ARTÍCULO ESPECIAL

Calcitonin gene-related peptide (CGRP) in the pathophysiology of gastrointestinal disorders — A key mediator in the gut-brain axis

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ABSTRACT

The "gut-brain axis" concept describes a bidirectional communication between the central nervous system and the gastrointestinal (GI) tract. This axis is key in keeping the physiological homeostasis of the GI tract and its dysfunction has been implicated in a number of neuropsychiatric and gut conditions. Several neurotransmitters are known to be involved in the function of the gut-brain axis. Our objective was to review and critically analyze the contribution of the calcitonin gene-related peptide (CGRP) to the physiology and pathophysiology of the gut-brain axis, with an emphasis on the fresh, basic, clinical evidence supporting an outstanding role for this neuropeptide. This article presents a narrative review based on recent literature and original data previously published by our research group. CGRP is considered a pivotal molecule and the first biomarker of migraine, a debilitating disease combining digestive and neurological symptoms. A number of recent experimental and clinical data support a relevant protective role for CGRP, and in particular for beta-CGRP, the isoform located in the enteric nervous system, in appropriate gut-brain axis functioning and in the pathophysiology of several gut diseases, including conditions such as diverticular disease, acute infectious diarrhea and inflammatory bowel disease. Exemplifying its adaptable behavior, circulating beta-CGRP levels are increased in patients with acute diarrhea in the setting of COVID-19, or reduced already in the early phases of inflammatory bowel disease. In addition, beta-CGRP antagonism may explain constipation as seen with the new CGRP antagonists used in the preventive treatment of frequent migraine. These evidences indicate a relevant role of CGRP for gut-brain axis functioning and call for analyzing a potential role of CGRP in other common diseases of the GI tract, comorbid with brain conditions, such as irritable bowel syndrome or chronic constipation.

Keywords: Constipation. Diarrhea. Calcitonin gene-related peptide. Gut-brain axis. Inflammatory bowel disease. Migraine.

THE GUT-BRAIN AXIS CONCEPT

There are at least 200 million neurons in the human gut. Although this enteric nervous system (ENS), "the second brain", contains a high proportion of the intestinal nervous structures and regulates gut functions autonomously, also extrinsic nerves connect the central nervous system (CNS) and the gut. These extrinsic neurons come from the dorsal root and nodose ganglia, as well as from the autonomic neurons that reside in the sympathetic and brainstem ganglia and modulate the

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activity of ENS (1-3). Dorsal root and nodose neurons function primarily as sensory neurons and possess receptors (4) such as the transient receptor potential vanilloid 1 (TRPV1), able to detect mechanical stretching and dietary or noxious stimuli (5). The "gut-brain axis" concept depicts, therefore, a two-way, afferent and efferent, communication system between the CNS and the gastrointestinal (GI) tract. CNS and GI tract cells develop simultaneously from the neural crest during pregnancy, remain connected via the autonomic nervous system for life, and secrete the same neurotransmitters (6). As an example, the brain is known to control GI movements and functions (sensory and secretion) via the hypothalamic-pituitary-adrenal axis in response to stress. On the other hand, the GI tract is believed to be able to affect a variety of CNS functions, and this efferent gut-brain arm has been involved in the pathophysiology of disorders such as depression-anxiety, neurodegenerative conditions, multiple sclerosis, and migraine (7,8). Inflammatory mediators, nutritional compounds, and/or the gut microbiota profile can influence this complex gut-brain interaction. Migraine is an excellent model of this interaction (9,10). First, GI symptoms are relevant in the presentation of migraine or of its variants, such as cyclic vomiting syndrome. Second, there is an increased frequency of several GI disorders in patients with migraine compared to the general population. Irritable bowel syndrome, *Helicobacter pylori* infection, gastroparesis, celiac disease, some hepatobiliary disorders, and inflammatory bowel disease (IBD) have been linked to the occurrence of migraine (9,11-13).

