Altered neuro-endocrine–immune pathways in the irritable bowel syndrome: the top-down and the bottom-up model

Cristina Stasi, Massimo Rosselli, Massimo Bellini, Giacomo Laffi & Stefano Milani

Journal of Gastroenterology

ISSN 0944-1174

J Gastroenterol
DOI 10.1007/s00535-012-0627-7

Springer

J Gastroenterol
DOI 10.1007/s00535-012-0627-7

REVIEW

Altered neuro-endocrine–immune pathways in the irritable bowel syndrome: the top-down and the bottom-up model

Cristina Stasi · Massimo Rosselli · Massimo Bellini · Giacomo Laffi · Stefano Milani

Received: 10 January 2012 / Accepted: 4 June 2012

Abstract The interaction between the brain and the gut as a pathological mechanism of functional gastrointestinal disorders has been recently recognized in the pathophysiology of the irritable bowel syndrome. Communication between central nervous system and enteric nervous system is two-directional: the brain can influence the function of the enteric nervous system and the gut can influence the brain via vagal and sympathetic afferents. In patients with irritable bowel syndrome, symptoms may be caused by alterations either primarily in the central nervous system (top-down model), or in the gut (bottom-up model), or in a combination of both. The brain–gut axis may be stimulated by various stressors either directed to the central nervous system (exteroreceptive stress) or to the gut (interoceptive stress). Particularly, clinical evidence suggest that in complex and multifactorial diseases such as irritable bowel syndrome, psychological disorders represent significant factors in the pathogenesis and course of the syndrome. Neuroimaging techniques have shown functional differences between central process in healthy subjects and patients with irritable bowel syndrome. Moreover, a high prevalence of psychological/psychiatric disorders have been reported in IBS patients compared to controls. Several data also suggest an alteration of neuro-endocrine and autonomic output to the periphery in these patients. This review will examine and discuss the complex interplay of neuro-endocrine–immune pathways, closely associated with neuropsychiatric disorders.

Keywords Stress · Corticotropin releasing hormone · Mast cells · Exteroreceptive stress · Interoceptive stress

Abbreviations

HPA	Hypothalamic–pituitary–adrenal axis
HANS	Hypothalamic–autonomic nervous system axis
IBS	Irritable bowel syndrome
PVN	Paraventricular nucleus
ACC	Anterior cingulated cortex
CNS	Central nervous system
PTSD	Post-traumatic stress disorder
EMS	Emotional motor system
GC	Glucocorticoid
CRH	Corticotropin-releasing hormone
NY	Neuropeptide Y
ACTH	Adrenocorticotropic hormone
MR	Mineralocorticoid receptor
GR	Glucocorticoid receptor
D-IBS	Diarrhea-predominant IBS
EC	Enterochromaffin cell
C-IBS	Constipation-predominant IBS

Introduction

Studies on the interaction between central nervous system and gastrointestinal system have clarified the pathophysiology of complex neurobiological response of body to

C. Stasi (✉) · M. Rosselli · G. Laffi
Dipartimento di Medicina Interna, University of Florence, Viale G.B. Morgagni, 85, 50134 Florence, Italy
e-mail: cristina.stasi@unifi.it

M. Bellini
Unit of Gastroenterology, Department of Internal Medicine, University of Pisa, Pisa, Italy

S. Milani
Department of Clinical Pathophysiology, University of Florence, Florence, Italy

Published online: 06 July 2012

stress, highlighting the importance of the hypothalamic–pituitary–adrenal (HPA) (Fig. 1) and hypothalamic–autonomic nervous system (HANS) axes (Fig. 2). The physiological response to stress in healthy subjects is limited to the time of exposure to a stressful event. On the contrary, the effect of adaptation in genetically predisposed subjects can lead both to the exacerbation of the disease process already in progress and to the onset of new diseases [1–3].

