Journal of Neuroimmune Pharmacology (2020) 15:57–73
https://doi.org/10.1007/s11481-019-09834-5

INVITED REVIEW

Targeting the Dopaminergic System in Autoimmunity

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Received: 4 December 2018 / Accepted: 8 January 2019 / Published online: 19 January 2019

Abstract

Dopamine has emerged as a fundamental regulator of inflammation. In this regard, it has been shown that dopaminergic signalling pathways are key players promoting homeostasis between the central nervous system and the immune system. Dysregulation in the dopaminergic system affects both innate and adaptive immunity, contributing to the development of numerous autoimmune and inflammatory pathologies. This makes dopamine receptors interesting therapeutic targets for either the development of new treatments or repurposing of already available pharmacological drugs. Dopamine receptors are broadly expressed on different immune cells with multifunctional effects depending on the dopamine concentration available and the pattern of expression of five dopamine receptors displaying different affinities for dopamine. Thus, impaired dopaminergic signalling through different dopamine receptors may result in altered behaviour of immunity, contributing to the development and progression of autoimmune pathologies. In this review we discuss the current evidence involving the dopaminergic system in inflammatory bowel disease, multiple sclerosis and Parkinson's disease. In addition, we summarise and analyse the therapeutic approaches designed to attenuate disease development and progression by targeting the dopaminergic system.

Keywords Dopamine · Inflammatory bowel disease · Multiple sclerosis · Parkinson's disease · Dopamine receptors

Introduction

Autoimmunity is a complex condition where the immune system is unable to distinguish between self and non-self-antigens due to the loss of immune tolerance. To date, 81 autoimmune diseases have been identified with an overall prevalence of 5%, constituting a serious health issue worldwide (Hayter and Cook 2012). Extensive research has shown dopaminergic pathways as key regulators of autoimmunity (Pacheco 2017; Pinoli et al. 2017), especially in inflammatory bowel disease (IBD) (Pacheco et al. 2014; Contreras et al. 2016), multiple sclerosis (MS) (Prado et al. 2012; Prado et al. 2013; Cosentino et al. 2016; Osorio-Barrios et al. 2018; Prado et al. 2018), and Parkinson's disease (PD) (Gonzalez et al. 2013; Christiansen et al. 2016; Elgueta et al. 2017; Kustrimovic et al. 2018).

Dopamine is a catecholaminergic neurotransmitter present in central and peripheral tissues involved in sodium balance, blood pressure, renal function, glucose homeostasis, voluntary movement, cognition, reward, sleep, memory, sympathetic regulation and retinal processes (Beaulieu and Gainetdinov 2011; Pinoli et al. 2017). It is mainly synthesized in the brain from the precursor L-dihydroxyphenylalanine (L-DOPA). Other sources of active dopamine are some immune cells, such as dendritic cells and T cells (Pacheco et al. 2014; Levite 2016; Papa et al. 2017) and some gut commensals, such as *Clostridium* species (Asano et al. 2012). There are five distinct receptors to which dopamine binds with different affinities. The D1-like subtype comprises D1 dopamine receptor (DRD1) and DRD5, whilst the D2-like subtype comprises DRD2, DRD3 and DRD4 (Vallone et al. 2000; Beaulieu and Gainetdinov 2011; Pinoli et al. 2017). The D1-like subtype is often coupled to the $G\alpha_{s/olf}$ family of G proteins that stimulate cyclic adenosine monophosphate (cAMP) production, whereas the D2-like subtype classically activates the $G\alpha_{i/o}$ family of G proteins to inhibit cAMP production (Beaulieu and Gainetdinov 2011). Stimulation of one or more of these receptors has been implicated either in promoting or dampening the development or progression of autoimmune diseases. The present review integrates the current literature about dopaminergic pathways involved in IBD, MS and PD.

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Inflammatory Bowel Disease

Epidemiology of Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an umbrella term used to describe a group of chronic inflammatory conditions triggered by the break of immune tolerance in the gastrointestinal tract. The most common pathologies falling under this term are Crohn's disease (CD) and ulcerative colitis (UC) (Mayer 2010; Pacheco et al. 2014). Results from gene-expression studies highlight IBD as one the most complex autoimmune diseases affecting at least 163 loci along the human genome, some of them shared by both CD and UC (Jostins et al. 2012). Inflammatory lesions in CD patients are generally transmural, multifocal and contain granulomas. They can affect the entire gastrointestinal tract from the mouth to the anus. In the case of UC patients, inflammation is superficial and limited to the colon (Brown and Mayer 2007; Pacheco et al. 2014). IBD is associated with abdominal pain, weight loss, diarrhoea, passage of blood or mucus or both (Baumgart and Sandborn 2007), as well as alternating phases of relapse and remission, increasing the risk of developing intestinal cancer (Geremia et al. 2014). IBD prevalence fluctuates between 605 and 827 cases per 100.000 individuals in Europe and North America with an estimated health-care cost of €4.6–5.6 billion annually (Burisch et al. 2013; Ng et al. 2018).

Physiopathology of Inflammatory Bowel Disease

Development and progression of IBD involves several signalling pathways interacting simultaneously, such as impairment of barrier function and loss of permeability (i.e. defective tight junctions in the intestinal epithelial cell layer), altered immune response (T lymphocyte signalling) (Izcue et al. 2009; Martini et al. 2017), environmental factors (i.e. smoking and intestinal microbiota) (Bernstein et al. 2006; Mayer 2010) and genetic predisposition (i.e. IL-23 receptor and ATG16L mutations) (Rioux et al. 2007; Mayer 2010). Current understanding of IBD pathobiology comes from the use of different experimental animal models, which resemble one or two major characteristics of the disease (Kiesler et al. 2015).

One of the first events occurring during IBD is the disruption of the intestinal epithelial barrier permeability, which allows bacterial breakthrough and development of intestinal inflammation (Olson et al. 2006). Studies with both mouse strains, IL-10 deficient and senescence-accelerated mouse (SAMP), which develop spontaneous colitis and ileitis while aging respectively, have shown that dysregulated epithelial barrier response precedes intestinal inflammation in vivo (Madsen et al. 1999; Olson et al. 2006). Moreover, different subsets of mesenchymal cells present in the gut lamina propria undergo remodeling processes during chronic gut inflammation, which may contribute to either epithelial barrier breakdown or repair and regeneration (Kinchen et al. 2018). Defective T cell signalling is another well characterized event leading to the development of IBD (Powrie and Mason 1990). In the T cell transfer model of colitis, regulatory T cells (Tregs) maintain intestinal homeostasis preventing disease development, whereas effector T cells (Teff) promote gut inflammation in the presence of triggering intestinal microbiota (Powrie and Mason 1990; Izcue et al. 2009). Moreover, a subtype of Teff, namely Th17 cells, have shown substantial plasticity with both protective and pathogenic functions following IBD (Feng et al. 2011; Gagliani et al. 2015). For example, in the presence of TGF-β1 the aryl hydrocarbon receptor promotes transdifferentiation of Th17 into Tregs, allowing resolution of inflammation following IBD (Gagliani et al. 2015). Whereas IL-17, IL-12, IL-23 and IFN-γ promote transdifferentiation of Th17 into Th1 cells leading to the development of a severe colitis (Feng et al. 2011; Nizzoli et al. 2018). Of note, the central role of Teff in promoting gut inflammation in IBD is carried out by recruiting and stimulating the function of cells from the innate immune system, such as neutrophils and monocytes/macrophages. On the other hand, the key anti-inflammatory activity of Tregs is exerted by dampening Teff function. Furthermore, several other immune pathways involving myeloid antigen-presenting cells of the intestine have been described to contribute to the development and progression of IBD. In experimental models of acute colitis, ablation of dendritic cells has a time-dependent effect, leading to either amelioration or exacerbation of disease progression (Berndt et al. 2007). Recently, IL-33 has been shown to ameliorate colitis development by stimulating differentiation of goblet cells and macrophage switching from an inflammatory to anti-inflammatory phenotype (Seo et al. 2017).

Dopaminergic Mechanisms Involved in Inflammatory Bowel Disease

Dopamine has been detected in the gastrointestinal tract of humans and mice, where is involved in gastrointestinal motility and gut homeostasis (Zizzo et al. 2016). It is produced by the mesenteric tissue (Eisenhofer et al. 1997), gut microbiota (Asano et al. 2012) and enteric nerves (Pacheco et al. 2014). Under inflammatory conditions, such as those found in IBD, the levels of this catecholamine are dysregulated both in humans and animal models (Table 1). In biopsy specimens of inflamed gut mucosa from IBD patients, dopamine levels are reduced compared to healthy controls (Magro et al. 2002). A similar situation has been observed in experimental rodent models of IBD (Magro et al. 2004; Tolstanova et al. 2015). This decrease in dopamine levels has been attributed to the IFN-γ-mediated inhibition on L-DOPA uptake by epithelial cells (Magro et al. 2004), decreased expression levels of tyrosine hydroxylase (TH) - the enzyme that synthesizes dopamine -, and reduced expression of the dopamine transporter (DAT) in the colon (Tolstanova et al. 2015).

