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SPECIAL FEATURE REVIEW

Dopaminergic regulation of inflammation and immunity in Parkinson's disease: friend or foe?

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease affecting 7–10 million people worldwide. Currently, there is no treatment available to prevent or delay PD progression, partially due to the limited understanding of the pathological events which lead to the death of dopaminergic neurons in the *substantia nigra* in the brain, which is known to be the cause of PD symptoms. The current available treatments aim at compensating dopamine (DA) deficiency in the brain using its precursor levodopa, dopaminergic agonists and some indirect dopaminergic agents. The immune system is emerging as a critical player in PD. Therefore, immune-based approaches have recently been proposed to be used as potential antiparkinsonian agents. It has been well-known that dopaminergic pathways play a significant role in regulating immune responses in the brain. Although dopaminergic agents are the primary antiparkinsonian treatments, their immune regulatory effect has yet to be fully understood. The present review summarises the current available evidence of the immune regulatory effects of DA and its mimics and discusses dopaminergic agents as antiparkinsonian drugs. Based on the current understanding of their involvement in the regulation of neuroinflammation in PD, we propose that targeting immune pathways involved in PD pathology could offer a better treatment outcome for PD patients.

Keywords: immunotherapy, inflammatory diseases, neuroimmunology

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive disease, which affects up to 10 million people worldwide.[1] It is characterised by a combination of motor and non-motor manifestations. Motor symptoms include tremor, rigidity and bradykinesia, which are associated with the loss of dopaminergic neurons in the *substantia nigra* (SN). The pathophysiology of the disease in other structures, both in the central and peripheral nervous systems, accounts for the wide spectrum

of non-motor manifestations, which may further contribute to other autonomic disturbances.[2] The hallmarks of PD include neuronal loss and the formation of Lewy bodies, which consist of intracytoplasmic inclusions in the surviving neurons that is mainly composed of abnormal aggregations of a highly soluble unfolded protein α-synuclein (α-syn).[3] Despite intense research since its identification in 1988, the physiologic functions of α-syn are still debated, but the protein is known to be genetically and neuropathologically linked with PD.[4,5] Furthermore, α-syn is expressed in many different tissues, including blood, cerebrospinal fluid (CSF) and the enteric nervous system. It is recognised as a potential diagnostic biomarker as well as a therapeutic target for PD.[6,7] Interestingly, the presence of the PD-specific protein α-syn induces activation of immune cells and inflammatory responses in the CNS and the periphery, leading to neuronal loss both in α-syn mouse models of PD and in humans.[8–12] Indeed, although the causes of neurodegeneration in PD remain inconclusive, the immune system is increasingly standing out as a pivotal factor in PD pathogenesis. This suggests that the immune system could provide potential biomarkers and novel therapeutic strategies.[9,13,14]

Drugs currently representing the mainstay of PD therapy are levodopa (or L-dopa) and dopaminergic agonists, which predominantly provide their beneficial effects on motor symptoms by counteracting dopamine (DA) deficiency in the brain.[15] Apart from controlling motor activity in the central nervous system (CNS), dopaminergic pathways are also largely involved in the regulation of immune responses in the brain and in the periphery.[16–19] Therefore, using dopaminergic agents as antiparkinsonian drugs could potentially dampen neuroinflammation in PD, which has yet to be investigated. This review aims to illustrate immune responses that are found to be altered in PD and to explore dopaminergic modulation of these immune responses.

PD AND THE IMMUNE SYSTEM: PATHOLOGICAL MECHANISMS AND THERAPEUTIC TARGETS

Neuroinflammation is a complex inflammatory process occurring in the CNS, which involves both the brain intrinsic immune defence and immune cells from the periphery.[20] Although the cause-effect mechanisms remain elusive, neuroinflammatory processes are undoubtedly involved in neuronal cell death in PD.[21,22] Brain imaging from PD patients showed high levels of activated microglia and astroglia,[23–26] with increased production of proinflammatory cytokines, such as tumour necrosis factor (TNF)-α, interleukin (IL)-1β, interferon (IFN)-γ, IL-6[27,28] and reactive oxygen and nitrogen species (ROS/RNS).[29] Besides local inflammation induced by resident neuroglia, numerous studies on peripheral blood and CSF from patients with PD suggest there were alterations in inflammatory molecules and immune cell populations.[30] Dysfunction of the blood–brain barrier (BBB) has been found in PD[31] and may be one of the possible routes of immune infiltration into the brain, which initiate or exacerbate neuroinflammation and perpetuate the neurodegenerative process.[8] The $CD8^+$ and $CD4^+$ T lymphocytes are the most frequently identified cells in the PD brain and are positively correlated with neuronal death.[12,32–35] Alterations of peripheral $CD4^+$ T lymphocytes are frequently reported in PD.[36–39] PD patients have been found to have decreased percentages of $CD45RA^+$ naïve $CD4^+$ T cells and T regulatory (Treg) cells,[36,39–41] and increased percentages of memory and effector T cells,[38,42,43] especially the Th1 and Th17 subsets.[38–41,43–45] Increased Th1 cells correlated with higher Unified Parkinson's Disease Rating Scale (UPDRS) motor scores.[40] Both preclinical and clinical evidence thus supports the idea that reprogramming $CD4^+$ T cells towards an anti-inflammatory phenotype may exert a neuroprotective effect in PD.[46,47]

The findings of monocytic infiltration in PD are inconsistent.[48–51] Therefore, it is still a debate that whether and to what extent monocytes can infiltrate the CNS and contribute to dopaminergic neuron loss in PD.[52–55] However, these cells were found to displace a proinflammatory phenotype, which positively correlates with disease state and severity.[48,56]

Dendritic cells (DCs) represent a key link between the innate and adaptive immune systems.[57] In particular, tolerogenic DCs have a crucial role in immune tolerance *via* the induction and maintenance of Treg cells.[58] A recent study reported that the level of tolerogenic DCs was decreased in patients with PD.[59] Preclinical studies on a mouse model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD demonstrated that adoptive transfer of tolerogenic bone marrow-derived DCs (BMDCs) led to an increase in splenic Treg cell numbers, and attenuated neuroinflammation and neurodegeneration.[47,60,61] In addition, circulating and

immature populations of DCs, including myeloid and plasmacytoid DCs, were found to be decreased in PD patients, which was associated with increased impairment of motor functions.[62]

Natural killer (NK) cells could also directly regulate T cell responses through cytokine secretion.[63–67] An increase in NK cells in the peripheral blood of PD patients has been reported in several studies, suggesting their association with the risk and severity of the disease and an inclination towards activation in PD patients compared to healthy subjects.[64,68–71]

Although B cells have not been detected in the brain,[33] their level was found to be decreased in the peripheral blood of PD patients.[36,37,39] Moreover, deposits of IgG immunoglobulins were found in dopaminergic neurons of PD patients, even in those containing Lewy bodies.[72] Similarly, antibodies against glial and neuronal antigens were found in serum and CSF of PD patients.[73] These include anti-α-syn and anti-GM1-ganglioside antibodies which are potentially associated with the familial variants and the tremor-dominant form of PD, respectively.[74] Although B cells and autoantibodies can contribute to neuroinflammation,[75] vaccination with human alpha-synuclein (halpha-syn) has been found to stimulate the production of antibodies which promotes the degradation of halpha-syn aggregates in the brain, leading to protection against Lewy body disease.[76]

DOPAMINERGIC MODULATION OF IMMUNE RESPONSES IN THE CNS AND IN THE PERIPHERY IN PD

DA is a crucial neurotransmitter and DA-signalling pathways are involved in the modulation of immune cell functions.[16–77] Immune cells can synthesise, store, uptake and metabolise DA since they express (i) the tyrosine hydroxylase (TH); (ii) the vesicular monoamine transporter 2 (VMAT2); (iii) the dopamine transporter (DAT) and (iv) the monoamine oxidase (MAO) and the catechol-O-methyltransferase (COMT).[78–81] Moreover, immune cells express all subtypes of dopamine receptors (DR)[17,82–85] (Figure 1). The DRs consist of the D1-like receptor subfamily (D1DR, D5DR) and the D2-like receptor subfamily (D2DR, D3DR, D4DR), which are coupled with the stimulatory protein Gα and the inhibitory Gαi/o protein,[86,87] respectively. Indeed, DA and its mimics may affect different immune components involved in neuroinflammation.[88,89] The nucleotide-binding oligomerisation domain-like receptor pyrin domain-containing (NLRP)3 inflammasome is one of these potential targets.[90–94] The renin–angiotensin system (RAS) could also be affected, with altered levels of angiotensin II (AII) and of its precursor angiotensinogen, as well as its two major receptors, AII type 1 (AT1) and type 2 (AT2).[95] The neuroprotective heat shock protein alpha B-crystallin (CRYAB),[88,96] NF-kB signalling pathway,[90–93,97,98] nicotinamide adenine dinucleotide phosphate (NADPH) oxidase[95,97] could also be influenced by DA, as well as intracellular signalling *via* mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK1/2) and p38 MAPK.[99–102] Targeting these pathways or associated molecules could potentially modulate immune cell functions, including cell proliferation, adhesion, migration, apoptosis and the production of pro-inflammatory mediators. The following subsections summarise studies on dopaminergic modulation of immune cells *via* DRs in the inflammatory processes in PD (Tables 1 and 2), and discuss potential application of DA and its mimics in PD treatments.

DR-dependent mechanisms

The dopaminergic modulation of immune functions is predominantly DR-dependent, involving either or both D1-like DR[79,91,93,94,101–107] and D2-like DR,[84,95,96,100,108–117] in CNS (Table 1) and peripheral immune cells (Table 2). In CNS, activation of microglia and astrocytes *via* both D1-like and D2-like DR stimulates an anti-inflammatory response, resulting in neuroprotective effects which could be applied in PD treatments.[93,94,96,109] DA and D1DR signalling in cultured murine microglia and astrocytes indeed suppresses NLRP3 inflammasome activation, which leads to the inhibition of caspase-1 activation, IL-1β, IL-18 and NO production[93,94,118] (Table 1). Similarly, the D2-like receptor agonist quinpirole attenuated LPS-induced NO secretion by rat and mice microglia.[119] Furthermore, both D1DR and D2DR agonists inhibit the pro-inflammatory AT1/NADPH-oxidase/superoxide axis and microgliosis in LPS-treated microglia, which could offer a potential anti-inflammatory strategy in PD.[95,120] Similarly, DA was shown to reduce LPS-induced phagocytic activity only in activated microglia, *via* the downregulation of ERK1/2, while it

