

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2021 December 14; 27(46): 7866-8039



**FRONTIER**

- 7866 Imaging of the chemotherapy-induced hepatic damage: Yellow liver, blue liver, and pseudocirrhosis  
*Calistri L, Rastrelli V, Nardi C, Maraghelli D, Vidali S, Pietragalla M, Colagrande S*
- 7894 Hepatic pseudolesions caused by alterations in intrahepatic hemodynamics  
*Kobayashi S*

**REVIEW**

- 7909 Enteric nervous system and inflammatory bowel diseases: Correlated impacts and therapeutic approaches through the P2X7 receptor  
*Magalhães HIR, Castelucci P*

**MINIREVIEWS**

- 7925 COVID-19 and gut immunomodulation  
*Roy K, Agarwal S, Banerjee R, Paul MK, Purbey PK*
- 7943 Transmembrane serine protease 2 and angiotensin-converting enzyme 2 anti-inflammatory receptors for COVID-19/inflammatory bowel diseases treatment  
*Lashgari NA, Momeni Roudsari N, Momtaz S, Abdolghaffari AH*
- 7956 T cells in pancreatic cancer stroma  
*Goulart MR, Stasinou K, Fincham REA, Delvecchio FR, Kocher HM*
- 7969 COVID-19 status quo: Emphasis on gastrointestinal and liver manifestations  
*Bhurwal A, Minacapelli CD, Orosz E, Gupta K, Tait C, Dalal I, Zhang C, Zhao E, Rustgi VK*

**ORIGINAL ARTICLE****Basic Study**

- 7982 Recombinant protein *Schistosoma japonicum*-derived molecule attenuates dextran sulfate sodium-induced colitis by inhibiting miRNA-217-5p to alleviate apoptosis  
*Zhang LC, Wu XY, Yang RB, Chen F, Liu JH, Hu YY, Wu ZD, Wang LF, Sun X*

**Retrospective Cohort Study**

- 7995 Digestive system involvement and clinical outcomes among COVID-19 patients: A retrospective cohort study from Qatar  
*Khan MU, Mushtaq K, Alsoub DH, Iqbal P, Ata F, Chaudhry HS, Iqbal F, Balaraju G, Maslamani MAA, Varughese B, Singh R, Ejji KA, Kaabi SA, Kamel YM, Butt AA*

- 8010** Life prognosis of sentinel node navigation surgery for early-stage gastric cancer: Outcome of lymphatic basin dissection

*Kinami S, Nakamura N, Miyashita T, Kitakata H, Fushida S, Fujimura T, Iida Y, Inaki N, Ito T, Takamura H*

**CORRECTION**

- 8031** Erratum: Author's research-fund support notation correction. Mass forming chronic pancreatitis mimicking pancreatic cystic neoplasm: A case report *World J Gastroenterology* 2018; Jan 14; 24 (2): (297-302)

*Jee KN*

**LETTER TO THE EDITOR**

- 8033** Surveillance strategies for precancerous gastric conditions after *Helicobacter pylori* eradication: There is still need for a tailored approach

*Shahini E, Maida M*

**ABOUT COVER**

Editorial Board Member of *World Journal of Gastroenterology*, Rashmi Kaul, PhD, Professor of Immunology, Department of Biochemistry and Microbiology, Oklahoma State University - Center for Health Sciences, 1111 West, 17th Street, Tulsa, OK 74107, United States. rashmi.kaul10@okstate.edu

**AIMS AND SCOPE**

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

**INDEXING/ABSTRACTING**

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Hua-Ge Yan, Production Department Director: Yan-Jie Ma, Editorial Office Director: Ze-Mao Gong.

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Andrzej S Tarnawski, Subrata Ghosh

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

December 14, 2021

**COPYRIGHT**

© 2021 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

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

Henrique Inhauser Riceti Magalhães, Patricia Castelucci

**ORCID number:** Henrique Inhauser Riceti Magalhães [0000-0001-9151-8160](https://orcid.org/0000-0001-9151-8160); Patricia Castelucci [0000-0002-7475-5962](https://orcid.org/0000-0002-7475-5962).

**Author contributions:** Magalhães HIR was responsible for the literature review and analysis and wrote the review; Castelucci P performed the critical interpretation and revised the manuscript for intellectual content.

**Conflict-of-interest statement:** The authors declare no conflicts of interest for this article.

**Supported by** the São Paulo Research (FAPESP, Brazil), No. 2014/25927-2 and No. 2018/07862-1; and the National Council for Scientific and Technological Development (CNPq, Brazil).

**Country/Territory of origin:** Brazil

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**  
Grade A (Excellent): A

**Henrique Inhauser Riceti Magalhães**, Department of Surgery, School of Veterinary Medicine and Animal Sciences, University of São Paulo, São Paulo 08000-000, Brazil

**Patricia Castelucci**, Department of Anatomy, Institute of Biomedical Sciences, University of São Paulo, São Paulo 08000-000, Brazil

**Corresponding author:** Patricia Castelucci, MHS, PhD, Associate Professor, Associate Research Scientist, Lecturer, Department of Anatomy, University of São Paulo, Av. Dr Lineu Prestes, 2415, São Paulo 08000-000, Brazil. [pcastel@usp.br](mailto:pcastel@usp.br)

## 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

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

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

Grade B (Very good): 0  
 Grade C (Good): 0  
 Grade D (Fair): 0  
 Grade E (Poor): 0

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Received:** July 10, 2021

**Peer-review started:** July 10, 2021

**First decision:** August 19, 2021

**Revised:** August 19, 2021

**Accepted:** November 25, 2021

**Article in press:** November 25, 2021

**Published online:** December 14, 2021

**P-Reviewer:** Xu B

**S-Editor:** Wang LL

**L-Editor:** A

**P-Editor:** Wang LL



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.

**Citation:** Magalhães HIR, Castelucci P. Enteric nervous system and inflammatory bowel diseases: Correlated impacts and therapeutic approaches through the P2X7 receptor. *World J Gastroenterol* 2021; 27(46): 7909-7924

**URL:** <https://www.wjgnet.com/1007-9327/full/v27/i46/7909.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v27.i46.7909>

## 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 haptening 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 (< <sup>1</sup> ); VIP (< <sup>1</sup> ); S100 β (< <sup>1</sup> )		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)

<sup>1</sup>Count 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 (> <sup>1</sup> ) 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] <sup>2</sup>	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)	

<sup>1</sup>Change in count without percentage information.

<sup>2</sup>Data 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
Gulbransen <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- $\alpha$ , IL-1 $\beta$  and NF- $\kappa$ B, 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- $\kappa$ B activation, Caspase-1 expression, and concentrations of TNF and IL-1 $\beta$  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.