Current evidence supports the idea that gut microbiota exerts dramatic effects on the development and functions of the CNS, possibly via the vagus nerve (14,15). More than 100 trillion microorganisms live in our intestine, the biggest population of commensal microorganisms of all body surfaces, and the gut-associated lymphoid tissue houses three quarters of the immune cells in our body (16). This complex microbial environment is separated from the host by a layer of intestinal columnar epithelial cells. Vagal afferents, containing receptors for signaling molecules released in this environment, are close to these mucosal immune cells and project to the nucleus tractus solitarius, interestingly the brain nucleus responsible for the control of nausea and vomiting, two pivotal migraine symptoms. From this brainstem nucleus second-order neurons project to cortical and subcortical regions, including the dorsal motor nucleus of the vagus, which provides the vagal motor output to the GI tract (1-4). Psychological or physical stress factors may induce changes in the microbiota profile as a result of increased synthesis of corticotropin-releasing hormone in the hypothalamus, which induces cortisol secretion from the adrenal glands, and leads to changes in gut permeability. This abnormal permeability modifies the physiological homeostasis of microbiota and finally results in dysbiosis. In the opposite direction, primary dysbiosis of the GI tract microbiota releases neurotransmitters and proinflammatory molecules that can activate the hypothalamic-pituitary-adrenal axis via vagal afferents (9,10,14-16) (Fig. 1). The human body may try