Table 1 Alterations of the dopaminergic system involved in autoimmune pathologies

	Inflammatory bowel disease/	Cell type or tissue affected	Alteration	Ref
Experimental model	Chemically-induced colitis using 2,4,6-trinitrobenzene sulphonic acid (TNBS) in rats.	Inflamed gut mucosa.	Decreased dopamine and L-DOPA levels in TNBS-treated group compared to control group.	(Magro et al. 2004).
	Chemically-induced colitis using sulfhydryl alkylator iodoacetamide in rats and IL-10 deficient mice.	Colonic tissue.	Decreased TH and DAT protein levels in the IBD group versus control.	(Tolstanova et al. 2015).
	Experimental *colitis*by *adoptive transfer of naive (CD45RB^{hi}).*	$CD4^+$ T cells.	Transference of naive DRD3-deficient $CD4^+$ T cells ameliorates body weight loss and mucosal inflammation. Furthermore, DRD3 deficiency in $CD4^+$ T cells leads to a reduction in IFN-γ production.	(Contreras et al. 2016).
Humans	CD and UC patients.	Inflamed gut mucosa.	Dopamine levels are reduced in IBD patients compared to healthy patients, either by impaired synthesis or reduced storage of this neurotransmitter.	(Magro et al. 2002).
	CD patients.	Genomic DNA isolated from whole blood samples.	Polymorphism in the DRD2, results in decreased receptor expression, associated with development of refractory CD.	(Magro et al. 2006).
Experimental model	Multiple sclerosis Myelin oligodendrocyte glycoprotein 35–55 peptide (pMOG)-induced EAE in wild-type (WT) and DRD5 knockout mice.	Dendritic cells.	DRD5 deficiency, either whole-body or on dendritic cells, reduced severity of EAE by decreasing infiltration of $CD4^+$ T cells producing IL-17 in the brain and spinal cord compared to the WT group. Stronger effects were observed when DRD5 was absent on dendritic cells.	(Prado et al. 2012).
	pMOG-induced EAE.	Dendritic cells.	Dopamine contained in dendritic cells stimulates DRD5 in an autocrine loop, attenuating STAT3 phosphorylation, and thus increasing IL-12 and IL-23 production, favouring a higher generation of pathogenic Th1 and Th17 cells infiltrating the CNS and a stronger severity in EAE.	(Prado et al. 2018).
	pMOG-induced EAE.	$CD4^+$ T cells.	DRD5-signalling in naive $CD4^+$ T cells favours a Th17-driven inflammatory response, promoting the development of EAE. DRD5-signalling in Tregs increases their suppressive activity in late stages of EAE, attenuating disease severity.	(Osorio-Barrios et al. 2018).
Humans	Relapsing-remitting MS patients.	PBMCs.	Low mRNA and protein levels of DRD5 in MS patients compared to healthy controls.	(Giorelli et al. 2005).
	Relapsing-remitting MS patients.	PBMCs.	Increased production of catecholamines, mRNA levels of TH and DRD5, and decreased mRNA levels of DRD2 in MS patients compared to 12-month treatment IFN-β.	(Zaffaroni et al. 2008).
	Relapsing-remitting MS patients.	Tregs and Teff.	IFN-β treatment decreased mRNA expression of TH, and DRD5 in Tregs compared to MS patients before starting the IFN-β treatment. Furthermore, IFN-β treatment increased DRD5 and TH mRNA expression in Teff.	(Cosentino et al. 2012).
	Patients diagnosed with clinically isolated syndrome.	PBMCs and Tregs.	Upregulation of DRD3 and DRD5 mRNA expression in PBMCs and Tregs, respectively, correlate with the risk of developing MS after 12-months of clinically isolated syndrome.	(Cosentino et al. 2016).
	Relapsing-remitting MS patients.	PBMCs.	Signaling through D2-like and D1- like receptors either stimulated or reduced IL-17 production, respectively.	(Melnikov et al. 2016).
	Relapsing-remitting MS patients.	Non-classical monocytes.	Increased number of non-classical monocytes expressing dopamine receptors versus healthy controls.	(Prado et al. 2018).
Experimental model	Parkinson's disease MPTP-induced PD.	Potentially dopaminergic neurons.	DRD3 protein expression was reduced following MPTP intoxicated macaque. Levodopa-treated primates overexpressed DRD3 in the brain, especially in the dyskinetic group.	(Bezard et al. 2003).
	MPTP-induced PD.	Potentially dopaminergic neurons.	DRD2 mRNA levels increased following MPTP intoxication in macaque. Levodopa treatment normalizes DRD2 mRNA levels in dyskenetic compared to the control group. DRD3 and DRD1 signalling correlates with LID.	(Guigoni et al. 2005).
	MPTP-induced PD.	Potentially dopaminergic neurons in the midbrain.	Reduced dopamine, DOPAC and HVA levels in the striatum of MPTP treated animals compared to control-treated group. Mice devoid of $CD4^+$ T cells are more resistant to MPTP-induced dopamine neuronal loss.	(Brochard et al. 2009).
	MPTP-induced PD.	$CD4^+$ T cells and microglia.	Mice bearing DRD3-deficiency on $CD4^+$ T cells are protected of neurodegeneration of dopaminergic neuron in comparison with mice bearing WT $CD4^+$ T cells.	Gonzalez et al. 2013.
	6-OHDA-induced PD.	Medium spiny neurons (MSN).	MSN expressing either DRD1 or DRD2 have a reduced number of spines following PD.	(Suarez et al. 2016)
	6-OHDA-induced PD.	Dopaminergic neurons.	GSK2606414 treatment increased survival of dopaminergic neurons and dopamine levels in the substantia nigra by inhibition of RNA-like endoplasmic reticulum kinase. This drug leads to attenuation of motor deficits compared to the vehicle treated group.	(Mercado et al. 2018).
Humans	PD patients.	Not addressed.	Striatal reduction of dopamine levels in postmortem brains of PD patients.	(Ehringer and Hornykiewicz 1998).
	PD patients.	Dopaminergic neurons.	Downregulation of genes involved in PD (e.g. PARK gene family, PINK1, AT4).	(Simunovic et al. 2009).
	PD patients.	Dopaminergic neurons.	Progressive loss of TH and DAT expression in postmortem brain samples of PD diagnosed patients compared to healthy controls.	(Kordower et al. 2013).

Another hallmark of IBD, where the dopaminergic system plays a relevant role, is the altered T cell signalling. This process might be mediated by the release of dopamine stored in endogenous compartments of Tregs, which subsequently acts in an autocrine/paracrine manner stimulating DRD5, attenuating their suppressive activity and thereby, leading to upregulation of Teff function (Cosentino et al. 2007). Dopamine receptors are present in the gut mucosa and adjacent tissues. For instance, DRD1 and DRD2 have been found mainly located in some subsets of sub-mucosal and myenteric neurons. On the other hand, DRD3 and DRD5 are present in both the nerve ending layer of the intestine wall and the gut mucosa, whereas DRD4 is located in the mucosal layer (Li et al. 2006; Zizzo et al. 2016). Signalling through the DRD3 has been shown to act as a negative regulator of Th2 differentiation, promoting a Th1 phenotype in a chronic model of IBD induced by the transfer of naive $CD4^+$ T cells into T lymphopenic recipient mice (Contreras et al. 2016). The negative regulation of Th2 differentiation exerted by DRD3 in $CD4^+$ T cells involves the upregulation of SOCS5, (Contreras et al. 2016) and the reduction of cAMP levels and attenuation of late extracellular signal-regulated kinase (ERK) phosphorylation (Franz et al. 2015). In contrast, signalling mediated by DRD5 in $CD4^+$ T cells leads to an early increase of ERK phosphorylation which potentiates T cell activation (Franz et al. 2015).

According to the involvement of the dopaminergic system in maintaining gut homeostasis, the development of IBD in some cases has been associated with genetic predisposition involving polymorphisms and mutations of different components of the dopaminergic system. For instance, D1-like receptor gene polymorphisms have been associated with $CD4^+$ T cell counts and proper Tregs function in the blood of healthy patients (Cosentino et al. 2015; Cosentino et al. 2018). Moreover a genetic polymorphism in the DRD2 has been associated with susceptibility to develop refractory CD in patients (Magro et al. 2006).

Current and Future Treatments for Inflammatory Bowel Disease

The main goal of IBD treatment is to relieve symptoms, diminish the inflammatory response, allow lesions to heal and prevent relapse. Current therapeutic approaches include the use of pharmacological drugs to inhibit inflammation, stimulate anti-inflammatory pathways, disturbance of T cell function, inhibition of leukocyte recruitment, among others. In severe cases, surgical management is recommended (Brown and Mayer 2007). However, no treatment strategy is free of side effects. Importantly, some studies performed in animal models have highlighted the importance of targeting dopamine receptors to attenuate IBD progression (Table 2). For example, in adult mice dopamine acts as an endogenous inhibitor of intestinal motility, promoting relaxation, mainly through D2-like receptors (Zizzo et al. 2016). This observation, has led to the use of pharmacological drugs targeting D2-like receptors for the management of gastrointestinal motor disorders (Tonini et al. 2004). Of note, is important to mention that chronic blockade of central DRD2 has been associated with the development of extrapyramidal reactions and hyperprolactinaemia (Tonini et al. 2004).