---

## REFERENCES

- 1 Nagy N, Goldstein AM. Enteric nervous system development: A crest cell's journey from neural tube to colon. *Semin Cell Dev Biol* 2017; **66**: 94-106 [PMID: 28087321 DOI: 10.1016/j.semcdb.2017.01.006]
- 2 Furness JB, Callaghan BP, Rivera LR, Cho HJ. The enteric nervous system and gastrointestinal innervation: integrated local and central control. *Adv Exp Med Biol* 2014; **817**: 39-71 [PMID: 24997029 DOI: 10.1007/978-1-4939-0897-4\_3]
- 3 Bayliss WM, Starling EH. The movements and innervation of the small intestine. *J Physiol* 1899; **24**: 99-143 [PMID: 16992487 DOI: 10.1113/jphysiol.1899.sp000752]
- 4 Furness JB. The Enteric Nervous System. Oxford: Blackwell Publishing, 2006: 1-102 [DOI: 10.1002/9780470988756]
- 5 Furness JB. The enteric nervous system and neurogastroenterology. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 286-294 [PMID: 22392290 DOI: 10.1038/nrgastro.2012.32]
- 6 Gershon MD. The Second Brain. New York: Harper Collins, 1998 [DOI: 10.1080/15299716.2010.500969]
- 7 De Giorgio R, Guerrini S, Barbara G, Stanghellini V, De Ponti F, Corinaldesi R, Moses PL, Sharkey KA, Mawe GM. Inflammatory neuropathies of the enteric nervous system. *Gastroenterology* 2004; **126**: 1872-1883 [PMID: 15188182 DOI: 10.1053/j.gastro.2004.02.024]
- 8 Gershon MD. Developmental determinants of the independence and complexity of the enteric nervous system. *Trends Neurosci* 2010; **33**: 446-456 [PMID: 20633936 DOI: 10.1016/j.tins.2010.06.002]
- 9 Spear ET, Mawe GM. Enteric neuroplasticity and dysmotility in inflammatory disease: key players and possible therapeutic targets. *Am J Physiol Gastrointest Liver Physiol* 2019; **317**: G853-G861 [PMID: 31604034 DOI: 10.1152/ajpgi.00206.2019]
- 10 Liu Y, Liu X. Research progress of P2X7 receptor in inflammatory bowel disease. *Scand J Gastroenterol* 2019; **54**: 521-527 [PMID: 31056977 DOI: 10.1080/00365521.2019.1609077]
- 11 Giaroni C, Knight GE, Ruan HZ, Glass R, Bardini M, Lecchini S, Frigo G, Burnstock G. P2 receptors in the murine gastrointestinal tract. *Neuropharmacology* 2002; **43**: 1313-1323 [PMID: 12527481 DOI: 10.1016/s0028-3908(02)00294-0]
- 12 Ren J, Bertrand PP. Purinergic receptors and synaptic transmission in enteric neurons. *Purinergic Signal* 2008; **4**: 255-266 [PMID: 18368519 DOI: 10.1007/s11302-007-9088-5]
- 13 Kolachala VL, Bajaj R, Chalasani M, Sitaraman SV. Purinergic receptors in gastrointestinal inflammation. *Am J Physiol Gastrointest Liver Physiol* 2008; **294**: G401-G410 [PMID: 18063703 DOI: 10.1152/ajpgi.00454.2007]
- 14 Antonioli L, Colucci R, Pellegrini C, Giustarini G, Tuccori M, Blandizzi C, Fornai M. The role of purinergic pathways in the pathophysiology of gut diseases: pharmacological modulation and potential therapeutic applications. *Pharmacol Ther* 2013; **139**: 157-188 [PMID: 23588157 DOI: 10.1016/j.pharmthera.2013.04.002]
- 15 Savio LEB, de Andrade Mello P, da Silva CG, Coutinho-Silva R. The P2X7 Receptor in

- Inflammatory Diseases: Angel or Demon? *Front Pharmacol* 2018; **9**: 52 [PMID: 29467654 DOI: 10.3389/fphar.2018.00052]
- 16 **Linden J**, Koch-Nolte F, Dahl G. Purine Release, Metabolism, and Signaling in the Inflammatory Response. *Annu Rev Immunol* 2019; **37**: 325-347 [PMID: 30676821 DOI: 10.1146/annurev-immunol-051116-052406]
  - 17 **Linden DR**, Couvrette JM, Ciolino A, McQuoid C, Blaszyk H, Sharkey KA, Mawe GM. Indiscriminate loss of myenteric neurones in the TNBS-inflamed guinea-pig distal colon. *Neurogastroenterol Motil* 2005; **17**: 751-760 [PMID: 16185315 DOI: 10.1111/j.1365-2982.2005.00703.x]
  - 18 **Lomax AE**, Fernández E, Sharkey KA. Plasticity of the enteric nervous system during intestinal inflammation. *Neurogastroenterol Motil* 2005; **17**: 4-15 [PMID: 15670258 DOI: 10.1111/j.1365-2982.2004.00607.x]
  - 19 **Gulbransen BD**, Bashashati M, Hirota SA, Gui X, Roberts JA, MacDonald JA, Muruve DA, McKay DM, Beck PL, Mawe GM, Thompson RJ, Sharkey KA. Activation of neuronal P2X7 receptor-pannexin-1 mediates death of enteric neurons during colitis. *Nat Med* 2012; **18**: 600-604 [PMID: 22426419 DOI: 10.1038/nm.2679]
  - 20 **Sairenji T**, Collins KL, Evans DV. An Update on Inflammatory Bowel Disease. *Prim Care* 2017; **44**: 673-692 [PMID: 29132528 DOI: 10.1016/j.pop.2017.07.010]
  - 21 **Bray J**, Fernandes A, Nguyen GC, Otleay AR, Heatherington J, Stretton J, Bollegala N, Benchimol EI. The Challenges of Living with Inflammatory Bowel Disease: Summary of a Summit on Patient and Healthcare Provider Perspectives. *Can J Gastroenterol Hepatol* 2016; **2016**: 9430942 [PMID: 27446878 DOI: 10.1155/2016/9430942]
  - 22 **Mikocka-Walus A**, Knowles SR, Keefer L, Graff L. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. *Inflamm Bowel Dis* 2016; **22**: 752-762 [PMID: 26841224 DOI: 10.1097/MIB.0000000000000620]
  - 23 **GBD 2017 Inflammatory Bowel Disease Collaborators**. . The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020; **5**: 17-30 [PMID: 31648971 DOI: 10.1016/S2468-1253(19)30333-4]
  - 24 **Gershon MD**. The enteric nervous system: a second brain. *Hosp Pract (1995)* 1999; **34**: 31-32, 35 [PMID: 10418549 DOI: 10.3810/hp.1999.07.153]
  - 25 **Wood JD**. Enteric Nervous System: Neuropathic Gastrointestinal Motility. *Dig Dis Sci* 2016; **61**: 1803-1816 [PMID: 27142673 DOI: 10.1007/s10620-016-4183-5]
  - 26 **Goyal RK**, Hirano I. The enteric nervous system. *N Engl J Med* 1996; **334**: 1106-1115 [PMID: 8598871 DOI: 10.1056/NEJM199604253341707]
  - 27 **Hansen MB**. The enteric nervous system I: organisation and classification. *Pharmacol Toxicol* 2003; **92**: 105-113 [PMID: 12753424 DOI: 10.1034/j.1600-0773.2003.t01-1-920301.x]
  - 28 **Brookes SJ**. Classes of enteric nerve cells in the guinea-pig small intestine. *Anat Rec* 2001; **262**: 58-70 [PMID: 11146429 DOI: 10.1002/1097-0185(20010101)262:1<]
  - 29 **Stöhr P**. Zusammenfassende ergebnisse über die mikroskopische innervation des magen-darmkanals. *Ergeb Anat Entwicklungsgesch* 1952; **34**: 250-401 [DOI: 10.1007/978-3-7091-5436-6\_5]
  - 30 **Furness JB**, Clerc N, Lomax AE, Bornstein JC, Kunze WA. Shapes and projections of tertiary plexus neurons of the guinea-pig small intestine. *Cell Tissue Res* 2000; **300**: 383-387 [PMID: 10928268 DOI: 10.1007/s004410000210]
  - 31 **Dogiel AS**. Über den Bau der Ganglien in den Gefl echten des Darmes und der Gallenblase des Menschen und der Säugetiere. *Arch Anat Physiol Leipzig Anat Abt Jg* 1899; 130-158 [DOI: 10.1007/bf02976730]
  - 32 **Pompolo S**, Furness JB. Ultrastructure and synaptic relationships of calbindin-reactive, Dogiel type II neurons, in myenteric ganglia of guinea-pig small intestine. *J Neurocytol* 1988; **17**: 771-782 [PMID: 3230396 DOI: 10.1007/BF01216705]
  - 33 **Hendriks R**, Bornstein JC, Furness JB. An electrophysiological study of the projections of putative sensory neurons within the myenteric plexus of the guinea pig ileum. *Neurosci Lett* 1990; **110**: 286-290 [PMID: 2325901 DOI: 10.1016/0304-3940(90)90861-3]
  - 34 **Song ZM**, Brookes SJ, Costa M. All calbindin-immunoreactive myenteric neurons project to the mucosa of the guinea-pig small intestine. *Neurosci Lett* 1994; **180**: 219-222 [PMID: 7535407 DOI: 10.1016/0304-3940(94)90524-x]
  - 35 **Furness JB**, Trussell DC, Pompolo S, Bornstein JC, Smith TK. Calbindin neurons of the guinea-pig small intestine: quantitative analysis of their numbers and projections. *Cell Tissue Res* 1990; **260**: 261-272 [PMID: 2357722 DOI: 10.1007/BF00318629]
  - 36 **Furness JB**. Types of neurons in the enteric nervous system. *J Auton Nerv Syst* 2000; **81**: 87-96 [PMID: 10869706 DOI: 10.1016/s0165-1838(00)00127-2]
  - 37 **Gallego D**, Mañé N, Gil V, Martínez-Cutillas M, Jiménez M. Mechanisms responsible for neuromuscular relaxation in the gastrointestinal tract. *Rev Esp Enferm Dig* 2016; **108**: 721-731 [PMID: 26938735 DOI: 10.17235/reed.2016.4058/2015]
  - 38 **Costa M**, Brookes SJ, Hennig GW. Anatomy and physiology of the enteric nervous system. *Gut* 2000; **47** Suppl 4: iv15-9; discussion iv26 [PMID: 11076898 DOI: 10.1136/gut.47.suppl\_4.iv15]
  - 39 **Kunze WA**, Furness JB. The enteric nervous system and regulation of intestinal motility. *Annu Rev Physiol* 1999; **61**: 117-142 [PMID: 10099684 DOI: 10.1146/annurev.physiol.61.1.117]

