Involvement of dopaminergic signaling in the cross talk between the renin-angiotensin system and inflammation

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Abstract
The renin-angiotensin system (RAS) is a fundamental regulator of blood pressure and has emerged as an important player in the control of inflammatory processes. Accordingly, imbalance on RAS components either systemically or locally might trigger the development of inflammatory disorders by affecting immune cells. At the same time, alterations in the dopaminergic system have been consistently involved in the physiopathology of inflammatory disorders. Accordingly, the interaction between the RAS and the dopaminergic system has been studied in the context of inflammation of the central nervous system (CNS), kidney, and intestine, where they exert antagonistic actions in the regulation of the immune system. In this review, we summarized, integrated, and discussed the cross talk of the dopaminergic system and the RAS in the regulation of inflammatory pathologies, including neurodegenerative disorders, such as Parkinson’s disease. We analyzed the molecular mechanisms underlying the interaction between both systems in the CNS and in systemic pathologies. Moreover, we also analyzed the impact of the commensal microbiota in the regulation of RAS and dopaminergic system and how it is involved in inflammatory disorders. Furthermore, we summarized the therapeutic approaches that have yielded positive results in preclinical or clinical studies regarding the use of drugs targeting the RAS and dopaminergic system for the treatment of inflammatory conditions. Further understanding of the molecular and cellular regulation of the RAS-dopaminergic cross talk should allow the formulation of new therapies consisting of novel drugs and/or repurposing already existing drugs, alone or in combination, for the treatment of inflammatory disorders.

Keywords Renin-angiotensin system · Dopamine · Inflammatory disorders · Parkinson’s disease · Inflammatory bowel diseases · Chronic kidney disease

Abbreviations
ACE Angiotensin-converting enzyme
AngI Angiotensin I
AngII Angiotensin II
Ang(1–7) Angiotensin (1–7)
ATR1 Type 1 AngII receptor
ATR2 Type 2 AngII receptor
CNS Central nervous system
COMPT Catechol-O-methyltransferase
DRDn Dopamine receptor Dn

DSS Dextran sodium sulfate
IBD Inflammatory bowel diseases
IL-1n Interleukin 1n
MasR Mas receptor
MPTP 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
RAS Renin-angiotensin system
Th1 T-helper 1n
TH Tyrosine hydroxylase
TNF-α Tumor necrosis factor α
WT Wild-type
βAR β-adrenergic receptor
β2AR β2-adrenergic receptor
6-OHDA 6-hydroxydopamine

Introduction
Inflammatory diseases include a huge number of pathologies that involve the perturbation immune homeostasis, causing
systemic or local inflammation in the organism. These disorders represent a serious issue world-wide, involving life-long debilitating symptoms. Their incidence in the western hemisphere has enhanced in the last decade due to increased life span, environmental pollutants, lifestyle, and changes in diet, reaching about 5–7% among its inhabitants and affecting almost 24 million people in the USA [1]. Nevertheless, those statistics are based on a list of 80 pathologies classified as inflammatory disorders, which excludes many diseases with an inflammatory component, such as neurodegenerative and cardiovascular diseases. Importantly, genetic and environmental factors may contribute to the development and progression of inflammatory disorders, including the renin-angiotensin system (RAS) and the catecholaminergic system, among others [2–6]. The RAS is composed by a group of hormones and enzymes that together regulate both blood pressure and inflammation (Fig. 1). The system consists on a molecule called angiotensinogen, which is secreted by the liver into the blood stream. Angiotensinogen is then converted into angiotensin I (AngI) by the action of renin, and in turn, AngI might be converted into angiotensin II (AngII) in a reaction catalyzed by the angiotensin-converting enzyme 1 (ACE1). AngII has the ability to stimulate type 1 AngII receptors (ATR1) as well as type 2 AngII receptor (ATR2). The stimulation of ATR1, which is expressed in the kidneys, blood vessels, heart, and central nervous system (CNS), promotes increased blood pressure and favors the development of inflammation [7]. Conversely, stimulation of ATR2, which is expressed in kidney, adrenal gland, and the brain, induces anti-inflammatory effects and reduces blood pressure [7]. In addition, AngII might be further processed by angiotensin-converting enzyme 2 (ACE2) to yield a peptide called angiotensin (1–7) (Ang(1–7)). Ang(1–7) in turn may stimulate the Mas receptor (MasR), exerting anti-inflammatory and regenerative effects [8–10]. Importantly, in addition to the systemic RAS, several local RAS have been also identified in individual organs, where it plays a role not only in the homeostasis of blood pressure but also in the regulation of local immune response [11–14].

