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Enteric nervous system and inflammatory bowel diseases: Correlated impacts and therapeutic approaches through the P2X7 receptor

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Abstract

The enteric nervous system (ENS) consists of thousands of small ganglia arranged in the submucosal and myenteric plexuses, which can be negatively affected by Crohn's disease and ulcerative colitis - inflammatory bowel diseases (IBDs). IBDs are complex and multifactorial disorders characterized by chronic and recurrent inflammation of the intestine, and the symptoms of IBDs may include abdominal pain, diarrhea, rectal bleeding, and weight loss. The P2X7 receptor has become a promising therapeutic target for IBDs, especially owing to its wide expression and, in the case of other purinergic receptors, in both human and model animal enteric cells. However, little is known about the actual involvement between the activation of the P2X7 receptor and the cascade of subsequent events and how all these activities associated with chemical signals interfere with the functionality of the affected or treated intestine. In this review, an integrated view is provided, correlating the structural organization of the ENS and the effects of IBDs, focusing on cellular constituents and how therapeutic approaches through the P2X7 receptor can assist in both protection from damage and tissue preservation.

Key Words: Chemical coding; Enteric nervous system; Gastroenterology; Inflammatory bowel diseases; P2X7 receptor; Purinergic signaling

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Core Tip: This review summarizes the impacts caused by inflammatory bowel diseases

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on enteric nervous system cells and brings together the findings of the most recent literature on therapeutic approaches through the P2X7 receptor. Despite the great advancement of knowledge in the field, data on the mechanisms and effects of neuronal loss during colitis are still scarce. Furthermore, clinical trials that would make the use of P2X7 receptor antagonists in human patients feasible are lacking. In the laboratory, the results of animal models reinforce that the P2X7 receptor may be an important future target for the treatment of intestinal disorders.

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INTRODUCTION

The gastrointestinal (GI) tract is a set of organs responsible for performing several complex functions that are essential for an individual's survival, including mainly food transportation, the digestion and absorption of nutrients, and the secretion of water, electrolytes, and mucus[1]. In the GI tract, there is an extensive intrinsic nervous system responsible for the control and coordination of local motility, the movement of fluids through the mucous epithelium, changes in blood flow, and interactions with the immune system[2]. Sometimes, this influence continues even if there is complete separation of the GI tract from the central nervous system (CNS)[2,3].

The enteric nervous system (ENS) is composed of thousands of small ganglia interconnected by their neural fibers and is arranged in two plexuses. The myenteric plexus is located between the fibers of the muscular layer throughout the GI tract, and the submucosal plexus is located in the submucosal layer of the small and large intestines[2,4,5]. Thus, the ENS shares many synaptic and ultrastructural characteristics of the neuronal interrelationship of the GI tract and the CNS[6], with many similarities demonstrated between them, which are reflected in neurological diseases[7]. Enteric innervation has been widely studied, and when preserved and functionally active, enteric innervation is considered equally essential to life as CNS innervation[8].

The study of the ENS has progressed from a healthy context to several pathological models, identifying neuroplastic changes that possibly contribute to modifying intestinal and perception functions in GI disorders[9]. It has been found that purinergic neurotransmission also plays a fundamental role in preserving the internal balance of these organs[10], interacting directly with motor and secretory functions[11] by the expression of several of its receptors on neurons located in the ENS[12]. In addition, the purinergic signaling pathway has also been widely recognized as a fundamental component in the course of inflammation during intestinal diseases[10,13,14].

In this context, the P2X7 receptor appeared to be one of the most correlated representatives in studies of infectious and inflammatory diseases[15]. The most striking differences in the P2X7 receptor in comparison to other purinergic receptors arise not only from its structural conformation but also from a sensitivity that is 10 to 100 times lower for its functional activation, suggesting it as a "danger" detector for tissue damage[16]. Therefore, a better understanding of the behavior of the P2X7 receptor and how it could be affected or modulated in some specific cases is sought, for example, in the treatment of Crohn's disease and ulcerative colitis - inflammatory bowel diseases (IBDs) that cause neuronal death in the ENS and compromise the functionality of the affected organs[17-19].