- 40 **Bornstein JC**, Costa M, Grider JR. Enteric motor and interneuronal circuits controlling motility. *Neurogastroenterol Motil* 2004; **16** Suppl 1: 34-38 [PMID: 15066002 DOI: 10.1111/j.1743-3150.2004.00472.x]
- 41 **Tonini M**, Costa M. A pharmacological analysis of the neuronal circuitry involved in distension-evoked enteric excitatory reflex. *Neuroscience* 1990; **38**: 787-795 [PMID: 1980147 DOI: 10.1016/0306-4522(90)90071-b]
- 42 **Furness JB**, Jones C, Nurgali K, Clerc N. Intrinsic primary afferent neurons and nerve circuits within the intestine. *Prog Neurobiol* 2004; **72**: 143-164 [PMID: 15063530 DOI: 10.1016/j.pneurobio.2003.12.004]
- 43 **Furness JB**, Clerc N, Vogalis F, Stebbing MJ. The enteric nervous system and its extrinsic connections. In: Yamada T, Alpers DH, editors. *Textbook of Gastroenterology*. Philadelphia: Lippincott Williams, 2003: 12-34 [DOI: 10.1002/9781444303254.ch2]
- 44 **Heanue TA**, Pachnis V. Enteric nervous system development and Hirschsprung's disease: advances in genetic and stem cell studies. *Nat Rev Neurosci* 2007; **8**: 466-479 [PMID: 17514199 DOI: 10.1038/nrn2137]
- 45 **Chalazonitis A**, Rao M. Enteric nervous system manifestations of neurodegenerative disease. *Brain Res* 2018; **1693**: 207-213 [PMID: 29360466 DOI: 10.1016/j.brainres.2018.01.011]
- 46 **Sasselli V**, Pachnis V, Burns AJ. The enteric nervous system. *Dev Biol* 2012; **366**: 64-73 [PMID: 22290331 DOI: 10.1016/j.ydbio.2012.01.012]
- 47 **Langley JN**. The autonomic nervous system: Part 1. Cambridge: Heffer, 1921 [DOI: 10.1093/brain/26.1.1]
- 48 **Shapiro JM**, Subedi S, LeLeiko NS. Inflammatory Bowel Disease. *Pediatr Rev* 2016; **37**: 337-347 [PMID: 27482063 DOI: 10.1542/pir.2015-0110]
- 49 **Shivashankar R**, Lichtenstein GR. Mimics of Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2018; **24**: 2315-2321 [PMID: 29947781 DOI: 10.1093/ibd/izy168]
- 50 **Loddo I**, Romano C. Inflammatory Bowel Disease: Genetics, Epigenetics, and Pathogenesis. *Front Immunol* 2015; **6**: 551 [PMID: 26579126 DOI: 10.3389/fimmu.2015.00551]
- 51 **Liu Y**, Zhao J, Zhao Y, Zong S, Tian Y, Chen S, Li M, Liu H, Zhang Q, Jing X, Sun B, Wang H, Sun T, Yang C. Therapeutic effects of lentinan on inflammatory bowel disease and colitis-associated cancer. *J Cell Mol Med* 2019; **23**: 750-760 [PMID: 30472806 DOI: 10.1111/jcmm.13897]
- 52 **Kaplan GG**. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 720-727 [PMID: 26323879 DOI: 10.1038/nrgastro.2015.150]
- 53 **Ke P**, Shao BZ, Xu ZQ, Chen XW, Liu C. Intestinal Autophagy and Its Pharmacological Control in Inflammatory Bowel Disease. *Front Immunol* 2016; **7**: 695 [PMID: 28119697 DOI: 10.3389/fimmu.2016.00695]
- 54 **Ishisono K**, Mano T, Yabe T, Kitaguchi K. Dietary Fiber Pectin Ameliorates Experimental Colitis in a Neutral Sugar Side Chain-Dependent Manner. *Front Immunol* 2019; **10**: 2979 [PMID: 31921214 DOI: 10.3389/fimmu.2019.02979]
- 55 **Barrett JC**, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, Bitton A, Dassopoulos T, Datta LW, Green T, Griffiths AM, Kistner EO, Murtha MT, Regueiro MD, Rotter JI, Schumm LP, Steinhardt AH, Targan SR, Xavier RJ; NIDDK IBD Genetics Consortium, Libioulle C, Sandor C, Lathrop M, Belaiche J, Dewit O, Gut I, Heath S, Laukens D, Mni M, Rutgeerts P, Van Gossom A, Zelenika D, Franchimont D, Hugot JP, de Vos M, Vermeire S, Louis E; Belgian-French IBD Consortium; Wellcome Trust Case Control Consortium, Cardon LR, Anderson CA, Drummond H, Nimmo E, Ahmad T, Prescott NJ, Onnie CM, Fisher SA, Marchini J, Ghori J, Bumpstead S, Gwilliam R, Tremelling M, Deloukas P, Mansfield J, Jewell D, Satsangi J, Mathew CG, Parkes M, Georges M, Daly MJ. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008; **40**: 955-962 [PMID: 18587394 DOI: 10.1038/ng.175]
- 56 **de Souza HS**, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 13-27 [PMID: 26627550 DOI: 10.1038/nrgastro.2015.186]
- 57 **Frolkis A**, Dieleman LA, Barkema HW, Panaccione R, Ghosh S, Fedorak RN, Madsen K, Kaplan GG; Alberta IBD Consortium. Environment and the inflammatory bowel diseases. *Can J Gastroenterol* 2013; **27**: e18-e24 [DOI: 10.1155/2013/102859]
- 58 **Ni J**, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD: causation or correlation? *Nat Rev Gastroenterol Hepatol* 2017; **14**: 573-584 [PMID: 28743984 DOI: 10.1038/nrgastro.2017.88]
- 59 **Baj A**, Moro E, Bistoletti M, Orlandi V, Crema F, Giaroni C. Glutamatergic Signaling Along The Microbiota-Gut-Brain Axis. *Int J Mol Sci* 2019; **20** [PMID: 30934533 DOI: 10.3390/ijms20061482]
- 60 **Vedamurthy A**, Ananthkrishnan AN. Influence of Environmental Factors in the Development and Outcomes of Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)* 2019; **15**: 72-82 [PMID: 31011301]
- 61 **Molodecky NA**, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142**: 46-54.e42; quiz e30 [PMID: 22001864 DOI: 10.1053/j.gastro.2011.10.001]
- 62 **Kotze PG**, Underwood FE, Damião AOMC, Ferraz JGP, Saad-Hossne R, Toro M, Iade B, Bosques-Padilla F, Teixeira FV, Juliao-Banos F, Simian D, Ghosh S, Panaccione R, Ng SC, Kaplan GG. Progression of Inflammatory Bowel Diseases Throughout Latin America and the Caribbean: A Systematic Review. *Clin Gastroenterol Hepatol* 2020; **18**: 304-312 [PMID: 31252191 DOI: 10.1016/j.cgh.2020.05.011]

