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REVIEW ARTICLE

Role of neurotransmitters in immune-mediated inflammatory disorders: a crosstalk between the nervous and immune systems

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Abstract
Immune-mediated inflammatory diseases (IMIDs) are a group of common heterogeneous disorders, characterized by an alteration of cellular homeostasis. Primarily, it has been shown that the release and diffusion of neurotransmitters from nervous tissue could result in signaling through lymphocyte cell-surface receptors and the modulation of immune function. This finding led to the idea that the neurotransmitters could serve as immunomodulators. It is now manifested that neurotransmitters can also be released from leukocytes and act as autocrine or paracrine modulators. Increasing data indicate that there is a crosstalk between inflammation and alterations in neurotransmission. The primary goal of this review is to demonstrate how these two pathways may converge at the level of the neuron and glia to involve in IMID. We review the role of neurotransmitters in IMID. The different effects that these compounds exert on a variety of immune cells are also reviewed. Current and future developments in understanding the cross-talk between the immune and nervous systems will undoubtedly identify new ways for treating immune-mediated diseases utilizing agonists or antagonists of neurotransmitter receptors.

Keywords Neurotransmitters · Immune-mediated inflammatory disorders

Introduction

Immune-mediated inflammatory diseases (IMIDs) are a diverse group of common, chronic, and complex disorders which are characterized by dysregulation of the normal immune response causing chronic inflammation of targeted organs or systems. One underlying manifestation of this immune dysregulation is the relative over-expression and inappropriate activation of pro-inflammatory mediators, such as IL-12, IL-6, or TNF alpha, whose actions lead to pathological consequences [1]. IMIDs might lead to end-organ damage that is associated with disability and high mortality [2]. Although the etiology of this disease is unknown, its pathogenesis is multifactorial including environmental factors, dietary habits, and infectious mediators in patients with a genetic predisposition [3]. The pathogenesis of immune-mediated inflammatory diseases, such as multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), Alzheimer's disease (AD), and Parkinson's disease (PD) may involve hormonal and neural mediators that link the immune and nervous system [4]. MS is an autoinflammatory demyelinating disease affecting the central nervous system (CNS) and characterized by inflammation, immune dysregulation, and immune overactivity. Experimental autoimmune encephalomyelitis (EAE) is a primarily mouse model used as an experimental model of MS [5].

RA is the most common autoinflammatory disease characterized by chronic joint inflammation, articular bone erosion, and consequently joint destruction that can lead to complete loss of function [6].

IBD is a chronic intestinal inflammatory condition. Two major types of IBD are ulcerative colitis and Crohn's disease [7]. The interaction between the gut mucosal immune system and the enteric nervous system (ENS) plays an important

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role in IBD [8]. Furthermore, IBD as a chronic inflammatory disease may impact the mammalian GI tract [9].

AD is a progressive neurodegenerative disease of the CNS and the most common form of dementia characterized by progressive loss of memory and other cognitive functions. Evidence now suggests that the pathogenesis of AD is not restricted to neuronal activity, but may involve strong interactions with immunological mechanisms in the brain [10].

PD is a progressive and degenerative nervous system disorder characterized by the death of dopaminergic neurons in the substantia nigra. Preclinical investigations indicated the role of neuroinflammation in the pathophysiology of PD [11].

The nervous and endocrine systems are closely linked to the immune system [4]. The interaction between the neuroendocrine and immune systems is necessary to maintain homeostasis of the whole body in an appropriate manner, by responding to environmental changes [12]. The neuroendocrine system regulates immunity and inflammation primarily via releasing neural mediators including neurotransmitters, neuropeptides, and endocrine hormones as they regulate a broad spectrum of physiological processes [13]. The immune system can affect nervous and endocrine systems through secreting immunocompetent substances including cytokine [14]. The pathogenesis of several IMIDs might involve immunocompetent substances and neural mediators that link the immune and nervous systems [15, 16].

Neurotransmitters are synthesized and released from nerve endings into the synaptic cleft. As well to be produced by neurons, neurotransmitters are produced by other cells, including lymphocytes and other immune system cells, and also release as a hormone into the blood [17]. The expression of several receptors for different neurotransmitters on the immune cell surface suggested that neurotransmitters show a physiological effect in the regulation of the immune response. It also demonstrates that the dysregulation of the activity of the neurotransmitter's receptors has been involved in the development of autoinflammatory disease [18]. Moreover, the expression of neurotransmitter receptors on the immune cell surface and the expression of cytokine receptors on cells from the nervous system reveal new capacities of bidirectional communication networks between the central nervous and the immune systems (Table 1) [19].

Bidirectional neuroimmune communication has considered the nervous system as a central partner of the immune system in the regulation of inflammation [21]. Neuronal pathways, like the vagus nerve-based inflammatory reflex, are physiological regulators of immune function and inflammation [22]. In competition, the neuronal function is changed in conditions categorized by immune dysregulation and inflammation [21]. Under normal conditions, this bidirectional regulatory system forms a negative feedback loop, which keeps the immune system and CNS in homeostatic balance [23]. Disturbance of these regulatory systems can lead to either overactivation of immune responses and inflammatory disease, or over suppression of the immune system and increased susceptibility to infectious disease [24].