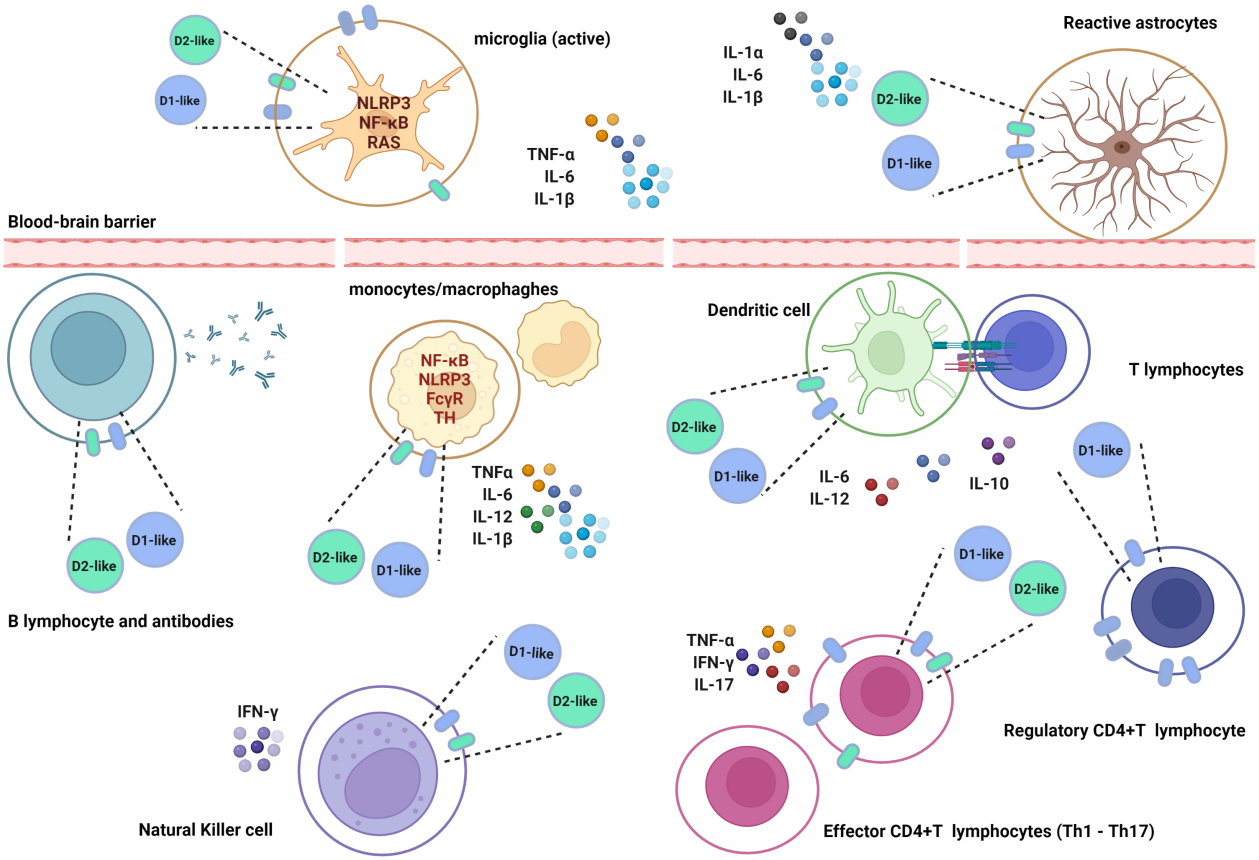

Figure 1. Dopaminergic modulation of immune responses in PD: DR-dependent mechanism. Human and animal immune cells in the CNS and the periphery express all subtypes of dopamine receptors (DR): the D1-like receptor subfamily (D1DR, D5DR) and the D2-like receptor subfamily (D2DR, D3DR, D4DR). DA and dopaminergic mimetics target different immune components involved in neuroinflammation *via* a DR-dependent mechanism: the nucleotide-binding oligomerisation domain-like receptor pyrin domain-containing (NLRP)3 inflammasome, the renin–angiotensin system (RAS), NF-kB signalling pathway ultimately impacting cell proliferation, adhesion, migration, apoptosis and the production of mediators (cytokines, NO). Microglia and astrocytes in CNS, and monocyte/macrophage, DC, T and B lymphocytes, naïve or polarised according to anti-inflammatory (Treg) or pro-inflammatory (Th1–Th17) phenotypes, and NK cells in the periphery all may be affected by D1-like and D2-like receptor activation. Both pro-inflammatory and anti-inflammatory roles have been observed depending on the type of immune cells, the species-specificity (human or animal) or the specific state of the inflammatory condition. The figure was created with BioRender.com.

increased p38MAPK activity *via* phosphorylation of Ser83 of paxillin in resting microglia.[99] Importantly, only the activation of ERK1/2 was blocked by spiperone, a prevalent D2-like DR antagonist.[99] However, other studies also suggested D2-like DR increase microglia chemotaxis in elderly human cultures and TNF-α mRNA levels in mouse microglia in unstimulated conditions.[84,111] Furthermore, it is worth mentioning that, on the one hand, deficiency of D3DR signalling led to an enhanced expression of pro-inflammatory cytokines (TNF-α and IL-1β) in response to LPS stimulation and an increased production of the anti-inflammatory mediator Fizz1 (found in inflammatory zone 1) in the presence of the anti-inflammatory stimulus IL-4.[108] On the other hand, inhibition of D3DR signalling is also associated with decreased expression of inducible nitric oxide synthase (iNOS) together with the rise in Fizz1 production in mixed glial cells, both *in vitro* and *in vivo*.[108] Thus, the pro-inflammatory or anti-inflammatory nature of nearby stimuli can affect dopaminergic immunomodulatory activity.[108] There is also evidence that supports the existence of heterogeneous subpopulations of microglia which respond differently to neurotransmitters and stimuli, depending on their receptor pattern expression.[121] In addition, triggers such as LPS, IFN-γ or IL-4, as well as factors including age or health status appear to modulate the responsiveness of microglia to other stimuli.[84,108,119,121,122] Therefore, under

Table 1. Dopaminergic modulation of immune cells in CNS

Immune target	Experimental condition	[DA]- [DA AG]	DR	Mechanism	Ref.
DR-dependent mechanisms					
BV-2 microglial cells; Primary microglial cells from new-born mice	LPS-induced activation	DA (0.001, 0.1, 1100 μM) SKF-38393 (10 μM)	D1DR/D5DR	↓NO production by DA in a concentration-dependent way; ↓phosphorylation of ERK1/2; ↓phosphorylation of NF-κB	93
Primary cultured microglia and astrocytes from mice	LPS-primed cells treated for 3 h with DA and then stimulated with nigericin; MPTP-treated mice	DA (200 μM); A-68930 (NA)	D1DR > D5DR	↓NLRP3 inflammasome-mediated IL-1β production (by NLRP3 Ubiquitination *via* E3 Ubiquitin Ligase MARCH7); ↓dopaminergic neuron damage, IL-1β or IL-18 production and caspase-1 activation in MPTP mice treated with A-68930	94
Primary cultured rat and mice microglia	Resting and LPS-induced activation conditions	DA (0.01–10 μM); dihydrexidine (0.01–10 μM); quinpirole (0.01–10 μM)	D1-like and D2-like receptors	↓LPS-induced NO release in a concentration-dependent way; DA, dihydrexidine and quinpirole enhanced microglial migration in resting condition	119
Striatal astrocytes in mice	MPTP-treatment in D2DR-null mice, CRYAB-null mice and WT mice	Quinpirole (2 or 5 mg kg^{-1} i.p. at 8 h intervals before and after MPTP injection)	D2DR	↓$GFAP^+$ cells in WT mice; ↑TH^+ neurons and levels of striatal DA in WT mice; ↓IL-1β, IL-2 and IL-6 mRNA levels in WT mice; No effect in D2DR-null mice, CRYAB-null mice	96
Primary mouse astrocytes cultures	LPS and ATP-induced cell activation	LY171555 (10, 20, 40 μM); Quinerolane (10, 50, 100 μM)	D2DR	↓IL-1β and caspase-1 in a concentration-dependent way	109
Striatal astrocytes in mice	MPTP-treatment in β-arrestin2 KO mice and WT mice	LY171555 (5 mg kg^{-1} i.p., daily for 11 days)	D2-like receptors β-arrestin2-dependent pathway	↓IL-1β and caspase-1 by LY171555 in WT mice but not in β-arrestin2 KO mice	109
N9 microglial cell line culture; Primary culture rat microglia	Resting condition; LPS-induced activation	DA (8 μM); SKF-38393 (10 μM); quinpirole (10 μM)	D2-like mediated effects in unstimulated and activate condition; D1-like mediated effects just in activated condition	↑AT2 and ↓AT1 mRNA levels by DA in unstimulated condition; ↓AT1 mRNA and NADPH activity and ↑AT2 mRNA by SKF-38393 and quinpirole in activated condition	95
C6 astroglial cell line culture; Primary rat astroglial cultures	Unstimulated condition	Quinpirole (10 μM)	D2DR	↓levels of angiotensinogen; ↓AT1 and ↑AT2 expression	95
BV-2 microglia cells; Primary microglial cells from mice	Unstimulated condition and LPS-induced activation	DA (2 μM)	D4DR-D2DR-D3DR > D1-like receptors; (spiperone alleviated the suppressive effect of DA on ERK1/2 activation in activated microglia)	↓ERK1/2 activation after LPS treatment; ↓phagocytic activity in activated microglia	99
Microglia isolated from mice striatal tissue	Unstimulated condition	DA (0.1 μM); quinpirole (1 μM); quinpirole (i.p. 0.5 mg kg^{-1}; 24 h and 1 h before harvesting)	D2-like receptors	↑TNF-α mRNA by DA on microglial cultures and by quinpirole in isolated microglia	111
Human elderly microglia cultures	Unstimulated condition	DA (0.1 μM)	D2-like receptors	↑microglial chemotaxis	84

(Continued)

Table 1. Continued.

Immune target	Experimental condition	[DA]- [DA AG]	DR	Mechanism	Ref.
Midbrain/striatal astrocytes cultures from mice	Unstimulated condition; cell cultured with LPS or IL-4	DA (0.1 μM); PD128097 (0.02 μM)	D3DR	↑iNOS expression by DA and PD128097 in unstimulated condition; ↓D3DR transcription after LPS treatment, but no change after IL-4	108
DR-independent					
N9 murine microglia cell	NO production induced by LPS or the combination of TNF-α and IFN-γ	DA (1 μM) co-incubation or 2 h pretreatment	DR independent. Alternative mechanism not detected	↓NO production and iNOS expression	118
BV-2 microglia cells; Primary microglial cells from mice	Resting condition and LPS-induced activation	DA (2 μM)	DR-independent; DAT and PMAT are involved in p38 by DA in resting microglia	↑number of stress fibres in resting and activated BV-2 cells; ↑p38MAPK activity in resting condition and ↓after LPS treatment; ↑Paxillin phosphorylation at Ser83 in resting microglia and ↓in activated microglia	99
BV-2 microglia cells; Primary mice microglial cells	LPS-induced activation	DA (1–100 μM; 24 h pre-treatment)	Autoxidation and formation of DAQ	↓TNF-α, IL-1β and IL-6 mRNA levels in a concentration- and pretreatment time-dependent manner, in the presence of tyrosinase, which catalyses the oxidation of DA to DAQ; DA 30 μM inhibited the transcriptional activity of NF-κB by reducing the nuclear translocation of NF-κB p65	98
BV-2 microglial cells	NO production induced by LPS or the combination of TNF-α and IFN-γ	DA (1-100 μM; pretreatment 1–24 h)	Autoxidation and formation of DAQ	↓NO production and iNOS expression in a concentration- and pretreatment time-dependent manner, in the presence of tyrosinase, which catalyses the oxidation of DA to DAQ	153

AG, Agonist; AT1/2, Angiotensin II Receptor Type 1/2; ATP, Adenosine Triphosphate; CRYAB, Alpha-crystallin B chain; DA, Dopamine; DAQ, Dopamine quinone; DAT, Dopamine Transporter; DR, Dopamine Receptors; ERK, Extracellular Signal-Regulated Kinases; GFAP, Glial fibrillary acidic protein; ICH, Spontaneous Intracerebral Haemorrhage; IFN, Interferon; IL, Interleukin; iNOS, inducible Nitric Oxide Synthase; KO, knockout; LPS, Lipopolysaccharide; MAPK, Mitogen-Activated Protein Kinase; MCP-1, Monocyte Chemoattractant Protein-1; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mRNA, Messenger Ribonucleic Acid; NA, Not Available; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of activated B cells; NLRP3, NOD-, LRR- and Pyrin Domain-Containing Protein 3; NO, Nitric Oxide; PMAT, Plasma Membrane Monoamine Transporter; TH, Tyrosine Hydroxylase; TNF, Tumour Necrosis Factor; WT, Wild Type.