- 10.1016/j.cgh.2019.06.030]
- 63 **Ng SC**, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, Wong TC, Leung VK, Tsang SW, Yu HH, Li MF, Ng KK, Kamm MA, Studd C, Bell S, Leong R, de Silva HJ, Kasturiratne A, Mufeeena MNF, Ling KL, Ooi CJ, Tan PS, Ong D, Goh KL, Hilmi I, Pisespongpa P, Manatsathit S, Rerknimitr R, Aniwan S, Wang YF, Ouyang Q, Zeng Z, Zhu Z, Chen MH, Hu PJ, Wu K, Wang X, Simadibrata M, Abdullah M, Wu JC, Sung JY, Chan FKL; Asia-Pacific Crohn's and Colitis Epidemiologic Study (ACCESS) Study Group. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. *Gastroenterology* 2013; **145**: 158-165.e2 [PMID: 23583432 DOI: 10.1053/j.gastro.2013.04.007]
  - 64 **Ng SC**, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]
  - 65 **Deepak P**, Fowler KJ, Fletcher JG, Bruining DH. Novel Imaging Approaches in Inflammatory Bowel Diseases. *Inflamm Bowel Dis* 2019; **25**: 248-260 [PMID: 30010908 DOI: 10.1093/ibd/izy239]
  - 66 **Xavier RJ**, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; **448**: 427-434 [PMID: 17653185 DOI: 10.1038/nature06005]
  - 67 **Torres J**, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017; **389**: 1741-1755 [PMID: 27914655 DOI: 10.1016/S0140-6736(16)31711-1]
  - 68 **Ungaro R**, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet* 2017; **389**: 1756-1770 [PMID: 27914657 DOI: 10.1016/S0140-6736(16)32126-2]
  - 69 **Wirtz S**, Popp V, Kindermann M, Gerlach K, Weigmann B, Fichtner-Feigl S, Neurath MF. Chemically induced mouse models of acute and chronic intestinal inflammation. *Nat Protoc* 2017; **12**: 1295-1309 [PMID: 28569761 DOI: 10.1038/nprot.2017.044]
  - 70 **Morris GP**, Beck PL, Herridge MS, Depew WT, Szewczuk MR, Wallace JL. Hapten-induced model of chronic inflammation and ulceration in the rat colon. *Gastroenterology* 1989; **96**: 795-803 [PMID: 2914642]
  - 71 **Kawada M**, Arihiro A, Mizoguchi E. Insights from advances in research of chemically induced experimental models of human inflammatory bowel disease. *World J Gastroenterol* 2007; **13**: 5581-5593 [PMID: 17948932 DOI: 10.3748/wjg.v13.i42.5581]
  - 72 **Chassaing B**, Aitken JD, Malleshappa M, Vijay-Kumar M. Dextran sulfate sodium (DSS)-induced colitis in mice. *Curr Protoc Immunol* 2014; **104**: 15.25.1-15.25.14 [PMID: 24510619 DOI: 10.1002/0471142735.im1525s104]
  - 73 **Bramhall M**, Flórez-Vargas O, Stevens R, Brass A, Cruickshank S. Quality of methods reporting in animal models of colitis. *Inflamm Bowel Dis* 2015; **21**: 1248-1259 [PMID: 25989337 DOI: 10.1097/MIB.0000000000000369]
  - 74 **Sanovic S**, Lamb DP, Blennerhassett MG. Damage to the enteric nervous system in experimental colitis. *Am J Pathol* 1999; **155**: 1051-1057 [PMID: 10514387 DOI: 10.1016/S0002-9440(10)65207-8]
  - 75 **Brierley SM**, Linden DR. Neuroplasticity and dysfunction after gastrointestinal inflammation. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 611-627 [PMID: 25001973 DOI: 10.1038/nrgastro.2014.103]
  - 76 **Stavelly R**, Abalo R, Nurgali K. Targeting Enteric Neurons and Plexitis for the Management of Inflammatory Bowel Disease. *Curr Drug Targets* 2020; **21**: 1428-1439 [PMID: 32416686 DOI: 10.2174/1389450121666200516173242]
  - 77 **Linden DR**. Colitis is associated with a loss of intestinofugal neurons. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G1096-G1104 [PMID: 22997196 DOI: 10.1152/ajpgi.00176.2012]
  - 78 **Cirillo C**, Sarnelli G, Cuomo R. Enteric nervous system abnormalities in ulcerative colitis. In: O'Connor MB. *Ulcerative Colitis - Epidemiology, Pathogenesis and Complications*. IntechOpen, 2011 [DOI: 10.5772/26176]
  - 79 **Boyer L**, Ghoreishi M, Templeman V, Vallance BA, Buchan AM, Jevon G, Jacobson K. Myenteric plexus injury and apoptosis in experimental colitis. *Auton Neurosci* 2005; **117**: 41-53 [PMID: 15620569 DOI: 10.1016/j.autneu.2004.10.006]
  - 80 **Bassotti G**, Villanacci V, Nascimbeni R, Cadei M, Fisogni S, Antonelli E, Corazzi N, Salerni B. Enteric neuroglial apoptosis in inflammatory bowel diseases. *J Crohns Colitis* 2009; **3**: 264-270 [PMID: 21172285 DOI: 10.1016/j.crohns.2009.06.004]
  - 81 **Colombel JF**, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52-65 [PMID: 17241859 DOI: 10.1053/j.gastro.2006.11.041]
  - 82 **Sandborn WJ**, Colombel JF, D'Haens G, Van Assche G, Wolf D, Kron M, Lazar A, Robinson AM, Yang M, Chao JD, Thakkar R. One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. *Aliment Pharmacol Ther* 2013; **37**: 204-213 [PMID: 23173821 DOI: 10.1111/apt.12145]
  - 83 **Perin RL**, Damião AOMC, Flores C, Ludvig JC, Magro DO, Miranda EF, Moraes AC, Nones RB, Teixeira FV, Zeroncio M, Kotze PG. VEDOLIZUMAB IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASES: A BRAZILIAN OBSERVATIONAL MULTICENTRIC STUDY. *Arq Gastroenterol* 2019; **56**: 312-317 [PMID: 31633731 DOI: 10.1590/S0004-2803.201900000-58]