Inflammation is a necessary response of the immune system to disturbed homeostasis caused by infection, injury, and trauma [25]. In addition to protecting the body, however, it can damage organs or lead to infectious and autoimmune inflammatory disorders including ankylosing spondylitis, psoriasis, psoriatic arthritis, Behcet's disease, arthritis, IBD, and allergy, as well as many cardiovascular, neuromuscular, and infectious diseases [26].

Over the past decades, evidence has accumulated clearly demonstrating a pivotal role for neuroendocrine-derived control mechanisms of immune function and specifically the role of neurotransmitters in the regulation of inflammation. Here, we review an assortment of neurotransmitters that modify the immune system. Understanding these mechanisms discloses the potential to use targeted neuromodulation as a therapeutic approach for treating inflammatory and autoimmune disorders. These findings and the current clinical investigation of neuromodulation in the treatment of inflammatory diseases describe the developing field of bioelectronic medicine.

Acetylcholine

Acetylcholine (ACh) is one of the old and abundant neurotransmitters in the body released from nerve terminals of postganglionic parasympathetic neurons and functions in both the central and peripheral nervous systems [27]. There are two core classes of acetylcholine receptors (AChR): nicotinic acetylcholine receptors (nAChR) and muscarinic acetylcholine receptors (mAChR) [28]. ACh, synthesized and released by the parasympathetic nerves, directly affects immune cells via muscarinic and nicotinic acetylcholine receptors and involves in the changes in central and peripheral inflammation [29]. In immune cells, signaling by ACh is mediated by these receptors [30]. Acetylcholine exerts an anti-inflammatory effect on macrophages, basophils, and mast cells via α7-nicotinic acetylcholine receptors (α7nAChRs) [31], receptors on inflammatory macrophages. Furthermore, ACh implicates in the anti-inflammation through inhibition of NF-κB nuclear translocation and down-regulation of ongoing inflammatory cytokine synthesis [32]. It has been also indicated that non-neuronal cells including immune cells can directly produce and release ACh, which may induce biological functions in an autocrine or paracrine manner [33]. In immune cells, ACh is accompanied by the expression of acetylcholinesterase and nicotinic/muscarinic

Table 1 The interaction between neurotransmitters and immune systems [17, 20]

Mechanism	Receptors identified on immune cells	Immune cells targets	Name
Acetylcholine (Ach)	Macrophages, basophils, and mast cells	α7-Nicotinic acetylcholine receptors (α7nAChRs)	Inhibition of NF-κB nuclear translocation and down-regulating ongoing inflammatory cytokine synthesis
5-Hydroxytryptamine (5-HT) or serotonin	T cells, dendritic cells, eosinophils, platelets, natural killer cells, and monocytes	5HT1, 5HT1A,5-HT1B, 5-HT2A, 5-HT3, 5-HT3A and 5-HT7	Neutrophil recruitment and T-cell activation
Dopamine (3-hydroxytyramine)	T cells and B cells, dendritic cells (DCs), macrophages, neutrophils, and natural killer (NK) cells	DRD2, DRD3, DRD4, and DRD5	Regulation of the activity, migration, differentiation, and proliferation of immune cells
Gamma-aminobutyric acid (GABA)	Monocyte,macrophage, neutrophil, T cells, B cells	$GABA_A$ and $GABA_B$ R	Inhibition of cytokine secretion, alteration of cell proliferation, and migration of the cells
Glutamate	T cells, B cells, macrophages, and dendritic cells	mGluR1, mGluR5, AMPA, NMDA	Proliferation of the lymphocytes and production of cytokines
Noradrenaline	Macrophage, monocyte, dendritic cells, natural killer cells, T cells, B cell	Adrenergic	Reduction of production of pro-inflammatory mediators including tumor necrosis factor-α, interleukin-1β, and inducible nitric oxide synthase activity
Substance P	NK cells, T and B cells, eosinophils, mast cells, macrophages, microglia, astrocytes, and dendritic	NK1	Regulation of T cell proliferation, differentiation, and migration of innate immune cells
Endocannabinoids	B cells, NK cells, macrophages, polymorphonuclear cells, T cells	CB2	Suppression of lymphocytes and T cell function
Endorphins	Monocytes, dendritic cells, natural killer cells, T cells, B cells	μ, δ, κ	Influence on antibody synthesis, lymphocyte proliferation, and natural killer cytotoxicity

acetylcholine receptors and, as one of the immunomodulatory signals, plays a key role in the regulation of immune function by triggering signals that affect differentiation, antigen presentation, or cytokine production in immune cells [30]. Accumulating evidence has suggested the presence of a strong association between cholinergic signaling and IMID [34]. Since acetylcholinesterase (AChE) inactivates acetylcholine, Li et al. reported that inhibition of acetylcholinesterase can show positive effects in the treatment of autoimmune diseases [35]. Serum levels of ACh are higher in MS patients and appear to associate with better disease outcomes, and also higher serum levels of ACh have been shown in MS patients receiving treatment than in treatment-naïve patients. These results propose that augmentation of cholinergic signaling in MS patients may ameliorate their symptoms [36]. Zabrodskii proposed that the interaction between ACh and the α7nAChR on monocytes, macrophages, and neutrophils is responsible for the cholinergic anti-inflammatory mechanism. Also, ACh treatment may diminish the blood levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 in mice [37].