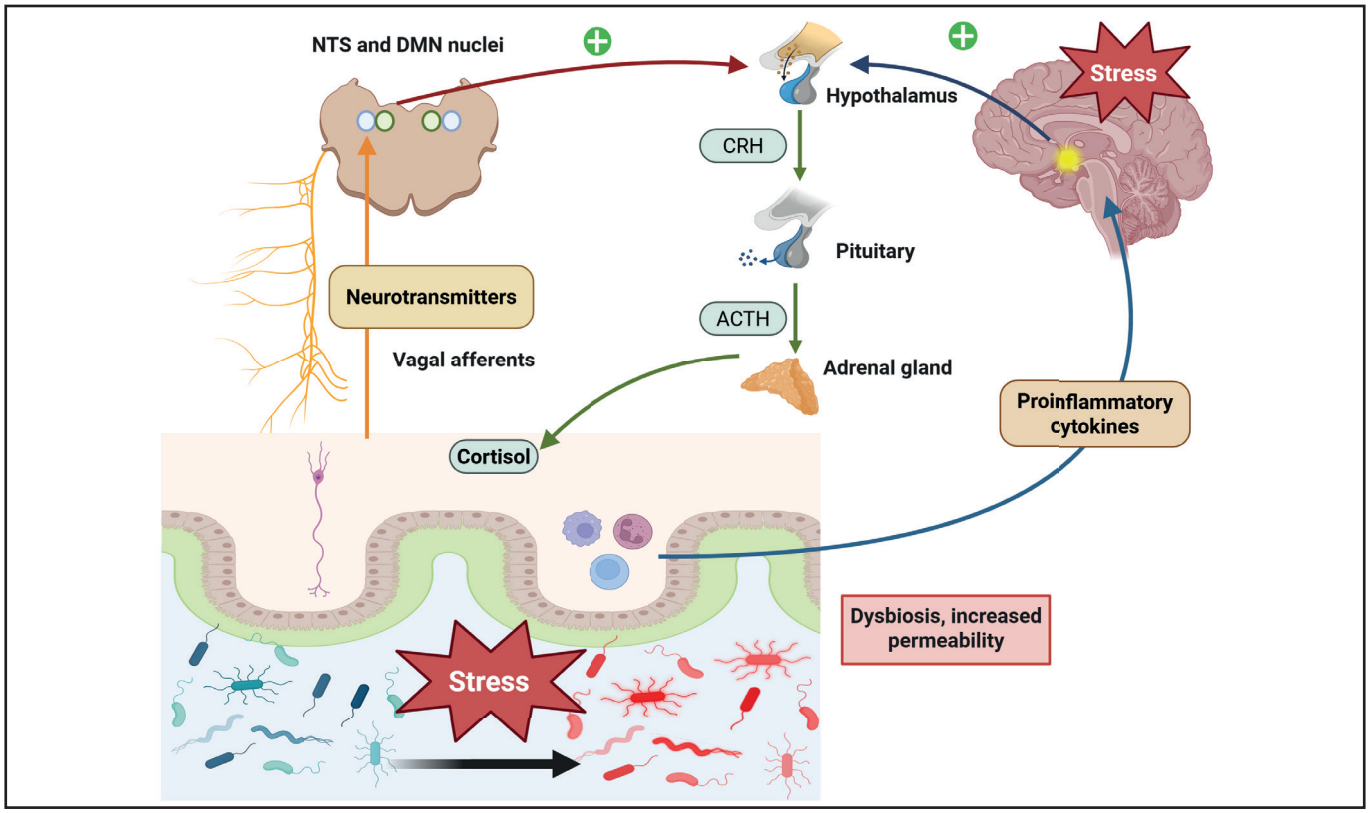

Fig. 1. *Gut-brain axis response to stress. Stress induces changes in the microbiota and alters intestinal permeability, which then activates both immune cells and sensory vagal afferents. Vagal afferents activate NTS and then project to subcortical regions and the DNM as well as subcortical regions. Neurotransmitters and inflammatory cytokines, as well as mental health conditions such as stress or anxiety, can activate the hypothalamic-pituitary-adrenal axis. Cortisol release prolongs increased intestinal permeability and dysbiosis in the gut. NTS: nucleus tractus solitarius, DMN: dorsal motor nucleus, CRH: corticotrophin-releasing hormone, ACTH: adrenocorticotropic hormone. Figure created with Biorender.com.*

to inhibit this release of inflammatory compounds by promoting stress-induced steroid responses, but such responses increase dysbiosis ultimately. The activation of TRPV1+ neurons, responsible for detecting noxious visceral signals to the nervous system, plays a pivotal role in this interaction between neurons and the immune system by inducing a decrease in ROR+ regulatory T cells (Treg). These cells play a protective role in pain via the release of anti-inflammatory cytokines such as IL-10, and production of endogenous opioids including proenkephalin (5).

Above, we briefly reviewed the anatomical basis and the key role of the intestinal microbiota and inflammation in the gut-brain axis, but it should not be forgotten that int the end, this connection is mediated by chemical compounds. A number of molecules, including classical neurotransmitters such as serotonin, dopamine, acetyl-choline, glutamate or gamma-aminobutyric acid, or peptides, such as neuropeptide Y, vasoactive intestinal peptide, pituitary adenylate cyclase-activating peptide, substance P or alpha-melanocyte-stimulating hormone, are released in the GI tract, exhibit a variety of antimicrobial, proinflammatory and anti-inflammatory effects, and are thus speculatively believed to be involved in this bidirectional gut-brain interaction (14,17,18). Interestingly, it has been very recently demonstrated, in a seminal paper, that spinal afferent TRPV1+ neurons mediate Treg changes via the neuropeptide calcitonin gene-related peptide (CCRP) (5).

In this article we discuss the contribution of calcitonin gene-related peptide (CGRP) to the physiology and pathophysiology of the gut-brain axis, with an emphasis on the fresh, basic, and clinical evidence supporting an outstanding role for this neuropeptide.

CALCITONIN GENE-RELATED PEPTIDE BIOLOGY

Discovered in 1982, CGRP is a multifunctional peptide described as the result of the alternative splicing of the calcitonin gene (*CALCA* in humans) transcript, hence its name (19). This first form of CGRP was designated alpha-CGRP as opposed to beta-CGRP, encoded in a different gene (*CALB*) with a different regulation and expression pattern to alpha-CGRP (20). These two isoforms of the peptide differ in 3 out of 37 amino acids in their sequence. Both alpha and beta-CGRP share a common structure and belong to the calcitonin family of peptides, also comprised by calcitonin, amylin, adrenomedullin 1, and adrenomedullin 2/intermedin. Both alpha and beta-CGRP bind to the CGRP receptor, a heterodimer formed of G-protein calcitonin receptor-like receptor (CLR) with the receptor activity-modifying protein 1 (RAMP1), which activates adenylyl cyclase and cAMP-dependent pathways (21-23). These increases in intracellular cAMP activate protein kinase A, which results in the phosphorylation of multiple downstream targets, including potassium-sensitive ATP channels, extracellular signal-related kinases, and transcription factors such as cAMP-responsive element-binding protein. There is a second receptor that may potentially respond to CGRP, the amylin receptor AMY1, which consists of RAMP1 and the calcitonin receptor (23). There is little colocalization of CGRP with CGRP receptors as CGRP is expressed in unmyelinated C-fibers and its receptor in myelinated Aδ fibers (24).