The immune system can also be modulated by the action of neurotransmitters, which have been extensively involved as mediators in neuro-immune communication. In particular, dopamine, a catecholaminergic neurotransmitter, has been consistently involved in the control of inflammation [15]. In this regard, dopamine plays an important role in the regulation of immune responses in the brain [16–20] and the gut [21, 22]. Dopaminergic regulation of immunity is exerted by the stimulation of dopamine receptors expressed on immune cells, including dendritic cells [23–25], T cells [26–28], and B cells among other cellular types [29, 30]. Dopaminergic effects are triggered by the stimulation of five different G protein-coupled receptors (GPCRs) expressed on the cell surface, which vary in their affinities for the ligand and are classified into two subtypes depending on their sequence homology, pharmacologic behavior, and signaling pathways coupled: type 1 dopamine receptors (including DRD1 and DRD5) and type 2 dopamine receptors (including DRD2, DRD3, and DRD4) [6]. It is noteworthy that high-affinity dopamine receptors (DRD3, DRD4, and DRD5), which are selectively stimulated by low dopamine concentrations (in the range of 20–500 nM), promote pro-inflammatory responses in the adaptive [20, 22, 27, 28, 31, 32] and innate immune cells [23–25, 33]. Conversely, the stimulation of low-affinity dopamine receptors (DRD1 and DRD2), which are exclusively stimulated by high dopamine levels (in the range of 1–10 μM), induces anti-inflammatory effects in the immune system [34, 35].

Anomalies in the dopaminergic regulation of these neuroimmune interaction have been associated to several autoimmune and neurodegenerative diseases [6, 19, 36]. Indeed,
polymorphisms in some dopamine receptors have been identified as genetic risk factors for Parkinson’s disease [37, 38] and inflammatory bowel diseases [39] as well as increased fibrosis and kidney inflammation, independently of blood pressure [40, 41]. Furthermore, dopamine is also involved in the regulation of blood pressure, renal function, cognition, and voluntary movements [42, 43], thus suggesting a potential communication between dopaminergic signaling and either local or systemic RAS. Here, we analyzed the communication between RAS components, the immune system, and dopaminergic signaling in the context of homeostasis, inflammation, and neurodegenerative disorders.

Modulation of inflammation by dopamine and RAS

Dopamine is a catecholaminergic neurotransmitter with immunomodulatory effects in the CNS and in the periphery. Dysregulation in the dopaminergic system affects both innate and adaptive immunity, contributing to the development of autoimmune and neurodegenerative disorders [6]. In this regard, changes of dopamine levels have been associated with inflammatory conditions, including inflammatory bowel diseases [44, 45], Parkinson’s disease [46], and sepsis [34]. These changes in dopamine concentration are critical for the modulation of immune responses by promoting a shift in the type of dopamine receptors stimulated. Dopamine receptors are expressed on several immune cell populations [47] where they modulate fundamental processes required for the development of immune responses, such as antigen presentation [24, 33], effector cell differentiation [22, 27], regulatory T cell function [31, 48], and leukocyte migration [49, 50].

Inflammation is often mediated by the inflammasome, a group of proteins that becomes activated and assembled in response to both microbial inflammation and endogenous danger signals, such as tumor necrosis factor α (TNFα) and reactive oxygen species [51–53]. Its activation plays a critical role in the initiation and development of systemic immune responses by promoting the secretion of pro-inflammatory cytokines, including interleukin 1β (IL-1β) and IL-18 [54, 55]. The NLRP3 inflammasome, which is highly expressed in macrophages, is strongly regulated by dopamine. In this regard, the stimulation of the DRD1 triggers a rise of cAMP and the consequent ubiquitination and degradation of NLRP3 in macrophages, thus dampening inflammation [35]. Consequently, exercise-induced dopamine secretion by the vagus nerve ameliorates inflammation by reducing serum levels of TNFα in a mouse model of endotoxiaemia [56]. According to these findings, the in vitro stimulation of splenocytes with a dopaminergic agonist type 1 attenuated TNFα production. Conversely, TNFα production was increased by splenocytes upon treatment with a dopaminergic antagonist type 1. In the same direction, administration of fenoldopam, a type 1 dopaminergic agonist, ameliorated systemic inflammation and attenuated hyperglycemia in diabetic septic mice by inhibiting p65NF-kB phosphorylation and reducing serum TNFα [57]. Taken together, these findings suggest that stimulation of low-affinity dopamine receptors in immune cells attenuates systemic inflammation.