- 84 **Rosen MJ**, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. *JAMA Pediatr* 2015; **169**: 1053-1060 [PMID: 26414706 DOI: 10.1001/jamapediatrics.2015.1982]
- 85 **Di Virgilio F**, Dal Ben D, Sarti AC, Giuliani AL, Falzoni S. The P2X7 Receptor in Infection and Inflammation. *Immunity* 2017; **47**: 15-31 [PMID: 28723547 DOI: 10.1016/j.immuni.2017.06.020]
- 86 **Cao F**, Hu LQ, Yao SR, Hu Y, Wang DG, Fan YG, Pan GX, Tao SS, Zhang Q, Pan HF, Wu GC. P2X7 receptor: A potential therapeutic target for autoimmune diseases. *Autoimmun Rev* 2019; **18**: 767-777 [PMID: 31181327 DOI: 10.1016/j.autrev.2019.06.009]
- 87 **Rajendran M**, Dane E, Conley J, Tantama M. Imaging Adenosine Triphosphate (ATP). *Biol Bull* 2016; **231**: 73-84 [PMID: 27638696 DOI: 10.1086/689592]
- 88 **Boué-Grabot E**, Blum D, Ceruti S. Editorial: Purinergic Signaling in Health and Disease. *Front Cell Neurosci* 2020; **14**: 15 [PMID: 32116561 DOI: 10.3389/fncel.2020.00015]
- 89 **Yamamoto K**, Sokabe T, Matsumoto T, Yoshimura K, Shibata M, Ohura N, Fukuda T, Sato T, Sekine K, Kato S, Isshiki M, Fujita T, Kobayashi M, Kawamura K, Masuda H, Kamiya A, Ando J. Impaired flow-dependent control of vascular tone and remodeling in P2X4-deficient mice. *Nat Med* 2006; **12**: 133-137 [PMID: 16327800 DOI: 10.1038/nm1338]
- 90 **Burnstock G**. Vessel tone and remodeling. *Nat Med* 2006; **12**: 16-17 [PMID: 16397544 DOI: 10.1038/nm0106-16]
- 91 **Franke H**, Krügel U, Illes P. P2 receptors and neuronal injury. *Pflugers Arch* 2006; **452**: 622-644 [PMID: 16645849 DOI: 10.1007/s00424-006-0071-8]
- 92 **Burnstock G**. Physiology and pathophysiology of purinergic neurotransmission. *Physiol Rev* 2007; **87**: 659-797 [PMID: 17429044 DOI: 10.1152/physrev.00043.2006]
- 93 **Abbracchio MP**, Burnstock G, Verkhratsky A, Zimmermann H. Purinergic signalling in the nervous system: an overview. *Trends Neurosci* 2009; **32**: 19-29 [PMID: 19008000 DOI: 10.1016/j.tins.2008.10.001]
- 94 **Burnstock G**. Purine and pyrimidine receptors. *Cell Mol Life Sci* 2007; **64**: 1471-1483 [PMID: 17375261 DOI: 10.1007/s00018-007-6497-0]
- 95 **Burnstock G**. Purinergic nerves. *Pharmacol Rev* 1972; **24**: 509-581 [PMID: 4404211]
- 96 **Burnstock G**. A basis for distinguishing two types of purinergic receptor. In: Straub RW, Bolis L, editors. Cell Membrane Receptors for Drugs and Hormones: A Multidisciplinary Approach. New York: Raven, 1978: 107-118 [DOI: 10.1016/0014-5793(79)81367-8]
- 97 **Burnstock G**, Kennedy C. Is there a basis for distinguishing two types of P2-purinoceptor? *Gen Pharmacol* 1985; **16**: 433-440 [PMID: 2996968 DOI: 10.1016/0306-3623(85)90001-1]
- 98 **Abbracchio MP**, Burnstock G. Purinoceptors: are there families of P2X and P2Y purinoceptors? *Pharmacol Ther* 1994; **64**: 445-475 [PMID: 7724657 DOI: 10.1016/0163-7258(94)00048-4]
- 99 **Mehta N**, Kaur M, Singh M, Chand S, Vyas B, Silakari P, Bahia MS, Silakari O. Purinergic receptor P2X7: A novel target for anti-inflammatory therapy. *Bioorg Med Chem* 2014; **22**: 54-88 [DOI: 10.1016/j.bmc.2013.10.054]
- 100 **Abbracchio MP**, Burnstock G, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Knight GE, Fumagalli M, Gachet C, Jacobson KA, Weisman GA. International Union of Pharmacology LVIII: update on the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy. *Pharmacol Rev* 2006; **58**: 281-341 [PMID: 16968944 DOI: 10.1124/pr.58.3.3]
- 101 **North RA**. Molecular physiology of P2X receptors. *Physiol Rev* 2002; **82**: 1013-1067 [PMID: 12270951 DOI: 10.1152/physrev.00015.2002]
- 102 **Roberts JA**, Vial C, Digby HR, Agboh KC, Wen H, Atterbury-Thomas A, Evans RJ. Molecular properties of P2X receptors. *Pflugers Arch* 2006; **452**: 486-500 [PMID: 16607539 DOI: 10.1007/s00424-006-0073-6]
- 103 **Burnstock G**, Knight GE. Cellular distribution and functions of P2 receptor subtypes in different systems. *Int Rev Cytol* 2004; **240**: 31-304 [PMID: 15548415 DOI: 10.1016/s0074-7696(04)40002-3]
- 104 **Kobayashi K**, Yamanaka H, Noguchi K. Expression of ATP receptors in the rat dorsal root ganglion and spinal cord. *Anat Sci Int* 2013; **88**: 10-16 [PMID: 23179910 DOI: 10.1007/s12565-012-0163-9]
- 105 **Wang L**, Feng D, Yan H, Wang Z, Pei L. Comparative analysis of P2X1, P2X2, P2X3, and P2X4 receptor subunits in rat nodose ganglion neurons. *PLoS One* 2014; **9**: e96699 [PMID: 24798490 DOI: 10.1371/journal.pone.0096699]
- 106 **Puchalowicz K**, Baranowska-Bosiacka I, Dziedziczko V, Chlubek D. Purinergic signaling and the functioning of the nervous system cells. *Cell Mol Biol Lett* 2015; **20**: 867-918 [PMID: 26618572 DOI: 10.1515/cmble-2015-0050]
- 107 **Burnstock G**. Introduction to purinergic signalling in the brain. In: Barańska J, editor. Glioma Signaling: Advances in Experimental Medicine and Biology. Cham: Springer, 2020: 1-12
- 108 **Christofi FL**, Zhang H, Yu JG, Guzman J, Xue J, Kim M, Wang YZ, Cooke HJ. Differential gene expression of adenosine A1, A2a, A2b, and A3 receptors in the human enteric nervous system. *J Comp Neurol* 2001; **439**: 46-64 [PMID: 11579381 DOI: 10.1002/cne.1334]
- 109 **Gao N**, Hu HZ, Zhu MX, Fang X, Liu S, Gao C, Wood JD. The P2Y purinergic receptor expressed by enteric neurones in guinea-pig intestine. *Neurogastroenterol Motil* 2006; **18**: 316-323 [PMID: 16553587 DOI: 10.1111/j.1365-2982.2005.00754.x]
- 110 **Castelucci P**, Robbins HL, Poole DP, Furness JB. The distribution of purine P2X(2) receptors in the guinea-pig enteric nervous system. *Histochem Cell Biol* 2002; **117**: 415-422 [PMID: 12029488 DOI: 10.1007/s00418-002-0404-4]
- 111 **Van Nassauw L**, Brouns I, Adriaensen D, Burnstock G, Timmermans JP. Neurochemical