Pharmacological modulation of the dopaminergic system in animal models of IBD highlights DRD2 as a promising target for the development of future treatments (Table 2). In this regard, it has been shown that DRD2 agonists, such as quinpirole and cabergoline, attenuate IBD severity by reducing nitric oxide production, recruitment of neutrophils in the intestine (Oehlers et al. 2017), and vascular permeability (Tolstanova et al. 2015). It is noteworthy that quinpirole is also a DRD3 agonist, although its affinity for this receptor is considerable lower than the affinity for DRD2 ($K_i \approx 4{,}8$ and 24 nM for DRD2 and DRD3 respectively) (Seeman and Van Tol 1994). Interestingly, another study also found attenuation of IBD using beberine, a non-selective antagonist of both D1- and 2 like receptors (Kawano et al. 2015). Beberine treatment decreased the secretion of IFN-γ and IL-17 from lymphocytes of the mesenteric lymph nodes of DSS-treated mice, leading to reduced intestinal inflammation (Kawano et al. 2015), thus suggesting a relevant role not only for DRD2, but also for other dopamine receptors in the control of gut inflammation.

Importantly, case reports of successful repurposing of pre-existing drugs to indirectly target the dopaminergic system have shown promising therapeutic results in CD and UC patients (Kast and Altschuler 2001; Furlan et al. 2006; Check et al. 2010, 2011a). The use of dextroamphetamine sulphate and clonidine, commonly used in the treatment of narcolepsy and hypertension, respectively, ameliorates some symptoms and colonic histopathological abnormalities in IBD patients (Furlan et al. 2006; Check et al. 2010, 2011a), by either reducing the hyperfunction (Check et al. 2011a) or attenuating the hypofunction of both the sympathetic and parasympathetic nervous systems (Check et al. 2011b). In this regard, CD has been associated with parasympathetic hyperactivity and sympathetic neuropathy (Check et al. 2011b), whilst the opposite alterations have been reported for UC, including sympathetic hyperactivity with parasympathetic dysfunction (Check et al. 2011a). Thereby, these facts might partially explain why these two drugs were reported to exert positive outcomes even though they have opposite functions. In the same line, the anti-depressant bupropion, has shown therapeutic effects in IBD patients that do not respond to conventional treatments (Kast and Altschuler 2001) (Table 2). The authors suggested that these drugs might exert their main protective effects indirectly targeting central dopamine receptors, the β-adrenergic receptor or reduction of TNF-α levels (Lechin et al. 1985; Furlan et al. 2006). However, properly designed double-

Table 2 Targeting dopaminergic system as therapeutic approaches for the treatment of autoimmune disorders

	Inflammatory bowel disease	Pharmacological target	Effect	Ref
Animal model	Iodoacetamide-induce UC in rats.	DRD2/DRD3 agonist (Quinpirole).	Quinpirole treatment reduced disease activity index, vascular permeability and size of colonic lesions and ulcers, compared to the saline-treated group.	(Tolstanova et al. 2015).
	IL-10 deficient mice.	DRD2/DRD3 agonist (Quinpirole).	Quinpirole-treated mice had reduced spleen and colonic weight compared to the saline-treated group.	(Tolstanova et al. 2015).
	Iodoacetamide-induce UC in rats.	DRD2 agonist (Cabergoline).	Cabergoline-treated group had lower disease activity and reduced size of colonic lesions.	(Tolstanova et al. 2015).
	Chemically-induced colitis using dextran sodium salt (DSS) in mice.	Antagonist of D1- and D2-like receptors (Berberine).	Berberine ameliorate body weight loss and reduced colon shrinkage in DSS-treated mice compared to control group. It also decreased the secretion of IFN-γ and IL-17 from mesenteric lymph nodes.	(Kawano et al. 2015).
	Chemically-induced colitis using TNBS and DSS in zebra fish.	DRD2 agonist (Cabergoline).	Cabergoline treatment reduced neutrophils infiltration and nitric oxide production in the intestine, compared to control group.	(Oehlers et al. 2017).
Humans	Case report CD patient.	Cathecholamine re-uptake (Bupropion).	Bupropion-treated CD patients (a female and a male) developed susceptibility to CD remission.	(Kast and Altschuler 2001).
	Case report UC patient.	Autonomic nervous system (Dextroamphetamine sulfate).	Dextroamphetamine sulfate treatment ameliorated some symptoms of UC.	(Check et al. 2011a).
	Study with UC and control patients.	Sympathetic activity (Clonidine).	Clonidine-treated UC patients presented a reduction of the abnormally increased sympathetic activity.	(Furlan et al. 2006).
Animal model	Multiple sclerosis			
	Inoculation of guinea pig spinal cord homogenate together with Freud's adjuvant.	DRD2 agonist (bromocriptine).	Bromocriptine treatment reduced both severity and duration in acute EAE compared to control-treated rats.	(Dijkstra et al. 1994).
	Myelin proteolipid protein (139–151 amino acids)-induced EAE.	D2-like (L750667) and D1-like (SCH23390) receptor antagonists.	L750667-treated mice developed an accelerated EAE, which quickly resulted in death, compared to the control group. SCH23390 treatment attenuated disease development leading to increased IFN-γ and reduced IL-17 production compared to the control group.	(Nakano et al. 2008).
	Inoculation of rat spinal cord homogenate together with Freud's adjuvant.	Agonist of DRD2 and 5-HT_{1A} receptor (Arylpiperazine).	Arylpiperazine treatment attenuated development of EAE, by reducing infiltration of immune cells and production of inflammatory mediators, and apoptosis.	(Popovic et al. 2015).
	pMOG-induced EAE.	Dopamine DRD2/DRD3 agonist (Pramipexole).	High dose of Pramipexole treatment lead to a reduction of inflammatory cell infiltration, astrogliosis, demyelination, reactive oxygen species in the spinal cord and brain, and no neurological development of EAE.	(Lieberknecht et al. 2017).
Humans	Case report relapsing-remitting MS patients.	DRD2 agonist (bromocriptine).	Bromocriptine-treated MS patients (a female and a male) experienced a reduction of paroxysmal symptoms.	(Khan and Olek 1995).
	Relapsing-remitting MS patients.	Antagonist of D1-like (SCH-23390) or D2-like (sulpiride) receptors.	In PBMC cultures from MS patients, sulpiride stimulated production of IL-17, whereas SCH-23390 reduced it, compared to cultures from healthy controls.	(Melnikov et al. 2016).
	Relapsing-remitting MS patients.	DRD2 antagonist (domperidone).	Pilot trial, phase II randomized, open-label, single-blind trial of domperidone for remyelination in MS patients (ongoing).	NCT02493049.
	Secondary progressive MS (SPMS) patients.	DRD2 antagonist (domperidone).	Phase II open-label, single-arm futility trial of domperidone in reducing disability progression in SPMS (ongoing).	NCT02308137.
Animal model	Parkinson's disease			
	MPTP-induced PD.	Partial agonist of DRD3 (BP 897) (nafadotride or ST 198).	BP 897 treatment attenuated dyskinesia without affecting therapeutic effects of levodopa treatment compared to the placebo group. Nafadotride or ST 198 treatments reduced incidence of dyskinesia leading to reappearance of PD symptoms compared to the placebo group.	(Bezard et al. 2003).
	MPTP-induced PD.	Antagonist of DRD4 (L-745,870).	L-745,870 treatment reduced levodopa-induced dyskinesia in macaques compared to levodopa treated group.	(Huot et al. 2012).
	6-OHDA-induced PD.	Agonist of DRD3 (SK609).	SK609 treatment reduced development of PD motor symptoms compared to levodopa and vehicle treated rats. In addition, use of SK609 in combination with levodopa attenuated LID.	(Simms et al. 2016)
	MPTP-induced PD and 6-OHDA induced PD in mice	Antagonist of DRD3 (PG01037).	PG01037 treatment attenuated loss of dopaminergic neurons and terminals in the substantia nigra pars compacta and striatum, compared to vehicle treatment. In addition, PG01037 treatment led to improvement of motor outcomes.	(Elgueta et al. 2017).
	6-OHDA-induced PD.	Antagonist of DRD3 (PG01037).	PG01037 treatment in DRD1-defcient mice reduced dyskinesia, and expression of downstream DRD1 genes induced by levodopa treatment.	(Solis et al. 2017).
Humans	PD patients.	DRD3 and DRD4 antagonist (buspirone).	Phase I randomized placebo-controlled to evaluate safety, tolerability and efficacy of buspirone in combination with amantadine in reducing L-DOPA-induced involuntary movements.	NCT02589340.
	PD patients	Restoration of dopaminergic neurons. iPSC-derived dopaminergic neurons).	Phase I/II ongoing in Japan.	(doi: https://doi.org/10.1038/d41586-018-07407-9)

blinded randomized trials are needed to assess the effectiveness and safety of repurposing these drugs in IBD. The involvement of the dopaminergic system in the control of gut homeostasis, alterations of the dopaminergic system associated to IBD and the therapeutic approaches targeting dopaminergic system as treatment for IBD are integrated in the illustration shown in Fig. 1.