Activation of the cholinergic system via α7 nAChR can reduce experimental autoimmune encephalomyelitis (EAE) that was associated with a decrease in the level of neuroinflammation in the CNS. Furthermore, the expression of immune cell markers was changed by α7 nAChR agonist, GAT107, treatment which provoked a significant decrease in macrophages, dendritic cells, and B cells, as well as a diminution in anti-myelin oligodendrocyte glycoprotein (MOG) antibodies. In addition, GAT107 directly activates α7 nAChR in murine macrophage cells. GAT107 can attach the cholinergic anti-inflammatory path for long-lasting and wide-ranging modification and downregulation of neuroinflammation in EAE. α7 nAChR activation exhibits a long-lasting widespread therapeutic effect on the immune response and disease course and, hence, shows the therapeutic management of inflammatory autoimmune diseases [38].

Dimethyl fumarate exhibits anti-inflammatory impacts on MS which is activated by ACh via alpha-7 nicotinic acetylcholine receptors (α7 nAChR) [39]. In the MS hippocampus, the activity and expression of choline acetyltransferase, the acetylcholine-synthesizing enzyme, was diminished. MS-specific cholinergic imbalance in the hippocampus may be the target of future treatment choices for memory deficit in this disease [40]. ACh is involved in the modification of central and peripheral inflammation. ACh stimuli stimulate immune cells as well as astrocytes and microglia through activation of cholinergic receptors. Cholinergic alterations may contribute to the dysregulated inflammatory processes of MS. Recent therapeutic ways for MS are according to anti-inflammatory drugs. Furthermore, cholinesterase inhibitors or ACh agonists may display a novel therapeutic approach in MS [41].

Signaling by ACh defends against IBD in rodents since decrement of AChE activity ameliorated experimental colitis in rats [42], and nicotine treatment blocked dextran sulfate sodium (DSS)-induced colitis in mice [43, 44]. Intriguingly, though activation of muscarinic signaling suppresses experimental colitis in mice, this effect is lost in animals exposed to either vagotomy or splenectomy [45, 46]. The muscarinic signaling in the nervous system moderates splenic immune cells to strongly change their inflammatory potential. Cholinergic may facilitate the clearance of the colitogenic mucosa-associated bacteria; though, the application of prosecretory drugs would increase irritating diarrheal signs. Therefore, cholinergic medication could be valuable in the future for ulcerative colitis managing but cautions should be taken about the timing and period of its usage which may cause different results [47]. Agonist of the cholinergic anti-inflammatory pathway inhibits colonic inflammatory action by downregulation of the TNF-α production and inhibition of NF-κB activation, which shows that moderating the cholinergic anti-inflammatory pathway may be a novel possible management for IBD [48].

Al-Khotani A and et al. investigated a possible anti-inflammatory effect of Ach. The results of this study showed that ACh decreases native and TNF-stimulated IL-6 release from RA human fibroblast-like synoviocytes. This finding could point to one pathway of how ACh exerts its previously shown anti-inflammatory effects, which in turn points to an important role for ACh in local regulation of the inflammatory activity in RA [49]. Studying a model of RA showed that immune cell function is regulated by the cholinergic system and, at least in part, mediated by the α7nAChR [29].

5-hydroxytryptamine or serotonin

Serotonin, which is also known as 5-hydroxytryptamine (5-HT), is an important multifunctional monoamine neurotransmitter derived from L-tryptophan via a rate-limiting reaction catalyzed by tryptophan hydroxylase 1 (TPH1) [50]. TPH1 catalyzes the conversion of tryptophan into 5-HT and is found only in 5-HT–producing cells [51]. 5-HT regulates a wide variety of functions in the CNS and the periphery through the engagement of seven types of cell surface receptors (HTR1–7) [52]. Most of the 5-HT in our body, and all of the peripheral 5-HT, is predominantly synthesized and secreted by enterochromaffin (EC) of the gastrointestinal mucosa [53]. Peripheral 5-HT plays an important role in peripheral tissues, including the immune system [54]. There is a growing body of evidence suggesting that the immune system can be regulated by the action of 5-HT on immune cells expressing 5-HT receptors (5-HTRs) and almost all immune cells express at least one serotonin component, including T cells, dendritic cells, natural killer cells, and

monocytes [55]. In recent years, the immunoregulatory role of serotonin is well established. For example, serotonin modifies both neutrophil recruitment and T-cell activation [56]. Furthermore, monocytes/macrophages' cytokine secretion and also suppression of the release of TNF-α and IL-1β can be mediated by activating serotonin receptors [55]. Evidence demonstrates that Tph1 is a potent regulator of immunity and Tph1 deficiency intensifies neuroinflammation in models of experimental autoimmune encephalomyelitis [57]. Studies have found that 5-HT is involved in the regulation of immunoinflammatory pathways and peripheral 5-HT levels and signaling have been changed in individuals with arthritis [58, 59]. Also, 5-HT could be directly involved in RA physiopathology through the regulation of the Th17/T-regulatory cell balance and osteoclastogenesis. The absence of peripheral 5-HT, in a murine model of RA, intensifies the clinical score, osteoclast differentiation, and the inflammatory response, while the addition of 5-HT in exvivo cultures restores the Th17 profile [58]. Recent investigations also suggest that 5-HT can play an important role in the pathogenesis of IBD. Changes in 5-HT signaling, including EC cell numbers and 5-HT content, have been demonstrated in patients with both Crohn's disease and ulcerative colitis [60, 61]. The recent study revealed a novel function of 5-HT in the regulation of gut inflammation concerning the recruitment of inflammatory cells and activation of proinflammatory cytokine production in TPH1-deficient ($TPH1^{-/-}$) mice [62]. The results of the current study revealed that a lack of 5-HT reduces the severity of inflammation in experimental colitis and this diminution can be reversed by the reformation of 5-HT synthesis in the gut.