Well-known biological functions of CGRP include vasodilation (it being the most potent vasodilator known), immunomodulation, angiogenesis, and nociceptive signaling (21,22). Alpha-CGRP is expressed in areas of the central nervous system such as dorsal roots, autonomic and trigeminal ganglia, and primary sensory neurons, which explains its key role in nociception and particularly in migraine pathophysiology. In fact, CGRP levels (and more specifically alpha-CGRP levels) have been proposed as the first migraine biomarker (25,26). Beta-CGRP is mainly found within intrinsic intestinal neurons in the myenteric plexus, which are capsaicin-insensitive. Beta-CGRP concentration in the intestine is seven times higher than that of alpha-CGRP (27,28). Therefore, theoretically, it may be assumed that data about gut CGRP are mostly referring to beta-CGRP, though studies did not differentiate between alpha and beta-isoforms until very recently (29), which explains why the role of beta-CGRP in the GI system has remained obscure. Immune cells in the GI tract also contain CGRP (30). CGRP receptors are located in several components of the GI tract, including vessels, muscle layers, mucosa, endocrine cells, immune cells, and nerves. This peptide is thought to have several GI functions, discussed in the next section; its role in increasing peristalsis as well as ion and water secretion has been well demonstrated (21,22).

CALCITONIN GENE-RELATED PEPTIDE IN EXPERIMENTAL MODELS OF GASTROINTESTINAL DISORDERS

CGRP functions in the human GI tract are mainly inferred from experimental studies, animal models, and ex-vivo specimens, but specific literature regarding CGRP actions on GI physiology is scarce.

In the stomach, CGRP has been shown to regulate acid secretion through gastrin and somatostatin. In experimental models, CGRP has been shown to increase somatostatin and decrease gastrin release in response to drops in gastric pH, and its blockage decreases somatostatin release and increases gastrin, which may indicate a role in the regulatory response to acid mediated by gastric G and D cells (31). Furthermore, in experimental models of gastroduodenal ulcers induced by ethanol, CGRP mediates tissue healing, mainly through acid regulation and local vasodilation (32).

One of the many functions of CGRP is the regulation of GI motility. CGRP is released by local afferent neurons as a mechanism of intrinsic motility regulation, and also via extrinsic primary afferent neurons as an external motility regulator, with both types of neurons usually responding to external stimuli. CGRP then activates interneurons and ultimately motor neurons, which may result in either inhibitory or excitatory muscle stimulation with prokinetic properties. This has been described in animal models, where CGRP release was found to occur in response to colon distension, mucosal stimulation, or muscle stretching, resulting in increased GI motility (33,34). To support this evidence, external infusion of CGRP in healthy volunteers triggers the development of not only migraine-like headache, but also GI symptoms such as diarrhea, abdominal discomfort, nausea and/or vomiting (35). This CGRP-induced diarrhea can be reversed by CGRP antagonists (36).

One of the most interesting functions of CGRP in the GI tract is immunity regulation and neurogenic inflammation, showing that sensory neurons in the GI tract can modulate both immune response and pain perception. In acute infection such as by *Salmonella enterica*, CGRP is released in the dorsal root ganglia in response to infection (37). Furthermore, transgenic alpha and beta CGRP knock-out (KO) mice show adult-onset spontaneous colitis and increased intestinal damage when using a dextran sodium sulfate experimental model of colitis (38). Interestingly, these beta-CGRP KO mice increase alpha-CGRP release in the dorsal root ganglia to maintain CGRP supply to the gut, but fail to control damage, which suggests a potential role of beta-CGRP in gut homeostasis. Furthermore, proteomic analysis shows that beta-CGRP KO mice have a different protein expression profile in the colon tissue, with changes in the coagulation-fibrinolytic system, and an increase in immunoproteasome expression compared to wild-type and alpha-CGRP KO mice. In other models of induced colitis such as by instillation of trinitrobenzene sulfonic acid in a group of rats, blocking CGRP, but not of substance P, increased ulcer index and mucosal damage as compared to control rats (39).

