

## Neuroimmunomodulation by gut bacteria: Focus on inflammatory bowel diseases

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### Abstract

Microbes colonize the gastrointestinal tract are considered as highest complex ecosystem because of having diverse bacterial species and 150 times more genes as compared to the human genome. Imbalance or dysbiosis in gut bacteria can cause dysregulation in gut homeostasis that subsequently activates the immune system, which leads to the development of inflammatory bowel disease (IBD). Neuromediators, including both neurotransmitters and neuropeptides, may contribute to the development of aberrant immune response. They are emerging as a regulator of inflammatory processes and play a key role in various auto-immune and inflammatory diseases. Neuromediators may influence immune cell's function *via* the receptors present on these cells. The cytokines secreted by the immune cells, in turn, regulate the neuronal functions by binding with their receptors present on sensory neurons. This bidirectional communication of the enteric nervous system and the enteric immune system is involved in regulating the magnitude of inflammatory pathways. Alterations in gut bacteria influence the level of neuromediators in the colon, which may affect the gastrointestinal inflammation in a disease condition. Changed neuromediators concentration *via* dysbiosis in gut microbiota is one of the novel approaches to understand the pathogenesis of IBD. In this article, we reviewed the existing knowledge on the role of neuromediators governing the pathogenesis of IBD, focusing on the reciprocal relationship among the gut microbiota, neuromediators, and host immunity. Understanding the neuromediators and host-microbiota interactions would give a better insight in to the disease pathophysiology and help in developing the new therapeutic approaches for the disease.

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**Core Tip:** Dysbiosis in gut bacteria is a well-established factor, and the abnormality in the enteric nervous system is an emerging aspect that influences the gut inflammation. Both of them contribute to inflammatory bowel disease (IBD) pathogenesis by modulating the host immune response. Through this review, we linked the two pathological mechanisms and explained how neuroimmunomodulation by gut bacteria play a crucial role in IBD. We elaborated all the known neuromediators produced by gut bacteria and the role of each neuromediator as well as the respective gut bacteria in inflammatory signaling pathways especially in IBD.

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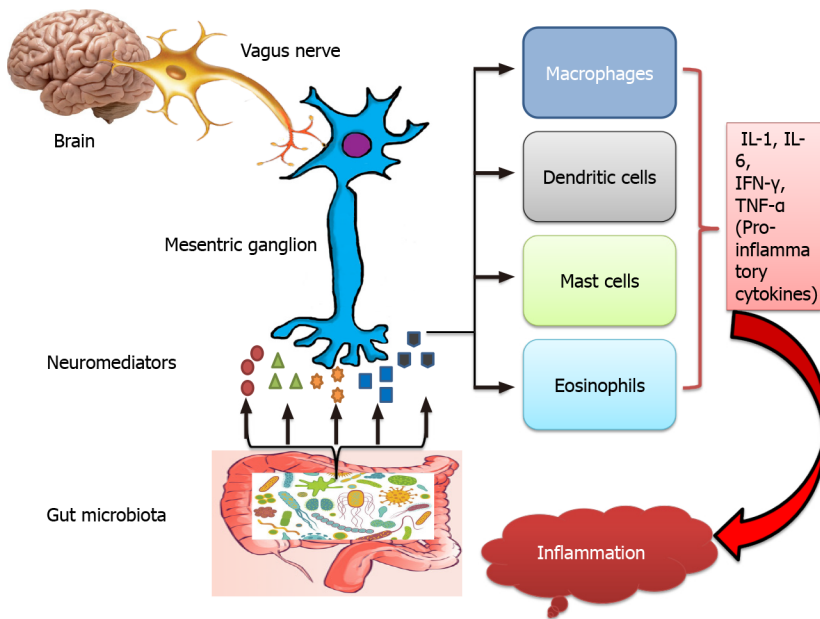
## INTRODUCTION

The gastrointestinal tract (GIT) is equipped with the most extensive immune system, and the largest network of neurons outside the central nervous system (CNS) called the enteric nervous system (ENS). Sometimes, ENS also referred to as “brain in gut” because it does not require any intermediate input from the brain for its functioning. The structure of ENS is organised into two Plexi, myenteric plexus and submucosal (Meissner’s) plexus. Myenteric plexus is located between the longitudinal and circular muscle of muscularis propria and regulates the intestinal motility. Submucosal plexus is located in the submucosa of the intestine and regulates secretion, absorption, and blood flow[1]. Neurons of these Plexi releases various neurotransmitters that regulate the secretory and motor functions of GIT. During inflammatory bowel disease (IBD), there are morphological, histological, and immunohistochemical abnormalities in the ENS which causes neuronal hyperplasia, necrosis, ganglion, and axonal degeneration, alteration in synthesis and release of neurotransmitters. It leads to a defect in the secretory and motor functions of GIT[2].