The great impact of Crohn's disease and ulcerative colitis is that both are capable of influencing all areas of patients' lives, from school and work to social and family life, affecting patients' productivity in each area[20]. In addition, when these conditions are poorly controlled, they can have negative effects on psychosocial well-being[21], increasing even the rates of anxiety and depression according to the severity of the conditions[22]. Worryingly, the occurrence of IBDs cases worldwide increased from 3.7 million to over 6.8 million between 1990 and 2017[23], which makes an individual approach with strong multidisciplinary care increasingly important, as this type of

approach could offer a higher quality of life even for individuals of different ages[20].

Thus, this review aimed to provide an integrated view of the structural organization of the ENS and the deleterious effects arising from IBDs, focusing on the cellular constituents and how therapeutic approaches through the P2X7 receptor can assist in both protection from damage and tissue preservation.

THE ENTERIC NERVOUS SYSTEM

The ENS, also known as the "second brain"[6,24], acts in an essential way in the motility of the esophagus, stomach, and small and large intestines[4,6], modulating the different contraction types of each organ[25]. In addition, the functions of endocrine and exocrine secretion, control of local blood flow, and regulation of inflammatory and immune processes are also related to ENS function[26].

The enteric neural circuit is organized as an interconnected network of enteric neurons and glial cells[4] throughout the entire GI tract and bile and pancreatic ducts [27]. The enteric neural circuit is arranged in two plexuses: the submucosal plexus, which in large mammals is present in two individualized levels (outer/inner) and is located in the outer connective tissue layer and the inner mucosal layer, and the myenteric plexus, located between the longitudinal and circular muscle layers[2,4,5, 28].

Within this complex innervation system, in humans, there are approximately 400 to 600 million neurons[5] grouped into several ganglia that connect[2] through the primary interganglionic tracts, which characterize the primary plexus[4,5]. The secondary and tertiary plexuses are also present in the myenteric plexus, represented by thinner filaments that are arranged parallel to the fibers of the circular musculature [29] and by even thinner filaments that branch among the constituents of the primary plexus[30]. This extensive neuronal network ends up projecting itself toward various effector structures, such as muscular and immune cells and blood vessels[27].

As proposed by Aleksandr S. Dogiel in 1899, the morphological classification of enteric neurons can be based on their conformation and dendritic distribution. Dogiel described type I cells as flattened, slightly elongated, with an angled or star-shaped contour, and, as remarkable characteristics, as having only one axon and four to 20 Lamellar dendrites that frequently extend at a short distance from the cell body[31].

Type II neurons have large round or oval cell bodies and eccentric nuclei[31], and the surface is grooved by bundles of neural fibers[32]. The main characteristic of type II neurons is the presence of several axonal processes that are emitted either directly from the cell body (multipolar neuron) or from a single initial process that branches into short subsidiary axons (pseudounipolar neurons)[4,33]. Such structures run toward the mucosa[34] and sometimes also provide collateral innervation to the submucosal ganglia[35].

Additionally, enteric neurons can also be identified as intrinsic primary afferent neurons (IPANs), interneurons, and motor neurons[4], classified into at least 18 subtypes and using more than 30 neurotransmitters in their synapses[28,30]. Of these neurotransmitters, acetylcholine (ACh) and nitric oxide (NO) stand out as the most abundant[27], as well as adenosine-5'-triphosphate (ATP)[26], vasoactive intestinal polypeptide (VIP), and substance P (SP)[36]. It is not rare that the same chemical compound stimulates neurons that perform distinct functions[26].

IPANs (classified as Dogiel type II) are recognized for responding to chemical stimuli, mucosal deformation and GI muscle tension, translating these signals into a neural impulse that will trigger a local motor reflex[37]. Altogether, IPANs represent approximately 14% and 30% of the neurons of the submucosal and myenteric plexuses, respectively. IPANs often project to form synapses with myenteric interneurons, motor neurons of the longitudinal and circular muscles[38], and with other IPANs[4].