The exploration of the underlying regulatory mechanisms of intestinal inflammation as mediated by CGRP, depending on the environment in which CGRP is released, has shown that the neuropeptide can exert either proinflammatory or anti-inflammatory actions. For example, in migraine, CGRP is released in the leptomeningeal space, activating mast cells and macrophages and liberating proinflammatory cytokines such as tumor necrosis factor alpha or interleukin 6 (40,41). In the gut, TRPV1+ sensory neurons from the dorsal root ganglia respond to nociceptive signals and release CGRP and substance P. These neurons can regulate macrophages, ROR+ Treg or type 2 innate lymphoid cells in the gut, promoting T helper 2 lymphocyte immune responses, which are key for gut homeostasis and defense (5). Chronic activation of these neurons in chronic pain or inflammation downregulates ROR+ Treg cells, which mediate pain perception, and increases local vasodilation and mast cell degranulation. In colon biopsies of patients with ulcerative colitis, CGRP concentration is associated with M2 macrophage response, with a positive correlation between CGRP mucosal levels and concentrations of anti-inflammatory cytokines such as transforming growth factor beta, and a negative correlation with proinflammatory cytokines such as gamma interferon, interleukin 1 beta or tumor necrosis factor alpha (42). Moreover, CGRP increases chloride secretion in the colon as well as mucus production by goblet cells, favoring barrier protection functions in the mucosa (43).

In summary, CGRP is involved in multiple physiological "protective" processes within the GI tract, including gastric ulcer healing, local vasodilation, prokinetic activity, stimulation of intestinal mucus production, reinforcement of the intestinal barrier, and most notably, the regulation of the immune system and neurogenic inflammation (Table 1 and Fig. 2).

Table 1. *Physiological effects of CGRP in the GI tract*

Location	Functions
Stomach	- Regulation of gastric acid secretion through vagal afferents (alpha-CGRP) - Local vasodilation and tissue healing (both isoforms)
Small bowel/ Colon	- GI motility regulation (both inhibitory and excitatory functions, but mainly prokinetic effects, beta- CGRP isoform) - Local vasodilation (both isoforms) - Nociception (both isoforms, mostly alpha-CGRP) - Immune regulation of neurogenic inflammation (both isoforms) - Chloride secretion, colon (both isoforms) - Stimulation of intestinal mucus production (both isoforms)