The neurotransmitters and neuropeptides released from ENS can alter various immune cell functions. Immune cells residing in colon express various receptors for neurotransmitters, and once neurotransmitter binds to these receptors, there would be an initiation of signal transduction pathways of cytokine production[3]. These cytokines, in turn, bind to their specific receptors, expressed on sensory nerve fibers to trigger neuronal response, thus establishing a bidirectional communication. This bidirectional cross-talk between ENS and the enteric immune system is crucial to maintain visceral homeostasis. This cross-talk regulates the magnitude of inflammatory response *via* the production of cytokines, disruption of epithelial tight junctions, neutrophil recruitment, phagocytosis, modification in lymphocyte differentiation, and ultimately cell death ensues[4].

During the early postnatal life, ENS undergoes extensive development in parallel to the colonisation of gut microbiota and maturation of mucosal immune system in GIT. In germ-free mice, structural and functional abnormalities of the ENS have been observed, which suggests the role of gut microbiota in ENS development. Microbiota interacts with the nervous system through modulation of neurotransmitters production. Indeed, bacteria have been found to have the capability to produce a range of significant neurotransmitters in the gut. Therefore, gut microbiota fine-tunes the interaction between enteric nervous and immune system by altering the level of neuromediators (Figure 1).

A more thorough understanding of the interactions among neuromediators, inflammation, and neuromediators producing gut microbiota is required to ensure the effectiveness of neuromediators as a treatment option for IBD. Herein, we review the current knowledge of the role of neuromediators and bacteria that produce neurome-



**Figure 1 Modulation of cross-talk between the enteric nervous system and the enteric immune system via gut bacteria.** Gut microbiota and vagus nerve stimulate mesenteric ganglion (enteric neuron) to produce neuromediators. Neuromediators act on various immune cells and influence their ability to release pro-inflammatory cytokines. During inflammatory bowel disease, dysbiosis in gut microbiota and abnormality in the enteric nervous system affect the level of neuromediators that results in overproduction of pro-inflammatory cytokines and promote inflammation. IL: Interleukin; TNF- $\alpha$ : Tumour necrosis factor- $\alpha$ ; IFN- $\gamma$ : Interferon- $\gamma$ .

diators which might be a potential option in the treatment of IBD.

## NEUROMEDIATORS AND IBD

A variety of neuropeptides and neurotransmitters are known to involve in the pathogenesis of IBD. Neuropeptides such as substance P (SP), neurotensin (NT), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), corticotrophin-releasing hormone (CRH), galanin (GAL) and calcitonin gene-related peptides (CGRP) and neurotransmitters like serotonin, nitric oxide (NO), acetylcholine, noradrenaline (NA) and  $\gamma$ -aminobutyric acid (GABA) regulates inflammatory processes by employing immunomodulatory pathways. Role of each of these neuromediators are briefly summarized in [Table 1](#).

### SP

SP is released from neurons and also from inflammatory cells like lymphocytes, macrophages, and dendritic cells. It acts by binding to the neurokinin-1 receptor (NK-1R). It plays a vital role in the amplification of inflammatory response by inducing the release of cytokines, reactive oxygen species, and stimulates leukocyte recruitment. Increased level of SP has been observed in the colon of IBD patients and, in the synovial fluid and serum of rheumatoid arthritis (RA) patients. Also, the enhanced expression of NK-1R was reported in the colon of IBD and synoviocytes of RA patients. SP has pro-inflammatory effects in epithelial and immune cells and contributes to many inflammatory diseases, including sarcoidosis, asthma, chronic bronchitis, RA, and IBD[5]. However, in murine models of colitis, SP plays a regulatory action[6]. In a recent study, SP was observed as an accelerator for healing the dextran sodium sulfate (DSS)-induced damaged intestine *via* inhibiting inflammatory responses through the modulation of cytokine expression[7].

### NT

NT is a tridecapeptide, a pro-inflammatory neuropeptide widely distributed in the