There is clinical evidence that in a complex and multifactorial disease such as irritable bowel syndrome (IBS), psychological disorders represent significant factors in the pathogenesis and course of the syndrome [1]. Recently, in the pathophysiology of IBS, the importance of the interaction between brain and gut (brain–gut axis) has been recognized within the so-called "biopsychosocial model", in which the stress-related psychological disorders are the main factors able to modulate motility and visceral perception [4, 5]. The body's response to stress is generated by a network of integrative brain structures, in particular subregions of the hypothalamus (paraventricular nucleus, PVN), amygdala and periaqueductal gray. These brain areas receive input from peripheral and cortical structures, such as medial prefrontal cortex and subregions of the anterior cingulated cortex (ACC) and insula [1]. In fact, the polymodal association and the transformation of the percept in awareness depend on the frontal cortex. However, the connection between perceived inputs and the body's responses depends on the kind of emotion which results from the evaluation process. This phase depends on the amygdala, which is know to be necessary for the formation of aversive associations to novel places and events [6].

This review will examine and discuss the complex interplay between neuro-endocrine–immune pathways, closely associated with neuropsychiatric disorders.

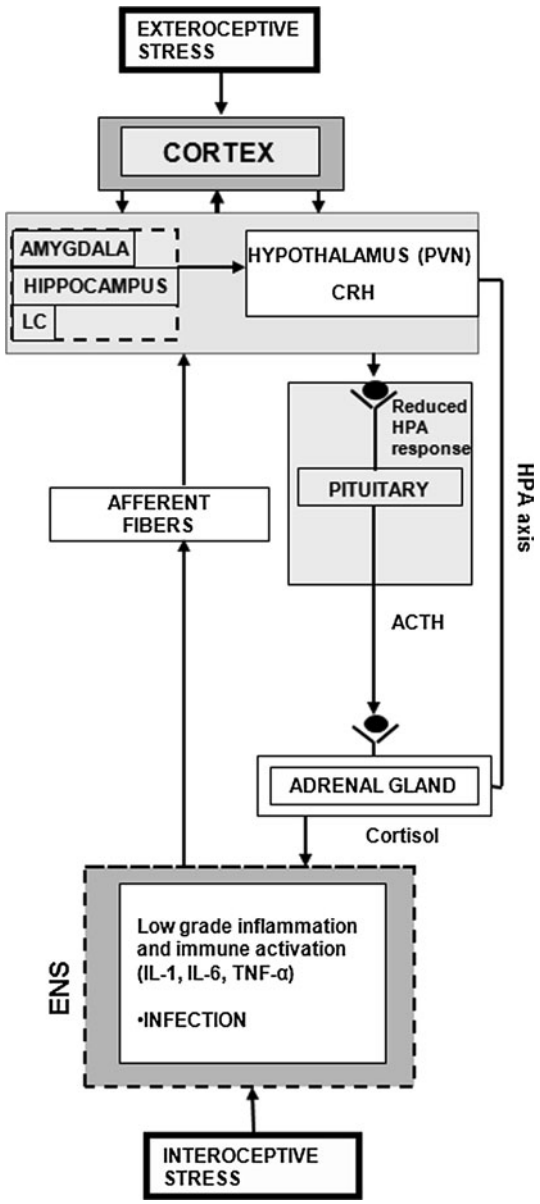

Fig. 1 The two-directional HPA axis communication in IBS pathophysiology: The top-down and the bottom-up model. Chronic exteroceptive stress on the cortex can cause an abnormal activation of brain areas (particularly amygdala, hippocampus, locus coeruleus) and a decreased HPA response, resulting in reduced cortisol release. This favors an increased immune response toward luminal antigens and consequent low grade inflammation (top-down model). In turn, this low grade inflammation, associated with the release of interleukins and TNF-α, may cause the activation of cerebral circuits by afferent fibers. Similarly, infections can cause increased permeability with subsequent immune activation and release of interleukins and TNF-α, that activate afferent cerebral circuits (bottom-up model). *HPA* hypothalamic–pituitary–adrenal axis, *LC* locus coeruleus, *CRH* corticotropin-releasing hormone, *ACTH* adrenocorticotropic hormone, *ENS* enteric nervous system

Neuropsychiatric disorders

The presence of psychological and/or psychiatric disorders leads to an exacerbation of symptoms and a greater demand for medical aid [7]. Lydiard et al. [8] confirm a mutual interaction between IBS and psychiatric disorders. In a recent study, Thijssen et al. [9] showed that in a total of 268 patients, anxiety and depression disorders were present in 30 and 22 % of IBS patients, respectively. A multicentre study also showed high prevalence of physical and sexual abuse among patients with IBS (31.6 %) compared to patients with organic digestive diseases (14.0 %) and to control subjects (7.6 %). Many of these patients had benefit from psychotherapy [10]. Patients with IBS reported an increase of symptoms severity in association with acute psychosocial stress. Complete or partial remission followed the resolution of psychosocial stress [11]. Chronic and severe stress may result in long-term changes in areas of the brain that cause symptoms associated with IBS, such as pain and visceral hypersensitivity. In animal models,

