interaction maintains cell homeostasis and physiological levels of dopamine. The pathological shift of AT<sub>1</sub>R expression from the membrane/cytoplasm to the nucleus reflects the disease process and contributes to secondary neurodegeneration due to increased oxidative stress. Interestingly, this shift can be observed relatively early. An altered ratio of membrane/cytoplasm to nuclear AT<sub>1</sub>R expression has already been observed in patients with a neuropathological diagnosis of PD who had not yet developed clinical manifestations or significant dopaminergic neurodegeneration (267). Yet to date, a potential re-distribution of other AT receptors in the brain of human PD patients has rarely been explored. However, ACE2 cleaves AngII and AngI to Ang1-9 and Ang1-7, respectively, and thereby shifts the RAS away from the proinflammatory main axis to the more anti-inflammatory side axis. Altogether, the RAS is a complex system that may be

amenable to therapeutic modulation. The potential of targeting the RAS in PD and AD has therefore been discussed in considerable detail in dedicated review articles (123, 261).

Of note, unwanted alterations in the subtle balance between the pro- and the anti-inflammatory axis of the RAS occur during COVID-19 infections, where ACE2 is the main entry receptor for the pathogenic SARS-CoV-2 virus (268). Neurological consequences of the strong inflammation observed in severe COVID-19 remain to be studied.

## 5 CONCLUSIONS/OUTLOOK

Even 200 years after the first description of PD, its pathophysiology is still far from being fully understood. Fortunately, research towards a causal treatment of PD has made substantial progress in the last 15 years. Realizing that (systemic) inflammation plays an essential role of PD, at least in its maintenance, might pave the way for new therapeutic pathways. Knowledge transfer from classical inflammatory diseases or diseases that lead to inflammatory processes will likely have a major impact on the therapy of PD, and allow new



**FIGURE 2** | Illustration of the renin-angiotensin system (RAS) and the different interactions of the renin-angiotensin-[aldosterone] system RAAS substrates on receptors. - Created with BioRender.com.

development and/or a repurposing of drugs that are already available. In addition, research in early diagnostics for PD is important. Ideally, neurodegeneration can be halted by initiating treatment before severe symptoms have developed. Skin biopsy or sleep analysis, along with new serum/liquor parameters, might lead to a sensitive and specific early diagnosis of PD. In turn, this should open up an earlier treatment window for future PD patients. Treating early with well-tolerated neuroprotective/anti-inflammatory agents certainly holds great promise for this devastating disease.

## AUTHOR CONTRIBUTIONS

AG - Conceptualization, Visualization, Writing - original draft, Writing - review & editing, RM - Writing - review & editing, JWu - Writing - original draft, JW - Writing - review & editing, CWI - Conceptualization, Supervision, Writing - review &

editing. All authors contributed to the article and approved the submitted version.

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