**Table 1** List of neuromediators and their role in gut inflammation

Neuromediator	Distribution	Binding receptor	Function
SP	Neurons and inflammatory cells like lymphocytes, macrophages, and dendritic cells	NK-1R	Exerts pro-inflammatory effects in epithelial and immune cells and contributes to inflammatory diseases. In murine model of colitis, it plays regulatory role
NT	Nervous system and intestine	NTR1	Recognized as an immunomodulator. By interacting with immune cells, it enhances the chemotaxis and induces the cytokine release to modulate the immune response. In IBD, it exerts its pro-inflammatory effects by promoting the expression of miR-210 in intestinal epithelial cells
NPY	Central and peripheral nervous system and immune cells	Out of five receptors of NPY, NPY1 is known to play a crucial role in immunomodulation	Regulates various immune cell functions such as T helper cell differentiation, neutrophil chemotaxis, natural killer cell activity, and granulocyte oxidative burst and NO production. In the gut, NPY is known to exert pro-inflammatory effects
VIP	Neuronal and lymphoid cells	VIPR1 and VIPR2	Identified as an anti-inflammatory molecule. administration of VIP nanomedicine in the form of VIP-SSM are capable of alleviating the symptoms of DSS- induced mice model of colitis
GAL	Vasculature, immune cells and colonic epithelial cells	GAL (1-3) receptor	Exerts anti-inflammatory effects in TNBS induced colitis model by reducing the expression and activity of iNOS
CRH	Immune cells	CRH-R1 and CRH-R2	It acts as a pro-inflammatory peptide. The expression pattern of CRH 1 and CRH 2 varies in ulcerative colitis. Inhibition of CRH1 and overexpression of CRH2 may have the therapeutic potential in IBD
CGRP	Sensory nerves projecting to the lymphoid organs, airways, and pulmonary neuroendocrine cells	CGRP receptors	CGRP negatively regulates innate immune responses and thus has potential anti-inflammatory effects. Its expression reduced in the colon of an animal model of colitis
NA	Nerves innervating the peripheral lymphoid organs	Adrenergic $\alpha$ and $\beta$ receptors	immunomodulatory effect of NA is administered <i>via</i> cAMP. Activation of NA receptors that stimulate cAMP resulting in a shift toward Th2 responses which are anti-inflammatory and neuroprotective whereas decreased cAMP stimulates Th1 responses resulting in cell destruction and inflammation
Acetylcholine	Central and peripheral nervous system, immune cells, keratinocytes, endothelial cells, urothelial cells of the urinary bladder, airways and epithelial cells of the placenta	Nicotinic and muscarinic receptors	Muscarinic receptors mediate pro-inflammatory responses and nicotinic receptors enhance anti-inflammatory responses. Treatment of UC <i>via</i> nicotine suggests the role of the cholinergic pathway in colonic inflammation
NO	Neuron synapses and immune cells	NO does not act <i>via</i> receptors. its specificity for target cell depends on its concentration, its activity and response, and territory of target cells	NO is oxidised to reactive nitrogen oxide species which mediate most of the immunological effects. It regulates the growth, functional activity, and death of immune cells. It acts as a biomarker for monitoring disease activity due to its increased serum concentration during the active phase of both UC and CD and reduced concentration during the inactive phase of the disease
Serotonin or 5-HT	Central nervous system and EC cells of GIT	5-HT receptor	It promotes activation of lymphocytes and secretion of pro-inflammatory cytokines. It activates the signalling molecules of the NF- $\kappa$ B pathway during gut inflammation
GABA	Nervous system and immune system	GABA- AR and GABA-BR	GABA has several effects on immune cells, including modulation of cytokine secretion, regulation of cell proliferation, and migration. Activation of GABA-A receptor aggravates DSS induced mice model of colitis

SP: Substance P; GABA:  $\gamma$ -aminobutyric acid; 5-HT: 5-hydroxytryptamine; EC: Enterochromaffin; NF- $\kappa$ B: Nuclear factor  $\kappa$ B; NO: Nitric oxide; NA: Noradrenaline; CD: Crohn’s disease; UC: Ulcerative colitis; cAMP: Cyclic adenosine monophosphate; CGRP: Calcitonin gene-related peptide; IBD: Inflammatory bowel disease; CRH: Corticotropin-releasing hormone; iNOS: Inducible nitric oxide synthase; GAL: Galanin; TNBS: 2,4,6-trinitrobenzenesulfonic acid; VIP: Vasoactive intestinal peptide; SSM: Sterically stabilised micelles; NPY: Neuropeptide Y; NK-1R: Neurokinin-1 receptor; NTR1: Neurotensi receptor 1; DSS: Dextran sodium sulfate.

nervous system and intestine. It binds to NT receptor 1 (NTR1) which is a high-affinity receptor and expressed in neurons, immune cells, colonic epithelial cells and colon cancer cell lines. It regulates various peripheral processes including gut motility, intestinal epithelial cell proliferation, secretion, and vascular smooth muscle activity, but recently it is recognized as an immunomodulator. NT interacts with leukocytes, dendritic cells and peritoneal mast cells, inducing the release of cytokines and enhancing chemotaxis in order to modulate the immune response. The elevated level

of NT and increased expression of NTR1 have been reported in the colonic mucosa of the experimental model of colitis and ulcerative colitis (UC) patients. NT is implicated in various acute and chronic inflammatory diseases, including lung and intestinal inflammation[8-11]. In IBD, NT exerts its pro-inflammatory effects by promoting the expression of miR-210 in intestinal epithelial cells[12].

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## NPY

NPY is a peptide of 36 amino acids and produced abundantly by the central and peripheral nervous system and also by immune cells. Neuronal functions of NPY include modulation of blood pressure, nociception, anxiety, and appetite. It also has diverse effects on innate and adaptive immunity, including immune cell migration, cytokine release from macrophages and T helper cells, and antibody production. Out of five receptors of NPY, NPY<sub>1</sub> is known to play a crucial role in immunomodulation. To modulate inflammation, NPY regulates various immune cell functions such as T helper cell differentiation, neutrophil chemotaxis, natural killer cell activity, and granulocyte oxidative burst and NO production. In the gut, NPY is known to exert pro-inflammatory effects. Several clinical studies reported the role of NPY in immune or inflammatory disorders such as arthritis, asthma, and IBD[4,13-15].