The interneurons of the ENS (classified as Dogiel type I) are interposed with the IPANs and motor neurons[26], acting as mediators that are activated by the first neuron after a stimulus is received in the mucosa[27,39,40]. Thus, four neuronal types have been reported: one ascending (5%)[38], related to the pathways of the propulsive reflexes[41]; and three descending[38], related to local motility reflexes (5%), the conduction of the migratory myoelectric complex in the small intestine (4%), and secretomotor reflexes (2%)[4,30]. The interconnection of motor, secretory, and vasomotor pathways was suggested on the basis of the double projection of some of these neural fibers in both the submucosal and myenteric plexuses[38].

Motor neurons (classified as Dogiel type I) mark direct connections with muscle cells and, according to their neurotransmitter, can be classified as excitatory by

acetylcholine transferase (ChAT) labeling or as inhibitory by neuronal nitric oxide synthase (nNOS) labeling[4,5,36]. In addition, Furness *et al*[30] classified motor neurons as secretomotor/vasodilator neurons (60%), secretomotor neurons that are not vasodilators (29%), and neurons that innervate only enteroendocrine cells. On the basis of distribution analysis, it is already known that this neuronal class is also present in both enteric plexuses[2].

In summary, neurons of the submucosal plexus innervate the mucosal epithelium and submucosal arterioles to control and maintain water and electrolyte balance, luminal secretion and vascular tone, whereas the myenteric plexus promotes motor innervation of both layers of the muscle region[5], controlling the reflex pathways of the motor complex[42]. However, it is worth noting that the former is present only in the small and large intestines, whereas the latter is found continuously from the initial esophageal region to the internal anal sphincter[4].

The great difference in ENS innervation is that because the enteric ganglia possess all the necessary components to generate and complete a complex reflex circuit (IPANs, interneurons, and motor neurons)[28,43], the ENS has the capacity to regulate GI functions even in the absence of extrinsic neural connections[43]. Therefore, several authors have confirmed that ENS action can occur independently of the CNS[4,24,26,36,44,45], even though the latter often initiates or modulates some of the actions of the ENS[18,24,26].

However, according to Furness[5] and Furness *et al*[2], this autonomy does not actually occur. There are dependencies through interactions between local enteric reflexes, reflexes that pass through sympathetic ganglia, and reflexes that pass in return to the CNS[2,5]. Conveniently, these connections can be classified as vagal and thoracolumbar spinal, being represented by pre-enteric neurons that terminate inside the enteric ganglia, controlling and modifying the activities of neurons present there, or even by direct innervation of effector regions, *e.g.*, the striated skeletal muscles of the esophagus and the sphincters of the GI tract[2].

All this structural and functional complexity characterizes the ENS as the largest and most varied division of the peripheral nervous system[46], leading initially John N. Langley[47] to recognize the ENS no longer as a distribution of parasympathetic postganglia but rather as a distinct segment of the autonomic nervous system that, due to its prominence, should stand alongside the sympathetic and parasympathetic divisions.

INFLAMMATORY BOWEL DISEASES AND THEIR IMPACTS ON THE ENTERIC NERVOUS SYSTEM

IBDs, classically subdivided into Crohn's disease and ulcerative colitis[48,49], are complex and multifactorial disorders characterized by chronic and recurrent inflammation of the intestine[50,51]. Usually, debilitating[48], these disorders reach their peak onset in patients between the ages of 15 and 30 years[52], who, on a purely individual basis, may alternate between periods of symptomatic flares and clinical remission[49].

Although the etiology of IBDs is not yet fully understood[53,54], a growing body of evidence has suggested that the occurrence of IBDs is related to genetic predispositions[55,56] and aberrant immune responses in the face of various environmental triggers[56,57], including antigens from the gut microbiota[56,58,59], poor dietary habits, and high antibiotic consumption in childhood and adolescence[57,60]. Worryingly, an increase in both the incidence and prevalence of IBDs has been reported worldwide[23,52,61,62], but this increase is even more pronounced in newly industrialized countries with more westernized societies[63,64].