Clinical efficacy of tropisetron, a 5-HT3 receptor antagonist, on an immune-based animal model of IBD and in patients with chronic inflammatory joint diseases and soft tissue rheumatism has been documented. It is likely that the protective effects of tropisetron on TNBS-induced colitis, at least partly arise from the ability of this drug the blockade 5-HT3 receptors [63]. All of the mentioned studies show that the regulation of immune cells by 5-HT in the pathogenesis of autoimmune diseases provides a new pointcut for the treatment of autoimmune diseases.

Specified bacteria in the gut can yield serotonin. In mammals, gut microbiota-derived serotonin can work locally in the intestinal tract or enter the blood circulation and enhance blood–brain barrier permeability and hence influences brain function [64]. Gut-derived serotonin through modification of gut microbiota composition impacts intestinal immune response and susceptibility to colitis. Therefore, the serotonin-microbiota axis is a potential new therapeutic target in intestinal inflammatory disorders [65].

Dysregulation of gut-derived serotonin and kynurenic pathways was detected in several neurodegenerative disorders such as AD [66]. Gut microbes impact the metabolism of tryptophan. Restoration of the intestinal microbiome to a healthy composition in patients with AD will significantly slow down the development of neurodegeneration by depressing the level of inflammatory reactions and/or amyloidogenesis [66].

Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatments for major depressive disorder in MS [67]. SSRIs induce a reduction of the clinical signs of experimental MS, by limitation of pro-inflammatory cytokine release (IFN-γ, TNF-a, IL-6, IL-7) and dropping T-cell proliferation. Diminishing stress-related relapses is of severe importance for attaining a significant delay in the start of severe weakening and hence agents like SSRIs that show efficiency in this field should be extremely considered as a complementary therapeutic option for all MS patients [68]. SSRIs exhibit a neuroprotective and anti-inflammatory effect in EAE animals. In EAE animals, SSRIs decrease the synthesis of inflammatory cytokines like IFN-γ, TNF-α, IL-6, IL-10, and IL-2 and upregulate the synthesis of anti-inflammatory mediators like IL-4 [69].

Previous studies show the positive effect of the long-lasting administration of SSRI antidepressants in delaying the development of AD and improving patient performance [70]. Furthermore, SSRIs reduced the objective signs of IBD [71].

Serotonin-norepinephrine reuptake inhibitors (SNRI) such as venlafaxine reduced the secretion of pro-inflammatory cytokines such as TNF-a, IFN-γ, and IL-6, therefore decreasing inflammation in the CNS, though regulating NK cell and T-cell gene expression in MS patients. Pro-inflammatory cytokines such as TNF-a, IFN-γ, IL-6, Ccl5, and IL-12 were downregulated while CNS inflammation was also diminished by venlafaxine which shows its efficacy in MS. Venlafaxine is useful through decrement or augmentation of mRNA expression of pro-inflammatory and anti-inflammatory factors, respectively [68].

Dopamine

Dopamine, 3-hydroxytryptamine, is a catecholaminergic neurotransmitter and peripheral chemical mediator that is associated with critical functions in a variety of neurological and peripheral processes [72]. Dopamine is not only synthesized by cells of the central nervous system but also in types of immune cells, and under certain conditions can be released by these cells and result in autocrine and paracrine effects [73], suggesting that dopamine functions as a bidirectional mediator between the central nervous system and the immune system. Growing research increasingly supports the key role of dopamine in the suppression of the immune system and suggested that dopamine functions as a fundamental regulator of inflammation [74]. Multifunctional effects of dopamine are mediated by the activation