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## VIP

VIP is a 28 amino acid neuropeptide, produced by neuronal cells and lymphoid cells. It controls the homeostasis of the immune system by carrying out a wide range of immunological functions. Recently, it has been identified as an anti-inflammatory molecule. It is reported to inhibit pro-inflammatory cytokines and chemokines production from macrophages, dendritic cells, and microglial cells. Furthermore, VIP reduces the expression of costimulatory molecules on antigen-presenting cells, resulting in the promotion of Th2 type responses and reduction in Th1 type responses. VIP has been considered as a promising target for the treatment of autoimmune as well as acute and chronic inflammatory diseases such as multiple sclerosis, RA, Crohn's disease (CD), septic shock, or autoimmune diabetes[4,16-18]. Recombinant VIP analogue protects the intestinal mucosal barrier function effectively in rats. This analogue of VIP ameliorates 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colonic injury and inflammation through downregulating the expression of tumour necrosis factor- $\alpha$  and upregulating the interleukin (IL)-10 expression[15,19]. Though the administration of VIP shown anti-inflammatory effect but its therapeutic use is restricted due to its rapid degradation and continuous infusion. Recently, the administration of VIP nanomedicine in the form of sterically stabilized micelles has been observed to overcome the barriers and are capable of alleviating the symptoms of DSS-induced mice model of colitis[20].

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## GAL

GAL is a 30 amino acid long sensory neuropeptide known to attenuate neurogenic inflammation. Among the receptors (GAL1-3), GAL-3 is most abundantly expressed on the vasculature, and immune cells and GAL-1 is the only receptor expressed in colonic epithelial cells. Various studies indicate the role of GAL-3 in inflammatory disease conditions. GAL-1 has multiple recognition sites for nuclear factor  $\kappa$ B (NF- $\kappa$ B), and its expression is increased in colonic tissues of IBD patients. NF- $\kappa$ B is a significant player in IBD; thus, specific antagonists of GAL-1 may be used in the treatment of IBD. Administration of GAL in the TNBS-induced colitis model exerts anti-inflammatory effects by reducing the expression and activity of inducible NO synthase (iNOS)[21]. GAL may act as an immunomodulatory peptide because of its ability to sensitize natural killer cells and polymorphonuclear neutrophils towards pro-inflammatory cytokines. In neutrophil-dominated autoimmune arthritis, activation of GAL-3 can be considered as a substantial anti-inflammatory pathway. In multiple sclerosis, GAL-2 agonist has been reported to be a promising therapeutic target[22-26].

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## CRH

CRH is 41 amino acid neuropeptide, produced by various immune cells to regulate immune/inflammatory responses. This locally produced CRH in the peripheral organs, also called peripheral CRH. Peripheral CRH is expressed in various inflamed sites where it acts as a pro-inflammatory peptide. It is also found in the testes, adrenal medulla, ovaries, GIT, cardiovascular system, spinal cord, pancreas, lung, endometrium, and placenta. It has also shown pro-inflammatory effects in the female reproductive system. CRH exerts its biological effects by CRH-Receptor R1 and CRH-R2. CRH and CRH-Rs are known to be expressed in several components of the immune system and regulates various inflammatory phenomena. Due to its pro-inflammatory properties, the antagonist of CRH has been proposed as a potential therapeutic target in the treatment of allergic conditions (asthma, eczema, urticaria) and also in the treatment of lower gastrointestinal inflammatory diseases (chronic inflammatory bowel syndromes, irritable bowel disease, and UC)[23,27]. The expression pattern of CRH-1 and CRH-2 is found to be altered in UC. Based on their differential expression, their therapeutic role is advocated in IBD. Inhibition of CRH-1 and overexpression of CRH-2 may have the therapeutic potential[28]. Activation of CRH-1 signaling upregulates the production of vascular endothelial growth factor-A *via* cyclic adenosine monophosphate (cAMP) response-element binding protein (CREB) transcriptional activity, which results in inflammatory angiogenesis in the gut. Therefore by targeting CREB inactivation, symptoms of colitis may be ameliorated[29]. CRH is also reported to enhance gut permeability by activating mast cells that worsen the IBD pathogenesis. Thus blocking CRH receptors with appropriate antagonists can inhibit mast cell activation and may be considered as a promising therapeutic target for chronic gastrointestinal inflammatory diseases, including IBD[30,31].

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## CGRP

CGRP is a 37 amino acid peptide that is expressed by sensory nerves projecting to the lymphoid organs, airways, and by pulmonary neuroendocrine cells. Peripheral CGRP is a vasodilator and responsible for acute neurogenic inflammation. It upregulates the expression of IL-10 and inhibits activation of NF- $\kappa$ B by acting on innate immune cells. It also inhibits the production of pro-inflammatory cytokines and presentation of antigens to T cells by directly acting on dendritic cells and macrophages. CGRP negatively regulates innate immune responses and thus has potential anti-inflammatory effects. Available pieces of evidence suggest CGRP contributes to limiting tissue damage in liver inflammation, joint inflammation, and also in chronic obstructive pulmonary disease. Decreased level of CGRP was observed in the colon of an animal model of colitis which suggests its role in intestinal inflammation[32-36].