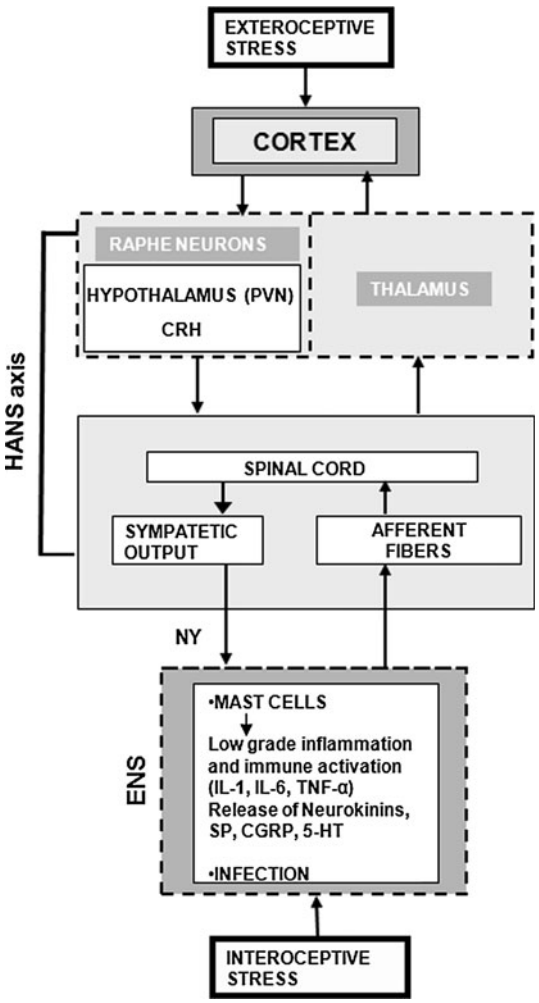

Fig. 2 The two-directional HANS axis communication in IBS pathophysiology: the top-down and the bottom-up model. Exteroceptive stress on the cortex can cause the activation of the HANS axis, in this case represented by hypothalamus and sympathetic efferents, thereby inducing the release of NY. This peptide may activate mast cells, resulting in low grade inflammation associated with the release of IL-1, IL-6, TNF-α. In turn, inflammation stimulates the local release of neurokinins, SP, CGRP, 5-HT (top-down model). Similarly, interoceptive stress factors such as infections may activate ascending pathways. Nerve terminations are largely located in the medial portions of the thalamus with direct connection to the hypothalamus (bottom-up model). Raphe nuclei may inhibit or facilitate nociceptive signal. *PVN* paraventricular nucleus, *CRH* corticotropin-releasing hormone, *HANS* hypothalamic–autonomic nervous system axis, *NY* neuropeptide Y, *ENS* enteric nervous system, *SP* substance P, *CGRP* calcitonin gene related peptide, *5-HT* serotonin

maternal separation causes alterations of the intestinal barrier function, altered balance in enteric microflora, exaggerated stress response and visceral hypersensitivity, such as in IBS [12]. Such results suggest that the presence of physical or sexual abuse and psychological disorders can lead to a chronic state of amplification of symptoms, which originates either at the level of the central nervous system (CNS) (hypervigilance on physical perception) or at the visceral level (hypersensitivity and hypermotility). In fact, IBS patients have a high prevalence of post-traumatic stress disorders (PTSD) and a higher psychiatric comorbidity than patients with no history of trauma. Irwin et al. [13], studying 50 consecutive IBS patients, showed that 54 % reported psychiatric diagnosis at some time in their lives, 44 % a trauma history, 36 % PTSD. The role of psychological factors, emotional state and modulation of CNS in the pathophysiology of IBS has been confirmed by the fact that symptoms are improved by psychotherapy, hypnosis, hypnotherapy and drugs active at central level such as anxiolytics, selective serotonin reuptake inhibitors and tricyclic anti-depressants [14–17].