of dopamine receptors (DRs), a class of G protein-coupled receptors expressed on various cell types in various organs and tissues [75]. There are five different subtypes of DRs, including DRD1, DRD2, DRD3, DRD4, and DRD5 which are grouped into 2 subgroups: (1) the D1-like dopamine receptors D_1 and D_5, which activate adenylate cyclase and (2) the D2-like dopamine receptors D_2, D_3, and D_4, which inhibit adenylate cyclase [76]. Most types of immune cells including T cells and B cells, dendritic cells (DCs), macrophages, neutrophils, and natural killer (NK) cells, express dopamine receptors, and other dopamine-related proteins, allowing them to actively reply to dopamine. It may show that dopaminergic immunoregulation is a vital part of proper immune function [77]. Dysregulated dopaminergic signaling through different dopamine receptors has been implicated in the development and progression of different autoimmune and inflammatory disorders [78]. Hoeger et al. demonstrated that dopamine induces an anti-inflammatory mechanism during renal inflammation. In this study, the brain-dead animal group that was treated with dopamine showed a down-regulated level of cytokine-induced neutrophil chemoattractant 1 (CINC-1) compared with controls [79]. Another study revealed that dopamine dose-dependently inhibits the production of the chemokines Gro-α, ENA-78, and IL-8 in proximal tubular epithelial cells [80, 81]. Different studies highlight the emerging role of dopamine on the systemic immune response as well as on abnormal bone remodeling and synovial inflammation, both in humans and in different animal models of arthritis [6]. Some studies have shown an increase in serum dopamine in patients with RA [82, 83], although conflicting results have been shown that dopamine was localized with DCs in the synovial tissue of RA (RASFs) patients and significantly increased in RASFs and dopamine released by DCs induces IL-6-dependent IL-17 production and leading to aggravation of synovial inflammation of RA [84]. Another observation in both animal models of arthritis and patients with RA suggests increased expression of dopamine receptors D1 and D5 in RASFs and this augmented expression may result in anti-inflammatory effects [82]. Lina van et al. revealed that mobility of fibroblasts from patients with chronic arthritides was performed under DR-stimulation, thus suggesting a functional role for dopamine in fibroblast activity in RA [85]. Recent findings indicate a strong increase of D_1DR expression on B cells, as well as a significant increase of dopamine in PBMCs from female RA patients and involvement of the dopaminergic pathway in the immune response in these patients [86]. Therefore, the synovial dopaminergic pathway might represent a new therapeutic target for future treatment approaches in RA. Dopamine and its receptors may be involved in IBD. Dopamine levels display a reduction in biopsy specimens of inflamed gut mucosa from IBD patients and animal models [87, 88]. The association of dopamine receptor polymorphism with IBD has been shown, in this regard, several polymorphisms of dopamine D2 receptor were evaluated in IBD patients (Crohn's disease and ulcerative colitis) and healthy controls. A 2 A 2 polymorphism represented a 2.5 times lower risk for development of refractory Crohn's disease (CD) than A 1 A 1 and A 1 A 2 carriers suggesting the involvement of DA receptor in CD that represent a novel target for therapy. Refractory CD patients exhibited lower disease duration than non-refractory ones and hence more aggressive disease [89]. Results showed that the dopaminergic system might implicate IBD by changes in the T cell signaling [90]. Dopaminergic regulation has emerged a relevant role in the control of MS and EAE development [91]. Dopamine production and expression of D5R (D1-like DR) are reduced in peripheral blood mononuclear cells (PBMC) from MS patients compared with PBMCs from healthy subjects and is affected by treatment with interferon (IFN)-β [92]. In chronic progressive MS or relapsing–remitting MS, the evidence demonstrated that dopamine production is reduced in stimulated lymphocytes [93]. Also, the studies displayed that dopamine decreases proliferation, IFN-γ secretion, and matrix metalloproteinase-9 production of activated PBMCs in healthy donors, but not in MS patients [94]. Deregulation of D1-like DRs expression in Tregs and T effector obtained from MS patients supports the involvement of dopaminergic pathways in MS pathogenesis and suggests new therapeutic targets in autoimmune disorders [93].

Pramipexole (PPX), a dopamine D2/D3 receptor-preferring agonist with a potent anti-inflammatory activity and suppressing immune cell responses, prevents EAE development and may represent a novel therapeutic strategy for slowing MS progression and the control of major symptoms [95].

Dopamine mostly exists in the colonic lumen of the GI tract. In humans, more than 50% of dopamine is synthesized in the gut, and peripheral dopamine levels can be regulated by the gut microbiota [64]. The perturbations of the gut-microbiota-brain axis impact PD development and targeting this axis may be a therapeutic approach for PD [96]. Chronic inflammation in the intestine by the gut microbes increases neurodegeneration and the probability of PD [97]. Gut microbiota suppresses the inflammation of the substantia nigra in chronic PD by protecting the function of dopamine neurons [98]. Furthermore, gut microbiota comprises intrinsic enzymatic activity that is highly contributed to dopamine metabolism, facilitating dopamine synthesis [99].

Gamma-aminobutyric acid (GABA)

GABA is the major inhibitory neurotransmitter in the mammalian CNS produced by decarboxylation of the amino acid glutamate by glutamate decarboxylase enzyme

(GAD), which includes two isoforms GAD65 and GAD67 [92]. After being secreted by neurons, GABA performs its function by engaging with GABA receptor subtypes [100]. There are two pharmacologically and molecularly types of GABA receptors: $GABA_A$ and $GABA_B$. $GABA_A$ receptors are pentameric ligand-gated ion channels whereas $GABA_B$ receptors are heterodimeric G protein-coupled receptors [101]. $GABA_A$ can be formed by assembling the $\alpha 1-6$, $\beta 1-3$, $\gamma 1-3$, δ, ε, θ, π, and $\rho 1-3$ subunits. In contrast, the $GABA_B$ receptor is normally composed of two isoforms. Certain immune cells may also produce GABA and express GABA receptors. The binding of GABA to these receptors initiates chemical signaling and promotes the immune regulatory responses that lead to a decrease in the inflammatory response and inhibit autoimmune diseases.

Several recent studies have shown that GABA has some effects on the immune cells for instance activation or inhibition of cytokine secretion, alteration of cell proliferation, and migration of the cells. The immune cells entered the brain and encounter GABA released by the immune cells themselves [102]. GABA signaling is complicated in the modulation of immune responses, mostly via negative regulation of T cell proliferation and the production of pro-inflammatory cytokines through downregulation of some related signaling pathways. Thus, the GABAergic system has great potential to inhibit inflammatory responses. These findings indicate that the components of the GABAergic system have a pharmacological effect and can be a new therapeutic target for inflammatory and autoimmune diseases [103].