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## NA

NA is a primary neurotransmitter of the sympathetic nervous system, released from nerves innervating the peripheral lymphoid organs. Some evidence suggests that the immunomodulatory effect of NA is administered *via* cAMP. NA influences immune response directly by alteration in expression of adrenergic  $\beta$  receptors on macrophages or indirectly by alteration in level of endogenous NA. Activation of  $\alpha$ 2 adrenoceptors located on sympathetic nerve terminals results in decreased extracellular NA concentration by a negative feedback effect. Activation of NA receptors that stimulate adenylate cyclase to produce cAMP resulting in a shift toward Th2 responses which are anti-inflammatory and neuroprotective whereas decreased cAMP stimulates Th1 responses resulting in cell destruction and inflammation[3,37]. The use of the  $\alpha$ 2-adrenoceptor antagonist might be a novel therapeutic approach for the management of colitis[38].

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## ACETYLCHOLINE

Previously it was thought that acetylcholine is synthesised by only neurons of the parasympathetic and sympathetic nervous system, but now it is established that

acetylcholine is also synthesized by immune cells, keratinocytes, endothelial cells, urothelial cells of the urinary bladder, airways and epithelial cells of the placenta. Acetylcholine released from these cells has been reported to modulate local inflammatory processes. Muscarinic and nicotinic are the two receptor subtypes of acetylcholine. T-cells express both subtypes and activation of each subtype exhibit differential effect. Muscarinic receptors mediate pro-inflammatory responses and nicotinic receptors enhance anti-inflammatory responses. Acetylcholine binds to  $\alpha 7$  nicotinic receptors thus inhibits the release of pro-inflammatory cytokines from macrophages, and it is referred to as “cholinergic anti-inflammatory pathway”. Acetylcholinesterase is an enzyme that catabolizes acetylcholine; thus, inhibitors of acetylcholinesterase may be considered for attenuating inflammation. In the murine model of sepsis, levels of pro-inflammatory cytokines can be brought down by injecting acetylcholinesterase inhibitors intraperitoneally. Reduced level of acetylcholine has been observed in multiple sclerosis, which is characterized by heightened inflammation. In mice, lacking the  $\alpha 7$  subunit of the nicotinic acetylcholine receptor ( $\alpha 7nAChR^{-/-}$ ), the severity of colitis was found to be enhanced[39]. Treatment of UC *via* nicotine also suggests the role of the cholinergic pathway in colonic inflammation. Acetylcholine is well evident to play an essential role in acute or chronic inflammation or autoimmune diseases, including RA[40,41].

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## NO

NO is a major non-adrenergic non-cholinergic potent neurotransmitter at the neuron synapses. It is involved in the regulation of apoptosis. NO is a gaseous signaling molecule, synthesized by many cells that are involved in immunity and inflammation. However, low levels of NO gives an anti-inflammatory effect and maintain homeostasis but overproduction of NO induces inflammation and causes tissue destruction. The key enzyme involved in NO synthesis is iNOS-2. At high concentrations, NO is oxidized to reactive nitrogen oxide species which mediate most of the immunological effects. NO does not act *via* receptors, its specificity for target cell depends on its concentration, its activity and response, and territory of target cells. In the cardiovascular system, it induces vasodilation. It also regulates the growth, functional activity, and death of various cells including T lymphocytes, atrial premature complexes, neutrophils, mast cells, NK cells, and most importantly macrophages, which release NO in high concentration. Available information suggests that it contributes to the pathogenesis of inflammatory diseases of joint, gut and lungs[37,42,43]. NO may act as a biomarker for monitoring disease activity due to its increased serum concentration during the active phase of both UC and CD and reduced concentration during the inactive phase of the disease[44].

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## SEROTONIN OR 5-HYDROXYTRYPTAMINE

Five-hydroxytryptamine (5-HT) is a monoamine neurotransmitter and hormone which is traditionally recognized by its functions in the CNS where it is known to regulate sleep, appetite, mood, body temperature, metabolism, and sexuality. The majority of 5-HT is localized to the intestine and tryptophan hydroxylase (TPH1) enzyme catalysis the synthesis of serotonin in enterochromaffin (EC) cells of GIT. EC cells produce 5-HT more than all neuronal and other sources combined. 5-HT is reported to promote activation of lymphocytes and secretion of pro-inflammatory cytokines[45]. 5-HT is considered a potent immunomodulator and it can affect various immune cells including dendritic cells, macrophages, lymphocytes, enteric epithelial cells, and endothelial cells through 5-HT receptors and also *via* a process of serotonylation. During intestinal inflammation, 5-HT is known to mediate activation of signaling molecules of the NF- $\kappa$ B pathway[46]. Upregulated TPH1 and downregulated serotonin transporter (5-HTT) expression leads to increased 5-HT availability resulting in enhanced 5-HT signalling, which is associated with inflammation in CD[47]. The role of 5-HT is not only limited to intestinal inflammation, but the alteration in its levels has also been observed in patients with RA and allergic airway inflammation[37,48].