Table 2. Dopaminergic modulation of immune cells in the periphery

Immune target	Experimental condition	[DA]- [DA AG]	DR	Mechanism	Ref.
DR-dependent mechanisms					
Mice BMDMs	LPS-primed cells treated for 3 h with various doses of DA or A-68930 and then stimulated with nigericin	DA (150, 200, 300 μM); A-68930 (150, 200, 300 μM)	D1R > D5R	↓NLRP3 inflammasome activation by reducing IL-1β and cleaved caspase-1; ↓IL-1β and IL-18 secretion	94
Mice BMDMs	LPS-primed cells treated for 3 h with various doses of DA and then stimulated with nigericin	DA (500, 600, 700 μM)	D2R	↓TNF-α secretion	94
RAW264.7 cells	2 h pre-treatment with various doses of DA before LPS-induced activation	DA (10, 100, 1000 μM)	NA	↓IL-1β, IL-6, TNF-α and iNOS expression; ↓NLRP3 and caspase-1 expression	92
Mice BMDMs	Pam3CSK4-induced inflammasome-independent TLR inflammatory activation	DA (10, 50, 150, 250, 400 μM); A-68930, or SKF-38393 (20 μM)	D5R	↓IL-6 and TNF-α at the mRNA and protein levels in a concentration-dependent manner; ↓NF-κB signalling pathway	91
Primary human monocyte-derived macrophages	Primary human monocyte-derived macrophages from donors either positive or negative for CMV	DA (1 μM)	NA	↓IκB levels; ↑phosphorylated p65 levels and NF-κB nuclear translocation, mainly in CMV^+cells; ↑NLRP3 levels ↑IL-1β intracellular levels, without any effect on its secretion; DA potentiates ATP-mediated release of IL-1β, not through an oxidative mechanism	90
Primary human monocyte-derived macrophages	Cells obtained from HS. Unstimulated condition and LPS-induced stimulation	DA (0.001, 0.01, 0.1, 1 μM)	D1-like receptors	↑IL-6, IL-1β and IL-18 secretion in unstimulated condition; ↑CCL2, CXCL8, CXCL9 and CXCL10 in unstimulated condition; ↓LPS-induced production of IL-10	125
Primary human monocyte-derived macrophages	Cells obtained from HS. Unstimulated condition and LPS-induced stimulation	DA (0.02, 0.2, 2, 20 μM)	NA	DA modulates macrophage cytokine secretion in unstimulated (↑IL-6, ↑CCL2) and LPS-induced macrophage (↑IL-6, ↑CCL2, ↑CXCL8, ↑IL-10, ↓TNF-α)	126
Human CD14+CD16+ monocyte	Cells from HS, treated with M-CSF for 3 days to induce maturation/activation	DA (0.1, 0.5, 1 μM); SKF38393 (0.001, 0.01, 0.1 μM)	D1-like receptors	↑migratory activity; ↑cell accumulation and adhesion	127
Murine BMDMs; Human peripheral blood mononuclear cells cultures	Human cells from HS. LPS-induced activation and IFN-γ	DA (500, 750 μM); quinpirole (2.5, 5, 10 μM)	D2R	↓TNF-α, IL-1β and IL-6 mRNA levels by DA on human PBMCs; ↓iNOS, TNF-α, IL-1β and IL-6 mRNA levels by quinpirole concentration-dependently on BMDMs; ↓$TNFα^+$ or $iNOS^+$ macrophages and ↑$CD206^+$ macrophages by quinpirole; ↓NADPH oxidase activation, ROS production, NF-κBp65, NLRP3, cleaved caspase1 and mature IL-1β, as well as the secretion of IL-1β and IL-18 by quinpirole on BMDMs	97
Human $CD4^+$ and $CD8^+$ T cells cultures	Cells from HS, stimulated with IL-2	DA (0.01–0.08 μM)	D1-like receptors	↓proliferation by DA 0.01–0.08, but no by DA at lower concentration (0.01–0.02 μM)	106

(Continued)

Table 2. Continued.

Immune target	Experimental condition	[DA]- [DA AG]	DR	Mechanism	Ref.
Human $CD4^+$ and $CD8^+$ T cells cultures	Cells from HS, stimulated with IL-2	DA (0.01–0.02 μM); DA (0.04–0.08 μM)	D1-like receptors	↓proliferation by DA 0.04–0.08 μM on $CD8^+$T cells more than $CD4^+$T cells; ↓cytotoxic activity of T cells by DA 0.04–0.08 μM; ↑intracellular cAMP correlates with the degree of inhibition of IL-2-induced cell proliferation	107
Jurkat cells and human normal peripheral lymphocytes	Cell mitogen-stimulation with anti-CD3/anti-CD28	SKF 82526 (0.05–6 μM)	D1-like receptors cAMP-mediated mechanism	↓concentration-dependent cell proliferation just on normal peripheral lymphocytes	132
Jurkat cells and human normal peripheral lymphocytes	Cell mitogen-stimulation with anti-CD3/anti-CD28	Quinpirole (0.001–6 μM)	D2-like receptors	↓concentration-dependent cell proliferation just on normal peripheral lymphocytes; Inhibited phosphorylation of ZAP-70 by quinpirole just in activated normal T cells	132
Human peripheral T lymphocytes cultures	Cells from HS. Cell stimulation with anti-CD3	DA (0.007–0.033 μM)	D2R, D3R	↓proliferation in a concentration-dependent manner; ↓IL-2, IFN-γ and IL-4 release in a concentration-dependent manner; inhibitory effect on Lck and Fyn abrogated by D2DR and D3DR antagonists	117
Human T cells cultures	Cells from HS. Cell stimulation with anti-CD3/anti-CD28	PD 168077 maleate salt 1 μM; ABT 724 trihydrochloride 1 μM	D4R	↓anti-CD3/CD28-mediated T cell proliferation; ↓expression of the early activation markers CD69 and CD25 like that of the resting cells; ↓IL-2 secretion; KLF2 expression in activated T cells associated with down-regulation of ERK1/ERK2	115
Mouse splenocytes	Splenocytes stimulation with LPS or ConA	SKF38393 or LY171555 (1, 5, 10 μg kg^{-1} i.v.); SKF38393 or LY171555 (0.001–10 μM)	D1-like and D2-like receptors	↑splenocytes proliferation after *in vivo* treatments; ↑splenocytes proliferation by SKF38393 or LY171555 0.001–1 μM *in vitro*; ↓splenocytes proliferation by SKF38393 or LY171555 10 μM *in vitro*	133
Human $CD8^+$T regulatory cells/ PBMCs co-culture (1:1)	Cells from HS, stimulated with anti-CD3/anti-CD28	DA (0.01 μM); SKF-38393 (0.01 μM)	D1-like receptors	↓functional $CD8^+$ Treg by DA in presence of D2 AT or by SKF-38393 on $CD8^+$T cells; ↓$CD8^+$T reg suppressive effect on PBMC proliferation by DA or SKF-38393	103
Human $CD4^+CD25^+$ regulatory T cells/T effector cells co-cultures (1:1)	Cells from HS, stimulated with PHA or anti-CD3/anti-CD28	DA (0.05298 ± 0.01692) μM released by cultured $CD4^+CD25^+$ regulatory T cells in culture medium after 1 h treatment with reserpine (1 μM); DA 1 μM	D1-like receptors	↓suppressive effect of Treg on Teff proliferation ↑cAMP levels by DA 1 μM in Tregs; inhibition of IL-10 and TGF-β production on Tregs by reserpine	79
Murine $CD4^+CD25^+$/ $CD4^+CD25^-$ T-cells co-cultures	Cell stimulation with anti-CD3 and IL-2 *in vitro*; Optic nerve crush injury in BALB/c mice (*in vivo*)	DA (10 and 0.1 μM); DA (0.4 mg kg^{-1}) after nerve crush injury; DA (10 μM)	D1-like receptors	↓Treg-suppressive activity on Teff proliferation; ↓CTLA-4 expression and IL-10 production on Treg; ↓phospho-ERK1/2 in Treg; ↑neuronal survival after optic nerve crush injury	102
Human peripheral blood lymphocytes	Cells from HS stimulated with pokeweed or alloantigens	BIM 53097 (0.1 μM)	D2R	↓proliferation; ↓IFN-γ and IL-6 secretion	114

(Continued)

Table 2. Continued.

Immune target	Experimental condition	[DA]- [DA AG]	DR	Mechanism	Ref.
Human T lymphocytes	Cells from HS under unstimulated/ normal conditions	DA (0.01–100 μM); SKF 38393 7-Hydroxy-DPAT; quinpirole	D1-like receptors; D3R, D2R	↑TNF-α in a time- and dose-dependent manner by DA, SKF 38393 and 7-Hydroxy-DPAT; ↑IL-10 in a time- and dose-dependent manner by DA, SKF 38393 and quinpirole	138
Murine lymphocytes cultures	Cell stimulation with ConA	Quinpirole (0.01, 0.1 μM)	D2-like receptors	↓T-bet, IFN-γ and IL-2 levels; ↑GATA-3, IL-4 and IL-10 levels; ↓ROR-γt and IL-22 levels; ↑Foxp3 and TGF-β levels	110
Murine lymphocytes cultures	Cell stimulation with ConA	SKF38393 (0.01 μM)	D1-like receptors	↓IFN-γ production	200
Murine lymphocytes cultures	Cell stimulation with ConA	Quinpirole (0.001–10 μM)	D2-like receptors ↓intracellular cAMP content and CREB phosphorylation	↓proliferation in a concentration-dependent way; ↓IFN-γ and ↑IL-4	200
Human peripheral blood mononuclear cells cultures	Cell stimulation with anti-CD3/ anti-CD28 of HS and MS patients	DA (10 μM)	D2-like receptors	↓IL-17 and IFN-γ production in HS and MS	112
Murine $CD4^+$T cells cultures	Cell-stimulation with anti-CD3/ anti-CD28	PD128907 0.05 μM	D3R	↑IL-2 production; ↑Th1 differentiation	113
Human lymphocytes	Cells from HS under unstimulated condition or stimulated with PHA and IL-2	Quinpirole (0.1–10 μM)	D3R	↓IL-4 and Il-10 production; ↑IFN-γ production; ↑CD25 and ↓CXCR3	139
Human and mouse peripheral naive $CD8^+$ T cells	Human cells from HS. Resting condition	DA (0.0001, 0.001, 0.01, 0.1, 1 μM); DA (0.1 nmol i.p.)	D3R	↑migratory activity in a concentration-dependent way; α4β1 and α5β1 integrin activation and adhesion to fibronectin; activation of LFA-1 and adhesion to ICAM-1; *In vivo* mobilisation of naive $CD8^+$ T cells and homing to lymph nodes	116
Human peripheral T lymphocytes	Unstimulated condition	DA 0.01 μM; pergolide 0.01 μM; bromocriptine 0.01 μM	D2R, D3R	α4β1 and α5β1 integrin activation and adhesion to fibronectin	143
Human peripheral CD8+ T lymphocytes	Unstimulated and activation by anti CD3/anti-CD28 Abs	DA 1 μM	D3R	↑migratory activity and adhesion in unstimulated condition, but not in activated state	144
Splenocytes, NK cells, B cells, neutrophils, monocytes, peritoneal Macrophages and BM-DCs from C57BL/6 mice	Cell stimulation with LPS	DA (1, 10 μM); A77636 (10, 100 μM); Quinpirole (10, 100 μM)	D2, D3, D4 > D1, D5	↓IFN-γ, IL-1β and TNF-α secretion by DA, A77636 and quinpirole; ↑IL-10 secretion by DA; ↓ERK1/2 phosphorylation and p38MAPK by A77636; ↑CXCL1 secretion by DA on NK cells and peritoneal Macrophages	100

(Continued)

Table 2. Continued.