Commonly, the symptoms of IBDs may include abdominal pain, diarrhea, rectal bleeding, and weight loss. Ulcerative colitis primarily affects the rectum and is limited to the superficial part of the large intestine mucosa[48], and Crohn's disease is manifested by transmural lesions that may extend from the mouth to the anus, promoting possibly irreversible damage[65]. Sometimes the appearance of and gradual increase in intestinal ulcers associated with cumulative destructive effects can cause stenosis, fistulas, and colorectal cancer[66-68]. Therefore, it is clear that IBDs have an expressive influence on the quality of daily life in these patients[20,21].

In this sense, several efforts are being made to more closely mimic these diseases in the laboratory through the use of animal models, either to understand the relationship between their pathophysiological components or to identify the mechanisms and drugs that mitigate the symptomatology[69]. For this, two main substances have been

used quite satisfactorily for colitis induction: dextran sulfate sodium (DSS) and 2,4,6-trinitrobenzene sulfonic acid (TNBS). DSS is a soluble polysaccharide supplied in drinking water and chemically interferes with gut mucosal barrier integrity, allowing the dissemination of luminal antigens into underlying tissue. TNBS is a reagent administered rectally in combination with ethanol that disrupts the mucosal barrier, allowing TNBS to induce colitis by haptenating colonic proteins, causing them to become preferential targets for immune cells. In both cases, the onset of acute or chronic lesions is dependent on the concentration and/or the frequency of the administration of each substance[69-73].

Specific to the ENS, reports have pointed out that intestinal inflammation can cause functional and structural changes in neurons[74-76] and necrosis, apoptosis and degeneration in enteric ganglia[17,18,77]. In fact, different authors have already demonstrated important variations in the cell number and neuronal profile of inflamed areas when compared to healthy tissues (Tables 1 and 2). In addition, damage to intestinal innervation during the inflammatory course may cause organ functional losses through modifications in motility patterns, increased excitability with changes in synaptic transmission in neural microcircuits, inadequate secretory responses of the epithelium to incoming stimuli[18,78], and enteric cell death from dependence on multiple caspases[19,79,80]. Despite this, little is still known about the mechanisms behind the loss of enteric innervation linked to IBDs[76].

In view of the therapeutic management of IBDs, the introduction of anti-TNF agents has positively marked this path[81-83], especially as they favor the healing of the mucosal layer with increases in its growth with stimulation[84], and as they demonstrate a greater safety of use when compared to conventional protocols[81,82]. In this same context, the P2X7 receptor is also emerging as a very important medical target for the prevention and treatment of these disorders[10], possibly in a similar way to the above, since its continuous activation may worsen the local inflammatory response[85,86]. However, little is known about the real involvement between the activation of this purinergic receptor and the subsequent cascade of events and how all these activities associated with chemical signaling interfere with the functionality of the affected or treated intestine.

THE PURINERGIC RECEPTORS

ATP is the central nucleotide of body metabolism[87], one of the most abundant molecules in living cells[88], and despite being recognized as an energy substrate[87], ATP also acts systemically in conjunction with adenosine and adenosine diphosphate (ADP). As an example, ATP presents actions in the control of vascular tone and remodeling[89,90] and in growth, differentiation[91], and cell communication[87,88,92,93].

Initially recognized for its fundamental role in several intracellular biochemical processes, the function of ATP as a neurotransmitter was greatly questioned when proposed by Geoffrey Burnstock in 1972[94]. In any case, the discovery of purinergic neurons - as they were named in reference to their relation with purine nucleotides[95] - answered the questions generated about the existence of neurons that are neither cholinergic nor adrenergic[36], and a high level of evidence has been reached on purinergic neurons in the scope of physiological and pathophysiological scientific research[92].