## GABA

GABA is an amino acid that is synthesised by decarboxylation of the glutamate with the help of enzyme glutamic acid decarboxylase. It is a classical neurotransmitter and best studied in CNS where it acts as an inhibitory neurotransmitter. Recently it has been found that the immune system is capable of synthesising GABA. GABA has several effects on immune cells, including modulation of cytokine secretion, regulation of cell proliferation, and migration. It can regulate immune responses in various autoimmune and inflammatory diseases such as multiple sclerosis, RA, psoriasis, and type 1 diabetes[49]. Reduced GABAergic signaling is reported to contribute in the pathogenesis of IBD[50]. However, a recent study demonstrated the aggravation of DSS-induced colitis through activation of GABA-A receptor[51].

## NEUROMEDIATORS PRODUCING GUT MICROBIOTA AND IBD

Several commensal gut bacteria have emerged as the producers of a variety of neuromediators. These neuromediators are the result of the metabolism of indigestible fibres by gut bacteria. Many bacteria genera are recognised to produce different neuromediators. *Bacillus* family is reported to contribute to the synthesis of dopamine, various species of *Bacteroides*, *Parabacteroides*, *Lactobacillus* and *Bifidobacteria* are known to produce GABA. Similarly, serotonin is produced by *Enterococcus*, *Streptococcus*, and *Escherichia* families. Some species of *Lactobacilli* are involved in acetylcholine synthesis. Some species of *Bacillus* and *Escherichia* also produce noradrenaline[52].

### *Bacillus*

Despite the low abundance of *Bacillus* species in the human gut, it has many beneficial effects, including probiotic features in GIT. Administration of *Bacillus subtilis* in DSS-induced mice model of colitis attenuated the gut inflammation and dysbiosis of gut microbiota[53]. It balances the pro and anti-inflammatory cytokines during disease conditions. It has also shown its protective effects in IBD patients[54]. *Bacillus* is reported to produce bioactive metabolites, including neurotransmitters, that further affect the host inflammatory responses[55].

### *Bacteroidetes*

*Bacteroidetes* is one of the most dominant genera of gut microbiota. It is comprised of *Bacteroides*, *Parabacteroides*, and *Alistipes*. In IBD patients, a low abundance of *Bacteroidetes* has been observed. *Bacteroidetes* confer protection against colitis by expressing polysaccharide A, which can induce the growth of regulatory T cell[56]. Various species of *Bacteroidetes* including *Bacteroides fragilis*, *Bacteroides vulgatus*, *Bacteroides ovatus*, *Bacteroides thetaiotamicron*, *Parabacteroides*, *Alistipes indistinctus*, *Alistipes finegoldii* and *Alistipes putredinis* are evident to produce GABA[57,58]. Administration of these species in LPS induced intestinal epithelial cells and animal model of colitis ameliorated colonic inflammation[59,60]. Significant reduction in the severity of gut inflammation in DSS induced mice model of colitis have been observed after oral administration of *Parabacteroides distasonis*[61].

### *Bifidobacterium*

*Bifidobacteria* is considered the early colonisers of human GIT. The beneficial effects of this genus are very well established[62]. It is widely used in the preparation of probiotics and reported to exert anti-inflammatory effects. Many species such as *Bifidobacterium dentium*, *Bifidobacterium breve*, *Bifidobacterium bifidum* are found to produce GABA[58]. These species, together with some other species like *Bifidobacterium longum*, *Bifidobacterium adolescentis* are known to confer beneficial effects to IBD patients by inhibiting the NF-κB activation, blocking pro-inflammatory cytokines expression and ultimately attenuating the inflammation[63,64].

### *Enterococcus*

*Enterococcus* primarily resides in the small and large intestine of human GIT. The strains of *Enterococcus* represent approximately 1% of human faecal flora. *Enterococcus faecalis* and *Enterococcus faecium* are the two dominant species found in the human gut[65]. *Enterococcus* is comprised of both commensals as well as nosocomial pathogens. However, commensals have shown several beneficial effects including antimicrobial properties, by releasing bacteriocins and genetically they are very distinct from pathogenic but still, they are not considered safe due to its pathogenic strains. *Entero-*



*coccus* is found to be actively involved in the biosynthesis of serotonin[66]. Increased abundance of *Enterococcus faecalis* has been observed in IBD patients where it contributes toward pathogenesis[67]. In IL-10 knockout mice, *Enterococcus faecium* can also induce IBD[68]. Daily administration of probiotic strain of *Enterococcus faecium* in combination with *Lactobacillus helveticus* 416 and *Bifidobacterium longum* ATCC 15707 is known to relieve the symptoms in DSS-induced colitis in rats[69].

### **Escherichia**

*Escherichia coli* is the regular inhabitant of human GIT. It is the most diverse member of gut microbiota which can act like commensal, probiotic, and pathogenic as well. Increased abundance of *Escherichia* is evident in several mouse models of colitis[70]. A newly identified pro-inflammatory strain of *Escherichia coli* (*E. coli*), adherent-invasive *E. coli* is detected in UC, CD and colorectal cancer. It is highly prevalent and associated with CD pathogenesis as compared to UC[71,72]. *E. coli* Nissle 1917 (EcN) is reported to produce serotonin and also enhance its bioavailability by interacting with the host. Clinical trials demonstrated the beneficial role of EcN in maintaining the UC in remission phase[73-75]. Serotonin signalling was reported to be altered in IBD patients[76]. Some strains of *E. coli* are found to exacerbate the gut inflammation, which suggested the strain-specific effects of *E. coli*[77].