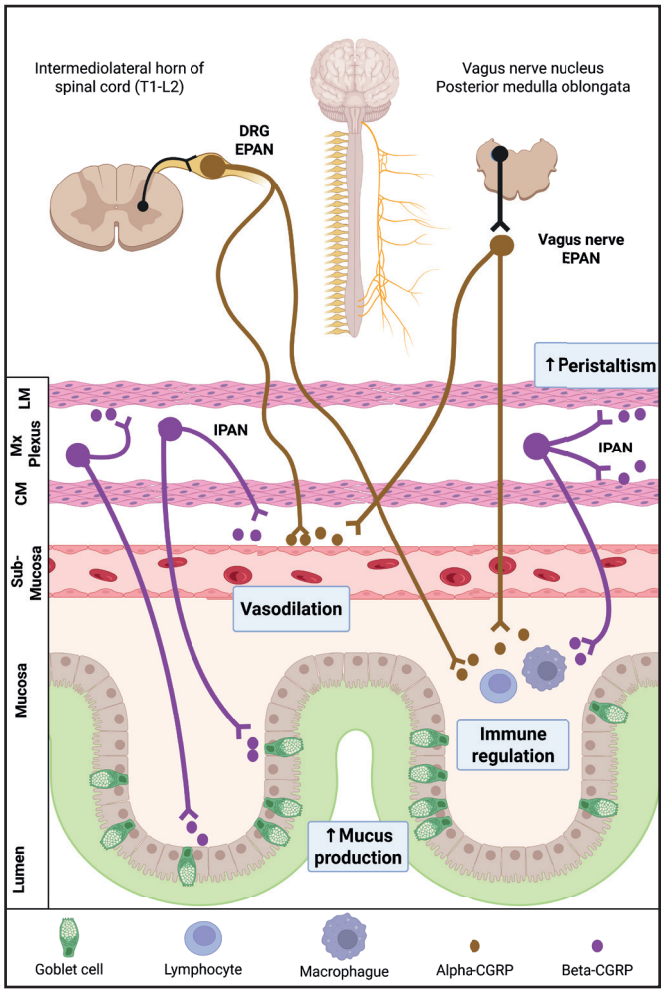

Fig. 2. *Summary of CGRP release and functions in the GI tract. First-order neurons originate in the intermediolateral horn of the spinal cord (T1-L2), and the vagus nerve nucleus in located in the posterior medulla oblongata. From there, they connect with EPANs, which originate from the DRG and vagus nerve, respectively. EPANS release alpha-CGRP, contributing to immune regulation and local vasodilation. Beta-CGRP is released by IPANs located in the myenteric plexus. IPANs release beta-CGRP to stimulate peristalsis and mucus production, as well as vasodilation and immune regulation similar to alpha-CGRP functions. DRG: dorsal root ganglia, EPAN: extrinsic primary afferent neurons, IPAN: intrinsic primary afferent neurons, LM: longitudinal muscle layer, CM: circular muscle layer, Mx plexus: myenteric plexus. Figure created with Biorender.com.*

CALCITONIN GENE-RELATED PEPTIDE IN HUMAN GI DISORDERS

As pointed out above, CGRP levels have been proposed as first biomarker for migraine, a debilitating disease with patent GI symptoms (25,26). There are strong arguments supporting a key role of CGRP in migraine, a disease typically exhibiting several GI manifestations such as nausea, vomiting, abdominal pain, or diarrhea (44). First, CGRP levels are increased during migraine attacks (45,46) and interictally in several fluids in patients with chronic migraine (47-50). Second, intravenous infusion of CGRP leads to migraine-like headache and diarrhea (35). Finally, modern, selective anti-CGRP drugs are highly effective as migraine treatment, even in patients refractory to conventional drugs (51,52); interestingly, the most frequent adverse event associated with these anti-CGRP therapies is constipation (52,53).

While the relationship of CGRP, and particularly alpha-CGRP, with migraine has been well-demonstrated for years, until very recently the evidence for a role of CGRP in the pathophysiology of human GI disorders was scarce (Table 2). The first study was published in 2019 and, using quantitative fluorescence microscopy, showed that CGRP levels were reduced by 52 % in patients with symptomatic diverticular disease. Conversely, CGRP receptors were upregulated by 41 % in the enteric ganglia, and colonic longitudinal smooth muscle displayed an increased response to exogenous CGRP application, suggesting a hypersensitization mechanism to decreased CGRP levels in ENS (54). These results illustrate that an imbalance in neuromuscular transmission is a major pathophysiological factor for diverticular disease, and suggest that CGRP is an important molecular mediator in this condition.

Table 2. *Summary of current data on CGRP and human GI tract diseases*

Condition	Main finding	Reference
Diverticular disease	- CGRP levels reduced by 52 % in enteric ganglia by quantitative fluorescence microscopy	54
COVID-19 infection	- Increase in alpha and beta-CGRP circulating levels	55
	- Increase in alpha-CGRP circulating levels in patients with headache	56
	- Selective increase in beta-CGRP levels in patients with diarrhea	57
Diverticular disease and IBD	- Genetic sharing at *CALCA/CALCAB** genes	59
IBD	- Increase in alpha-CGRP circulating levels, mainly in patients with comorbid migraine	60
	- Reduction in circulating beta-CGRP levels in early phases of IBD	61
Constipation with anti-CGRP	- Normal alpha-CGRP circulating levels	62
	- Decrease in patients with emergent constipation	62

* *CALCA/CALCAB* are the genes encoding two isoforms of CGRP.

The recent COVID-19 pandemic has provided an excellent model to test the role of CGRP in aspects of the pathophysiology of some of its clinical manifestations, which could also be extrapolatable to other human diseases. Interestingly, leaving aside respiratory symptoms, migraine-like headache and diarrhea are the two most common neurological and GI manifestations, respectively. As an inflammatory mediator, CGRP has been shown to be released in the acute phase of COVID-19 inpatients (55). This increase was seen for the two CGRP isoforms but, interestingly, circulating alpha-CGRP levels were mainly increased in patients exhibiting headache (56) and beta-CGRP levels were increased in general, but selectively in patients who suffered from COVID-19 diarrhea (57). These data confirm a role of alpha-CGRP in the pathophysiology of headache, but also indicate that beta-CGRP may help to explain the mechanism behind COVID-19-induced diarrhea.