According to Burnstock[96], the presence of purinergic receptors was implicit in the hypothesis of this class of neurotransmission, and these receptors were classified into two types: P1 by the use of adenosine and P2 by the use of ATP and ADP. However, only in 1985 was it proposed on pharmacological grounds that this second type could be further subdivided into two other larger families[97]: P2Y, coupled with G-protein; and P2X, coupled with ion channel-dependent ligands[98]. Four subforms are currently recognized for P1 receptors (A1, A2a, A2b, and A3)[99], eight for P2Y receptors (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, and P2Y14)[100], and seven for P2X receptors (P2X1-7)[101,102], making it plausible that purinergic receptors are the most abundant in mammalian tissues[103], found even in cells of neural origin[13,93,103-107].

In the ENS, the presence of purinergic receptors has been widely recognized in enteric neurons and glial cells of humans and other animal species[13,14,108]. In the guinea pig, the P2Y1 receptor has already been identified in the submucosal plexus of the ileum[109], and the P2Y2, P2Y6, P2Y12, P2X2, and P2X3 receptors have been identified in the submucosal and myenteric plexuses of the stomach, jejunum, ileum, and distal colon[110-114].

Table 1 Specific variations in cell number and neuronal profile area according to the respective chemical code observed in the submucosal plexus of the enteric nervous system

Ref.	Species	Colitis	Time	Submucosal plexus	Cellular chemical code (change in density compared to healthy tissues, %)	Cellular chemical code (change in profile area compared to healthy tissues, %)
Schneider <i>et al</i> [169]	Human	Crohn's disease	6.1±6,3 years	ChAT, nNOS, SP, and NSE (similar to); VIP (> 16%-CT)		N/A
Sigalet <i>et al</i> [170]	Rat	TNBS-50% ethanol	5 d	PGP9.5 (< ¹); VIP (< ¹); S100 β (< ¹)		N/A
da Silva <i>et al</i> [130]	Rat	TNBS-30% ethanol	24 h	P2X7 (< 21%-CT; < 13%-sham); Calret (< 11.7%-CT; < 8%-sham); Calb (< 34%-CT; < 30%-sham); HuC/D (< 33.4%-CT; < 28%sham); S100β (< 44.2%-CT; < 33%-sham)		Calbindin (< 25%-CT/sham)

¹Count change without percentage information.

TNBS: 2,4,6-trinitrobenzenesulfonic acid; N/A: Not applicable; (<): Cell count/area decreased; (>): Cell count/area increased; ir: immunoreactive; CT: Control group; Sham: Sham group; P2X7: P2X7 receptor; ChAT: Acetylcholine transferase enzyme-ir; nNOS: Neuronal nitric oxide synthase enzyme-ir; Calret: Calretinin-ir; Calb: Calbindin-ir; SP: Substance P-ir; VIP: Vasoactive intestinal polypeptide-ir; HuC/D and PGP9.5: Pan neuronal-ir; NSE: Neuron-specific enolase-ir; S100β: Protein β for calcium S100-ir labeling.

In mouse studies, P2X2, P2X3, and P2X5 receptors were identified in the submucosal and myenteric plexuses of the stomach, jejunum, ileum, and colon[11,115-117]. In rats, P2X2 and P2X3 receptors have been demonstrated in the submucosal and myenteric plexuses from the stomach to the large intestine and rectum[118-123], and P2X6 receptors have been demonstrated in the submucosal plexuses of the jejunum, ileum, and proximal and distal colon and in the myenteric plexuses of the stomach, ileum, and proximal and distal colon[124].

Specifically, the P2X7 receptor has also been visualized in the submucosal and myenteric plexuses of the colon of humans[19] and in the submucosal plexus of the ileum and the myenteric plexus of the stomach and small and large intestines of guinea pigs[125]. In mice, the presence of the P2X7 receptor was identified in the myenteric plexus of the colon[19] and in rats in the submucosal and myenteric plexuses of the esophagus, stomach, jejunum, ileum, large intestine, and distal colon [121,126-133]. Similar to the other purinergic receptors, the P2X7 receptor also presents a wide range of distributions in relation to enteric neurons with different chemical codes that integrate the ENS (Table 3).