GABAA receptor has a significant role in anti-inflammation by suppressing the expression of inflammatory cytokines [104]. For instance, the functional $GABA_A$ receptor in CD4 + T cells and macrophages inhibits the proliferation of antigen-specific T cells and the creation of IL-6, IL-12, IL-1β, and TNF-α [105–107]. Furthermore, the agonist of the $GABA_A$ receptor prevents the immune responses to stimulation, including cytotoxic immune responses and cutaneous delayed-type hypersensitivity [103]. GABA suppresses the plasma level of IL-6 through both $GABA_A$ and $GABA_B$ receptors, and the plasma level of IL-1β via the GABAA receptor. TNF-α induces the endocytosis of the $GABA_A$ receptor in mice and a high concentration of TNF-α upregulates the expression of the $GABA_A$ receptor [108]. It has been found that the activation of the GABAA receptor stops the release of TNF-α and IL-6 from alveolar macrophages [109].

GABA plays some important roles in autoimmune diseases like MS, type 1 diabetes, colitis, and RA and may moderate the immune response to infections [102]. GABA receptor transcripts are present in immune cells [106, 110, 111]. MS may be associated with diminished serum levels of GABA and its synthetic enzyme glutamic acid decarboxylase (GAD) [112]. Taken together, these clues demonstrate the use of GABAergic agonists in a mouse model of MS [113]. GABA agonist, progabide, is an effective antispastic agent that reduces spasticity in MS but increases motor weakness. The use of the drug, however, has adverse side effects such as fever and weakness which will likely limit progabide's therapeutic usefulness. DSS-induced colitis was aggravated by $GABA_A$ receptors, while the expression of pro-inflammatory cytokines was stopped. Activation of $GABA_A$Rs in colon mucosa disturbs the intestinal barrier and augments the intestinal permeability which facilitates inflammatory reactions in the colon. The suppression of pro-inflammatory cytokines results in inadequate bacteria eradication and further aggravated the bacteria invasion and inflammatory damage [114].

Oral GABA application can downregulate inflammatory responses in a mouse model of RA. Activation of peripheral GABA receptors may suppress the activity of T cell, B cell, and antigen-presenting cells and improve RA and other inflammatory diseases [115]. GABA by an inhibitory signal to the spinal cord may downregulate mitogen-activated protein kinase (MAPK) and limit proinflammatory cytokine production. This could diminish the RA by further proinflammatory cytokines [116].

Moreover, GABA is formed by the bacteria *Lactobacillus* and other species of the *Bifidobacterium* genus. Disturbances in their levels in the CNS may arise from the action of these neurotransmitters on the vagus and peripheral nerves that may lead to cognitive disorders such as AD [117].

Glutamate

Glutamate is an extremely abundant excitatory neurotransmitter and is important for many features of normal brain function. Glutamate activates ionotropic (ion channel-forming) and metabotropic (G protein-activating) glutamate receptors. In excess, however, glutamate is harmful and makes neuronal death by a massive calcium influx through ionotropic glutamate receptor channels, resulting in injury to mitochondria and activation of proapoptotic genes. Glutamate toxicity arises as part of the ischemic state in spinal cord injury, stroke, traumatic brain injury, and various diseases of the central nervous system, including AD, amyotrophic lateral sclerosis, PD, and MS [118]. A combination of low reuptake and elevated release of glutamate through glial cells during immune activation results in glutamate increment and causes abnormal extrasynaptic signaling by ionotropic and metabotropic glutamate receptors, ultimately leading to synaptic dysfunction and loss. It has been shown that high levels of inflammatory cytokines such as TNF and IL-1β released by activated inflammatory cells including microglia, astroglia, and macrophages result in rises of the synaptic glutamate and spillover of

the glutamate into the extrasynaptic space [119]. Inflammation results in clear increases in glutamate release and "spillover" of glutamate into the extrasynaptic space by decreasing the capacity of glial transporters to buffer glutamate [120]. Excessive activation of glutamate receptors in nigrostriatal neurons might cause cellular death via glutamate excitotoxicity and concomitant motor dysfunction in PD [121]. Glutamate activates intrasynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-d-aspartate receptors (NMDA) and extrasynaptic NMDA receptors. This results in atrophy and regression of dendritic spines and processes and loss of synaptic integrity, eventually causing neuronal loss, and suppression of neurotrophic protection from factors such as brain-derived neurotrophic factor (BDNF) [122, 123]. Furthermore, rises in extrasynaptic glutamate can activate presynaptic metabotropic glutamate receptors (mGluR2/3) causing decreases in synaptic glutamate transmission [124, 125]. Besides, changes in the ratio between synaptic and extrasynaptic activation of ionotropic receptors by glutamate may lead to the loss of synaptic fidelity and specificity of neurotransmission [126, 127].