### **Lactobacillus**

Despite having a low abundance, this genus is well known for its probiotic effects[74]. The population of *Lactobacillus* is either positively or negatively associated with many diseases, including IBD[78]. Significant reduction in the *Lactobacillus* population has been observed in UC patients, and there are reports suggested the improvement in clinical symptoms of UC patients after consuming food containing *Lactobacillus*. It showed a beneficial effect in intestinal inflammation by modulating Treg cells which maintain intestinal homeostasis by secreting anti-inflammatory cytokines[79]. Various species of *Lactobacillus* like *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus brevis*, *Lactobacillus reuteri* and *Lactobacillus rhamnosus* are reported to produce GABA[57].

Additionally, acetylcholine is also produced by various strains of *Lactobacillus*, especially *Lactobacillus plantarum*[80]. In a recent study, the effect of dietary probiotics is investigated in IBD induced murine model where *Lactobacillus rhamnosus* is observed as a significant producer of IL-10 and interferon- $\gamma$ [81]. Group of animal studies, human trials, and in vitro studies revealed that these species of *Lactobacillus* are involved in controlling inflammation either by inhibiting the NF- $\kappa$ B induced release of pro-inflammatory cytokines or by maintaining the intestinal barrier integrity[82-88].

### **Streptococcus**

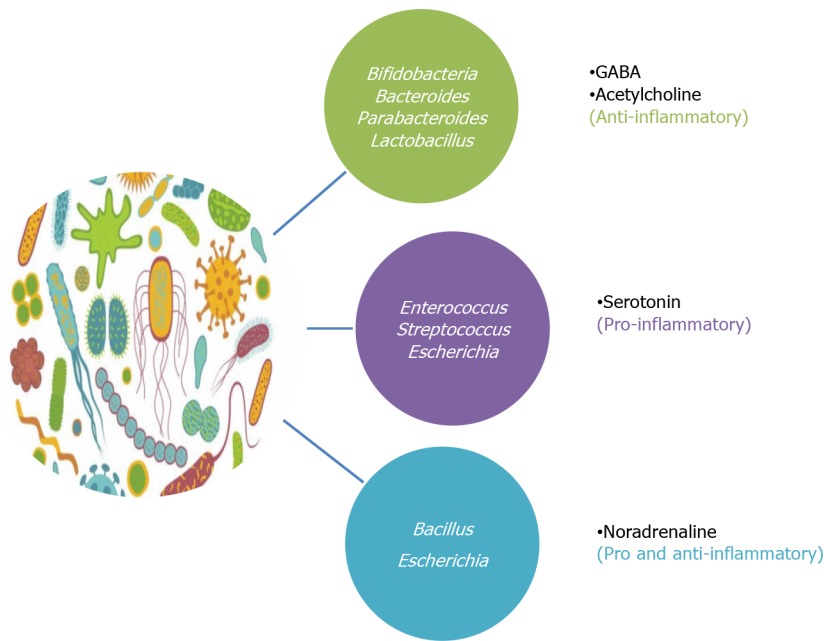
*Streptococcus* is a luminal microbial genus, dominant in the distal oesophagus, duodenum, and jejunum. The most common species are *Streptococcus salivarius*, *Streptococcus thermophilus*, and *Streptococcus parasanguinis*[89]. *Streptococcus* species, including *Streptococcus thermophilus* is reported to produce serotonin[90]. Increased abundance of streptococcus has been observed in IBD patients that indicated the involvement of this genus in the severity of IBD. *Streptococcus bovis* is found to be associated with colon cancer and IBD. *Streptococcus* is known to interact with immune cells and modulate the secretion of pro-inflammatory cytokines that could initiate the inflammatory response in different organs[91]. Recently, immunoglobulin enriched streptococcus is reported in IBD patients that implicate a prominent role of oropharyngeal bacteria in IBD pathogenesis by triggering host immune response[92].

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## **SIGNIFICANCE OF NEUROIMMUNOMODULATION BY GUT BACTERIA**

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Gut bacteria have been known to be crucial for human health. It deliberate number of benefits to the host, including digestion of indigestible carbohydrates that leads to the production of short-chain fatty acids (SCFA) and prevent the colonisation of pathogenic bacteria by producing antimicrobial peptides. SCFAs are involved in various functions like protection from epithelial injury, synthesise vitamins (vitamin B12, vitamin K and folic acid) and essential amino acids, regulate fat metabolism, boost intestinal angiogenesis, cause intestinal motility and promote proper development of immune system[93-95]. Studies conducted in IBD patients and mice models have indicated the central role of gut bacteria in the gut inflammation[96]. The new research in the field opens up new avenues to understand the IBD pathogenesis. Through