Immune target	Experimental condition	[DA]- [DA AG]	DR	Mechanism	Ref.
Human monocyte-derived dendritic cells (Mo-DCs)	Immature autologous Mo-DCs from HS treated with forskolin (10 μM) or DA antagonists (sulpiride, 0.1 μM; SHC-23390)	DA (0.1, 1, 10 μM)	D2-like receptors ↑induced transient $Ca2^{+}$ mobilisation and ↓cAMP	↑cAMP; ↑TH activity and DA synthesis and storage by DCs	105
Human naïve $CD4^{+}$ T cells	Cells from HS. Cell stimulation with anti-CD3/anti-CD28	DA (0.001–1 μM)	D1-like receptors	↑cAMP formation; ↑IL-4 and IL-5 secretion in a concentration-dependent-way; ↑GATA-3 mRNA expression	105
Bone marrow-derived DCs from wild type and D5RKO mice	LPS-induced activation	SKF38393 (0.001 μM)	D5R	↓LPS-induced ERK1/2 phosphorylation just in wild-type DCs; ↓IL-23, IL-12 in no-treated D5RKO DCs; ↓IL-2 production and proliferation of CD4+ T cells in presence of D5RKO DCs; ↓Th17 infiltration in EAE mice transferred with D5DR-KO DCs	101
NK cells from mouse spleen cultures	Cytotoxicity of NK cells against the YAC-1 lymphoma cell line	SKF38393 (0.1, 0.01 μM)	D1-like receptors	↑NK cell cytotoxicity by SKF38393; ↑D1/D5Rs expression, cAMP, CREB phosphorylation levels by SKF38393	149
NK cells from mouse spleen cultures	Cytotoxicity of NK cells against the YAC-1 lymphoma cell line	Quinpirole (0.1, 0.01 μM)	D2-like receptors	↓NK cell cytotoxicity by quinpirole; ↓D3R and D4R expression, cAMP content and CREB phosphorylation by quinpirole	149
Human $CD56^{+}$ NK cells cultures	Cells from HS. Cell stimulation with anti-CD3 and rIL-2	DA (0.001–10^{-12} μM); SKF 38393 (0.1 μM); quinpirole (20 μM)	D5R	↓proliferation by DA at 0.01, 10^{-6}, or 10^{-9} μM; ↓proliferation by SKF 38393, but not by quinpirole; ↓IFN-γ production by DA at 0.01 and 10^{-6} μM and SFK 38393; ↑miR-29a mRNA levels and ↓relative binding of p50 to miR-29a promoter by DA 0.01 μM and SKF 38393	104
DR-independent					
Spleen and thymus cells from BALB/c mice	Cell stimulation with ConA	DA (10 μM)	NA Alternative mechanism not detected	↓DNA synthesis	154

AG, Agonist; ATP, Adenosine Triphosphate; BALB, Bagg Albino; BM-DCs, Bone Marrow Derived Dendritic Cells; BMDMs, Mice Bone Marrow-Derived Macrophages; cAMP, Cyclic Adenosine Monophosphate; CCL2, Chemokine (C-C motif) Ligand 2; CMV, Cytomegalovirus; ConA, Concanavalin A; CREB, cAMP-Response Element Binding Protein; CTLA4, Cytotoxic T Lymphocyte Antigen 4; CXCL, Chemokine (C-X-C motif) Ligand; DA, Dopamine; DC, Dendritic cells; DNA, Deoxyribonucleic Acid; DR, Dopamine Receptor; EAE, Experimental Autoimmune Encephalomyelitis; ERK, Extracellular Signal-Regulated Kinases; Foxp3, Forkhead Box P3; Fyn, Tyrosine-protein kinase Fyn; GATA-3, GATA Binding Protein 3; HS, Healthy Subjects; i.v., intravenous; ICAM-1, Intercellular Adhesion Molecule-1; IFN, Interferon; IL, Interleukin; iNOS, inducible Nitric Oxide Synthase; KLF2, Krüppel-Like Factor 2; KO, knockout; Lck, Lymphocyte-specific protein tyrosine kinase; LFA-1, Lymphocyte Function-Associated Antigen 1; LPS, Lipopolysaccharide; M-CSF, Macrophage Colony-Stimulating Factor; MMP-9, matrix metalloproteinase-9; Mo, monocytes; mRNA, Messenger Ribonucleic Acid; MS, Multiple Sclerosis; NA, Not Available; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of activated B cells; NK, Natural Killers; NLRP3, NOD-, LRR- and Pyrin Domain-Containing Protein 3; PBMCs, Peripheral Blood Mononuclear Cells; PHA, Phytohaemaglutinin; PMA, Phorbol Myristate Acetate; ROR-γt, RAR-Related Orphan Receptor γt; ROS, Reactive Oxygen Species; ROS, Reactive Oxygen Species; T-bet, T-box transcription factor; Teff, T effector cells; TGF, Transforming Growth Factor; Th, T helper; TH, Tyrosine Hydroxilase; TLR, Toll-Like Receptor; TNF, Tumour Necrosis Factor; Treg, T regulatory cells; ZAP, Zeta-Chain-Associated Protein Kinase.

inflammatory conditions in PD, the activation of D3DR may enhance the inflammatory milieu, contributing to the neurotoxic effects. Indeed, systemic inhibition of D3DR-signalling attenuates nigrostriatal neurodegeneration and motor impairment in MPTP-intoxicated mice by favouring anti-inflammatory astrocyte phenotype but inhibiting microglia activation.[123,124]

Peripheral myeloid cells are similarly affected by DA and its analogues (Table 2). High concentrations of DA and the D1-agonist A-68930 reduced IL-1β and IL-18 secretion through inhibition of NLRP3 inflammasome activation in LPS-primed murine bone marrow-derived macrophages (BMDMs) and the macrophage-like RAW264.7 cells.[92,94] On the other hand, evidence from primary human monocyte-derived macrophages (hMDM) demonstrated that DA and D1DR activation increased the production of pro-inflammatory cytokines IL-6, IL-1β and IL- 18 in unstimulated conditions, allegedly by increasing NLRP3 inflammasome and NF-κB activation[90,125] as well as promoting CCL2 and CXCL8 expression, which are associated with migratory, cell accumulation and adhesion of human matured monocytes.[125–127] DA also affects Toll-like receptor (TLRs)-induced inflammatory responses by downregulating the NF-kB inflammatory signalling pathway and reducing IL-6 and TNF-α productions by macrophages through a signalling D5DR mechanism.[91,128] The controversial findings of DA and DR1-signalling in inflammatory responses of monocytes and macrophages could be due to different concentrations of DA being used in different studies.[91,92,94] The species variation in immune-related pathways, inflammatory responses and DRs expression could also be potential contributors to these controversial findings.[129] Indeed, the maturation/activation or inflammatory/disease-specific conditions may influence the expression and signalling of different DRs.[125–127] For example, expression of D5DR, but not other DRs, was significantly increased in peripheral blood mononuclear cells (PBMC) of S. aureus-infected patients.[91] The levels of D1DR and D5DR proteins in human monocytes were also found to be significantly increased with their maturation.[127] In addition, activation of DA and D1R-signalling also exacerbates the cytomegalovirus-induced inflammatory response.[90] These findings suggest that the expression of DRs could be altered in PD patients to promote inflammatory response *via* DA signalling. Furthermore, in a recent study, monocytes from PD patients were found to express a higher level of TH, the rate-limiting enzyme involved in DA biosynthesis, compared to the healthy controls. Indeed, TNF-α stimulation further increased both the number of TH^+ monocytes as well as the levels of TH per monocyte.[130] The increase in TH-positive peripheral immune cells raised many exciting questions: does this represent a compensatory mechanism due to DA deficiency, and how do DA-mediated immune responses contribute to PD development and progression.[131] Regarding species-specific differences, experimental evidence shows that stimuli towards a pro-inflammatory macrophage profile significantly upregulated the levels of dopamine D2-like receptors in human cells, while the same were decreased, together with D1-like DR, in murine BMDMs.[97] Nonetheless, D2DR activation was shown to reduce inflammatory responses in M1 macrophages obtained from both human PBMC and murine bone marrow-derived macrophages (BMDMs).[97] Similarly, high DA concentrations also reduced TNF-α secretion in a murine BMDM culture *via* D2-like DR activation.[94]

It has been reported that DA and the D1-like receptor activation evoke anti-inflammatory effects in human PBMC and $CD4^+$ T lymphocytes[106,107] (Table 2). In particular, D1DR signalling inhibited IL-2-induced proliferation and cytotoxicity in cultured human $CD4^+$ and $CD8^+$ T cells, by increasing intracellular cAMP levels. Similarly, D2-like DR signalling also reduces proliferation and secretion of IL-2, IFN-γ and IL-4 in human T cells *via* inhibition of T Cell Receptor (TCR) stimulation.[115,117,132] By contrast, administration of D1DR (SKF38393) or D2DR (LY171555) agonists in mice enhanced LPS- or concanavalin A-stimulated splenocyte proliferation.[133] A mouse model of experimental autoimmune encephalomyelitis (EAE) has shown that, DRD5-signalling confined to naïve CD4 T cells promoted the differentiation and proliferation of Th17 cells.[134] Interestingly, DRD5-signalling confined to Tregs also exacerbated their suppressive activity.[134] These findings suggest that DRD5 signalling might exert either a pro-inflammatory or anti-inflammatory effect, depending on the immune cell subsets it expresses on. DA and D1-like DR signalling was instead shown to reduce human $CD4^+$ and $CD8^+$ Treg-suppressive activity on T effector cells (Teff) and PBMC proliferation.[79,102,103] These contradictory findings suggest that, under different conditions, DA and DR signalling differentially regulate immune responses. Treatment of inflammatory conditions could therefore also impact DA-induced immune effects. Lower mRNA levels of

D5DR, D2DR and D4DR were reported in $CD4^+$ T cells from PD patients, compared to HS. Interestingly, D1DR and D5DR expression on naïve $CD4^+$ T cells negatively correlated with the disease severity.[38] Furthermore, the genetic polymorphisms in DR genes in PD alter dopaminergic modulation of the immune response.[135,136] In this regard, cAMP levels in lymphocytes and $CD4^+$ T regulatory cells, along with their suppressive functions, were affected by DR1 polymorphisms.[137] Therefore, further investigation in PBMC and T cells isolated from peripheral blood of PD patients is required to define the effects of D1-like DR activation. Treatment with DA induced secretion of TNF-α *via* D3DR, or IL-10 *via* D2DR, or both *via* D1/D5DR by T lymphocytes isolated from peripheral blood of healthy donors.[138] D2-like DR signalling inhibited T cell differentiation towards Th1 and Th17 pro-inflammatory phenotypes and decreased the production of the cytokines IFN-γ and IL-17,[110,112] while promoting the differentiation of anti-inflammatory $CD4^+$ Treg and Th2 cells and production of TGF-β, IL-10 and IL-4.[110] In contrast, D3DR signalling exerted pro-inflammatory effects by stimulating IL-2 production and Th1 differentiation.[113,139] Similarly, D3DR was found to favour Th1 differentiation and Th17 cells expansion in mice under chronic inflammatory conditions, suggesting DRD3-mediated signalling favours the inflammatory potential of $CD4^+$ T cells.[140] Similar to their effect on microglia, the systemic transfer of D3DR-antagonised $CD4^+$ T cells in a mouse model of PD (induced by the chronic administration of MPTP and probenecid) reduced motor impairment and the extent of microgliosis without significant effects on neurodegeneration and astrogliosis.[44] The inflammatory effect mediated by D3DR-expressing $CD4^+$ T cells on microglia *in vivo* is even more intriguing, suggesting it might directly contribute to neurotoxicity.[33,141,142] Indeed, DA signalling through D3DR and D2DR mediates integrin activation and adhesion to fibronectin and ICAM-1, enhancing human T cell adhesion and migration.[116,143,144] The expression of D3DR is increased in $CD4^+$ T cells of PD patients and D2-like DR on $CD4^+$ T memory and T effector cells positively correlates with increased motor symptoms according to appropriate clinical scores (UPDRS).[38] Further evidence demonstrates downregulation of DRD3 on naïve $CD4^+$ T cells in PD patients was correlated with disease activity.[44,145]