In another study, it was revealed that glutamate may sluggish PD development by postponing progressive dopamine neuron degeneration. Glutamate drives a regulatory T cell response that ameliorates neuroinflammation in a mouse model of this paralyzing disease. This increment of regulatory T cells is mediated by the mGluR4 expressed on dendritic cells, a cell type crucial for supporting an immune response [128]. Therefore, glutamate may play a defensive role in inflammatory neurodegenerative diseases. Also, a mGluR4 enhancer is used to reduce glutamate release in the brain and hence would be a treatment for PD [129]. Antagonists of NMDA receptors reverse motor symptoms, levodopa-induced dyskinesias, and neurodegeneration in PD models. While AMPA receptor antagonists display effectiveness in the treatment of levodopa-induced dyskinesias, AMPA receptor agonists display neuroprotection. Antagonists of mGluRs, as well as activators of group II mGluRs and mGluR4, protect against neurodegeneration. Taken together, glutamate receptors demonstrate exciting targets for the development of new pharmacological therapies for PD [130].

High amounts of glutamate, as a neurotoxin, are an indicator of the autoimmune neurological disease MS and may involve in its pathology. The glutamate receptor can inhibit autoimmunity development and defend against neuroinflammation in a mouse model of MS [128]. Therefore, glutamate may also have a defensive role and its receptor may show a therapeutic target. Excessive glutamate is released from leukocytes and activated microglia at the location of demyelination and axonal degeneration in MS plaques. Therefore, modification of glutamate release and transport, as well as blockade of receptors, may be appropriate targets for future therapeutic interventions [131].

NMDAR-enhancing agents can recover cognition in AD or PD patients. These studies show that glutamate metabolized by gut bacteria may impact the glutamate NMDAR and cognition in AD patients [132].

Norepinephrine

Norepinephrine (NE) limits microglial activation and diminishes the production of pro-inflammatory mediators including TNF-α, IL-1β, and inducible nitric oxide synthase activity. Therefore, noradrenaline inhibits the cytotoxicity of midbrain dopaminergic neurons by inflammatory stimuli [133]. Noradrenaline shows a bi-modal neuroprotective role in the brain in some neurodegenerative diseases through interactions with glial cells, predominantly by downregulating microglial pro-inflammatory gene expression [134, 135], and also through promoting a neurotrophic effect in the brain via astrocytic growth factor production [136].

Moreover, in the MS field, CNS noradrenaline deficiency impairs EAE [137]. Similarly, the serotonin noradrenaline reuptake inhibitor venlafaxine suppresses CD3, CD8, IL-12 p40, TNFα, IFN-γ, CCL2, and RANTES gene transcripts in the CNS lesions of an experimental adoptive myelin-specific T-cell model of EAE, while concomitantly upregulating BDNF expression in the inflamed spinal cord of these animals [138].

The main source of noradrenaline in the CNS originates from the locus coeruleus, situated in the lateral face of the fourth ventricle in the upper dorsolateral pontine tegmentum [139]. Noradrenaline released from locus coeruleus neurons activates adrenergic receptors of neurons and glial cells through adenylate cyclase and phospholipase C signal transduction. Noradrenaline can modify membrane potential, synaptic transmission, and excitability of neurons. In astrocytes, noradrenaline stimulates glycogen metabolism and calcium signaling, and blood vessels normalize blood flow and blood–brain barrier permeability. The locus coeruleus contributes to the regulation of arousal, memory, stress, attention [140, 141], neuroinflammation, neuronal survival, and neurogenesis [142].

Previous studies have shown that noradrenaline is neuroprotective and reduces inflammatory responses. Noradrenaline diminishes class II antigen and cytokine expression in astrocytes and attenuates expression of inducible nitric oxide synthase type 2 in astrocytes, microglia, and neurons [143]. In vivo, augmentation of noradrenaline using an alpha-2-adrenoceptor antagonist diminished inflammation by accumulated amyloid-beta. Furthermore, selective inhibitors of noradrenaline reuptake attenuated CNS cytokine and chemokine resulting from systemic endotoxin injection and

augmented anti-inflammatory cytokines. Noradrenaline also decreased neurotoxicity following inflammatory or excitotoxic stimuli. It has been shown that loss of locus coeruleus, noradrenergic neurons in some neurodegenerative diseases including AD and PD are augmented [143].

Depletion of NE provokes a neurotoxic proinflammation, reduces Aβ clearance, and negatively influences cognition-recapitulating main features of AD [144]. LC injury and NE deficiency decrease anti-neuroinflammatory molecules which normally limit cortical responses to amyloid-beta. Thus, LC loss is permissive for augmented inflammation and neuronal cell death in AD. Noradrenergic depletion potentiates beta-amyloid-induced cortical inflammation in AD [145]. The agonists of peroxisome proliferator-activated receptor-gamma (PPARgamma) can reverse the effect of noradrenergic depletion and beta-amyloid-induced cortical inflammation. These findings suggest one mechanism by which PPARgamma agonists could provide benefit in neurological diseases having an inflammatory component [146]. Inhibitors of NE transport and precursor of NE that are used for the treatment of neurologic and psychiatric disorders have been shown to treat animal models of AD and are now used for early-phase clinical trials in humans. Developing proinflammatory responses, weakening anti-inflammatory responses, restoration of NE, and decreasing Aβ degradation and clearance, LC degeneration, and NE loss are considered to slow neurodegeneration in animal models and may delay or reverse AD-related pathology. Inhibitors of noradrenaline reuptake limit neuroinflammation in the rat cortex following a systemic inflammatory challenge [144].