Multiple Sclerosis

Epidemiology of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disease induced by autoimmune response against the axonal myelin sheath in different areas of the brain and spinal cord, leading to a progressive neurological disability. It mainly affects young adults and involves more than 100 loci accounting for approximately 30% of the overall disease risk (International Multiple Sclerosis Genetics et al. 2013; Dendrou et al. 2015). There are also environmental risk factors (i.e. smoking and infectious agents) likely acting together with MS risk-conferring genes contributing to the development and progression of the diseases (Dendrou et al. 2015). The disease course and symptomatology are heterogeneous, including impairments of visual, sensory, motor, neurocognitive, and autonomic functions. The most common form affecting MS patients is relapsing-remitting MS, which is characterized by two alternating phases. In the first one there are neurological impairment and inflammation, followed by a remission period of clinical recovery (Dendrou et al. 2015). It has an overall prevalence of 58.3 per 100.000 individuals (Hayter and Cook 2012) with an estimated health-care cost of €42–53 million annually (Ernstsson et al. 2016; Buijs et al. 2018) depending on disease severity.

Physiopathology of Multiple Sclerosis

Experimental autoimmune encephalitis (EAE), the animal model of MS, has provided compelling evidence of the multicellular complexity of this autoimmune pathology that involves myelin-reactive $CD4^+$ T cells, imbalanced $CD8^+$ T cells, inflammatory B cells, and NK function, production of autoantibodies, and a genetic predisposition and non-genetic factors (Dendrou et al. 2015; Li et al. 2015; Laroni et al. 2016; Jelcic et al. 2018).

Th1 and Th17 cells producing IFN-γ and IL-17A respectively, are the main $CD4^+$ T cells subsets promoting inflammation in MS. Patients carrying the HLA-DR15 haplotype, the strongest genetic-risk factor for MS, have elevated self-

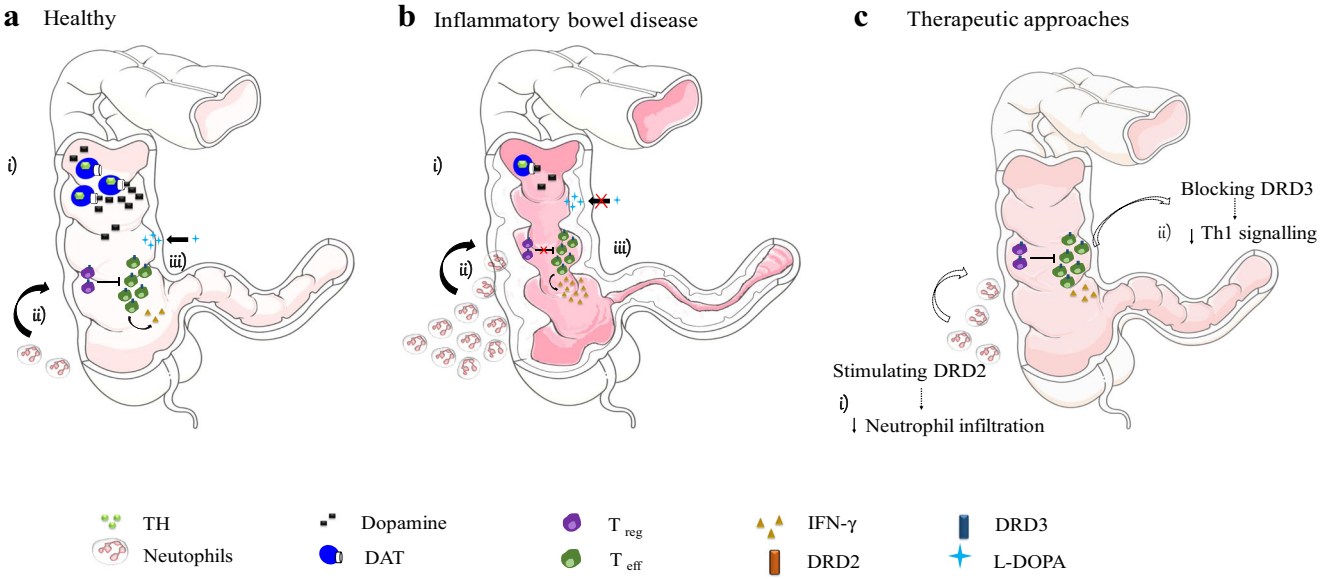

Fig. 1 Altered dopaminergic signalling and its pharmacological targets in inflammatory bowel disease. Schematic representation of dopaminergic components in the gut mucosa under homeostasis, IBD, and IBD exposed to therapeutic approaches targeting dopaminergic system. **a** In healthy conditions, dopamine, DAT and TH are present at optimal levels in the intestine (i). The extent of neutrophils infiltration in the gut mucosa is low (ii) and the ratio of Tregs-to-Teff is high in steady-state conditions (iii). **b** However, during IBD, the expression of TH and DAT is down-regulated and L-DOPA uptake is significantly decreased in the epithelium of the intestine, thus promoting a strong reduction in the levels of dopamine in the gut mucosa (i). Neutrophils infiltration and recruitment into the gut mucosa is increased (ii). Low dopamine levels favour the selective stimulation of DRD3 in Teff, promoting their expansion (reducing the Tregs-to-Teff ratio) and a strong production of IFN-γ (iii). **c** Pharmacological stimulation of DRD2 reduces neutrophil infiltration (i), whereas inhibition of DRD3 on $CD4^+$ T cells attenuates IFN-γ production, promoting a Th2 phenotype on these cells (ii). In both cases there is a significant reduction in mucosal inflammation, ameliorating colitis symptoms and thus, restoring the gain of proper body weight. Abbreviations: DA: dopamine, DAT: dopamine transporter, TH: tyrosine hydroxylase, T_{reg}: regulatory T cells, T_{eff}: effector T cells

reactive $CD4^+$ T cells compared to MS patients devoid of this haplotype (Jelcic et al. 2018). Myelin protein-derived antigens such as basic protein (MBP), proteolipid protein and myelin oligodendrocyte glycoprotein (MOG) have been suggested as the main targets recognized by autoreactive $CD4^+$ T cells in MS patients (Dendrou et al. 2015). Furthermore, $CD8^+$ T cells have been found in the white and grey matter of cortical demyelinating lesions of MS patients (Frischer et al. 2009). Interestingly, a pathogenic $CD8^+$ T cell subset expressing intermediate levels of CD161, which displays increased migratory properties, has recently been detected in the central nervous system (CNS) of MS patients (Nicol et al. 2018).

Other well-known players of MS are NK and B cells. Immune-modulating therapies targeting NK cells in MS, have suggested a relevant immune-regulatory role of these cells on $CD4^+$ T cell proliferation and activity, which is dysregulated during disease progression (Gross et al. 2016; Laroni et al. 2016). Addressing the relevance of B cells in MS, it has been shown that a single administration of rituximab (an anti-CD20 monoclonal antibody that mediates the depletion of B cells) reduced brain lesions and clinical relapses for 48 weeks (Hauser et al. 2008). In this regard, B cell subsets can play antibody-dependent or –independent pathogenic functions in MS. For example, the GM-CSF-producing B cell subset that activates inflammatory myeloid cells, is increased in MS patients compared to age and sex-matched healthy controls (Li et al. 2015). On the other hand, the memory B cell subset ($CD19^+CD27^+HLA\text{-}DR^{++}$ $RASGRP2^+$) contributes to T cell proliferation and homeostasis (Jelcic et al. 2018). These memory B cells can activate and propagate pathogenic T cells, which induce inflammation in the brain.

Dopaminergic Dysregulation in Multiple Sclerosis

Dopamine has been detected in the midbrain, hindbrain and spinal cord of mice (Sharples et al. 2014), where it has been involved in stabilization of ongoing locomotor activity, without affecting coordination on its own (Sharples et al. 2015), and controlling of micturition (Hou et al. 2016). Peripheral blood mononuclear cells (PBMC) of MS patients display altered expression of dopaminergic receptors (Giorelli et al. 2005; Prado et al. 2018), reduced expression of TH and production of dopamine (Zaffaroni et al. 2008), compared to healthy controls (Table 1). Furthermore, PBMCs from MS patients display higher IL-17 production compared to those obtained from healthy controls. This effect was mediated by in vitro activation of D2-like receptors and reverted by the stimulation of D1-like receptors (Melnikov et al. 2016). Interestingly, it has been shown that after 12 months of IFN-β treatment, alterations in the dopaminergic system of MS patients were reverted. In this regard, PBMC from IFN-β-treated MS patients display an increased production of catecholamines (norepinephrine, epinephrine and dopamine), higher mRNA levels of TH and DRD5, and a reduction of DRD2 mRNA levels, compared to their baseline levels before starting the treatment (Zaffaroni et al. 2008). Furthermore, in relapsing-remitting MS patients, IFN-β treatment reduced DRD5 and TH mRNA expression in Tregs compared to their baseline expression, thus, contributing to the recovery of normal suppressive function by abolishing dopamine-mediated inhibition of regulatory T cells function (Cosentino et al. 2012). Of note, although DRD3 mRNA levels were also reduced in Tregs following IFN-β treatment, it is unlikely that signalling through this receptor could be involved in proper regulatory T cell function given that functional impairment of Tregs has been associated to D1-like receptors activation (Cosentino et al. 2007).