The P2X7 receptor

The P2X7 receptor is a trimeric complex that typically contains 595 amino acids (594 in guinea pigs)[134,135]. The P2X7 receptor consists of two transmembrane domains (TM1 and TM2) linked by a large extracellular loop and by two intracellular domains known as the N-terminus and C-terminus[134,136]. The loop acts as a site for transition metal binding and assists in the activation of this receptor *via* ATP[136], allowing the channel formed by TM1 and TM2[86,135,137] to regulate the passage of calcium, sodium, and potassium[13,93,138]. The domains inside the cell modulate the functions and determine the kinetics of the depolarization and expansion of this channel[139]. It is worth noting that in the P2X7 receptor, the intracellular C-terminus is significantly longer than that in the other P2X receptors[134,136].

As another striking feature, the P2X7 receptor also demands higher concentrations of extracellular ATP for its activation than other purinergic receptors do[101], and this is a possible tissue "danger" sensor[101,140]. In response to inflammation[14,128], trauma or injury[91,141], the elevation of ATP causes a prolonged stimulus that induces the transition of the ion channel to a nonselective membrane pore[101,142,143], making the cell permeable to molecules up to 900 daltons[94,101,142,143]. In association, massive calcium influx[144] can contribute to cell death[85,137,145], with subsequent release of greater amounts of ATP[146-148].

Thus, in addition to its already recognized role in neurotransmission[141], the P2X7 receptor is also closely related to most diseases of the body[140], acting in multiple inflammatory processes[85,99,149,150], immune responses[10,85,86,99,149,151], metabolism and cell proliferation[149]. The P2X7 receptor may also be responsible for

Table 2 Specific variations in cell number and neuronal profile area according to the respective chemical code observed in the myenteric plexus of the enteric nervous system

Ref.	Species	Colitis	Time	Myenteric plexus	Cellular chemical code (change in density compared to healthy tissues, %)	Cellular chemical code (change in profile area compared to healthy tissues, %)
Boyer <i>et al</i> [79]	Mice	DNBS-50% ethanol	0.5 - 120 h	HuC/D (< 42%-CT)		N/A
Linden <i>et al</i> [17]	Guinea pig	TNBS-30% ethanol	2 - 12 h;1-56 d	HuC/D 12 and 24 h (< 15%-CT); HuC/D 6 and 56 d (< 20%-CT); ChAT, nNOS, calret and NeuN 6 d (=); VIP 6 (> ¹ and 56 d (No differences)		N/A
Sarnelli <i>et al</i> [171]	Rat	TNBS-50% ethanol	7 d	HuC/D (< 20%-CT)		N/A
Gulbransen <i>et al</i> [19]	Mice	DNBS-50% ethanol	48 h	HuC/D (< 32%-CT)		N/A
Linden[77]	Guinea pig	TNBS-30% ethanol	24 h	HuC/D (< approximately 20%-25%-CT)		N/A
Da Silva <i>et al</i> [129]	Rat	TNBS-30% ethanol	24 h	P2X7 (< 11%-CT); ChAT (< 34.9%-CT); nNOS (< 42.3%-CT; < 18%-sham); Calret (< 60.6%-CT; < 15%-sham); Calbindin (< 22.9%-CT); HuC/D (< 33.3%-CT; < 16%-sham); S100β (< 29.2%-CT; < 23%-sham)	nNOS (< 6.6%-CT/sham); ChAT (< 21.2%-CT/sham); Calbindin (>19%-CT); Calretinin (< 2%-sham)	
Souza <i>et al</i> [133,2]	Rat	TNBS-30% ethanol	24 h	P2X7 (< 10.6%-sham; < 20.4%-BBG); ChAT (< 34%-sham; < 13.9%-BBG); nNOS (< 22.9%-sham; < 22.2%-BBG); HuC/D (< 15.4%-sham; < 19.5%-BBG); GFAP (< 14.4%-sham; < 17.7%-BBG)	nNOS (< 12%-sham; < 8%-BBG); ChAT and HuC/D (No differences)	

¹Change in count without percentage information.