- identification of enteric neurons expressing P2X(3) receptors in the guinea-pig ileum. *Histochem Cell Biol* 2002; **118**: 193-203 [PMID: 12271355 DOI: 10.1007/s00418-002-0447-6]
- 112 **Poole DP**, Castelucci P, Robbins HL, Chiochetti R, Furness JB. The distribution of P2X3 purine receptor subunits in the guinea pig enteric nervous system. *Auton Neurosci* 2002; **101**: 39-47 [PMID: 12462358 DOI: 10.1016/s1566-0702(02)00179-0]
- 113 **Xiang Z**, Burnstock G. Distribution of P2Y2 receptors in the guinea pig enteric nervous system and its coexistence with P2X2 and P2X3 receptors, neuropeptide Y, nitric oxide synthase and calretinin. *Histochem Cell Biol* 2005; **124**: 379-390 [PMID: 16136347 DOI: 10.1007/s00418-005-0043-7]
- 114 **Xiang Z**, Burnstock G. Distribution of P2Y6 and P2Y12 receptor: their colocalization with calbindin, calretinin and nitric oxide synthase in the guinea pig enteric nervous system. *Histochem Cell Biol* 2006; **125**: 327-336 [PMID: 16195889 DOI: 10.1007/s00418-005-0071-3]
- 115 **Ruan HZ**, Burnstock G. The distribution of P2X5 purinergic receptors in the enteric nervous system of mouse. *Cell Tissue Res* 2005; **319**: 191-200 [PMID: 15551155 DOI: 10.1007/s00441-004-1002-7]
- 116 **Mizuno MS**, Crisma AR, Borelli P, Castelucci P. Expression of the P2X<sub>2</sub> receptor in different classes of ileum myenteric neurons in the female obese ob/ob mouse. *World J Gastroenterol* 2012; **18**: 4693-4703 [PMID: 23002338 DOI: 10.3748/wjg.v18.i34.4693]
- 117 **Mizuno MS**, Crisma AR, Borelli P, Schäfer BT, Silveira MP, Castelucci P. Distribution of the P2X<sub>2</sub> receptor and chemical coding in ileal enteric neurons of obese male mice (ob/ob). *World J Gastroenterol* 2014; **20**: 13911-13919 [PMID: 25320527 DOI: 10.3748/wjg.v20.i38.13911]
- 118 **Xiang Z**, Burnstock G. P2X<sub>2</sub> and P2X<sub>3</sub> purinoceptors in the rat enteric nervous system. *Histochem Cell Biol* 2004; **121**: 169-179 [PMID: 14767775 DOI: 10.1007/s00418-004-0620-1]
- 119 **Misawa R**, Girotti PA, Mizuno MS, Liberti EA, Furness JB, Castelucci P. Effects of protein deprivation and re-feeding on P2X<sub>2</sub> receptors in enteric neurons. *World J Gastroenterol* 2010; **16**: 3651-3663 [PMID: 20677337 DOI: 10.3748/wjg.v16.i29.3651]
- 120 **Paulino AS**, Palombit K, Cavriani G, Tavares-de-Lima W, Mizuno MS, Marosti AR, da Silva MV, Girotti PA, Liberti EA, Castelucci P. Effects of ischemia and reperfusion on P2X<sub>2</sub> receptor expressing neurons of the rat ileum enteric nervous system. *Dig Dis Sci* 2011; **56**: 2262-2275 [PMID: 21409380 DOI: 10.1007/s10620-011-1588-z]
- 121 **Girotti PA**, Misawa R, Palombit K, Mendes CE, Bittencourt JC, Castelucci P. Differential effects of undernourishment on the differentiation and maturation of rat enteric neurons. *Cell Tissue Res* 2013; **353**: 367-380 [PMID: 23644765 DOI: 10.1007/s00441-013-1620-z]
- 122 **Marosti AR**, da Silva MV, Palombit K, Mendes CE, Tavares-de-Lima W, Castelucci P. Differential effects of intestinal ischemia and reperfusion in rat enteric neurons and glial cells expressing P2X<sub>2</sub> receptors. *Histol Histopathol* 2015; **30**: 489-501 [PMID: 25400134 DOI: 10.14670/hh-30.489]
- 123 **Mendes CE**, Palombit K, Vieira C, Silva I, Correia-de-Sá P, Castelucci P. The Effect of Ischemia and Reperfusion on Enteric Glial Cells and Contractile Activity in the Ileum. *Dig Dis Sci* 2015; **60**: 2677-2689 [PMID: 25917048 DOI: 10.1007/s10620-015-3663-3]
- 124 **Yu Q**, Zhao Z, Sun J, Guo W, Fu J, Burnstock G, He C, Xiang Z. Expression of P2X<sub>6</sub> receptors in the enteric nervous system of the rat gastrointestinal tract. *Histochem Cell Biol* 2010; **133**: 177-188 [PMID: 19946698 DOI: 10.1007/s00418-009-0659-0]
- 125 **Hu HZ**, Gao N, Lin Z, Gao C, Liu S, Ren J, Xia Y, Wood JD. P2X(7) receptors in the enteric nervous system of guinea-pig small intestine. *J Comp Neurol* 2001; **440**: 299-310 [PMID: 11745625 DOI: 10.1002/cne.1387]
- 126 **Vanderwinden JM**, Timmermans JP, Schiffmann SN. Glial cells, but not interstitial cells, express P2X<sub>7</sub>, an ionotropic purinergic receptor, in rat gastrointestinal musculature. *Cell Tissue Res* 2003; **312**: 149-154 [PMID: 12684872 DOI: 10.1007/s00441-003-0716-2]
- 127 **Palombit K**, Mendes CE, Tavares-de-Lima W, Silveira MP, Castelucci P. Effects of ischemia and reperfusion on subpopulations of rat enteric neurons expressing the P2X<sub>7</sub> receptor. *Dig Dis Sci* 2013; **58**: 3429-3439 [PMID: 23990036 DOI: 10.1007/s10620-013-2847-y]
- 128 **Antonoli L**, Giron MC, Colucci R, Pellegrini C, Sacco D, Caputi V, Orso G, Tuccori M, Scarpignato C, Blandizzi C, Fornai M. Involvement of the P2X<sub>7</sub> purinergic receptor in colonic motor dysfunction associated with bowel inflammation in rats. *PLoS One* 2014; **9**: e116253 [PMID: 25549098 DOI: 10.1371/journal.pone.0116253]
- 129 **Da Silva MV**, Marosti AR, Mendes CE, Palombit K, Castelucci P. Differential effects of experimental ulcerative colitis on P2X<sub>7</sub> receptor expression in enteric neurons. *Histochem Cell Biol* 2015; **143**: 171-184 [PMID: 25201348 DOI: 10.1007/s00418-014-1270-6]
- 130 **Da Silva MV**, Marosti AR, Mendes CE, Palombit K, Castelucci P. Submucosal neurons and enteric glial cells expressing the P2X<sub>7</sub> receptor in rat experimental colitis. *Acta Histochem* 2017; **119**: 481-494 [PMID: 28501138 DOI: 10.1016/j.acthis.2017.05.001]
- 131 **Palombit K**, Mendes CE, Tavares-de-Lima W, Barreto-Chaves ML, Castelucci P. Blockage of the P2X<sub>7</sub> Receptor Attenuates Harmful Changes Produced by Ischemia and Reperfusion in the Myenteric Plexus. *Dig Dis Sci* 2019; **64**: 1815-1829 [PMID: 30734238 DOI: 10.1007/s10620-019-05496-8]
- 132 **Mendes CE**, Palombit K, Tavares-de-Lima W, Castelucci P. Enteric glial cells immunoreactive for P2X<sub>7</sub> receptor are affected in the ileum following ischemia and reperfusion. *Acta Histochem* 2019; **121**: 665-679 [PMID: 31202513 DOI: 10.1016/j.acthis.2019.06.001]
- 133 **Souza RF**, Evangelinellis MM, Mendes CE, Righetti M, Lourenço MCS, Castelucci P. P2X<sub>7</sub> receptor antagonist recovers ileum myenteric neurons after experimental ulcerative colitis. *World J*