In EAE, the animal model of MS, there are also several studies highlighting the role of D1-like dopamine receptors, specially DRD5, in the development of the disease (Nakano et al. 2008; Prado et al. 2012; Osorio-Barrios et al. 2018; Prado et al. 2018). In this regard, the complete DRD5-deficiency, or either confined to dendritic cells or bone marrow, has led to a delayed onset and less severe EAE compared to the control group (Prado et al. 2012; Osorio-Barrios et al. 2018; Prado et al. 2018). It has been suggested that DRD5 activation targets a broad spectrum of different immune cells with opposite functional outcomes depending on the disease stage. For example, it has been shown that stimulation of DRD5 present on dendritic cells increases the production of IL-12 and IL-23, thus promoting the differentiation of naïve $CD4^+$ T cells toward the Th1 and Th17 phenotypes early after the onset of the disease (Prado et al. 2012; Prado et al. 2018). This inflammatory effect was due to the release of dopamine contained in dendritic cells and the subsequent stimulation of DRD5-dependent inhibition of STAT3 phosphorylation in dendritic cells (Prado et al. 2018). Nevertheless, it has recently been shown that DRD5-signalling in Tregs favours a stronger suppressive activity in late stages of EAE (Osorio-Barrios et al. 2018). Furthermore, in apparent controversy, experiments performed in PBMCs obtained from MS patients and from healthy subjects carrying specific dopamine receptors polymorphisms have shown that stimulation of D1-like receptors in Tregs attenuates their suppressive activity (Cosentino et al. 2007; Cosentino et al. 2018). These discrepancies observed between studies performed in EAE and MS could be due to one or more of the following explanations: i) maybe the effects observed in human PBMCs were mediated by DRD1-stimulation rather than DRD5-activation; ii) DRD5-signalling could be coupled to different effects in human Tregs and mouse Tregs; iii) DRD5-mediated effects in Tregs might be different in those Tregs circulating in peripheral blood in comparison with those infiltrating the CNS. Anyway, irrespective of which of these hypotheses are correct, the evidence obtained from animal models and MS patients indicates an important regulatory role of D1-like dopamine receptors in the suppressive activity of Tregs.

Current and Future Treatments for Multiple Sclerosis

Long-standing treatments used for MS reduce relapses, but do not substantially halt disease progression and neuroaxonal damage. A recent study showed that increased DRD3 and DRD5 mRNA expression in regulatory T cells may be associated with the risk of developing MS in patients with clinically isolated syndrome (Cosentino et al. 2016) (Table 1). IFN-β treatment, which is associated with improvement of clinical MS manifestation, has been shown to involve increased production of catecholamines (norepinephrine, epinephrine and dopamine) and mRNA levels of DRD5, and a reduction of DRD2 mRNA levels in PBMC obtained from MS patients, suggesting that these alterations in the dopaminergic system might be involved in ameliorating the clinical course of the disease (Zaffaroni et al. 2008). In this regard, several studies have shown the therapeutic potential of targeting dopamine receptor using human PBMCs in vitro or the EAE animal model.

In monocyte-derived dendritic cells isolated from healthy volunteers, inhibition of D2-like or D1-like receptors can lead to a higher or lower IL-17 production, respectively, compared to non-treated cells (Nakano et al. 2008). Furthermore, EAE mice treated with a D2-like receptor antagonist developed an accelerated progression of EAE. In contrast, EAE mice treated with a D1-like receptor antagonist showed an improved clinical score compared to control group. The authors suggested that this therapeutic effect was mediated by a reduction of IL-17 production and increased IFN-γ secretion by T cells (Nakano et al. 2008).

According to the beneficial effect observed for D2-like dopamine receptors mediated signalling in EAE, the use of pharmacological agonists targeting DRD2, such as bromocriptine, arylpiperazine and pramipexole in MS or EAE have reported promising therapeutic results (Dijkstra et al. 1994; Popovic et al. 2015; Lieberknecht et al. 2017). Bromocriptine, a DRD2 agonist normally used to treat PD, has been shown to decrease EAE severity and duration compared to the control group (Dijkstra et al. 1994). Regarding the mechanism underlying, it is likely that bromocriptine treatment reduces the production of inflammatory cytokines, such as TNF-α, similarly to what has been observed under inflammatory stress induced by LPS inoculation (Mastronardi et al. 2001). Furthermore, mice treated with a high dose of pramipexole, a DRD2/3 agonist, did not develop neurological signs upon EAE induction. These animals presented a significant reduction in astrogliosis, demyelination, and production of reactive oxygen species in the CNS as well as an attenuated production of inflammatory cytokines in the draining lymph nodes (Lieberknecht et al. 2017). Although, the specific cell type responsible for the pramipexole-mediated therapeutic effect was not addressed in this study, it is likely that this drug affected multiple cell types concertedly, as D2-like receptors are expressed in several immune cells, including, lymphocytes, dendritic cells and astrocytes among others. Importantly, therapeutic effects targeting the dopaminergic system have been reported not only in EAE but also in human MS patients. In this regard, a case report of two MS patients showed that bromocriptine treatment alleviated paroxysmal symptoms (Khan and Olek 1995), potentially by reducing IL-17 production by $CD4^+$ T cells (Melnikov et al. 2016). Moreover, there are two ongoing phase II clinical trials using a DRD2/3 antagonist, domperidone, in patients with secondary progressive MS (NCT02308137) and in relapsing-remitting MS (NCT02493049) in Canada (see Table 2).

Interestingly, a recent study performed in the EAE animal model described an important DRD5-mediated dopaminergic autocrine loop in dendritic cells which promotes an inflammatory response and, consequently, a stronger severity in EAE development. In this regard, the depletion of dopamine contained in dendritic cells or the abolition of DRD5-signalling in dendritic cells attenuated significantly the development of EAE (Prado et al. 2018).

Interestingly, the use of psychostimulant drugs can modulate dopamine levels and $CD4^+$ T cell response in MS patients affected by fatigue and cognitive deficits. For instance, increased absolute number and percentage of peripheral blood $CD4^+$ T cells, the main players in MS pathology, have also been reported in patients with depression (Foley et al. 1992). In addition, the prevalence of depression in MS patients is much higher than general population, reaching a frequency of about 20% (Siegert and Abernethy 2005). Moreover, the treatment of patients with anti-depressive therapy has been associated with decreased T cell responsiveness to MOG. Thus, these results together suggest that depression could promote the pathogenic $CD4^+$ T cell response in MS (Mohr et al. 2001). Furthermore, 80–97% of MS patients experience fatigue, which arises due to dopamine imbalance in the CNS. In this regard, the use of amantadine or IFN-β, have shown not only to ameliorate fatigue, but also to increase extracellular dopamine levels (Melanson et al. 2010; Dobryakova et al. 2015). Thus, the evidence suggests the involvement of dopamine mediating a connection between depression and the pathogenic $CD4^+$ T cell response associated to MS.

There is increasing evidence that B cells are involved in the pathogenesis of MS. In this regard, a single administration of rituximab, which deplete B cells, can lead to a significant reduction of brain lesions associated to clinical relapses for 48 weeks (Hauser et al. 2008), and decreased frequency of autoreactive T cells present in peripheral blood of MS patients (Jelcic et al. 2018). Although, the role of dopaminergic signalling on B cells has not been yet studied in MS or EAE, it is likely that DRD2, DRD3 or DRD5, which have been found to be expressed on B cells (McKenna et al. 2002), might play a relevant role in the regulation of the autoimmune response involved in this disorder. Interestingly, DRD2 signalling in B cells negatively correlated

with disease progression in rheumatoid arthritis, another autoimmune disorder dependent of autoreactive T and B cells (Wei et al. 2015). Future studies should address the contribution of the dopaminergic system on B cell signalling and its involvement in autoimmunity. The alterations of dopaminergic system involved in MS/EAE and the therapeutic approaches targeting the dopaminergic system as treatment for MS are integrated in the illustration shown in Fig. 2.

Parkinson's Disease

Epidemiology of Parkinson's Disease

PD is the second most common chronic neurodegenerative disorder of the aging brain in the United States, affecting about 0.01–1.2% of the population between 45 and 65 years, respectively. With increasing life expectancy and the aging of the population, it has been estimated that approximately 1.34 million new cases will be diagnosed with PD by 2050 in the US. The annual costs are $22,800 per person in the US (Kowal et al. 2013). It is considered a multifactorial disease, including genetic (approximately 10–15%) (Thacker and Ascherio 2008; Ascherio and Schwarzschild 2016; Lunati et al. 2018) and environmental ones (i.e. exposure to solvents, pesticides) (Elbaz et al. 2016; Abbas et al. 2018). To date 15 causal genes and over 25 genetic risk factors have been identified (Verstraeten et al. 2015). Patients with PD can present a variety of clinical symptoms, including slowness of voluntary movements and rigidity, tremor, postural instability, cognitive impairment and dementia, originated from a loss of striatal dopaminergic innervations in the brain. Symptoms are often unilateral becoming more pronounced meanwhile the disease and age progresses (Verstraeten et al. 2015). Non-motor symptoms include olfactory, cognitive and autonomic impairments (De Virgilio et al. 2016). Of note, PD risk is lower among smokers, tea and coffee drinkers, people who perform physical activities, non-steroidal anti-inflammatory drug consumers, among others (Ascherio and Schwarzschild 2016). Parkinson's disease diagnosis is based on the presence of motor impairment, poor levodopa response, early dementia, ataxia, among others (Verstraeten et al. 2015).