²Data from ileum after colitis. DNBS: Dinitrobenzene sulfonic acid; TNBS: 2,4,6-trinitrobenzenesulfonic acid; N/A: Not applicable; (=): Similarity of cell count; (<): Cell count/area decrease; (>): Cell count/area increase; ir: Immunoreactive; CT: Control group; Sham: Sham group; BBG: Brilliant Blue G-treated animals group; P2X7: P2X7 receptor; ChAT: Acetylcholine transferase enzyme-ir; nNOS: Neuronal nitric oxide synthase enzyme-ir; Calret: Calretinin-ir; VIP: Vasoactive intestinal polypeptide-ir; HuC/D: Neuronal pan-ir; NeuN: Neuronal nuclear antigen-ir; GFAP: Glial fibrillary acid protein-ir; S100β: Protein β for calcium S100-ir labeling.

triggering the stimulation of necrosis and apoptosis after neurological injuries[85,152,153].

Most of the studies involving the ENS have demonstrated a decrease in the number of cells that are immunoreactive to the P2X7 receptor in the submucosal and myenteric plexus following ischemia/reperfusion in the ilea of rats [127,131,132] and intestinal inflammation in rats[128-130,133], mice, and humans[19]. Moreover, the alteration of these same neurons was observed in the ENS of the large intestine of rats subjected to undernourishment protein and renutrition[121].

Antonioli *et al*[128] also observed a higher intensity of immunofluorescence labeling of these cells in the myenteric ganglia of the distal colon of rats with experimentally induced colitis. These findings may reflect higher activation of the P2X7 receptor in the epithelium and lamina propria of the colon in response to inflammation[154] and in human patients with Crohn's disease or ulcerative colitis[155]. Moreover, it has already been shown that the P2X7 receptor also acts in regulating the activation of NF-κB[148,154] and in the release of proinflammatory cytokines (IL-1β, IL-6, IL-18, and TNF)[148,154,156]. In addition, higher colocalization rates between the P2X7 receptor and dendritic cells, T cells, and macrophages in the epithelium and lamina propria of the inflamed colon in humans have also been reported[155].

Thus, it is highlighted that the P2X7 receptor can promote the occurrence and progression of IBDs, altering the local biological behavior[10] and acting as a key factor in the pathogenesis of ulcerative colitis and Crohn's disease[19,154,157], sometimes even being responsible for neuronal loss[19,158]. Soon, effective pharmacological blockade of this receptor will emerge as a new target in the treatment of inflammatory conditions[99].

Table 3 Specific distribution of the P2X7 receptor in relation to cells with different chemical code that integrate the enteric nervous system

Ref.	Species	Tissue	Chemical cellular code (p2x7 receptor expression, %)	
			Submucosal plexus	Myenteric plexus
Hu <i>et al</i> [125]	Guinea pig	Ileum	ChAT, calret, NPY and SP	nNos, calret, calb, NPY, SP, and HuC/D
Hu <i>et al</i> [125]	Guinea pig	Stomach and intestines	N/A	nNos, calret, calb, NPY, SP, and HuC/D
Vanderwinden <i>et al</i> [126]	Rat	Stomach, jejunum, and colon	S100β	S100β
Gulbrandsen <i>et al</i> [19]	Human and mice	Colon	+	+
Girotti <i>et al</i> [121]	Rat	Large intestine	P2X7 in 100% of ChAT, calret, and calb; ChAT (22.5%), calret (35%) and calb (12.7%)	P2X7 in 100% of ChAT, nNOS, calret, and calb; ChAT (12.7%), nNOS (35.7%), calret (17.6%) and calb (8.3%)
Palombit <i>et al</i> [127]	Rat	Ileum	N/A	P2X7 in 100% of ChAT, nNOS, calret, and calb; ChAT (42.2%), nNOS (24.5%), calret (33.5%), and calb (10.7%)
Antonioli <i>et al</i> [128]	Rat	Distal colon	N/A	P2X7 in 100% of HuC/D
Da Silva <i>et al</i> [129]	Rat	Distal colon	N/A	P2X7 in 100% of ChAT, nNOS, calret, calb, and S100β
Da Silva <i>et al</i> [130]	Rat	Distal colon	P2X7 in 100% of calret, calb, HuC/D, and S100β	N/A

(+): P2X7 receptor positivity without cellular chemical code information; N/A: Not applicable; ir: Immunoreactive; ChAT: Acetylcholine transferase enzyme-ir; nNOS: Neuronal nitric oxide synthase enzyme-ir; Calret: Calretinin-ir; Calb: Calbindin-ir; NPY: Neuropeptide Y-ir; SP: Substance P-ir; HuC/D: Neuronal pan-ir; NF200: Neurofilament 200-ir; GFAP: Glial fibrillary acid protein-ir; S100β: Protein β for calcium S100-ir labeling.