Recent studies have confirmed that the prevalence of migraine, including chronic migraine, is increased in patients with IBD (58), and also that these two conditions share some genetic background (59). This comorbidity between migraine and IBD is a further example of the bidirectional relationship between the GI tract and CNS (9,10). The neural influence on inflammatory status in the GI tract has been well demonstrated, and CGRP exerts a relevant role in migraine and in gut mucosal homeostasis (9,10). Circulating alpha-CGRP levels are increased, as compared to healthy controls, both in patients with chronic migraine and in patients with IBD (60). These results could reflect an underlying chronic inflammation state, but also demonstrate that alpha-CGRP levels are not a totally specific migraine biomarker, though alpha-CGRP levels are further elevated in patients with IBD who also have a history of migraine. In contrast, circulating levels of beta-CGRP, the most abundant isoform in the human GI tract, are within the range of healthy controls in chronic migraine patients (47,48), but remain consistently low in the early phases of IBD, both in ulcerative colitis and in Crohn's disease (61). On the one hand, the increase in alpha-CGRP, mainly expressed in primary afferent neurons, both in migraine and IBD, reinforces the role of this CGRP isoform in nociception and, considering its effect on stomach motility, possibly in nausea/vomiting as well. On the other hand, the decrease in beta-CGRP levels already in the early phases of IBD would confirm a protective role for this CGRP isoform in keeping GI tract homeostasis in IBD. Whether this beta-CGRP reduction is a cause or a consequence of the mucosal damage occurring in IBD remains unknown. However, its early decrease in IBD and the varied protective actions of beta-CGRP in experimental models of colitis (see above) support a role for this isoform in the pathophysiology of IBD since its early stages, and calls for longitudinal studies testing beta-CGRP levels, both circulating and in intestinal biopsies, and IBD disease activity, and for analyzing gut homeostasis in migraine patients treated long-term with anti-CGRP medications, particularly in those with IBD or other intestinal comorbidities.

Constipation is the most frequent adverse event of the new preventive treatments for migraine that antagonize CGRP signaling (52,53). Our group has prospectively analyzed the

circulating levels of both isoforms of CGRP in migraine patients treated with CGRP antibodies (48). Compared to healthy controls, alpha-CGRP levels are increased before treatment with anti-CGRP monoclonal antibodies and normalize after 3 months of treatment, mainly in patients who show a clinical response, whereas pretreatment circulating beta-CGRP levels are in the range of the controls (48). However, beta-CGRP, but not alpha-CGRP, levels are significantly reduced after three months, selectively in patients with emergent constipation on CGRP antibodies (62). Again, these results suggest that antagonism of the alpha-CGRP isoform plays a relevant role in the nociceptive actions of anti-CGRP drugs, but not in the development of constipation. In contrast, the specific reduction in beta-CGRP levels seen in patients with emergent constipation indicates a role for beta-CGRP antagonism in the development of this adverse event and, going back to the link between diarrhea and increased beta-CGRP levels (57), shows an interesting chameleonic behavior of this isoform in different diseases of the GI tract, supporting an intrinsic role of beta-CGRP in their pathophysiology.

CONCLUSIONS

A number of recent experimental and clinical data support a relevant protective role for CGRP, and in particular for the beta-CGRP isoform, in the gut-brain axis and therefore in the physiology of the normal GI tract, as well as in the pathophysiology of several gut diseases, including conditions such as diverticular disease, acute infectious diarrhea, and IBD. Beta-CGRP antagonism seems a plausible explanation for the constipation seen with the new CGRP antagonists used in the preventive treatment of frequent migraine. These evidences call for analyzing a potential role of CGRP in other common diseases of the GI tract that are comorbid with brain conditions, such as irritable bowel syndrome, chronic constipation, or functional defecation. Based on the current data available, it seems reasonable to consider any potential clinical translational implications of these changes in CGRP isoforms. For example, a decrease in beta-CGRP isoform in conditions such as diverticulosis or IBD could be a straightforward biomarker for monitoring any disruptions of the physiological GI mucosal homeostasis, and CGRP antagonists could be helpful in the treatment of acute diarrhea; however, chronic CGRP blockade, as used now for recurrent migraine treatment, should include follow-up for delayed GI adverse events.

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