Neuroimaging techniques have shown functional differences between central processes in healthy subjects and patients with functional gastrointestinal disorders. Silverman et al. [18] were the first to compare healthy subjects with patients with IBS using positron emission tomography. They found activation in the left prefrontal cortex and a lack of correlation between the activation of the ACC and the intensity of perceived stimuli using rectal distension by balloon. This suggests that alterations in central mechanisms may result in a decreased inhibition through descending pain ways which may cause hyperalgesia in patients with IBS. On the contrary, Drossman et al. [19], using functional magnetic resonance imaging, found a correlation between the clinical symptoms of patient with IBS, hers psychological state and the activation of the ACC. The ACC activation correlated with anxiety, stressful life events, maladaptive coping and history of abuse [5]. In IBS patients, but not in controls, Mertz et al. [20] showed that pain led to greater activation of the ACC than nonpainful stimuli. The ACC, the pain's critical center, is part of the emotional limbic system; it mediates both positive and negative emotions, it integrates autonomic functions including the stress response of "flight or fight", and endocrine response and it is involved in memory of emotional experiences. Other studies have shown deactivation in the right hemisphere, within the posterior part of the insular cortex, the amygdala and the striatum (putamen) in patients with IBS compared to controls [21, 22]. These data suggest an up-regulation of afferent sensitivity to pain. The complexity of these pathophysiological mechanisms is linked to the role of these regions, that are abnormally activated.

As discussed previously, the integrative brain structures (PVN, amygdala and periaqueductal gray) provide outputs to the central, pituitary and pontomedullary nuclei, which mediate the neuroendocrine and autonomic output to the periphery, respectively [1]. This central stress circuit, called emotional motor system (EMS), is under feedback control through projections from the brainstem nuclei, particularly serotonergic (raphe nucleus) and noradrenergic

(locus coeruleus) and through circulating glucocorticoids, which exert an inhibitory control through the glucocorticoid (GC) receptor, located in the cerebral cortex and hippocampus [23]. The outputs of the EMS, which is activated in response to various kind of stress, include the response of the ascending via aminergica (serotonergic, noradrenergic and dopaminergic), the endogenous modulation of pain, the autonomic nervous system, and the HPA axis [1].

Corticotropin-releasing hormone: the key hormone in stress

The amygdala, which is part of the limbic system, regulates the release of hypothalamic corticotropin-releasing hormone (CRH) [24], the key hormone in the body's response to stress. In contrast to the action of CRH, neuropeptide Y (NY), located in the amygdala, in the hippocampus, and in some areas of the septum and locus coeruleus, has an anti-stress effect [25].

Although most of the neurons producing CRH are found in PVN, other CRH secreting neurons are located in the cingulate and prefrontal cortex, and in the insula which have multiple connections with the amygdala.

In the pituitary gland, CRH stimulates the cleavage of the precursor peptide proopiomelanocortin and the production of adrenocorticotropic hormone (ACTH) and beta-endorphin, secreted into the systemic circulation.

Adrenocorticotropic hormone then reaches the adrenal gland, stimulating the production of cortisol, which exerts a negative feedback on the hypothalamus, pituitary gland and especially on the hippocampus. The amygdala plays an essential role in the regulation of cortisol secretion induced by psychological stimuli.

The large number of nerve fibers that connect the amygdala with the hippocampus, mainly towards the latter, suggests that it acts in response to signals from the amygdala [6].

Corticotropin-releasing hormone neurons of the PVN project to brainstem and, in particular, to paragigantocellular nucleus and to locus coeruleus. The major contingent of CRH nerve fibers also project from the PVN to the intermediolateral cell column of the spinal cord, where all the preganglionic sympathetic fibers and the nucleus of the solitary tract organize the sympathetic cardiovascular reflexes.

For this reason, the functions of the structures innervated by the sympathetic nervous system are affected by the activity of CRH neurons that originate from the PVN.

The nerve fibers of the "central CRH" system play a key role in the integration of central adaptive behaviours, autonomic activity and HPA axis function [26]. The central injection of CRH can cause a physical and behavioural response similar to that observed in conditions of acute psychological stress [6, 27, 28]. CRH receptor 1 is limited primarily to the pituitary gland and to specific regions of the brain, whereas CRH receptor 2 is expressed in peripheral tissues including the gastrointestinal tract, the heart, the skeletal muscle, etc. [28, 29].