Dopamine and DR signalling also indirectly affect the functional activity of T lymphocytes through modulation of other immune cells, such as DCs and NK cells (Table 2).[63,146] Human DCs express DRs and are the major source of DA.[105,147] They produce different patterns of cytokines under different inflammatory stimuli.[63,100] Engagement with $CD4^+$ T cells induced DCs to release DA, which drives $CD4^+$ T cell polarisation towards the Th2 anti-inflammatory phenotype.[105] The dopaminergic modulation of DCs and their role in T cell differentiation and immune responses depends on different types of DR signalling. A mouse study reported that autocrine signalling through DC-derived DA and D5DR promoted the production of cytokines IL-23 and IL-12, thereby priming naïve $CD4^+$ T cell activation.[101] In other studies, antagonism of D1-like DR inhibited Th17 differentiation, accompanied by an increase of IFN-γ production.[147] In contrast, antagonism on D2-like DR in DCs promoted differentiation towards Th17 cells, while reducing Th1 polarisation.[147] In addition, the D2-like DR antagonist haloperidol decreased expression of the major histocompatibility complex (MHC) II, and the costimulatory molecules CD80 and CD86, thus inhibiting murine DC maturation and decreasing the release of IL-12 p40.[148] Furthermore, haloperidol-treated DCs suppressed the proliferation of Th1 immune responses in co-culture.[148] In NK cells DA exerts opposite effects, by activating different DR subtypes, positively or negatively coupled with the cAMP-PKA-CREB pathway.[149] In particular, D1-like DR signalling enhanced the cytotoxicity of mice NK cells against YAC-1 lymphoma cells through the cAMP-PKA-CREB signalling pathway, whereas D2-like signalling attenuated NK cell functions by decreasing cAMP levels.[149] However, DA did not have any impact on their effector functions or cytotoxic activity of human NK cells. Freshly purified human NK cells predominantly express D2-like DRs, but a prolonged stimulation with IL-2 induces a significant upregulation of D5DR, which subsequently inhibits the proliferation of and IFN-γ production by NK cells through DA signalling.[104] These findings highlight the differences in immune responses and neuronal signalling pathways between different species.[104]

DR-independent mechanisms

The DA-mediated effects on immune cell functions can also be DR-independent (Figure 2). Indeed, DA binds D3DR, D4DR and D5DR with the highest affinity, and D1DR, D2DR, DAT and α1-, α2-, β1-, β2-adrenoreceptors with a similarly lower affinity.[150] Similarly to DRs, adrenoreceptors

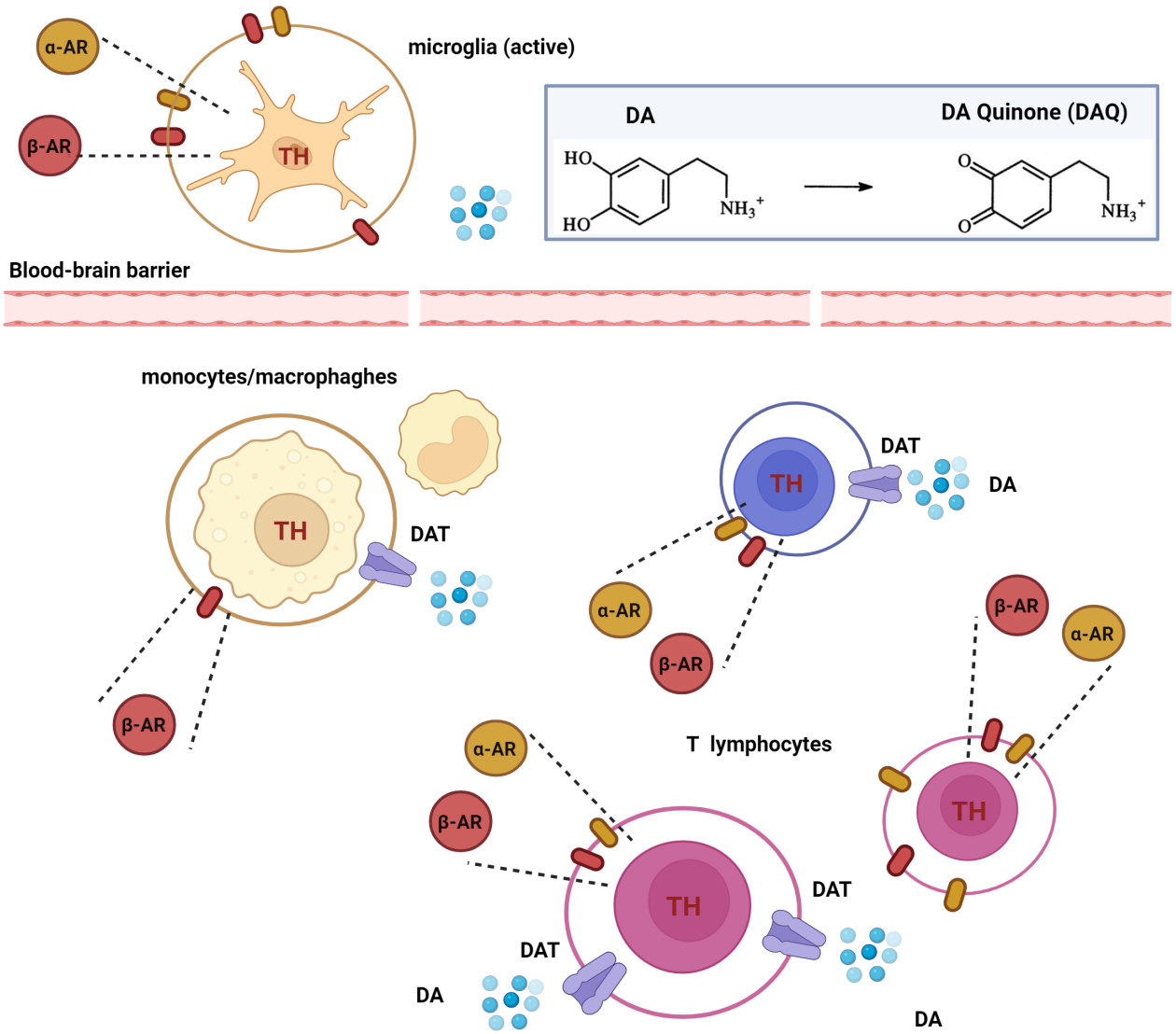

Figure 2. Dopaminergic modulation of immune responses in PD: DR-independent mechanism. (i) A and β- adrenoreceptors (AR) are expressed by human and animal immune cells and modulate their activity. (ii) Immune cells can synthesise and uptake DA since they express the tyrosine hydroxylase (TH) and the dopamine transporter (DAT). DAT and other transporters, such as the plasma membrane monoamine transporter (PMAT), can modulate DA activity on immune cells. (iii) Redox pathways and the generation of reactive oxygen metabolites, such as DA quinone (DAQ), are involved in DA-immune regulation. The figure was created with BioRender.com.

(AR) are expressed by immune cells and modulate their activity.[151] A study with murine macrophages showed that DA decreases LPS-induced IL-12p40 production *via* a β-AR-mediated mechanism[152] (Table 2). In addition, DA signalling through both α- and β-AR agonists was also found to lead to a decrease in NO production by LPS-treated N9 microglial cells[118] (Table 1). It has also been found that DA signalling can occur through Dopamine transporter (DAT) and other transporters, such as the plasma membrane monoamine transporter (PMAT).[101] Interestingly, same as TH expression in monocytes,[130] DAT expression in PBMCs from PD patients was also found to be increased.[131] Experimental evidence shows DA can modulate inflammation through redox pathways and the generation of reactive oxygen metabolites, such as DA quinone (DAQ).[98,153,154] For example, DA can reduce NO and iNOS production, TNF-α, IL-1β and IL-6 expression in the presence of tyrosinase, which catalyses the oxidation of DA to DAQ in both murine primary and microglial BV-2 cell line[98,153] (Table 1). Treating BV-2 cells with 30 μM DA in

the presence of 300 U mL^{-1} tyrosinase, which catalyses the oxidation of DA to DAQ, has been shown to attenuate the mRNA expression of pro-inflammatory cytokine in response to LPS stimulation.[98] Interestingly, another independent study shows that treating BV-2 cells with 100 μM DAQ increases the expression of genes associated with inflammation, indicating a pro-inflammatory effect of DAQ in microglial cells.[155] Although the resulting concentration of DAQ from DA conversion was not known, these contradictory findings suggest that the immune regulatory effects of DAQ are concentration dependent[98] (Table 2).

DOPAMINE REPLACEMENT THERAPY IN PD: L-DOPA AND DOPAMINERGIC AGONISTS

The current antiparkinsonian therapy focuses on treating motor symptoms. Antiparkinsonian drugs include dopaminergic agents, namely L-dopa and dopaminergic agonists, monoamine oxidase (MAO)-B and Catechol-O-methyltransferase (COMT) inhibitors and other drugs such as amantadine, centrally acting antimuscarinic drugs and istradefylline.[156,157] Despite the availability of different medications for PD, none of them can be considered as the best single treatment for the disease.[15,157] Pharmacological therapy is individually tailored, taking into account factors such as age, main symptoms, impairment severity and the occurrence of long-term therapy side effects.[158,159]

Dopaminergic agents aim at restoring altered dopaminergic activity at the striatal level and represent the main therapy for PD.[15] L-dopa represents the first-choice therapy due to its effectiveness in treating motor symptoms, especially bradykinesia and rigidity.[157] L-dopa is the precursor of the neurotransmitter DA, which is administered in this pro-drug form to exploit its ability to cross the BBB through the neutral amino acid transporter (Supplementary table 1). In clinical practice, L-dopa is almost always administered in fixed-combination formulation with a peripheral decarboxylase inhibitor, such as carbidopa (L-dopa/carbidopa 10: 1 or 4: 1) or benserazide (4: 1), to increase systemic L-dopa bioavailability, thus reducing the levodopa dose required to produce clinical effects.[157] Unfortunately, it is well known that more than half of treated patients develop long-term side effects, including L-dopa-induced dyskinesia (LID), dystonia and phases of non-response to therapy alternated with unpredictable periods of mobility (on/off phenomenon). The dose of L-dopa used in PD treatment is increasing over the years.[157,160,161] Dopaminergic agonists are used alone, typically in the early phase of the disease, or combined with L-dopa since they reduce the threshold of L-dopa effective concentration and facilitate the therapeutic response. Moreover, DA agonists also have the potential to delay the occurrence of motor complications induced by L-dopa.[157] Dopaminergic agonists are classified into ergot derivates, which include bromocriptine, pergolide, lisuride, cabergoline and non-ergolines including apomorphine, piribedil, pramipexole, ropinirole and rotigotine.[157] Dopaminergic agonists can cross the BBB and enter the brain without requiring any carrier-mediated transport. They are commonly D2-like agonists with different pharmacokinetic properties[158,162–166] (Supplementary table 1). Currently, the most used dopaminergic agonists in clinical practice are the non-ergolines, such as pramipexole and ropinirole which are used in immediate-release (IR) and extended-release (ER) formulations, and rotigotine which is used in a transdermal delivery patch formulation.[159]

The currently available drugs are safe and offer effective symptomatic treatments, and there is evidence that at least some of them could modify immune signalling in PD to mediate a neuroprotective effect.[167,168] Immunotherapy is increasingly regarded as an attractive strategy for PD treatment.[9,13,14] Therefore, considering the dopaminergic modulation of immune response in PD, the studies presented in the following section investigate the possible effects of L-dopa and dopaminergic agonists on the immune response (Table 3).