Physiopathological Features of Parkinson's Disease

The main hallmarks of PD are the reduction in striatal dopamine levels, loss of dopaminergic neurons in the substantia nigra projecting to the striatum (nigrostriatal pathway),

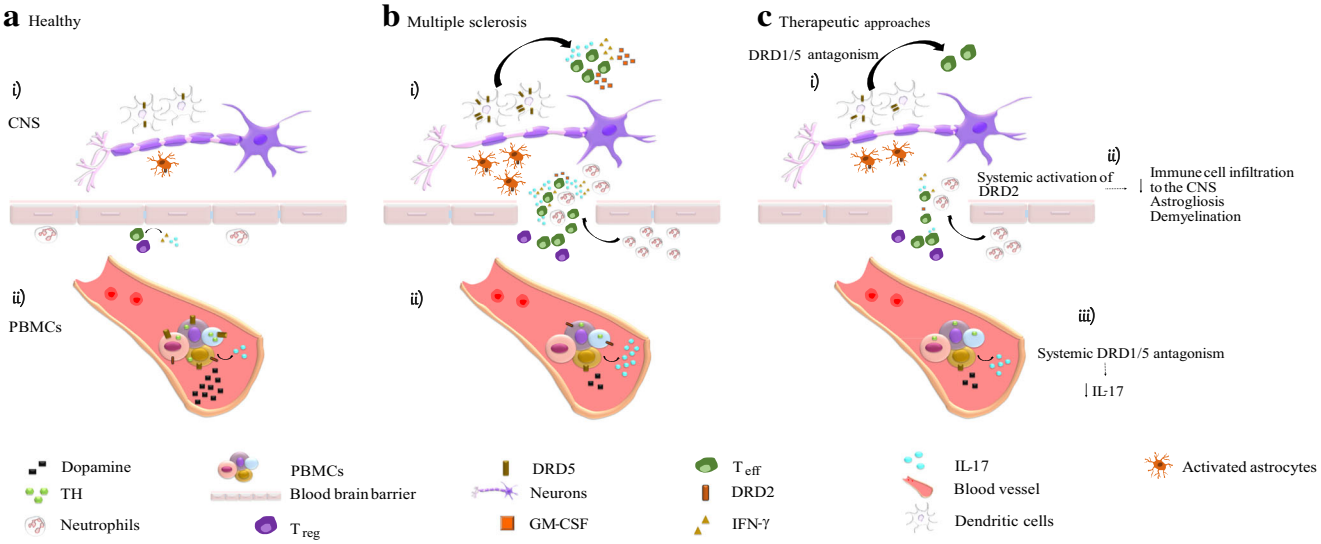

Fig. 2 Targeting the dopaminergic system in MS/EAE attenuates the pathogenic immune response, ameliorating disease manifestation. Scheme illustrating some immune and dopaminergic components of the CNS and PBMC under steady-state conditions, during MS, and in MS exposed to therapeutic approaches targeting dopaminergic system. **a** In homeostatic conditions some dendritic cells, which express DRD5, infiltrate the CNS and homeostatic astrocytes express DRD2 (i). PBMC do not infiltrate the CNS, express TH, synthesize dopamine and express the DRD5. It is noteworthy that stimulation of D1-like receptors attenuates the suppressive activity of Treg (ii). **b** Stimulation of DRD5 signalling on dendritic cells promotes a strong production of IL-12 and IL-23, inducing the differentiation of $CD4^+$ T cells into Th1 and Th17 phenotypes respectively in the CNS. Of note, pathogenic Teff not only produce IFN-γ and IL-17, but also the key pro-inflammatory cytokine GM-CSF (i). Reduction in TH expression and dopamine synthesis in PBMC, favour the stimulation of high affinity dopamine receptors. In this regard, the stimulation of D1-like receptors (presumably DRD5) on PBMCs also increases IL-17 production (ii). **c** Furthermore, the systemic administration of a D1-like antagonists (SCH23390) inhibits disease development by reducing the frequency of Teffs producing IL-17, IFN-γ and GM-CSF in the CNS (i). Stimulation of DRD2 also attenuates disease progression by reducing immune cell infiltration, astrogliosis, demyelination in the CNS (ii). (iii) The systemic administration of the DRD5 antagonist (SCH23390) also exerts an anti-inflammatory effect at the level of PBMC, by reducing IL-17 production. Abbreviations: CNS: Central nervous system, PBMCs: peripheral mononuclear cells, TH: tyrosine hydroxylase, T_{reg}: regulatory T cells, T_{eff}: effector T cells

generation of protein inclusions formed by the aggregation of misfolded α-synuclein (Lewy bodies) and impairment in the control of voluntary movements (Elbaz et al. 2016; Spillantini and Goedert 2018). Of note, not all PD patients present evident detection of Lewy bodies (Verstraeten et al. 2015), which adds more complexity to the understanding of the disease. The loss of dopaminergic neurons causes most of the motor symptoms observed in PD (Hirsch and Hunot 2009). Furthermore, non-dopaminergic neurons (e.g. norepinephrinergic, cholinergic and serotoninergic) are also affected in a lower degree in PD (Hirsch and Hunot 2009). There are several animal models that have allowed a better understanding of the disease development and progression, including those induced by dugs affecting mitochondrial respiration, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, annonacin, 6-hydroxydopamine (6-OHDA) (Hirsch and Hunot 2009), and those genetic animal models including the α-synuclein overexpression (Hallett et al. 2012) or those transgenic animals expressing mutant versions of proteins involved in mitochondrial and lysosomal homeostasis such as parkin, pink1, Dj-1, LRRK2, ATP13A2 among others (Winklhofer and Haass 2010).

Several mouse models of PD have shown a pivotal contribution of neuroinflammation, which is required to promote the loss of dopaminergic neurons in the substantia nigra. Importantly, it has been consistently shown that the infiltration and accumulation of peripheral T cells (CD4 and CD8) play a fundamental role favouring neuroinflammation in PD (Brochard et al. 2009). Neuroinflammation involves the activation and recruitment of microglial cells (Kurkowska-Jastrzebska et al. 1999) and astrogliosis (Brochard et al. 2009). It is noteworthy that a similar scenario has been observed in postmortem substantia nigra obtained from PD patients, including a strong T cell infiltration, microglial activation, astrogliosis and also the production of inflammatory factors (e.g. TNF-α, IL-1β) and autoreactive antibodies (McGeer et al. 1988; Damier et al. 1993; Chen et al. 1998; Brochard et al. 2009; Hirsch and Hunot 2009; Selvaraj et al. 2012; Mercado et al. 2018). According to the fundamental role of T cells in chronic neuroinflammation and to the pivotal role of neuroinflammation in the loss of dopaminergic neurons, it has been shown that loss of dopaminergic neurons of the nigrostriatal pathway and the progression of PD are dependent on $CD4^+$ but not $CD8^+$ T cell infiltration in the substantia nigra (Brochard et al. 2009; Gonzalez et al. 2013). In this regard, several lines of evidences have shown that PD involves an autoimmune response mediated by $CD4^+$ T cells specific to neo-antigens contained in Lewy bodies, including nitrated and phosphorylated forms of α-synuclein (Gonzalez et al. 2014, 2015). The generation of these neoantigens and their relevance triggering antigen-specific $CD4^+$ T cell mediated responses have been observed in both, animal models and human PD patients (Gonzalez and Pacheco 2014; Sulzer et al. 2017).

Role of Dopaminergic System in Parkinson's Disease

There are four major dopaminergic pathways in the mammalian brain, the nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular systems (Beaulieu and Gainetdinov 2011). Among them, the nigrostriatal is substantially affected during the development and progression of PD. The progressive degeneration of dopaminergic neurons of the nigostriatal pathway is accompanied by the reduction of striatal dopamine (Ehringer and Hornykiewicz 1998) and decreased levels of TH and DAT in both striatum and substantia nigra of PD patients compared to healthy controls. Interestingly, it has been determined that maximal reduction of dopaminergic neurons (quantidied as TH and DAT expression) was reached 4 years after the disease is diagnosed (Kordower et al. 2013). Furthermore, it has been shown that dopaminergic neurons of PD patients undergo a downregulation of different genes involved in mitochondrial and synaptic function, protein degradation, cell survival, and programmed cell death, oxidative stress-induced cell response and ubiquitin-proteasome system compared to dopaminergic neurons of the substantia nigra from control subjects (Table 1) (Simunovic et al. 2009).