- Gastrointest Pathophysiol* 2020; **11**: 84-103 [PMID: 32587788 DOI: 10.4291/wjgp.v11.i4.84]
- 134 **Surprenant A**, Rassendren F, Kawashima E, North RA, Buell G. The cytolitic P2Z receptor for extracellular ATP identified as a P2X receptor (P2X7). *Science* 1996; **272**: 735-738 [PMID: 8614837 DOI: 10.1126/science.272.5262.735]
- 135 **Sluyter R**. The P2X7 receptor. In: Atassi M, editor. *Protein Reviews. Advances in Experimental Medicine and Biology*. Singapura: Springer, 2017
- 136 **Liu X**, Ma W, Surprenant A, Jiang LH. Identification of the amino acid residues in the extracellular domain of rat P2X(7) receptor involved in functional inhibition by acidic pH. *Br J Pharmacol* 2009; **156**: 135-142 [PMID: 19068080 DOI: 10.1111/j.1476-5381.2008.00002.x]
- 137 **Zhang WJ**, Zhu ZM, Liu ZX. The role and pharmacological properties of the P2X7 receptor in neuropathic pain. *Brain Res Bull* 2020; **155**: 19-28 [PMID: 31778766 DOI: 10.1016/j.brainresbull.2019.11.006]
- 138 **North RA**, Jarvis MF. P2X receptors as drug targets. *Mol Pharmacol* 2013; **83**: 759-769 [PMID: 23253448 DOI: 10.1124/mol.112.083758]
- 139 **Coddou C**, Yan Z, Obsil T, Huidobro-Toro JP, Stojilkovic SS. Activation and regulation of purinergic P2X receptor channels. *Pharmacol Rev* 2011; **63**: 641-683 [PMID: 21737531 DOI: 10.1124/pr.110.003129]
- 140 **Burnstock G**. P2X ion channel receptors and inflammation. *Purinergic Signal* 2016; **12**: 59-67 [PMID: 26739702 DOI: 10.1007/s11302-015-9493-0]
- 141 **Sperlágh B**, Illes P. P2X7 receptor: an emerging target in central nervous system diseases. *Trends Pharmacol Sci* 2014; **35**: 537-547 [PMID: 25223574 DOI: 10.1016/j.tips.2014.08.002]
- 142 **North RA**, Verkhratsky A. Purinergic transmission in the central nervous system. *Pflugers Arch* 2006; **452**: 479-485 [PMID: 16688467 DOI: 10.1007/s00424-006-0060-y]
- 143 **Dubyak GR**. P2X7 receptor regulation of non-classical secretion from immune effector cells. *Cell Microbiol* 2012; **14**: 1697-1706 [PMID: 22882764 DOI: 10.1111/cmi.12001]
- 144 **Matyśniak D**, Nowak N, Chumak V, Pomorski P. P2X7 receptor activity landscape in rat and human glioma cell lines. *Acta Biochim Pol* 2020; **67**: 7-14 [PMID: 32187491 DOI: 10.18388/abp.2020\_2848]
- 145 **Ohishi A**, Keno Y, Marumiya A, Sudo Y, Uda Y, Matsuda K, Morita Y, Furuta T, Nishida K, Nagasawa K. Expression level of P2X7 receptor is a determinant of ATP-induced death of mouse cultured neurons. *Neuroscience* 2016; **319**: 35-45 [PMID: 26812038 DOI: 10.1016/j.neuroscience.2016.01.048]
- 146 **Burnstock G**. Pathophysiology and therapeutic potential of purinergic signaling. *Pharmacol Rev* 2006; **58**: 58-86 [PMID: 16507883 DOI: 10.1124/pr.58.1.5]
- 147 **Deaglio S**, Robson SC. Ectonucleotidases as regulators of purinergic signaling in thrombosis, inflammation, and immunity. *Adv Pharmacol* 2011; **61**: 301-332 [PMID: 21586363 DOI: 10.1016/b978-0-12-385526-8.00010-2]
- 148 **Wan P**, Liu X, Xiong Y, Ren Y, Chen J, Lu N, Guo Y, Bai A. Extracellular ATP mediates inflammatory responses in colitis via P2 × 7 receptor signaling. *Sci Rep* 2016; **6**: 19108 [PMID: 26739809 DOI: 10.1038/srep19108]
- 149 **Young CNJ**, Górecki DC. P2RX7 Purinoceptor as a Therapeutic Target-The Second Coming? *Front Chem* 2018; **6**: 248 [PMID: 30003075 DOI: 10.3389/fchem.2018.00248]
- 150 **Zhang Q**, Hu F, Guo F, Zhou Q, Xiang H, Shang D. Emodin attenuates adenosine triphosphate-induced pancreatic ductal cell injury in vitro via the inhibition of the P2X7/NLRP3 signaling pathway. *Oncol Rep* 2019; **42**: 1589-1597 [PMID: 31524270 DOI: 10.3892/or.2019.7270]
- 151 **Di Virgilio F**, Giuliani AL. Purinergic signalling in autoimmunity: A role for the P2X7R in systemic lupus erythematosus? *Biomed J* 2016; **39**: 326-338 [PMID: 27884379 DOI: 10.1016/j.bj.2016.08.006]
- 152 **Volonté C**, Amadio S, Cavaliere F, D'Ambrosi N, Vacca F, Bernardi G. Extracellular ATP and neurodegeneration. *Curr Drug Targets CNS Neurol Disord* 2003; **2**: 403-412 [PMID: 14683468 DOI: 10.2174/1568007033482643]
- 153 **Franke H**, Illes P. Involvement of P2 receptors in the growth and survival of neurons in the CNS. *Pharmacol Ther* 2006; **109**: 297-324 [PMID: 16102837 DOI: 10.1016/j.pharmthera.2005.06.002]
- 154 **Marques CC**, Castelo-Branco MT, Pacheco RG, Buongusto F, do Rosário A Jr, Schanaider A, Coutinho-Silva R, de Souza HS. Prophylactic systemic P2X7 receptor blockade prevents experimental colitis. *Biochim Biophys Acta* 2014; **1842**: 65-78 [PMID: 24184714 DOI: 10.1016/j.bbadis.2013.10.012]
- 155 **Neves AR**, Castelo-Branco MT, Figliuolo VR, Bernardazzi C, Buongusto F, Yoshimoto A, Nanini HF, Coutinho CM, Carneiro AJ, Coutinho-Silva R, de Souza HS. Overexpression of ATP-activated P2X7 receptors in the intestinal mucosa is implicated in the pathogenesis of Crohn's disease. *Inflamm Bowel Dis* 2014; **20**: 444-457 [PMID: 24412990 DOI: 10.1097/01.mib.0000441201.10454.06]
- 156 **Luna-Gomes T**, Santana PT, Coutinho-Silva R. Silica-induced inflammasome activation in macrophages: role of ATP and P2X7 receptor. *Immunobiology* 2015; **220**: 1101-1106 [PMID: 26024943 DOI: 10.1016/j.imbio.2015.05.004]
- 157 **Diezmos EF**, Bertrand PP, Liu L. Purinergic Signaling in Gut Inflammation: The Role of Connexins and Pannexins. *Front Neurosci* 2016; **10**: 311 [PMID: 27445679 DOI: 10.3389/fnins.2016.00311]
- 158 **Roberts JA**, Lukewich MK, Sharkey KA, Furness JB, Mawe GM, Lomax AE. The roles of purinergic signaling during gastrointestinal inflammation. *Curr Opin Pharmacol* 2012; **12**: 659-666