IMMUNE REGULATORY EFFECTS OF DOPAMINERGIC ANTIPARKINSONIAN DRUGS

L-dopa

In light of the immunomodulatory effects of DA, several studies have explored the link between alterations of immune responses in PD and the antiparkinsonian effects of dopaminergic agents, especially L-dopa.[36,37,39,41,169–171] One of the significant alterations in the peripheral immune system of PD patients is a reduction in T and

Table 3. Immune effects of dopaminergic antiparkinsonian drugs

Immune target	Experimental condition	Drug	DR	Mechanism	Ref.
L-dopa					
Cultured lymphocytes	PD patients on pharmacological treatment (drug-treated, n = 56) and untreated (n = 33). Cells were activated with PHA	L-dopa with a mean dose of 484 mg per day (50–1800 mg per day) alone (n = 8), L-dopa+ DA agonists (n = 28), with selegiline (n = 11), L-dopa with other agents (n = 5), DA agonists alone (n = 3), with selegiline (n = 8)	NA	↓PHA-induced Fas expression in $CD4^+CD25^+$ and, $CD4^+CD45RA^+$ T cells of L-dopa-treated patients	36
Lymphocytes	PD patients (n = 24) studied before and after medications	L-dopa/benserazide (300–800 mg per day) for 207 ± 12 days (195–219 days)	NA	↑$CD16^+$ lymphocytes in treated patients; ↓$CD19^+$ lymphocytes, and the ratios of CD4/CD8 and CD95/CD3 in treated patients	172
Peripheral blood lymphocytes	Cells from HS. Oxidative stress induced by H_2O_2	L-dopa (100 μM) alone or in combination with carbidopa 25 (μM)	NA	↓8-oxo-dG concentrations by L-dopa/carbidopa more than L-dopa alone; ↓micronuclei induction; ↑GSH/GSSG ratio; ↓malondialdehyde and protein carbonyl levels	176
Peripheral blood lymphocytes	Cells from HS. Oxidative stress induced by H_2O_2	L-dopa (20, 50, 100 and 150 μM) alone or in combination with carbidopa (12.5, 25, 37.5 μM)	NA	↓H_2O_2-induced DNA damage; ↓SOD1 and SOD2 mRNA levels by L-dopa without H_2O_2; ↑CAT mRNA levels by L-dopa without H_2O_2; ↓GPX3 mRNA levels by L-dopa without H_2O_2, except L-dopa 150 μM that ↑GPX3 mRNA levels prevent radical formation in a concentration-dependent manner	177
Peripheral blood mononuclear cells	PD patients (n = 24)	L-dopa treatment (499 ± 235.8 mg per day) consumed from 7 ± 4.6 years	NA	Significant negative correlation between L-dopa daily dosage and ROS production	173
Lymphocytes	PD patients	DA (0.1, 1, or 500 μM); L-dopa (200–1350 mg per day)	NA	↑caspase-3 activity by DA 1 μM; ↓caspase-3 activity by DA 500 μM; ↓Cu/Zn SOD levels by DA 1 and 500 μM, while DA 0.1 slightly increase. *In vivo* negative correlation between the daily intake of L-dopa and the lymphocyte levels of Cu/Zn SOD	174
Lymphocytes	PD patients	PD patients: untreated; treated with L-dopa, or with L-dopa + DA agonists	NA	↑caspase-3 activity in all PD groups; Further ↑caspase-3 activity in patients taking L-dopa, but tended to ↓in L-dopa + DA agonists patients; ↑Cu/Zn SOD levels in L-dopa-treated patients	175
Lymphocytes	PD patients under L-dopa treatment (n = 21), L-dopa + PPX (n = 20) or ROP (n = 12) or pergolide (n = 6) and untreated (n = 13)	L-dopa treatment alone (584.5 ± 259.5 mg per day); L-dopa (494.1 ± 188.7) + PPX (3.1 ± 1.3 mg per day) or ROP (21 ± 12.3 mg per day) or pergolide (3.9 ± 0.6 mg per day)	NA	↑caspase-3 activity, especially in L-dopa-treated PD patients; ↑Cu/Zn SOD levels; ↓Bcl-2 levels in the L-dopa/DA agonist group	178

(Continued)

Table 3. Continued.

Immune target	Experimental condition	Drug	DR	Mechanism	Ref.
Peripheral blood lymphocytes	PD patients (n = 9); Suspension of the L-dopa intake the day before the samplings (washout procedure). The 2nd and the 3rd samplings performed 90 and 180 min, respectively, after the therapy administration, according to the L-dopa half-life	L-dopa treatment (416.7 ± 291.5 mg per day) consumed from 8.7 ± 6.9 years	NA	↑DNA damage in washout conditions; ↓DNA damage after the intake of the L-dopa therapy, progressively up to 3 h from the administration	179
B cells	PD patients (n = 8) were assessed pre- and post- the onset.	L-dopa treatment (300 mg per day for 3 months)	NA	↓number of $CD19^+$ cells post commencement of medication; No effect of medication was observed for the other cell populations	37
Spleen mouse mononuclear cells cultures	T-cell stimulation with Con A; B-cell stimulation with LPS	L-dopa (100, 400 μM); DA (100, 400 μM)	NA	↑frequency of apoptotic cells in a concentration-dependent way; ↓proliferation and number of IgG- and IgM-producing cells; ↓IL-2, IL-6 and IFN-γ production	181
Spleen cell cultures from BALB/c mice	Cell stimulation with Con A or immobilised anti-CD3	L-dopa methyl ester 126 mg kg^{-1} s.c daily for 5 days; DA continuous infusion 5 μg kg^{-1}/h for 5 days	D2, D3, D4	↑proliferation by L-dopa; ↓IFN-γ-producing cells by L-dopa and by DA	182
T lymphocytes, DCs, Monocytes	Initially, untreated PD patients (n = 30) were evaluated at the baseline and after 1- and 2-year receiving antiparkinsonian treatments	L-dopa alone (250–1000 mg per day) and PPX/L-dopa combined (1.5–4.5/250–750 mg per day)	NA	↑T regulatory after 1 and 2 years of treatments; ↓B regulatory levels after 1 and 2 years of treatments, more with L-dopa compared with the combined treatment; ↑$CD8^+$T cells after 1 year and ↓after 2 years; ↑$ILT3^+$ DCs cells after 2 years of treatment; ↓SLAMF1-expressing DCs in L-dopa-treated patients than combo-treated patients and baseline; ↓frequency of IFN-γ producing Th1 cells and IL-17 and IL-6 producing Th17 cells after 2 years; ↑non-classical and classical monocytes including IL-10-producing classical monocytes after 2-year; ↑total and HLA-DR+ classical monocytes in L-dopa-treated patients; ↑levels of M1-like and M2-like monocytes after 2 years	170
$CD4^+$ T lymphocytes	PD patients: drug-treated, (n = 56) and untreated (n = 26)	L-dopa alone (n = 11), L-dopa + DA agents (n = 34), without (n = 19) or with rasagiline (n = 15), DA agonists alone (n = 4) or with rasagiline (n = 5) and 2 with other treatments	NA	No differences in absolute number of circulating $CD4^+$T cells, but the frequency of $CD4^+$T cells was higher in drug-treated patients; No differences in polarisation of T cells	39
$CD4^+$ T lymphocytes	PD patients on antiparkinsonian drugs (drug-treated n = 16) and untreated (drug-naïve; n = 37)	L-dopa alone (n = 8); L-dopa + DA agents (n = 19); DA agents alone (n = 4) or with rasagiline (6), and 17 taking DA agonists+ L-dopa, without (6) or with rasagiline (11)	NA	No differences in either absolute number or percentage of T naive, T memory and T effector cells; ↓D1, D5 and, D2 mRNA levels in PD-dt patients as well as less percentage of $CD4^+$ T cells $D1^+$ or $D3^+$ in naïve T cells, but not in T memory and effector cells	38

(Continued)

Table 3. Continued.

Immune target	Experimental condition	Drug	DR	Mechanism	Ref.
Lymphocytes	PD patients on pharmacological treatment (drug-treated, n = 30) and untreated (n = 34)	L-dopa alone (n = 15), L-dopa + DA agonists (n = 19), without (n = 12) or with selegiline (n = 7) for a mean time of 5 ± 3.7 years	NA	No correlation with L-dopa treatment, tendency towards an increase in lymphocytes count in patients treated with DA agonists + L-dopa	36
T and B lymphocytes, NKT cells	Initially untreated PD patients (n = 32) were evaluated at the baseline and after 1- (n = 22) and 2-year (n = 19) receiving antiparkinsonian treatments	L-dopa alone (NA); and L-dopa/PPX combined treatment (NA)	NA	Negative correlation between Tc1 and Tc2 cell levels and the H&Y scale score in patients treated with levodopa only after 2 years; Positive correlation between the levels of NKT cells with the MDS-UPDRS scale score in patients treated with levodopa only after 1 year; ↓IL-10+ plasma cells with a levodopa/pramipexole combination after 2 years of treatment	42
Peripheral blood mononuclear cells	DAT+ and TH+ PBMC-induced expression in MPTP and 6-OHDA mice	L-dopa (6.25 mg kg^{-1}, i.p.); L-Dopa/benserazide (6.25/10 mg kg^{-1}, i.p.)	NA	↓TH+ PBMC to baseline levels by L-dopa alone; ↓TH+ and DAT+ PBMC to baseline levels by L-dopa/benserazide	131
Striatal microglia in rats	6-OHDA induced lesion	L-dopa 6 mg kg^{-1} or 25 mg kg^{-1} twice daily (at 9 a.m. Benserazide was co-administered with L-dopa at a fixed dose of 15 mg kg^{-1} per injection; Bromocriptine 2.5 mg kg^{-1}/day	NA	No activation of microglia/macrophages could be seen in animals treated with high-dose or low-dose L-dopa and bromocriptine	188
Striatal microglia in rats	6-OHDA induced lesion	L-dopa/benserazide (6.25/15 mg kg^{-1} s.c. daily for 21 days)	NA	↑$Iba1^{+}$ microglia soma size and less branched morphology	194
Striatal microglia in rats	6-OHDA induced lesion	chronic pulsatile L-dopa (L-dopa p, 6 mg kg^{-1} s.c. daily for 2 weeks); chronic continuous L-dopa (L-dopa c, 12 mg kg^{-1} daily for 2 weeks)	NA	L-dopa p exacerbated microglia activation induced by 6-OHDA, also increasing TNF-α levels; L-dopa c restored TNF-α levels of activated microglia to physiological levels.	195
Striatal microglia in rats	6-OHDA induced lesion	L-dopa/benserazide (30/7.5 mg kg^{-1} daily for 21 days)	NA	↑OX-42 levels; ↑expression iNOS; ↑GFAP-immunoreactivity	196
Striatal astrocytes in rats	Rats with 6-OHDA lesion	L-dopa/carbidopa (100 mg o.s.) per day over a 20-day period, by day 21 post-lesion	NA	↑nitrite levels and 3-NT-immunoreactive-cells in SN and striatum; ↑ROD- and GFAP-immunoreactivity	197
Striatal microglia from macaque monkeys	MPTP-treatment	L-dopa/benserazide (100/25 mg p.o. daily for a month + L-dopa methyl ester/benserazide 15–30/50 mg kg^{-1} sc)	NA	L-dopa normalised microglial density and morphology; ↓monocytic infiltration	198
N9 murine microglia cell	LPS-induced activation	L-dopa (31.25, 62.5, 125, 250 μM)	NA	↓NO production	118
Mice striatum microglia	MPTP mice treated with LPS	50 mg kg^{-1} L-dopa and/or 5 mg kg^{-1} carbidopa i.p. once a day for 3 days	NA	↓NF-kB p65 level; ↓Iba1-positive cells and their morphological changes; ↓TNF-α, IL-1β and IL-6 mRNA levels in the striatum	199

(Continued)

Table 3. Continued.