It is important to consider that other catecholamines, including epinephrine and norepinephrine, also play an important role in the regulation of systemic inflammation both in humans and animal models. In this regard, initial studies showed that antiviral function of alveolar macrophages was dampened after exercise in experimental animals, an effect that was abrogated by adrenalectomy or by the administration of propranolol, thus suggesting the involvement of β-adrenergic receptors (βAR) [58]. Similarly, a study performed with human samples showed a decrease in LPS-induced TNFα production and a concomitant increase in IL-10 secretion by mononuclear cells after an acute exposition to epinephrine [59]. Further studies have provided genetic and pharmacologic evidence indicating that sympathetic activity reduces inflammation [60, 61]. Accordingly, it has been shown that norepinephrine stimulates β2AR in macrophages, promoting IL-10 secretion and attenuating the production of TLR-induced pro-inflammatory cytokines by these cells [60]. In consequence, the genetic deficiency of Adrb2 (the gene encoding for β2AR) in experimental animals resulted in exacerbated susceptibility to dextran sodium sulfate (DSS)-induced inflammatory colitis and increased lethality to LPS-induced endotoxiaemia [60]. Despite the acute sympathetic activity exerts a β2AR-mediated immunosuppressive effect on inflammation, it has been shown that prolonged time of exercise training leads to increased IL-12 production by macrophages in response to LPS. It was due to that prolonged sympathetic stimulation (i.e., 3 weeks of exercise training) induces a downregulation of β2AR in macrophages [62]. Altogether these studies illustrate the important immunosuppressive role of sympathetic activity contributing to the control of inflammation.

On the other hand, systemic immunomodulatory effects have been also associated with global RAS activation. In this regard, preclinical and clinical studies have shown that both ATR1 signaling and ACE activity promote inflammatory responses through mechanisms that are independent of blood pressure. For instance, global RAS is activated during atherosclerosis and unstable angina, inducing myocardial damage mediated by T cells. Of note, ACE and ATR1 expression has been shown upregulated in T cells obtained from patients with unstable angina [63]. Furthermore, T cells from these patients were cultured in the presence of AngII, ACE enzymatic activity was increased in the supernatant, indicating the activation of a positive feedback of the RAS in lymphocytes [63]. In the same direction, the systemic administration
of an ACE inhibitor, quinapril, showed an anti-inflammatory effect, decreasing immune cell accumulation and reducing pro-inflammatory cytokine production in renal tubules in a rodent model of immune complex nephritis [64]. Another key process involved in inflammation and regulated by RAS is leukocyte migration. In this regard, it has been shown that AngII-mediated ATR1-stimulation promotes migration of naïve T cells from the bloodstream into the spleen. Mechanistic analyses showed that systemic administration of AngII induces the overexpression of CCR9 and CD62L in naïve T cells and the secretion of CCL25 and CCL19 in the spleen of mice [65]. Another study has shown that exogenous AngII induced upregulation of cell surface molecules involved in T cell proliferation and migration, including CD69, CD25, and CCR5 [66]. Moreover, the same authors showed that AngII produced by T cells upon TCR stimulation showed that AngII produced by T cells upon TCR stimulation increased permeability due to epithelial disruption mediated by some pathobionts present in commensal bacteria [72–74]. Interestingly, it has been described that gut inflammation in IBD involves a sharp reduction of dopamine levels (up to 10 -fold change in the colonic mucosa), which results from epithelial disruption, loss of some neurons of the enteric nervous system, and dysbiosis [44, 75]. In this context, using a mouse model of IBD induced by the adoptively transfer of naïve T cells into lymphopenic mice, it was shown that DRD3-signaling in T-lymphocytes promoted Th1 differentiation, inhibited the Th2 differentiation, and favored the expansion of Th17 cells in the gut mucosa [22]. Of note, reduced dopamine levels associated to gut inflammation (50–100 nM) are consistent with a selective stimulation of DRD3, which display the highest affinity for dopamine [15]. Conversely, DRD2 signaling, which is triggered by 1–5 μM dopamine and therefore is impaired upon gut inflammation, has been involved in promoting suppressive activity of regulatory T cells [76] and favoring epithelial permeability [77]. Accordingly, the administration of DRD2 agonists, such as cabergoline and quinpirole, has been shown to dampen gut inflammation in animal models [76, 77]. In the same direction, a DRD2 allele associated with lower DRD2 expression has been related to increased risk of Crohn’s diseases [39]. Thus, current evidence indicates that DRD3 signaling promotes gut inflammation, whereas DRD2 stimulation ameliorates IBD. Regarding the involvement of the RAS system in IBD, it has been shown that a genetic mouse model, which overexpresses renin in the liver, develops a more severe form of TNBS-induced inflammatory colitis than that of wild-type (WT) littermates. Accordingly, increased expression of renin promotes gut epithelium disruption and accumulation of Th1 and Th17 subsets of T cells in the intestinal lamina propria. In addition, administration of the ATR1 antagonist, losartan, reduced the severity of the disease manifestation, reaching levels similar to that of the WT mice [78]. Furthermore, the analysis of biopsies of IBD patients treated with losartan showed that ATR1 antagonism resulted in lower levels of pro-inflammatory cytokines in the colonic mucosa when compared with control IBD patients [78]. Another study analyzed the interaction between the RAS and the dopaminergic system in gut inflammation using mice deficient in genes encoding for some dopamine receptors and RAS components involved in inflammation. The results showed that genetic deficiency of ATR1 resulted in increased expression of either type 1 and 2 dopamine receptors in the proximal colon. Moreover, an increased ratio of ATR1 to ATR2 was observed in the gut upon genetic deficiency of either DRD1 or DRD2 [79]. Thus, this study confirms a reciprocal negative regulation between the pro-inflammatory receptor ATR1 and the anti-inflammatory receptors ATR2, DRD1, and DRD2. Interestingly, the same authors also demonstrated that aged rats, which are associated...
with a pro-inflammatory state on the gastrointestinal tract, display higher levels of ATR1 expression and lower expression of ATR2 and DRD2 in the colon, differences that could be partially reverted by the administration of the ATR1 antagonist candesartan [79]. Taken together, these results indicate that gut homeostasis involves a reciprocal regulation between some components of the RAS and the dopaminergic system, which becomes dysregulated upon inflammation associated to IBD and ageing, resulting in increased pro-inflammatory signaling mediated by ATR1 and DRD3, and impaired anti-inflammatory signaling mediated by ATR2, DRD1, and DRD2.