Corticotropin-releasing hormone is involved in the central mechanisms by which stress inhibits gastric emptying and stimulates colonic motor function [27]. Inhibition by CRH antagonists [28] or experimental inactivation of CRH receptor 1 result in a decreased response to stress [29, 30], suggesting that hypersecretion of CRH in the brain may contribute to the pathophysiology of stress-related exacerbation of IBS [27].

Chronic stress and endocrine response

The hippocampus is considered the primary site for regulating the synthesis of glucocorticoids, because it contains the highest number of receptors for these hormones than any other organ. There are two types of adrenal steroid receptors: mineralocorticoid receptor (MR) and glucocorticoid receptor (GR). GRs, specific for glucocorticoids, have low affinity, while MRs have high affinity for both glucocorticoids and mineralocorticoids (aldosterone).

During stress, excessive cortisol secretion can be inhibited by hippocampal stimulation, suggesting that MRs may modulate of cortisol secretion, while GRs inhibit cortisol secretion in the presence of stressors stimuli [31].

Studies on HPA axis in patients with diarrhea-predominant IBS (D-IBS) have shown a decrease of plasma cortisol levels, an impaired cortisol response to ACTH and an increased vagal response to rectal distention [32].

On the contrary, Heitkemper et al. [33] reported higher levels of urine cortisol in IBS female patients than in controls.

Decreased levels of cortisol were instead found in patients with post-traumatic stress disorder (PTSD) [34, 35], implying either a desensitization of the GRs for cortisol or a desensitization of pituitary CRH-receptor. The diagnosis of PTSD is generally made in patients who have experienced particularly serious and violent emotional events such as the experience of battle, natural disasters, assault, rape and accidents. However, events which are usually insignificant for most individuals, in others may lead to PTSD because of the subjective meaning of the event.

The hypocortisolism first detected in patients with PTSD, was later found in subjects affected by chronic stress and in patients with autoimmune diseases, chronic pain, chronic fatigue syndrome, asthma, allergic diseases

[35], and fibromyalgia [36]. In some animal models it appears that repeated exposure to stress may cause a decrease in the response of the HPA axis, as an expression of usual stressful event. In fact, the pharmacological blockade of the MRs/GRs prevents the attenuation of the HPA response to an usual stressor. The decrease of HPA response does not appear to be correlated with a reduction of control function from the CNS that responds to stress. In this case the inhibition of the MRs/GRs should not prevent the manifestation of an attenuated response. It is believed that the MRs are involved in tonic regulation of basal HPA axis activity [31].

The reported persistence of chronic inflammatory enteric mucosa after eradication of infection, the increase of intestinal permeability, enterochromaffin cell (EC) hyperplasia [37], are all consistent with an inadequate physiological response to acute bowel inflammation, in particular in the presence of an inadequate cortisol response (and probably also with an altered sympathetic response).

It has been suggested that a downregulated cortisol response to intero- or exteroceptive stress may predispose IBS patients to chronic inflammatory conditions such as asthma, rheumatoid arthritis or inflammatory bowel disease [1]. This stress response is closely related with changes in brain activity consistent with an increased central release of norepinephrine, which is typical of patients with PTSD. The decreased response of the HPA axis may precede the onset of symptoms in patients with IBS and predisposes to the development of post-infectious IBS. In fact, more than 40 % of patients with IBS showed increased anxiety disorder [38], suggesting a "top-down" model of disease, where the alteration of central stress circuits in individuals are prepared and conducted by exteroceptive stress and may play a key role in the pathophysiology of the disease. In fact, psychosocial stress can influence the immune response though CRH-mediated activation of the HPA axis and some branches of autonomic nervous system. For example, it has been suggested that a hyporeactivity of HPA axis associated with an alteration of sympathetic modulation of immune function, may result in decreased immune surveillance [3], thus predisposing to post-infectious IBS [39].