Noradrenergic dysfunction accompanying non-motor signs of PD. Thus, loss of LC NE and subsequently its immune-modulatory and neuroprotective effects may worsen or even accelerate the progression of PD. It has been shown that LC-NE dysregulation may promote the progression of PD. Immune mediators including IL-1ß, TGFß, IFNγ, and IL-6 are augmented in the cerebral spinal fluid and nigrostriatal regions appear particularly sensitive to pro-inflammatory cytokines in PD. Neuroinflammation is demonstrable preceding signs of neuronal degeneration, signifying a potential early role for inflammation in PD pathogenesis [147]. Norepinephrine has been found in the gut microbiota, including *Escherichia coli*, *Bacillus subtilis*, *Bacillus mycoides*, *Proteus vulgaris*, and *Serratia marcescens* [64].

Substance P

Substance P as a peptide mainly formed by sensory neurons originates in the brainstem and dorsal horns of the spinal cord but is also more widely in the brain [148]. Substance P is a mediator of nociceptive stimuli, neurogenic inflammation, and neuroimmunoregulation [149, 150].

Substance P is produced by lymphocytes [151]. Substance P binds to cell surface G protein-coupled receptors of the neurokinin (NK) family including NK1, NK2, and NK3 [152, 153]. NK1 is expressed in neurons [154] and leads to intracellular signaling that regulates gene expression. Furthermore, NK1 is expressed by immune cells including NK cells [155], T and B cells [156], eosinophils, mast cells [157], macrophages [158], microglia, astrocytes [159], and dendritic cells [160]. In lymphocytes, NK1 regulates T cell proliferation, differentiation, and production of cytokines [161]. NK1R antagonists are attractive potential therapeutic agents in the treatment of different neurodegenerative diseases [162]. CP-96,345, a selective NK1R antagonist, reduces the clinical and histological signs of EAE [163].

Moreover, substance P causes the migration of innate immune cells including neutrophils by stimulating the synthesis of cytokines and the expression of cytokine receptors [164, 165]. In CNS trauma, pro-inflammatory cytokines [166] and immunomodulatory neuropeptides including substance P are elevated [167]. It has been shown that tachykinin antagonists by downregulation of cytokines can improve MS [152, 153, 168]. In disease states, substance P involves the maintenance of inflammation in MS by causing widespread infiltration of the CNS by macrophages, dendritic cells, T cells, and other immune cells [169, 170].

Endocannabinoids

Endocannabinoids, bioactive lipids of the brain [171], act on CB1 and CB2 receptors [172, 173]. Endocannabinoids have physiological roles in the immune system, metabolism, and locomotion [173, 174]. Endocannabinoids are released from activated T and B lymphocytes [175, 176]. Cannabinoid receptors are expressed in the ventral tegmental area and affect drug-seeking behavior [177]. CB2 cannabinoid receptors are expressed in cells of the immune system [173, 178]. Cannabinoids suppress autoreactive lymphocytes [179] and T-cell function [180]. In a mouse model of IBD, a CB2 agonist improved the disease [181]. Endocannabinoids have been shown to suppress T cell activity [182].

Cannabinoids are used in medicine [183, 184] and immunosuppression in autoimmune diseases [185] like rheumatic disease [186] and type 1 diabetes [187]. The endocannabinoid system (ECS) plays an important role in the immunomodulation of inflammation in IBD. The manipulation of the system through agonists and antagonists suggests a potential therapeutic role for ECS in IBD [188]. Results of recent studies have shown the modulatory effect of the endocannabinoid system in the control of symptoms and disease progression in MS. It has been widely reported that cannabinoids might be used to control MS symptoms and that they also might exert neuroprotective effects and slow down

disease progression [189]. In MS, cannabinoids are utilized for the treatment of spasticity but do not improve disease activity [190]. WOBE437, as a new class of ECS modulators and selective endocannabinoid reuptake inhibitors (SERIs), significantly reduced the severity of disease and accelerated recovery through CB1 and CB2 receptor-dependent mechanisms in EAE (C57BL/6 mice) and may represent a possible new venue for an effective MS treatment [191].

Endorphins

Endorphins or endogenous opioids include mainly beta-endorphin that is produced by the pituitary gland and the enkephalins that are produced more widely in the brain [192, 193]. Endorphins activate opioid receptors including mu, delta, and kappa of which the mu receptor (the morphine receptor) is best recognized [192, 194, 195]. Endorphins modify the response to pain and stress [196]. Endorphins are produced following social happiness and exercise [197]. Lymphocytes also release opioids that involve in analgesia in inflammation [198]. Activation of opioid receptors on lymphocytes leads to immune suppression [199–201]. There are studies that β-endorphins could control autoimmunity [202] and may play a role in the inhibition of carcinogenesis [203].

Conclusion

The pathogenesis of several IMIDs might involve immunocompetent substances and neural mediators that link the immune and nervous systems. The expression of several receptors for different neurotransmitters on the immune cell surface suggested that neurotransmitters play a physiological role in the regulation of the immune response. Various evidence has clearly shown a physiological role for neuroendocrine-derived control mechanisms of immune function and specifically the role of neurotransmitters in the regulation of inflammation. Understanding these mechanisms reveals possibilities to use targeted neuromodulation as a therapeutic approach for treating inflammatory and autoimmune disorders.

Declarations

Ethical approval N/A.

Informed consent N/A.

Registry and the registration no. of the study/trial N/A.

Animal studies N/A.

Conflict of interest The authors declare no competing interests.

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