**Interaction between RAS and dopaminergic system in neurodegenerative disorders**

Not only the kidney and the gut mucosa express local components of the RAS but also the brain, where it plays a key role regulating blood pressure and inflammation. In this regard, some components of the RAS have been identified in neurons and glial cells. Angiotensinogen and ACE activity have been found in astrocytes and neurons in particular areas of the brain [80, 81]. Although scarcely found in the brain, renin is seques-tered by the pro-renin receptor, which seems to constitute a key component required to propagate AngII actions in the CNS [82]. After conversion of angiotensinogen into AngI and then in AngII, the latter might stimulate ATR1 expressed in microglia, triggering increased production of nitric oxide species and oxidative damage [83]. Conversely, the dopaminergic stimulation of DRD2 in astrocytes dampens the pro-inflammatory and oxidative effects exerted by local RAS, by downregulating the expression of microglial ATR1 and reducing the astrocytic production of angiotensinogen [83] (Fig. 2).

A huge number of studies performed in human and animals has indicated that neuroinflammation plays a major role in the development and progression of neurodegenerative disorders, including Parkinson’s disease, Alzheimer’s disease, and multiple sclerosis [84]. According to the regulatory role of the RAS in neuroinflammation, emerging evidence has shown a relevant role of this system in neurodegenerative disorders. In this regard, the inflammatory features associated to the mouse model of Parkinson’s disease induced by 6-hydroxydopamine (6-OHDA) were significantly dampened by the administration of candesartan, an ATR1 antagonist [85]. Patients with Parkinson’s disease often show gastrointestinal problems many years before the manifestation of the motor symptoms. Braak and colleagues proposed that Parkinson’s disease is initiated in the gut by the generation of alpha-synuclein aggregates in response to pathogenic bacteria, and that these aggregates migrate later to the brain through the vagus nerve, being accumulated in the substantia nigra and ultimately promoting degeneration of neurons of the nigrostriatal pathway [86, 87].