Immune target	Experimental condition	Drug	DR	Mechanism	Ref.
DA agonists					
Primary mouse astrocytes cultures	LPS and ATP-induced activation	Bromocriptine (10, 50, 100 μM)	D2	↓IL-1β and caspase-1 in a concentration-dependent way	109
T-lymphocytes	PD patients: no-drug treated (n = 9); drug-treated with L-dopa (n = 4); L-dopa + DA agonists (n = 9); PPX alone (n = 1)	L-dopa (150–1200 mg per day); PPX (1.05–2.1 mg per day); ROP (150-1200 mg per day); ROT (300–400 mg per day)	NA	Upregulation of ATP synthase β subunit and proteasome β subunit type-2 downregulation by L-dopa: Upregulation of prolidase, Actin-related protein 2, F-Actin capping protein subunit β, proteasome activator complex subunit 1 and peroxiredoxin 6 and downregulation of tropomyosin α-3 chain and of an isoform of GAPDH by dopaminergic agonists	202
T lymphocytes, DCs, Monocytes	Initially untreated PD patients (n = 30) were evaluated at the baseline and after 1- and 2-year receiving antiparkinsonian treatments	L-dopa alone (250–1000 mg per day) and PPX/L-dopa combined (1.5–4.5/250–750 mg per day)	NA	↑T regulatory after 1 and 2 years of treatments; ↓B regulatory levels after 1 and 2years of treatments; ↑$CD8^+$T cells after 1 year and ↓after 2 years; ↑$ILT3^+$ DCs cells after 2 years of treatment; ↓frequency of IFN-γ producing Th1 cells and IL-17 and IL-6 producing Th17 cells after 2 years; ↑HLA-expressing classical monocytes after 2 years that negatively correlate with [PPX]; ↑levels of M1-like after 2 years that negatively correlate with [PPX]; ↓TGF-β-secreting Th3-type Treg after 2 years that negatively correlate with [PPX]	170
Peripheral blood mononuclear cells	PD patients: drug-naïve (n = 136); L-dopa treated (n = 83); piribedil or PPX treated (n = 38); L-dopa + DA agonist (n = 105); matched healthy control *In vitro* experiments on PBMC isolated from HS	PPX (NA *in vivo*; 10 μM *in vitro*)	NA	↑Nurr1 mRNA level by PPX *in vitro* and *in vivo*	171
Peripheral blood mononuclear cells	Unstimulated cells from HS	L-dopa (3043 μM); PPX (0.9 μM)	NA	↓IL-1β, IL-6, IL-8, IL-10 and TNF-α by L-dopa; ↓IL-6, IL-8 and TNF-α by PPX	184
Striatal microglia in mice	Lactacystin-PD model	PPX (0.1 mg kg^{-1} or 0.5 mg kg^{-1} i.p. daily 7 days before PD induction and for 28 days)	Partially D3	↓microglia and astrocytic activation by PPX at high and low dose	205
Mesencephalic astrocytes-SH-SY5Y interaction	SH-SY5Y cells treated with lactacystin and conditioned medium derived from PPX-treated astrocytes	PPX (10 μM)	D2, D3	↑SH-SY5Y cell viability; ↑BDNF in the conditioned medium of astrocyte cultures	24
Primary mice astrocyte cultures	LPS-induced activation	Bromocriptine (20 μM)	NA	↓extracellular TNF-α	206
Peripheral blood mononuclear cell cultures	Cells from HS, activated with PHA, ConA or PWM	Bromocriptine (0.15–15.3 μM)	NA	↓proliferation; ↓IL-2 production in a concentration-dependent way	207

(Continued)

Table 3. Continued.

Immune target	Experimental condition	Drug	DR	Mechanism	Ref.
Guinea pig macrophages	*In vivo*	Bromocryptine (0.005–0.5 μg kg^{-1}/day), leuprolide (0.005–0.5 μg kg^{-1}/day) and pergolide (0.001–0.250 μg kg^{-1}/day) for 7 days	D2 > D1	↑macrophage clearance of IgG-sensitised cells; ↑macrophage receptor FcγR1,2 responsivity	208
Microglia cell cultures from mice	LPS and IFN-γ-induced activation	PPX dihydrochloride (100 μM)	D2, D3	↑release of nitrite	122

6-OHDA, 6-hydroxydopamine ATP, Adenosine Triphosphate; BALB, Bagg Albino; BDNF, Brain-Derived Neurotrophic Factor; CAT, Catalase; CNS, Central Nervous System; Con A, Concanavalin A; DA, Dopamine; DAT, Dopamine Transporter; DCs, Dendritic Cells; DNA, Deoxyribonucleic Acid; dt, drug treated; EAE, Experimental Autoimmune Encephalomyelitis; FCγR, Fc-γ Receptors; GAPDH, Glyceraldehyde-3-phosphate Dehydrogenase; GFAP, Glial Fibrillary Acidic Protein; GPX, Glutathione Peroxidases; GSH, Glutathione; GSSG, Glutathione Disulphide; H&Y, Hohen & Yahr; H_2O_2, Hydrogen Peroxide; HS, Healthy Subjects; i.p., Intraperitoneal; Iba1, Ionised Calcium-Binding Adaptor Molecule 1; ICH, Spontaneous Intracerebral Haemorrhage; IFN, Interferon; Ig, Immunoglobulin; IL, Interleukin; ILT3, Immunoglobulin-like Transcript 3; iNOS, Inducible Nitric Oxide Synthase; L-dopa, Levodopa; LPS, Lipopolysaccharide; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mRNA, messenger Ribonucleic Acid; NA, Not Available; NF-κB, Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells; NK, Natural Killer; NO, Nitric Oxide; NT, Nitrotyrosine; Nurr1, Nuclear Receptor Related 1 Protein; PBMC, Peripheral Blood Mononuclear Cells; PD, Parkinson's Disease; PHA, Phytohemagglutinin; PPX, Pramipexole; PWM, Pokeweed mitogen; ROD, Relative Optical Density; ROP, Ropinirole; ROS, Reactive Oxygen Species; ROT, Rotigotine; SLAMF1, Signalling Lymphocytic Activation Molecule Family Member 1; SN, *substantia nigra*; SOD, Superoxide Dismutase; TGF-β, Transforming Growth Factor beta; Th, T helper; TH, Tyrosine Hydroxylase; TNF, Tumour Necrosis Factor; Treg, T regulatory cells.

B lymphocyte numbers, which is potentially due to cell apoptosis.[36,37,39,41,169] In a small group of patients treated with L-dopa, a reduced level of activation-induced apoptosis was found in naïve and memory T cells, compared to the healthy subjects.[169] Consistent with the potential antiapoptotic effect of L-dopa treatment, the combination of L-dopa and benserazide decreased the ratio of the apoptotic cell marker CD95 and the number of dead lymphocytes in PD patients.[172–175] The anti-apoptotic effect of L-dopa could be conceivably related to their anti-oxidative functions.[173–177] To evaluate the efficacy of L-dopa therapy on cellular oxidative stress in PD, several biomarkers are considered, such as increased ROS production, impairment of antioxidant defences like glutathione-(GSH) and a decline in DNA repair efficiency, which can ultimately trigger apoptosis.[176] PD patients treated with L-dopa showed an increase in the concentration of the anti-oxidative enzyme Cu/Zn superoxide dismutase (SOD), which may counteract the pro-apoptotic increase of caspase-3 levels in PD.[174,175,178] Moreover, extensive evidence suggests that L-dopa can act as a scavenger for ROS, thus protecting DNA from oxidative damage in peripheral blood lymphocytes.[38,175–177] Interestingly, both L-dopa and carbidopa may have different but complimentary antioxidant mechanisms.[176,177] L-dopa often acts as a scavenger for ROS, while carbidopa plays a crucial role in restoring the expression of key genes involved in antioxidant cellular processes.[177] Moreover, the ability of carbidopa to increase L-dopa half-life might also be related to its protective effect.[173,179]

Furthermore, L-dopa treatment also led to a decrease in the percentage of CD19 lymphocytes, suggesting it may exert an anti-proliferative effect on B cells.[172] Nevertheless, in other studies, stepwise regression modelling revealed that disease severity measured by Hoehn and Yahr (H&Y) scale is the most reliable prediction of B cell decrease.[37] Although studies in mice indicate that high concentrations of L-dopa reduce B cells proliferation and IgG production, this occurs at even lower doses in human malignant cells.[180,181] However, other *in vivo* studies reported that treatment with L-dopa augments the proliferative response of murine T lymphocytes in response to mitogenic stimuli *via* a D2-like DR mechanism.[182] As a result,

DR-signalling through receptors other than D2DR evokes opposite effects on lymphocyte proliferation.[180–182]

The administration of L-dopa or DA in mice also selectively decreased the number of splenic IFN-γ-producing cells *via* D2-like DR, suggesting that dopaminergic therapy might regulate Th1 and inflammatory responses, which are increased in PD.[182] In contrast, in a 2-year longitudinal study, L-dopa alone was found to decrease the levels of B regulatory cells and a subset of tolerogenic DCs, whereas the combination of pramipexole and L-dopa leads to a decrease in proinflammatory T cell subpopulations.[170] These findings suggest that L-dopa alone can promote inflammation, while exhibiting a clinically beneficial regulatory effect in combination with pramipexole in PD patients. These patients were also found to have increased levels of human leukocyte antigen-DR (HLA-DR)-expressing monocytes which have an increased antigen presentation capacity for T cell stimulation.[170] In addition, disease severity and duration also correlated with decreased B regulatory cells and increased HLA-DR monocytic expression, thus making it unclear whether these immune effects are PD-related or induced by L-dopa treatment.[37,183] Therefore, the lack of untreated patients with comparable disease severity and duration limits the interpretation of how L-dopa affects immune response in PD. For this reason, well-tailored *in vitro* studies using immune cells isolated from untreated PD patients at the onset of the disease should be considered for testing the immune effects of L-dopa at a concentration that is comparable to what was detected in the plasma of L-dopa-treated patients. Indeed, *in vitro* studies using PBMC from healthy subjects show that IL-1β, IL-6, IL-8, IL-10 and TNF-α production by PBMC were significantly decreased after treatment with L-dopa at a concentration that was 100× higher than its peak plasma concentration.[159,184] In addition, L-dopa treatment has also been shown to alter $CD8^+$ T cell (Tc) profiles in PD patients.[48] In fact, treatment with L-dopa revealed a negative correlation between the levels of proinflammatory $CD8^+$ T cells (Tc1) and IL-13 producing anti-inflammatory $CD8^+$ T cells (Tc2), as well as disease severity in patients after 2 years.[48] Remarkably, these decreased levels of Tc1 and Tc2 cells correlated with increased IL-17 producing CD8+ T cells (Tc17) after 2 years of treatment, which may contribute to the inflammatory response in PD.[42,45,185] Furthermore, after 1-year of treatment with L-dopa alone, a positive correlation between decreased levels of NK cells and disease severity measured by the UPDRS scale was reported.[48] L-dopa effects may be mediated by D1-like DR, as it has been shown that D1-like-DR signalling suppresses $CD8^+$ Treg functional responses,[103] exacerbates T-cell activation[138] and increases $CD4^+$ T cell differentiation towards a Th17 inflammatory phenotype.[134] However, it is worth mentioning that chronic use of dopaminergic agents in PD impacts protein expression of DRs, TH, DAT and downstream signalling pathways, in both PBMC and T cells, thereby potentially affecting the immunomodulatory potential of DA and dopaminergic agonists in PD.[38,131,186,187] In detail, treatment with L-dopa in PD reduced the expression of DRs to a basal expression level in PBMC[186] and mRNA levels of DRD5 and DRD2 in $CD4^+$ T cells.[38] In addition, in comparison with HS, peripheral lymphocytes from PD patients showed reduced intracellular Ca^{2+} production in response to mitogen-induced activation, and decreased cAMP levels, which are conceivably associated with L-dopa treatment.[187] Furthermore, experimental evidence revealed that PD patients treated with the mainstay pharmacological therapy (i.e. L-dopa, dopamine agonists) show a specific reduction of PBMC expressing DAT and TH in comparison with untreated patients, which was also confirmed in PD mouse models.[131] The treatments also affect the expression patterns of DAT and TH as L- dopa/benserazide treatment in mice restored baseline levels of both DAT and TH, whereas L-dopa alone only restored TH expression on PBMC.[131]