- [PMID: 23063457 DOI: 10.1016/j.coph.2012.09.011]
- 159 **Ribeiro T**, Oliveira JT, Almeida FM, Tomaz MA, Melo PA, Marques SA, de Andrade GM, Martinez AMB. Blockade of ATP P2X7 receptor enhances ischiatic nerve regeneration in mice following a crush injury. *Brain Res* 2017; **1669**: 69-78 [PMID: 28554806 DOI: 10.1016/j.brainres.2017.05.025]
- 160 **Arbeloa J**, Pérez-Samartín A, Gottlieb M, Matute C. P2X7 receptor blockade prevents ATP excitotoxicity in neurons and reduces brain damage after ischemia. *Neurobiol Dis* 2012; **45**: 954-961 [PMID: 22186422 DOI: 10.1016/j.nbd.2011.12.014]
- 161 **Diezmos EF**, Markus I, Perera DS, Gan S, Zhang L, Sandow SL, Bertrand PP, Liu L. Blockade of Pannexin-1 Channels and Purinergic P2X7 Receptors Shows Protective Effects Against Cytokines-Induced Colitis of Human Colonic Mucosa. *Front Pharmacol* 2018; **9**: 865 [PMID: 30127744 DOI: 10.3389/fphar.2018.00865]
- 162 **Figliuolo VR**, Savio LEB, Safya H, Nanini H, Bernardazzi C, Abalo A, de Souza HSP, Kanellopoulos J, Bobé P, Coutinho CMLM, Coutinho-Silva R. P2X7 receptor promotes intestinal inflammation in chemically induced colitis and triggers death of mucosal regulatory T cells. *Biochim Biophys Acta Mol Basis Dis* 2017; **1863**: 1183-1194 [PMID: 28286160 DOI: 10.1016/j.bbadis.2017.03.004]
- 163 **Eser A**, Colombel JF, Rutgeerts P, Vermeire S, Vogelsang H, Braddock M, Persson T, Reinisch W. Safety and Efficacy of an Oral Inhibitor of the Purinergic Receptor P2X7 in Adult Patients with Moderately to Severely Active Crohn's Disease: A Randomized Placebo-controlled, Double-blind, Phase IIa Study. *Inflamm Bowel Dis* 2015; **21**: 2247-2253 [PMID: 26197451 DOI: 10.1097/mib.0000000000000514]
- 164 **Wiley JS**, Sluyter R, Gu BJ, Stokes L, Fuller SJ. The human P2X7 receptor and its role in innate immunity. *Tissue Antigens* 2011; **78**: 321-332 [PMID: 21988719 DOI: 10.1111/j.1399-0039.2011.01780.x]
- 165 **Burnstock G**, Jacobson KA, Christofi FL. Purinergic drug targets for gastrointestinal disorders. *Curr Opin Pharmacol* 2017; **37**: 131-141 [PMID: 29149731 DOI: 10.1016/j.coph.2017.10.011]
- 166 **Kurashima Y**, Amiya T, Nochi T, Fujisawa K, Haraguchi T, Iba H, Tsutsui H, Sato S, Nakajima S, Iijima H, Kubo M, Kunisawa J, Kiyono H. Extracellular ATP mediates mast cell-dependent intestinal inflammation through P2X7 purinoceptors. *Nat Commun* 2012; **3**: 1034 [PMID: 22948816 DOI: 10.1038/ncomms2023]
- 167 **Kopp R**, Krautloher A, Ramírez-Fernández A, Nicke A. P2X7 Interactions and Signaling - Making Head or Tail of It. *Front Mol Neurosci* 2019; **12**: 183 [PMID: 31440138 DOI: 10.3389/fnmol.2019.00183]
- 168 **Franke H**, Verkhatsky A, Burnstock G, Illes P. Pathophysiology of astroglial purinergic signalling. *Purinergic Signal* 2012; **8**: 629-657 [PMID: 22544529 DOI: 10.1007/s11302-012-9300-0]
- 169 **Schneider J**, Jehle EC, Starlinger MJ, Neunlist M, Michel K, Hoppe S, Schemann M. Neurotransmitter coding of enteric neurones in the submucous plexus is changed in non-inflamed rectum of patients with Crohn's disease. *Neurogastroenterol Motil* 2001; **13**: 255-264 [PMID: 11437988 DOI: 10.1046/j.1365-2982.2001.00265.x]
- 170 **Sigalet DL**, Wallace L, De Heuval E, Sharkey KA. The effects of glucagon-like peptide 2 on enteric neurons in intestinal inflammation. *Neurogastroenterol Motil* 2010; **22**: 1318-e350 [PMID: 20718942 DOI: 10.1111/j.1365-2982.2010.01585.x]
- 171 **Sarnelli G**, De Giorgio R, Gentile F, Cali G, Grandone I, Rocco A, Cosenza V, Cuomo R, D'Argenio G. Myenteric neuronal loss in rats with experimental colitis: role of tissue transglutaminase-induced apoptosis. *Dig Liver Dis* 2009; **41**: 185-193 [PMID: 18635410 DOI: 10.1016/j.dld.2008.06.004]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-3991568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**Help Desk:** <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