Of note, the nigrostriatal pathway is an area of the brain involved in the control of voluntary movements; thereby, a classic symptomatic manifestation in advanced Parkinson’s disease is the motor impairment. The Braak’s hypothesis has been the starting point for many studies addressing the mechanisms by which processes associated to the gut mucosa might trigger neuroinflammation. In this regard, a study addressing the role of the cross talk between the dopaminergic system and the RAS in the context of the gut-brain axis has demonstrated that gut inflammation induced in mice by the administration of DSS results in downregulation of DRD2 and ATR2 expression and increased expression of ATR1 in the nigrostriatal pathway. Accordingly, the subchronic administration of DSS resulted in significant neurodegeneration of dopaminergic neurons of the substantia nigra and overexpression of the pro-inflammatory cytokine IL-1β and of AngII [88]. Interestingly, vagotomy reverted the changes in the expression ratio of ATR1/ATR2 and partially recovered the expression levels of the nigrostriatal IL-1β [88]. Of note, these changes in the local CNS RAS were previously shown to be toxic for dopaminergic neurons [89–91]. On the other hand, when nigrostriatal pathway was directly lesioned by the stereotaxic administration of 6-OHDA, the ratio of ATR1 to ATR2 and IL-1β expression was increased in the colonic mucosa; nevertheless, dopamine levels were increased in this tissue. Moreover, vagotomy did not reversed the inflammatory features observed in the colonic mucosa upon nigrostriatal lesion [88]. Thereby, these results indicate a bidirectional communication of inflammatory components in the colonic mucosa and the nigrostriatal pathway, which is dependent in the vagus nerve only in the gut-to-brain direction but not in the opposite direction (Fig. 3). In addition, a number of studies have indicated that the initial reduction of dopamine levels in the nigrostriatal pathway induce pro-inflammatory responses in this area of the brain [19]. It is noteworthy that initial aggregation of α-synuclein in nigrostriatal neurons observed in Parkinson’s disease results in decreased secretion of dopamine, even before neurodegeneration [92]. Due to the early reduction of nigrostriatal dopamine, the role of DRD3 in neuroinflammation has been explored in the context of Parkinson’s disease. In this regard, it has been shown that DRD3 signaling in CD4+ T cells infiltrating the substantia nigra favors Th1 and Th17 effector function [17, 20]. In addition, DRD3 signaling in astrocytes has been also involved in neuroinflammation. In this regard, genetic and pharmacologic evidence has recently shown that DRD3 signaling in astrocytes attenuates the production of the anti-inflammatory factor Fizz1 by microglial cells, thus promoting neuroinflammation [93]. Accordingly, the systemic treatment of mice with a selective DRD3 antagonist, PG01037, exerted a significant therapeutic effect reducing neuroinflammation and neurodegeneration in two different mouse models of Parkinson’s disease [16]. In addition, another couple of studies have addressed the
role of the low-affinity dopamine receptors in neuroinflammation associated to Parkinson’s disease. Using genetic and pharmacologic approaches, that study showed that DRD2 signaling in astrocytes induced the expression of the anti-inflammatory mediator αB-crystallin, which abolishes the development of neuroinflammation and neurodegeneration in a mouse model of Parkinson’s disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [94].

Another example of neurodegenerative disease that is affected by the dopaminergic system and RAS is multiple sclerosis (MS). MS is a CD4+ T cell-driven autoimmune disease characterized by the destruction of the myelin sheath on the axons of motor neurons. Myelin is targeted by the adaptive and innate immune system once the blood-brain barrier becomes permeable leading to the infiltration of immune cells into the CNS [95–97]. Experimental autoimmune encephalomyelitis (EAE) is a mouse model of MS which is elicited by the immunization with a peptide derived from the sequence of myelin oligodendrocyte glycoprotein (MOG35-55) and recapitulates several immunologic and pathological aspects of MS. Addressing the role of RAS in EAE, it has been shown an upregulation of AngII, ACE1, and ATR1 either in CD4+ T cells and macrophages infiltrating the CNS during the inflammatory process [98, 99]. Accordingly, the inhibition of ACE...
Consequently, expression of low-affinity dopamine receptors turns inflammatory arm of RAS in the gut by increasing ATR1/ATR2 balance. The loss of dopaminergic neurons in the brain induces an activation of the gut-brain axis. Gut and brain local RAS mediate inflammatory responses in their corresponding organs. Communication between the gut and the brain involves a number of immune mediators. The human body hosts more than 10-fold its own number of cells on intestinal microbiota, giving rise to the idea that it constitutes another organ of our body [103].