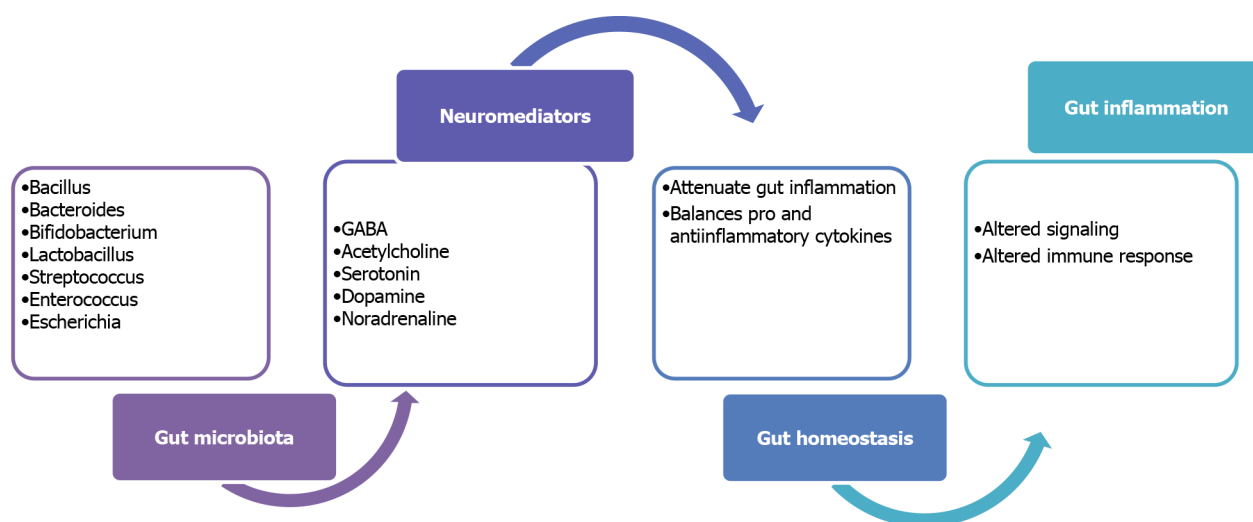
**Figure 2 Inter-relation of diverse gut microbiota and their respective neuromediators with gut inflammation.** Bacteria used as probiotics in inflammatory bowel disease (IBD) (green box) produces anti-inflammatory neuromediators ( $\gamma$ -aminobutyric acid, acetylcholine), bacteria having a detrimental role in IBD (purple box) releases pro-inflammatory neuromediator (serotonin) and bacteria having a debatable role in IBD (blue box) secrete neuromediator (noradrenaline) having both pro and anti-inflammatory properties. GABA:  $\gamma$ -aminobutyric acid.

numerous mechanisms, bacteria execute their part in disease pathogenesis. The revelation of secretion of neuromediators from gut microbes introduced a new area for research and a unique way of looking at the pathophysiology of IBD.

Neuromediators, apart from their classical neuronal functions, are currently being recognised as a pillar in maintaining the gut homeostasis. There are different sources of neuromediators in GIT, including enteric neurons, gut microbiota, immune cells and gut epithelial cells. Out of all the sources, microbial content is the only factor which can be extrinsically varied. Altering the neuromediators *via* gut bacteria can affect the gut physiology, signalling and immune cells secretions and function in GIT. The available literature on the signalling pathways of a variety of neuromediators and their respective gut bacteria in IBD indicated that the neuromediators released by bacteria being used as probiotic are having anti-inflammatory properties and bacteria which were reported to increase disease severity produce neuromediators with pro-inflammatory properties. For instance, GABA and acetylcholine are the anti-inflammatory neuromediators, produced by those bacteria which are very well established to attenuate gut inflammation in both DSS-induced mice model of colitis and IBD patients. Serotonin which is a pro-inflammatory neuromediator is produced by bacteria that are involved in the severity of IBD. Besides, noradrenaline, having both anti and pro-inflammatory properties, produced by two different types of bacteria, one having the beneficial role and other having the debatable role in IBD (Figure 2). This interrelation suggests that bacteria impart their effects in gut inflammation through releasing neuromediators as one of the mechanism.

## CONCLUSION

Neuromediators are emerging as essential players in IBD pathogenesis. These are influenced by the complex interaction of gut microbiota, host immunity, and intestinal epithelium. During gut inflammation or IBD, dysbiosis in gut microbiota and alteration in neuromediators complicate the mechanism of gut homeostasis resulting in perturbed equilibrium (Figure 3). In-depth mechanism of neuroimmunomodulation due to gut bacteria needs to be explored more, to settle the gut homeostasis during disease. These neuromediators may prove to be a great tool to clinicians in treating inflammatory diseases. Through this review, we summarized various neuromediators produced by different gut microbiota and their significance as an immunomodulatory entity in the colon. Using gut bacteria that can produce neuromediators having anti-



**Figure 3 Role of neuromediators producing gut microbiota during gut inflammation.** Gut microbiota produces various neuromediators that attenuate the gut inflammation by balancing the pro and anti-inflammatory cytokines to maintain gut homeostasis. During inflammation, dysbiosis in gut microbiota leads to alteration in respective neuromediators which may lead to altered the host immune response. GABA:  $\gamma$ -aminobutyric acid.

inflammatory properties for treating IBD patients may be a novel therapeutic approach and also the fertile area for future research.

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