THERAPEUTIC APPROACHES TO THE TREATMENT OF INFLAMMATORY BOWEL DISEASES THROUGH THE P2X7 RECEPTOR

Positive results from the use of P2X7 receptor antagonists have already been demonstrated in the treatment of ischiatic nerve lesions in mice[159], in brain infarction by middle cerebral artery occlusion in rats[160], and in ileal ischemia and reperfusion in rats[131]. During experimentally induced colitis, intraperitoneal application of Brilliant Blue G (BBG) significantly reduced weight loss in rats, the score of mucosal lesions observed through colonoscopy, the macro- and microscopic degrees of inflammation, the number of inflammatory cells, and the deposition of collagen fibers in this organ. Lower levels of P2X7 receptor expression in the epithelium and lamina propria and lower levels of cell apoptosis in the distal colon epithelium were also demonstrated by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. In addition, there was a stabilization of low concentrations of TNF-α, IL-1β and NF-κB, elementary members of this inflammatory process[154]. BBG was also effective in protecting intestinal regions distant from the inflammatory focus, as in the case of ileum in relation to distal colitis[56].

Moreover, in the context of colitis, various P2X7 receptor antagonists also slowed disease progression and reduced NF-κB activation, Caspase-1 expression, and concentrations of TNF and IL-1β in the mouse intestine[148]. Microscopic changes[148,154], changes in colonoscopy examination findings[154] and the loss of tight junctions due to inflammatory-cytokine-induced damage were also ameliorated[161]. In knockout (KO) mice, there was also an increase in specimen weight and reductions in histological lesions[155], with a greater preservation of the epithelial barrier, compared to wild-type (WT) animals[162]. Basically, there was no development of this disease in P2X7 receptor KO animals after the induction of inflammation[155,162].

Although all these therapeutic advances are exceptionally remarkable, only Eser *et al*[163] evaluated the use of some P2X7 receptor antagonists in humans with IBDs - a phase IIa study conducted specifically with patients in moderate to severe stages of Crohn's disease. According to the authors, the drug AZD9056 was well tolerated, and although it did not alter the concentrations of C-reactive protein or fecal calprotectin when compared to placebo, it caused a significant improvement in the Crohn's Disease

Activity Index (CDAI) and showing favorable effects on the remission of the disease and marked reduction in abdominal pain during the treatment period[163].

Taken together, this information reinforces the characterization of the P2X7 receptor as a promising target for the treatment of intestinal inflammatory conditions[14,127-133,148,154,155], especially in view of not only its wide expression in macrophages[10,164,165], mast cells[166] and T cells[10,162] but also its their strong involvement in the activation of caspases[167] and the release and regulation of transcription factors and pro-inflammatory cytokines[168,165].

CONCLUSION

It is concluded that IBDs are capable of aggressively and negatively affecting the cellular constituents of the ENS, and further studies are required in this area since knowledge in this area can still be considered, in a certain way, scarce. Studies of structural losses and/or structural deregulations in the enteric plexus may answer numerous questions about intestinal functionality, and therefore, the performance of these studies is of fundamental importance. Thus, it is also clear that the therapeutic approaches carried out through the P2X7 receptor have contributed to the advancement of this knowledge, but unfortunately: (1) We cannot fail to highlight that clinical trials with human patients are still lacking; (2) A better elucidation of the chemical signaling and functional regulation of immune cells upon the activation of this receptor is required; and (3) More quantitative studies on the structural components of the ENS involved in colitis and in its treatment are also required.

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