**Intestinal microbiota in the modulation of RAS and its role in inflammatory and metabolic diseases**

More than 5000 different species of bacteria and more than 100 trillion individual microbial cells inhabit our intestine. The human body hosts more than 10-folds its own number of cells on intestinal microbiota, giving rise to the idea that it constitutes another organ of our body [103]. Intestinal microbiota interacts with the organism by synthesizing metabolites, such as γ-aminobutyric acid (GABA) or short-chain fatty acids (SCFA), which exert their effects by stimulating specific receptors expressed on the host cells [104]. Of note, some of those metabolites, including SCFA, can only be obtained through gut microbiota-mediated food degradation. SCFA have acquired particular importance, as a relevant regulatory role in the development of inflammatory and neurodegenerative disorders has been consistently reported in the last 15 years [105–108]. Dietary fiber is mainly degraded into three different SCFA by the intestinal microbiota: acetate and propionate, which are mainly synthesized by the bacterial genus *Bacteroidetes*, and butyrate, produced by the *Firmicutes* genus [109]. Each of these molecules can act in the organism beyond the intestine by stimulating G protein-coupled receptors expressed in several type of cells in the host, including GPR41, GPR43, and GPR109a [75]. For instance, propionate has a protective role on the blood-brain barrier, promoting its integrity and reducing its permeability, thereby protecting the CNS from infections [110]. On the other hand, butyrate favors healing and promotes the structural integrity of the epithelial barrier of the gut mucosa, thus limiting bacterial translocation into the blood stream and thereby reducing the probability of gut inflammation [111]. At the same time, metabolites derived...
| Molecular target | Experimental model/pathology | Outcome | Reference |
|------------------|-----------------------------|---------|-----------|
| **Drugs targeting RAS** |
| Lisinopril ACE  | Alzheimer’s disease APP/PS1 transgenic mouse model | Lisinopril inhibited beneficial effect of ACE-overexpressing macrophages (low iNOS and TNFα and high IGF1) | [117] |
| Losartan/Enalapril ATR1/ACE | TGF-β KO mice Alzheimer’s disease-like model | Treatments restored reactivity to acetylcholine. Losartan reduced astrogliosis | [118] |
| Candesartan/Lisinopril ATR1/ACE | Haloperidol-induced dyskinesia in rat model | Co-administration of candesartan and lisinopril inhibited increase of TNFα and IL1β induced by haloperidol in the striatum and cortical regions of the rat brain | [119] |
| Candesartan ATR1 | LPS-induced neuroinflammation in rat model | Attenuation of microglial activation. Inhibition of pro-inflammatory cytokine production and NF-κB signaling | [120] |
| Losartan ATR1 | Rat model of chronic hypertension (hypertension correlates with increased risks of PD) | Intranasal administration of losartan increased brain IL-10 production, thus promoting neurogenesis by increasing choroid plexus cell proliferation | [121] |
| Candesartan ATR1 | Alzheimer’s disease transgenic APP mouse model | Candesartan administration decreased Iba-1 and GFAP expression in the brain | [122] |
| Candesartan/Telmisartan ATR1 | Alpha-synuclein-induced Parkinson’s disease mouse model | Co-administration of RAS inhibitory drugs decreased the expression of IL-6, IL1β, and iNOS in the substantia nigra and striatum of mice treated with adeno-associated virus encoding mutated alpha-synuclein | [123] |
| Losartan ATR1 | LPS-induced neuroinflammation in rat | Pre-treatment with losartan before LPS administration decreased brain IL-6, malondialdehyde, and nitric oxide metabolites, improving behavioral parameters | [124] |
| Telmisartan ATR1 | LPS-induced neuroinflammation in mouse | Telmisartan decreased the TNFα and iNOS expression in brain together with a decrease in the brain Aβ plate deposition | [125] |
| Perindopril ACE | LPS-induced neuroinflammation in mouse | Perindopril improved spatial and non-spatial memory, decreased Aβ deposition, and reduced TNFα, iNOS, and malondialdehyde expression | [126] |
| Telmisartan ATR1 | MPTP-induced Parkinson’s disease mouse model | Telmisartan induces the activation of PPAR-γ in microglia, imprinting an anti-inflammatory M2 phenotype | [127] |
| Candesartan ATR1 | 6-OHDA-induced Parkinson’s disease rat model | Administration of candesartan did not induce changes in dopamine nor dopamine receptors expression, suggesting ATR1 inhibition does not improve motor symptoms in Parkinson’s disease | [128] |
| Captopril ACE | MPTP-induced Parkinson’s disease mouse model | Activation of microglia was inhibited in the group treated with captopril | [129] |