Maturation and function of neurons in the nigrostriatal pathway are controlled by microRNA (miRNA)-133b, which is specifically expressed in midbrain dopaminergic neurons. It was undetectable in the midbrain of PD patients and in two different mouse models of PD (Kim et al. 2007). However, miRNA-133b deficient-mice do not develop PD, and present a normal number of midbrain dopaminergic neurons and no alterations in striatal dopamine levels and in motor performance (Heyer et al. 2012). Thus, these results suggest that reduction of miRNA-133b levels in dopaminergic neurons of the nigrostriatal pathway is induced as a consequence of the pathogenic process associated to PD, but it is not the cause of neurodegeneration. On the other hand, the expression of dopamine receptors has been shown to be differentially affected during the development of PD. In this regard, DRD3 expression has been consistently decreased in the striatum of MPTP intoxicated macaques (Bezard et al. 2003; Guigoni et al. 2005). Conversely, DRD2 mRNA levels are increased in the caudate nucleus and putamen of a macaque model of PD, without affecting the protein levels (Guigoni et al. 2005).

Dopaminergic signalling is not only affected during disease progression, but also after the treatment with levodopa (Table 2). For instance, it has been described that levodopa treatment increases DRD3 and DRD1 expression in striatal neurons of non-dyskinetic and dyskinetic groups (Bezard et al. 2003; Guigoni et al. 2005), whilst DRD2 mRNA recovers normal levels in dyskinetic macaques intoxicated with MPTP (Guigoni et al. 2005). Thus, whereas DRD3 signalling has been co-related with both development and attenuation of levodopa-induced dyskinesia (LID) (Bezard et al. 2003),

DRD1 signalling has been only directly associated with LID (Guigoni et al. 2005). Interestingly, it has been suggested the existence of a crosstalk between DRD1 and DRD3 during the development of dyskinesia. In this regard, a recent study performed in a mouse model of PD showed that levodopa treatment resulted in the overexpression of DRD3 in both DRD1 and DRD2 positive neurons. Furthermore, experiments performed with the DRD3 antagonist PG01037 and DRD1-deficient mice showed that inhibition of DRD1- and DRD3-signalling act synergistically attenuating the incidence of dyskinesia (Solis et al. 2017).

DRD3-signalling has also been shown to promote the development of PD by favouring neuroinflammation (Elgueta et al. 2017) and the pathogenic $CD4^+$ T cell response associated to PD (Gonzalez et al. 2013). In this regard, it has been described that the selective DRD3-stimulation in $CD4^+$ T-cells promotes a strong production of IFN-γ and TNF-α in the substantia nigra inducing the inflammatory M1 phenotype on the microglial cells and the consequent degeneration of the dopaminergic neurons of the nigrostriatal pathway in a mouse model of PD induced by MPTP (Gonzalez et al. 2013). Accordingly, it has been recently demonstrated that the systemic DRD3-antagonism results in a significant attenuation of neurodegeneration and in a significant reduction of motor impairment in two different mouse models of the disease (Elgueta et al. 2017). Furthermore, a recent study performed in the mouse model of PD induced by MPTP has shown that DRD1-signalling in microglial cells and astrocytes promoted a potent anti-inflammatory effect attenuating neurodegeneration of the nigrostriatal pathway. This potent effect was mediated by an increase in cAMP levels, which subsequently induced the ubiquitination and degradation of the NLRP3 inflammasome in glial cells (Yan et al. 2015). Another study addressing the role of dopaminergic signalling in glial cells in the regulation of neuroinflammation found that DRD2-signalling in astrocytes promotes a relevant anti-inflammatory effect mediated by αB-crystallin. In this regard, it was shown that mice bearing DRD2-deficiency confined to astrocytes presented an exacerbated susceptibility to MPTP-induced neurodegeneration and that wild type (WT) mice treated with a DRD2-agonist displayed attenuated neurodegeneration of the nigrostriatal pathway (Shao et al. 2013). Structural changes have been observed in the striatal microcircuit of a 6-OHDA mouse model of PD. Medium spiny neurons (MSN) expressing either DRD1 or DRD2 display a reduced number of spines, leading to an enhancement of excitability. Although, levodopa treatment recovered the number of spines in MSN expressing DRD2, these new spines are weak and insufficient to recover the loss of synaptic transmission (Suarez et al. 2014, 2016). Taken together these studies suggest that high dopamine levels, such as those found in the nigrostriatal pathway under homeostatic conditions, would promote the stimulation of low-affinity dopamine receptors, including DRD1 and DRD2, thus inducing anti-inflammatory effects and favouring homeostasis. Conversely, pathologic conditions involving decreased dopamine levels, such as those found in the nigrostriatal pathway of PD patients and animal models, would induce a selective stimulation of high-affinity dopamine receptors, specially DRD3 (displaying the highest affinity for dopamine), which exert inflammatory effects, favouring neuroinflammation and consequent neurodegeneration.

Treatment Options for Parkinson's Disease

To date, currently available pharmacological treatments for PD are geared to restore dopaminergic transmission, helping to alleviate symptoms. Nevertheless, these drugs do not affect the neurodegenerative process, thereby they do not cure or slow down disease progression. Some D2-like agonists, such as ropinirole or rotigotine have been used to increase the dopaminergic signalling in the striatum as a palliative therapy for PD, which improves motor symptoms. Some inhibitors of the enzymes that catabolize dopamine, including monoamine oxidase and catechol-O-methyltransferase, have also used to increase the availability of endogenous dopamine as a therapy to dampen motor impairment (Stoker et al. 2018). The drug most commonly used to treat PD is levodopa, the precursor of dopamine, which is administered together with dopa-decarboxylase inhibitors to increase the half-life of the drug and to limit the development of some side-effects (Stoker et al. 2018). This treatment is effective reducing motor symptoms, specially at early stages of the disease progression (Poewe et al. 2010). However, long-term levodopa treatment has been shown to involve the development of complications related to fluctuations in motor response and appearance of involuntary movements (dyskinesia) (Poewe 2010; De Virgilio et al. 2016), which have been associated with signalling through D1- and D2-like receptors (Bezard et al. 2003; Guigoni et al. 2005; Huot et al. 2012).

As discussed above, DRD1 and DRD2 signalling in glial cells has been associated with potent anti-inflammatory effects in animal models. Accordingly, it has been shown that the systemic administration of the DRD1-agonist A-68930 strongly attenuated the loss of dopaminergic neurons of the nigrostraiatal pathway in mice intoxicated with MPTP, an effect that was abrogated in DRD1-deficient mice (Yan et al. 2015). Similarly, according to the anti-inflammatory effect of DRD2-signalling in astrocytes, the systemic administration of the DRD2/DRD3-agonist quinpirole exerted a significant therapeutic effect reducing the extent of neuroinflammation and neurodegeneration of dopaminergic neurons of the substantia nigra in a mouse model of PD induced by MPTP (Shao et al. 2013).

Several studies in animal models of PD, have pointed to the DRD3 receptor as a potential target for the development of future therapies to either stop of slow-down the progression of the disease or to attenuate the emergence of side-effects associated with current treatments (Bezard et al. 2003; Elgueta

et al. 2017) (Table 2). In this regard, chronic pharmacological antagonism of DRD3 using PG01037 has been shown to significantly attenuate the loss of dopaminergic neurons of the nigrostriatal pathway, to abolish the development of motor impairment, and to reduce microglia activation in a mouse model of PD induced by the chronic administration of MPTP. Furthermore, the therapeutic effect of the systemic administration of PG01037 at the level of neurodegeneration was also reproduced in a mouse model of PD induced by the stereotaxic delivery of 6-OHDA (Elgueta et al. 2017). Interestingly, the therapeutic effect of PG01037 was accompanied by an increased astrogliosis (Elgueta et al. 2017), thus suggesting that DRD3-antagonism induces an exacerbated activation of astrocytes with anti-inflammatory properties. In this regards, neuronal death has been inversely correlated with the number of activated astrocytes in necropsies of PD patients (Damier et al. 1993). Moreover, an increased astrogliosis has been shown to constitute a critical process necessary to achieve tissue healing and functional recovery in models of spinal cord injury (Herrmann et al. 2008; Anderson et al. 2016). Since astrocytes are heterogeneous, future studies should point to dissect which astrocyte subpopulations are involved in controlling the beneficial effects of astrogliosis in PD, and to decipher the key factors involved in their turning on/off protective effects, as well as the relative contribution of DRD1, DRD2 and DRD3 signalling.

Addressing the therapeutic potential of DRD3 in avoiding LID in PD, a recent study showed that the administration of the DRD3-antagonist PG01037 reduced LID, an effect that was due to a synergistic crosstalk between DRD3 and DRD1 signalling (Solis et al. 2017). On the other hand, another study showed that the treatment of parkinsonian mice with the selective DRD3-agonist, SK609, led to a reduction in the development of motor impairment induced by 6-OHDA (Simms et al. 2016). Moreover, it has been shown that the administration of BP897, a partial DRD3 agonist and DRD2 antagonist, attenuated LID without affecting the therapeutic effects of levodopa in a macaque PD model. However, although the interaction of the drug with DRD2-mediated effects was limited, it could not be completely excluded from the effect observed. In addition, the use of two DRD3 antagonists, nafadotride or ST198 also reduced dyskinesia, but PD symptoms reappeared (akinesia, rigidity) (Bezard et al. 2003). A similar effect was observed using SK609 in combination with levodopa treatment in a rat model of PD, induced by L-DOPA (Simms et al. 2016). Moreover, the use of pramipexole in combination with levodopa treatment in PD patients has shown promising results alleviating LID (Utsumi et al. 2013). Taken together these results indicate that DRD3 signalling has a dual role, participating in the regulation of dyskinesia and also in the therapeutic action of levodopa.