Chronic stress and neuronal response

The two branches of the autonomic nervous system are anatomically and functionally integrated with the brain–gut axis and are responsible for homeostatic regulation of gastrointestinal function [40]. IBS and other functional gastrointestinal disorders are in fact associated with cholinergic and adrenergic autonomic dysfunction [40–43]. Increased sympathetic response in patients with IBS may be due to the increase of CRH expression. In fact, the projections descending from the pontine nucleus to the distal colon containing CRH may mediate the increase in distal colon motor response to stress or food, while the ascending projections to the locus coeruleus and to prefrontal cerebral cortex may be responsible for visceral hypersensitivity [1].

Heitkemper et al. [42] reported a significant increase in parasympathetic tone in women with D-IBS compared to constipation-predominant IBS (C-IBS).

Aggarwal et al. [40] found that cardio-vagal dysfunction is specifically associated to C-IBS, while D-IBS patients showed mainly adrenergic dysfunction of the sympathetic nervous system.

The changes in the frequency of high amplitude propagated contractions in the colon, presumably through alteration of colonic vagal regulation, may determine the predominant bowel habit of IBS [1].

The increase of sympathetic tone increases the levels of perception of gastrointestinal stimuli, without changing the reflex response [44]. HANS axis is an essential mediator of visceral response to central influences such as psychological stress [41].

Gupta et al. [45] also reported that in IBS patients, pain intensity and abdominal discomfort evocated by visceral and cutaneous stimuli are significantly higher than in controls. These data were similar to those found in other chronic pain disorders such as fibromyalgia [46], suggesting the presence of abnormalities in central nociceptive processing also in patients with IBS.

The psychological disorders that are known to be associated with functional gastrointestinal symptoms, are also capable of altering autonomic balance [41].

In fact, anxiety and depression are associated with lower parasympathetic activity, both in patients with IBS and in controls [47].

In patients with IBS, particularly those with post-infectious IBS, an up-regulation of immune function has been demonstrated. Clinical observations suggest that enteric infections may precede the development of IBS [39]; patients with ulcerative colitis in remission often have symptoms similar to IBS [48], supporting the inflammatory theory. In patients with D-IBS, an increased number of mast cells in the terminal ileum, ascending colon and rectum has also been found [49].

It was suggested that mast cells are involved in neurogenic inflammation. There are in fact pathological conditions characterized by the activation of mast cells in the absence of a clear exposure to allergens, such as chronic idiopathic urticaria, urticaria induced by heat, cold-induced urticaria, or cholinergic urticaria. Similarly, asthma episodes and activation of mast cells in patients with systemic mastocytosis may be induced by exercise and stress in the

absence of a known allergen [50]. In addition the degranulation of mast cells is associated with the activation of the autonomic nervous system (sympathetic branch) and with the release of neuropeptides, such as NY [51], which can modulate the activity of mast cells through specific receptors [52].

In fact, the activation of mast cells, mediated by NY in response to stress [51], may lead to an increase in intestinal permeability and visceral sensitivity, changes in mucus secretion and transport of water and electrolytes. On the other hand, the activation of sympathetic nervous system may serve to localize the inflammatory response with a subsequent selective suppression of Th1 responses and a Th2 shift toward dominance of humoral immunity [53].

The Th2 shift and the mast cell activation demonstrate that the interface between the gut lumen and immune system is under close control of the autonomic nervous system.

The top-down and the bottom-up model

Recently, the conceptual model of IBS pathophysiology increasingly recognizes the interactions between the brain and gut as a pathological mechanism of functional gastrointestinal disorders [5]. Communication between CNS and enteric nervous system in normal conditions is already two-directional, especially during disturbance of homeostasis.

In patients with IBS, symptoms may be caused either by alterations in the CNS (top-down model), or in the periphery (bottom-up model), or in a combination of both (Figs. 1, 2). The brain–gut axis may be stimulated by various stressors either directed to the CNS (exteroreceptive stress) or to the gut (interoceptive stress). In addition intestinal infections may alter the cortical response to visceral stimuli.