| Candesartan ATR1 | MPTP-induced Parkinson’s disease mouse model | Candesartan administration inhibited striatum levels of TNFα and decreased dopaminergic neurons death in the nigrostriatal pathway | [130] |
| Candesartan ATR1 | EAE in mouse | Candesartan administration during the first days of EAE-reduced demyelination in the optic nerve | [131] |
| Losartan/Quinapril ATR1/ACE | Mouse model of autoimmune thyroiditis in non-obese diabetic mouse | Neither of both drugs interfered with thyroiditis development, which correlated with unmodified inflammatory parameters. | [132] |
| Enalapril ACE | EAE in mouse | Oral administration of enalapril increased serum levels of bradykinin, reduced severity of EAE, and decreased Th17 cell infiltration to the CNS | [133] |
| Telmisartan ATR1 | Experimental autoimmune uveitis in mouse | Telmisartan suppressed uveitis by inhibiting T cell activation in the draining lymph nodes and their adhesion to the retina. Intracutal MCP-1 and ICAM-1 expression was reduced | [134] |
| Losartan ATR1 | Endotoxin-induced uveitis in rats | | [135] |
| Molecular target | Experimental model/pathology | Outcome | Reference |
|------------------|-----------------------------|---------|-----------|
| Losartan         | Reduced the production of TNFα and MCP-1 in a dose-dependent manner. Activation of NF-κB was reduced in the iris ciliary body. | Fenoldopam inhibits p65NF-kB phosphorylation leading to decreased TNFα production by splenocytes. Fenoldopam recues diabetic mice from polymicrobial peritonitis. | [57] |
| Fenoldopam       | Type 1 dopaminergic agonist  | Diabetic septic mouse | Treatment with Quinpiroli decreased size of colonic lesions, colon wet weigh, and permeability by inhibiting Akt pathway. | [77] |
| Quinpiroli       | DRD2/DRD3 agonist           | Iodoacetamide-induced colitis in rats | Treatment with Quinpiroli decreased colitis severity. | [77] |
| Cabergoline      | DRD2 agonist                | Iodoacetamide-induced colitis in rats | Treatment with Cabergoline decreased size of colonic lesions, colon wet weigh, and permeability. | [77] |
| A-68930          | DRD1 agonist                | Intracerebral hemorrhage in mouse | A-68930 reduced edema by inhibiting neutrophil infiltration to the CNS. Also reduced NLRP3, caspase-1, and IL1β. | [136] |
| LY171555         | DRD2 agonist                | MPTP-induced Parkinson’s disease mouse model | This drug inhibited the formation of NLRP3 in the MPTP model of Parkinson’s disease, decreasing the severity of the model. This was mediated by an inhibition of the secretion of IL1β in the midbrain. | [137] |
| Pramipexole      | DRD2/DRD3-preferred agonist | EAE in mouse | Intraperitoneal administration of Pramipexole prevents EAE development by inhibiting the production of IL17, IL1β, and TNFα in peripheral lymphoid tissue. | [138] |
| Berberine        | Pan-antagonist for Dopamine receptors | DSS-induced inflammatory colitis in mouse | Berberine ameliorates clinical score by reducing IFNγ and IL-17 secretion by cells in the mesenteric lymph nodes. | [139] |
| Quinpiroli       | DRD2/DRD3 agonist           | LPS-induced neuroinflammation in mouse | Quinpiroli reduces neuroinflammation in WT, but not in alpha-synuclein overexpressing mice. Reduction of inflammation was dependent on arrestin-β2 signaling. | [140] |
| Pramipexole      | DRD2/DRD3-preferred agonist | Formalin-induced and carrageenan-induced paw inflammation in mouse, TPA-induced ear edema in mouse | This drug reduced clinical scores on all these inflammatory models by attenuating neutrophil infiltration into the affected tissue. | [141] |
| Sulpiride        | Type 2 dopaminergic antagonist | Multiple sclerosis in human | Sulpiride inhibited the anti-inflammatory effects of dopamine observed in PBMC from MS patients. | [142] |
| PG01037          | DRD3 antagonist              | MPTP-induced Parkinson’s disease mouse model | PG01037 attenuated neurodegeneration and motor impairment on mice treated with MPTP by increasing astrogliosis in the substantia nigra and increasing ramifications of microglia. | [16] |
| SCH-23390        | Type 1 dopaminergic antagonist | RA synovial/SCID mouse | Administration of the drug reduced accumulation of IL-6 and IL-17 T cells and cartilage destruction. | [143] |
| Haloperidol      | Type 2 dopaminergic antagonist | RA synovial/SCID mouse | Administration of Haloperidol induced the accumulation of IL-6 and IL-17 T cells and cartilage destruction. | [143] |
| SCH-23390        | Type 1 dopaminergic antagonist | EAE in mouse | Attenuates disease manifestation by reducing Th17 differentiation in T cells. | [144] |