According to the relevance of dopaminergic drugs in attenuating LID in animal models of PD, some clinical trials are currently evaluating the therapeutic potential of these drugs in humans. In this regard, two clinical trials are evaluating the efficacy of buspiron, an antagonist of DRD3 and DRD4, alone or in combination with amantadine in reducing LID in the US (NCT02589340) and France (NCT02617017). However, buspirone is also a 5-HT_{1A} agonist, and probably its efficacy attenuating LID also depends on neurons expressing this receptor (Politis et al. 2014) and in the consequent effect on the firing rate of neurons from the subthalamic nucleus (Sagarduy et al. 2016).

The use of cell-based therapies to restore loss of dopaminergic neurons has also shown promising results (Ma et al. 2010; Kikuchi et al. 2017). In a non-human primate model of PD induced by MPTP, transplantation of dopaminergic neurons derived from induced pluripotent stem cell (iPSC) led to an improvement of symptoms with mild inflammation and recovery of midbrain dopaminergic neurons (Kikuchi et al. 2017). Prompted by these results, in October 2018 the first in-human trial of dopaminergic precursor cells implantation into the brain of a PD patient has begun in Japan. The surgeries aim to restore dopaminergic neuron deficit and motor abilities in six patients (doi: https://doi.org/10.1038/d41586-018-07407-9). Another line of research is the use of spinal cord stimulation to attenuate parkinsonian symptoms. Although it is not clear the exact mechanism involved in this process, it has been suggested that spinal cord stimulation may trigger structural changes in the nigrostriatal circuit leading to locomotor improvement (Santana et al. 2014; Yadav et al. 2014). The involvement of the dopaminergic system in homeostasis of the nigrostriatal pathway, alterations of dopaminergic system associated to PD and the therapeutic approaches targeting dopaminergic system as treatment for PD are integrated in the illustration shown in Fig. 3.

Conclusions and Future Perspectives

Alterations of the neuroimmune communications mediated by the dopaminergic system have been involved in the physiopathology of IBD, MS and PD. Taking into consideration the dopamine levels available in particular tissues in homeostasis or in inflammation, the differential expression of dopamine receptors in different immune cells, and the mechanisms by which dopaminergic signalling regulates the function of immune cells, the dopaminergic system becomes a very attractive therapeutic target to manipulate the pathogenic immune response involved in autoimmune disorders. A thorough understanding of the role of this neurotransmitter and signalling pathways associated, will in the future contribute not only to the repurposing of already available pharmacological drugs for the usage in autoimmune pathologies, but also to the development of new therapeutic strategies geared to target specific dopamine receptors in particular cell types, increasing the therapeutic efficacy and reducing adverse effects associated

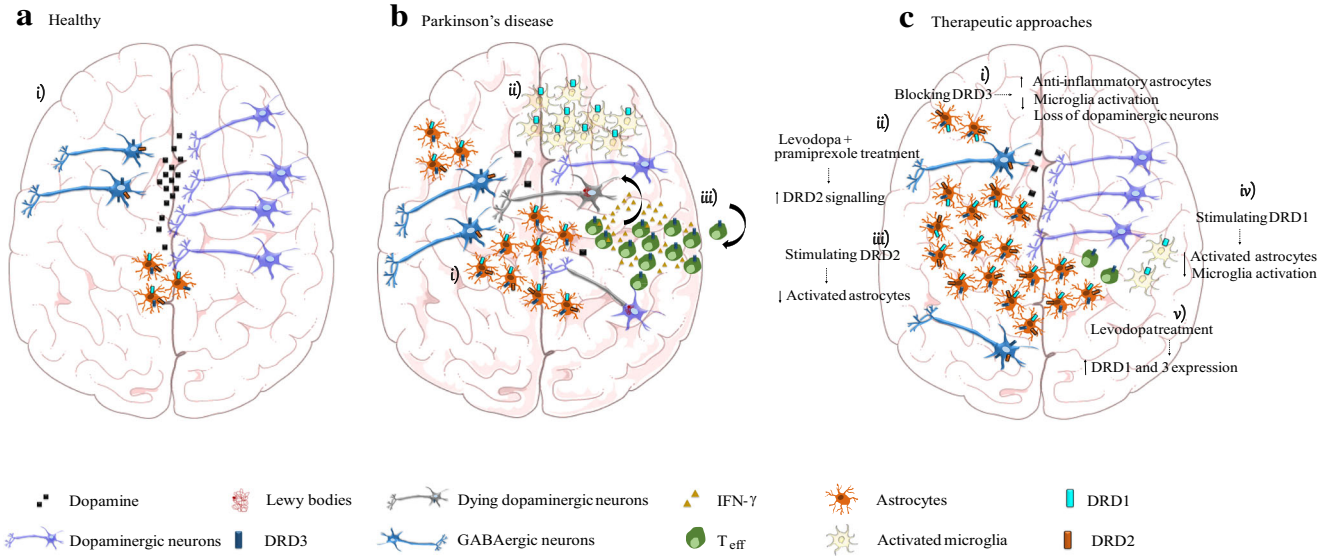

Fig. 3 Targeting the dopaminergic system as therapy for Parkinson's disease. Schematic representation of dopaminergic components in the nigrostriatal pathway under homeostasis, PD, and PD exposed to therapeutic approaches targeting dopaminergic system. **a** In healthy conditions, dopaminergic neurons located in the substantia nigra release dopamine in the striatum. Striatal GABAergic neurons, which regulate the control of voluntary movements, express DRD3 and DRD2 and respond to dopamine produced by neurons of the nigrostriatal pathway. Homeostatic astrocytes express DRD1 and DRD2, which exert anti-inflammatory effects (i). **b** In PD, there is an oxidative stress which leads to the generation of Lewy bodies and the progressive loss of dopaminergic neurons of the nigrostriatal pathway, and a consequent reduction of dopamine levels in the striatum (i). Decreased dopamine levels promote a shift from the stimulation of low-affinity dopamine receptors (DRD1 and DRD2) to a selective stimulation of high-affinity dopamine receptors (DRD3). Thus, GABAergic neurons receive attenuated input for DRD2 stimulation, triggering the motor impairment. In addition, microglial cells and astrocytes loss their anti-inflammatory stimulation mediated by DRD1 and DRD2, thus favouring neuroinflammation (ii). Lewy bodies stimulate Toll-like receptors in microglial cells, leading to further microglial activation and neuroinflammation. Moreover, Lewy bodies are captured by dendritic cells and presented to T cells in the cervical lymph nodes, triggering a $CD4^+$ T cell response specific to neo-antigens contained in Lewy bodies. Activated $CD4^+$ T cell acquire Teff phenotypes and infiltrate the brain. The selective stimulation of DRD3 expressed in Teff induces a strong IFN-γ production, which further contributes to induce a pro-inflammatory phenotype in microglial cells, increasing the extent of activated microglia and astrogliosis (iii). **c** The antagonism of DRD3-signalling attenuates IFN-γ-mediated pro-inflammatory effects of Teff, promotes activated astrocytes with anti-inflammatory properties, reduced microglial activation and thus dampening neurodegeneration (i). A combination of levodopa and pramiprexole, a DRD2/3 agonist, increases DRD2 expression and stimulation in GABAergic neurons, attenuating motor manifestations (ii). Moreover, the systemic administration of quinpirole, a DRD2/DRD3-agonist, promotes the DRD2-stimulation in astrocytes, inducing anti-inflammatory effects, dampening microglial activation and consequently attenuating neurodegeneration (iii). Similarly, the systemic administration of the DRD1-agonist A-68930, stimulates DRD1-signalling in microglial cells and astrocytes, triggering anti-inflammatory effects that attenuates neuroinflammation and the consequent neurodegeneration (iv). Levodopa, the current treatment to treat PD patients' symptoms, increases DRD3 and DRD1 expression in the brain (v), and when used in combination with pramiprexole increases DRD2 signalling (ii). Abbreviations T_{eff}: effector T cells

with current off-target drugs. This kind of therapy complemented with genome sequencing analysis usage for diagnosis, will reduce off-target effects among different patients affected by these autoimmune pathologies.

Acknowledgements This work was supported by *Programa de Apoyo a Centros con Financiamiento Basal* AFB-170004 (to Fundación Ciencia & Vida) from "Comisión Nacional de Investigación Científica y Tecnológica de Chile (CONICYT)" and by grants FONDECYT-1170093 (to R.P.) from "Fondo Nacional de Desarrollo Científico y Tecnológico de Chile", and MJFF-10332.01 (to R.P.) and MJFF-15076 (to R.P.) from Michael J. Fox Foundation for Parkinson Research. PV is supported by "Progama PostDoc Hinge" from Fundación Ciencia & Vida.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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