Besides their effects on immune regulation in the periphery, L-dopa also contributes to glial neuroinflammatory responses and long-term therapy side-effects, including LID.[188,189] The exact mechanism that causes LID and other motor complications has yet to be defined but increasing preclinical evidence suggests that glial cells are potential contributors.[189–191] Preclinical studies in rats demonstrated that immunomodulatory drugs, such as exogenous corticosteroids and thalidomide, may alleviate LID, reducing L-dopa-induced microgliosis and excessive TNF-α and IL-1β levels in the striatum, while restoring physiological levels of the anti-inflammatory cytokine IL-10.[192,193] L-dopa induced-motor complications may depend on dosage and administration regimens.[188] In fact, while Lindgren

and colleagues did not show any sign of activated microglia in the striatum with either high or low doses of L-dopa,[188] other studies demonstrated that chronic and pulsatile treatment with L-dopa induced dyskinesia and exacerbate microglia and astroglia activation, with an increase in proinflammatory mediators, such as TNF-α mRNA and iNOS, in a 6-hydroxydopamine (6-OHDA) rat model of PD.[194–197] Conversely, a chronic but continuous treatment with L-dopa was associated with normalised microglial density and morphology.[195] Converging *in vivo* evidence links a reduction in microglia activation, monocytic infiltration to chronic treatment with L-dopa in a monkey model of PD[198] (Table 3). Likewise, *in vitro* experiments reported that L-dopa has an inhibitory effect on microglial NO production.[118] Moreover, similar to DA, L-dopa alone or in combination with carbidopa exerts an anti- inflammatory effect on microglia by forming DAQ.[199]

L-dopa has been demonstrated to regulate immune responses in the periphery and CNS. In the periphery L-dopa reported anti-apoptotic and regulatory effects on antioxidant functions.[173,176,177,179] However, its effect on proliferation and lymphocytes polarisation seems to depend on the type of DR-signalling involved, with more profound anti-inflammatory effects mediated by D2-like receptors.[180–182] However, chronic treatment with L-dopa may also affect the protein expression of DRs thus potentially influencing its immune regulatory functions in PD.[38,186,187] The immune regulatory effect of L-dopa on CNS seems to depend on the drug administration regimens and the DR-independent mechanisms it acts through.[188,199] Thus, precisely managing L-dopa treatment regimens may limited side-effects while achieving neuroprotective outcomes.

DA agonists

Currently used dopaminergic agonists in PD are D2-like DR agonists. D2-like DR activation, especially D2R, exhibits anti-inflammatory effects that could counteract PD-associated neuroinflammation.[95,96,100,109,110,112,114,115,117,132,200] Indeed, both bromocriptine and ropinirole were shown to displace anti-inflammatory effects by inhibiting microglia and astroglia activation through β-arrestin-2- and CRYAB-dependent mechanisms, respectively.[109,201] Despite this, only a few studies have been carried out to test the effects of dopaminergic agonists on immune cell functions in PD. Among them, a proteomic study on circulating T cells from PD patients revealed limited effects on the immune system due to the long-term treatment with L-dopa and DA agonists.[202] Treatment with DA agonists pramipexole, ropinirole or rotigotine revealed potential antioxidant effects in T lymphocytes isolated from PD patients, by increasing expression of prolidase, whose plasmatic deficiency is related to oxidative stress in PD,[203] and peroxiredoxin 6, an enzyme with antioxidant activity.[202] Although the proteomic study showed no major effect in T lymphocytes of PD patients treated with DA agonists, a stratified analysis in a 2-year longitudinal study in PD patients treated with combined L-dopa/pramipexole reported that the frequencies of pro-inflammatory TNF-α- and IFN-γ-producing Th1 cells, IL-17- and IL-6-producing Th17 cells were decreased, whereas the frequencies of anti-inflammatory IL-13-producing Th2 cells, tolerogenic DCs and regulatory cells were increased.[170] In particular, pramipexole concentrations negatively correlated with the levels of pro-inflammatory M1 macrophages and positively correlated with the level of TGF-β-secreting Treg cells.[170] Nuclear receptor-related one protein 1 (Nurr1) is a transcription factor that maintains DA neuron functions and regulates neuroinflammation. Nurr1 expression has been reported to be negatively correlated with TNF-α, IL-1β, IL-6 and IL-10 cytokine production by PBMC from PD patients.[204] Treatment with pramipexole was also found to augment Nurr1 mRNA expression level in PBMC from PD patients.[171] Likewise, pramipexole has been reported to reduce IL-6, IL-8 and TNF-α production in human PBMC culture.[184] However, these PBMC were isolated from healthy subjects and that high concentrations of pramipexole were used which are not comparable to the ones detected in PD patients during therapy.[159] Similarly, inhibition of microglia and astrocyte activation by pramipexole has also been reported in a mice model of PD.[205] Accordingly, available studies reported that pramipexole reduces astroglia activation, inducing neuroprotective effects on human neuroblastoma SH-SY5Y cells.[24] Similarly, bromocriptine reduced TNF-α in LPS-induced murine primary cultured astrocytes[206] and reduced T lymphocyte proliferation and IL-2 production in human cells isolated from HS.[207] In PD patients, 1 and 2 years after disease onset, a combined treatment with L-dopa and pramipexole, but not with L-dopa alone, was linked with a further decrease of the

anti-inflammatory IL-10^{+} plasma B cells and this correlates with PD disease severity according to H&Y scale score, which is *used for the staging of the functional disability associated with Parkinson's disease*.[42] Additional studies also revealed that *in vivo* treatment with bromocriptine, leuprolide and pergolide increased Fc gamma receptor (FcγR) responsivity of guinea pig macrophages, thus enhancing the clearance of IgG-sensitised cells.[208] Remarkably, FcγR are also expressed on the surface of microglia and IgG-FcγR interaction was reported to play a role in microglia activation and consequently DA neurodegeneration in an α-syn mouse model of PD.[209] Converging evidence also proves the entry of activated, pro-inflammatory monocytes into the CNS, which are crucial for α-syn-induced neuroinflammation and neurodegeneration in a mouse model of PD.[10] Therefore, D2-like DR-induced FcγRs responsivity and enhanced clearance of IgG-sensitised cells in monocytes/macrophages may induce neurotoxic effects in PD.[10,209]

Overall, whether DA agonists have a neuroprotective or a harmful impact on PD requires further investigation. Moreover, the immune effect of rotigotine, one of the most used DA agonists, displays an affinity for D1-like DR differently than other agonists and deserves specific assessment.

Thus, understanding the role of dopaminergic substitution therapy on the immune pathways involved in PD would possibly allow for a more precise use of currently prescribed drugs and improved clinical management for PD.

CONCLUSIONS

Defining the impact of DA and dopaminergic agents on immune cells and on neuroinflammation is intricate, since both pro-inflammatory and anti-inflammatory roles have been observed. In fact, despite the specific DA-mediated mechanisms, distinguished by potentially involved DR and downstream signalling pathways, various factors can affect the final response, such as the type of immune cells, the species-specificity, or the specific inflammatory condition. Nevertheless, considering the extensive evidence demonstrating how dopaminergic modulation can regulate the immune functions involved in neuroinflammation, even in PD, using dopaminergic agents as the main antiparkinsonian treatment requires further evaluation for their clinical implications.

The available studies suggest that L-dopa/DA and dopaminergic agonists do influence different immune pathways involved in neuroinflammation in the CNS and the periphery. Indeed, L-dopa and DR agonists were reported to have anti-inflammatory activities. However, despite the potential of DA-mediated immune modulation in PD, the present studies have some common limitations, including the lack of untreated patients comparable for disease and age to treated patients and the lack of powerful biomarkers for specific immune alterations in PD. Diagnosis of PD occurs mainly after the onset of clinical symptoms and patients are immediately treated with dopamine replacement drugs. Indeed, due to the lack of specific tests exist which predict or corroborate the clinical diagnosis, the response to L-dopa therapy is often used to confirm the accuracy of PD diagnosis.[210] In addition, dopaminergic antiparkinsonian therapy exists not as a single best treatment but as a tailored drug combinations for each individual patient, and even more so in the advanced stages of the disease, when more than half of the patients develop long-term therapy side effects.[157,160] Therefore, the heterogeneity in pharmacodynamics and pharmacokinetic profiles of antiparkinsonian drugs, along with increasing doses during disease progression, makes deciphering any possible correlation with their immunomodulatory effects.[157,160]

The lack of specific biomarkers at different stages of PD limits the identification of the potential immune effect of dopaminergic substitution therapy. Moreover, confounding factors such as disease duration, severity and age should also be taken into consideration when evaluating the role of the immune system in PD. Indeed, immune processes in PD patients should be follow-up throughout the course of the disease, starting from the onset of the prodromal symptoms, such as sleep, olfactory and gastrointestinal dysfunctions, which can occur decades before motor symptoms.[2] In this way, specific immunological endpoints for immune activity and disease stages could be defined to characterise the effects of DA replacement therapy, and provide insights in understanding the impacts and involvement of immune processes in neuroinflammation and neurodegeneration in PD.

As explored in this review, DA and its analogues may have a crucial role in the modulation of proinflammatory functions in both peripheral and CNS immune cells. Taken together, given the overwhelming evidence proving immune

activation and inflammation to be the hallmarks of PD, targeting the immune system using anti-inflammatory interventions may offer potential therapeutic improvement for PD. Thus, further fine-tuned and longitudinal studies in PD patients to exploit the immunomodulating potential of PD drugs will allow more appropriate use of these drugs and precision design of the treatment approach for PD and, eventually, other neuroinflammatory disease.

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AUTHOR CONTRIBUTIONS

Alessia Furgiuele: Writing – original draft; writing – review and editing. **Frederico C Pereira:** Supervision; writing – original draft; writing – review and editing. **Stefano Martini:** Formal analysis; writing – review and editing. **Franca Marino:** Conceptualization; supervision. **Marco Cosentino:** Conceptualization; supervision.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.