*Abbreviations present in this table that were not previously defined in the main text: Aβ amyloid Aβ, APP amyloid precursor protein, DCs dendritic cells, GFAP glial fibrillary acidic protein, IGF1 insulin-like growth factor 1, iNOS inducible nitric oxide synthase, MCP-1 monocyte chemoattractant protein 1, PBMC peripheral blood mononuclear cells, PPAR-γ peroxisome proliferator-activated receptor γ, PSI presenilin 1, SCID severe combined immunodeficiency, RA rheumatoid arthritis, TPA 2-O-tetradecanoylphorbol-13-acetate.
from commensal bacteria might stimulate their receptors expressed in innate and adaptive immune cells, strongly regulating the immune response of the host [104]. Thus, the presence of some commensal bacterial populations in the gut contributes to the regulation of homeostatic processes in the organism. In this regard, it has been shown that depletion of intestinal microbiota through the action of wide-spectrum antibiotics enhances the sensitivity to insulin, modifying the outcome of some metabolic disorders, which suggest the possibility that commensal bacteria are able to interact with intestinal RAS [112]. Indeed, the administration of sodium butyrate to uninephrectomyzed rats attenuated the increase on arterial pressure induced by high AngII and significantly reduced the production of inflammatory cytokine, including TNFα and IL-6 [113]. Moreover, the expression of proteolytic enzymes, and debris protein derived from dying epithelial cells. Some of these peptides have shown to exert inhibitory effects on the activity of renin and ACE1 [114], thus modulating directly RAS in the gut and indirectly the dopaminergic intestinal system, as these systems are reciprocally regulated in the gut mucosa, as described above. In addition to the direct production of metabolites that might affect host physiology, intestinal microbiota can also influence the production of key regulators of immunity, including dopamine and norepinephrine [115, 116]. As previously mentioned in this review, either systemic or local dopamine levels have different effects in the modulation of the immune system, orchestrating either tolerogenic or inflammatory responses depending on the dopamine receptor that are preferentially being stimulated in adaptive or innate immune cells. However, further research is required to decipher how gut microbiota affects the different mechanisms involved in the interaction between the RAS and the dopaminergic system. The potential knowledge derived from these studies would give novel insight in the understanding of potential consequences of dysbiosis in the development of inflammatory affects, and in the design, combination or repurpose of dopaminergic drugs and RAS-targeting drugs as therapeutic approaches for inflammatory disorders

Conclusions and projections

Current evidence has shown a significant regulation of inflammation by RAS and dopaminergic system, as well as a complex interaction between both systems. Of note, the RAS and the dopaminergic system might trigger pro-inflammatory and anti-inflammatory outcomes systemically and in particular organs, including the kidney, the gut, and the brain. Whereas AngII-ATR1 axis exerts pro-inflammatory effects, the AngII-ATR2 and Ang(1–7)-MasR arm induces anti-inflammatory and regenerative processes. Similarly, DRD3 and DRD5 signaling promotes inflammatory effects, while DRD1 and DRD2 stimulation trigger anti-inflammatory effects. Furthermore, it has been shown that DRD1/DRD2 stimulation might exert inhibition of ATR1 signaling as well as attenuation of AngII synthesis. Conversely, ATR1 stimulation exerts downregulation of DRD1 expression. Thus, both systems regulate each other reciprocally. Further insight at the cellular and molecular level is needed in order to elucidate the detailed mechanisms of interaction by which changes on RAS or dopaminergic components control inflammation in the kidney, the gut, the brain, and systemically. Several preclinical studies have demonstrated the use of RAS inhibitors and dopaminergic drugs for the treatment of neurodegenerative and inflammatory diseases (Table 1). It is noteworthy that the lack of selectivity for dopaminergic drugs represents a challenge for the design of new drugs or other therapeutic approaches for targeting specific dopamine receptors as therapy for inflammatory disorders. Another interesting projection that arises from this study is that the combination of drugs targeting different components of the RAS and dopaminergic system could potentially reach synergistic outcomes as therapeutic strategies for the treatment of inflammation. Furthermore, the potential identification of heteromeric receptors conforded by protomers from different systems would open the possibility of development of new pharmacologic tools to be tested as therapeutic approaches for inflammatory disorders.

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