The function of the gastrointestinal tract is modulated by both the intrinsic and the extrinsic nervous system. The intrinsic innervation consists of the enteric nervous system (ENS), including the myenteric and submucosal plexus. The extrinsic innervation is provided by the autonomic nervous system (sympathetic and parasympathetic) and is two-directional: the brain can influence the function of ENS through the autonomic nervous system, and gut may influence the brain via the intrinsic primary afferent neurons, whose cell bodies are located in cranial and dorsal nerve root ganglia [54]. In particular, vagal afferents mediate non-nociceptive sensations, including local reflexes such as gastric accommodation and gastro-colic reflex, while sympathetic afferents mediate nociceptive sensations. The sympathetic nerve endings are located in the muscle and serosa of the intestine, where the relaxation and stretching can cause muscle activation in pain conditions. In contrast, vagal terminals are located more superficially, primarily in the mucosa and submucosa, where low-intensity stimuli, such as nutrients, can cause an activation. The visceral nerve endings are localized in the dorsal horn of the spinal cord, where all the viscerosomatic afferents are found [55]. The ENS provides local reflexes, such as migrating motor complex and peristaltic reflexes and receives some input from the CNS via the sympathetic and parasympathetic nervous system [54].

Visceral hypersensitivity, which is a characteristic of IBS, may be related to bowel dysfunction or distorted processing, representation and modulation of gut signals in the brain [55, 56] or to a chronic disorder of serotonin metabolism, altered serotonin receptor sensitivity, exaggerated sensitivity of peripheral afferent nerve fibers, and spinal hyperalgesia [54, 55, 57, 58].

Some patients with IBS show increased sensitivity or increased visceral perception of intestinal distension. Whitehead et al. [59] reported that patients with IBS have significantly elevated levels of anxiety, interpersonal sensitivity, depression, hostility, and somatization of affect. However, there were no significant trait differences between patients with diarrhea and those with constipation.

In other studies, an increased sensitivity to colon and rectum distension was observed in patients with IBS and D-IBS compared to healthy subjects [14, 60] while patients with C-IBS showed conflicting results [61, 62]. However, significant differences in pain threshold did not emerge from a comparison between patients with D-IBS and C-IBS [63].

Intraluminal distension or inflammation promotes the release of 5-HT from EC of the enteric mucosa. The 5-HT by interacting with 5-HT receptor, regulates sensory, motor and secretory functions of the digestive system [57] through the intrinsic and extrinsic nervous system.

The 5-HT stimulates the 5-HT_3 and 5-HT_4 receptors located on primary afferent neurons of vagal and splanchnic fibers, which mediate both sensory and motor responses [54, 64].

Nociceptive signals project from the viscera to specific laminae in the spinal cord dorsal horn. The synaptic input activates a specific second-order neuron from spinal cord to thalamus. The axons of these cross to the opposite side in the spinal cord and continue to the thalamus. Third-order neurons connect the thalamus to the primary somatosensory area of cerebral cortex.

The bulbo-spinal tract, triggered by nociception, carries descending projections from the periaqueductal gray matter and raphe neurons in the dorsal horn neurons, which inhibit or facilitate nociceptive signal. The descending bulbospinal pathways use serotonin, noradrenergic and opioid transmitters.

Several gastrointestinal tachykinins are involved in gastrointestinal function and have been implicated in the modulation of visceral pain sensitivity.

In the gastrointestinal tract, substance P (SP) and neurokinin A (NKA), two neuropeptides belonging to the family of tachykinins, are expressed both in intrinsic neurons and extrinsic primary afferent nerve fibers originating from dorsal root ganglia [65]. Tachykinins bind and activate three different types of tachykinin receptors (NK1, NK2 and NK3). SP and NKA mediate or comediate slow synaptic transmission and modulate neural excitability via stimulation of NK3 and NK1 receptors. The imbalance of tachykinins could play an important role in the gastrointestinal dismotility associated with stress and pain [66, 67].

An experimental study of Leng et al. [68] demonstrated that cold restriction stress following transient intestinal infection triggered the down regulation of acetylcholine and up-regulation of substance P in the ileum of wild-type controls.

Stead et al. [69], studying the microanatomical relationship between mast cells and enteric nerves in the intestine of normal and nematode infected rats intestine, found that 77 % of mast cells in close proximity to subepithelial nerves contain SP and/or calcitonin-gene-related peptide (CGRP). CGRP is also found in spinal afferent neurons and intrinsic enteric neurons, with excitatory and inhibitory effect on smooth muscle [70].

Neurokinin A, SP, and CGRP are normally expressed at high levels in spinal cord, whereas SP and 5-HT are normally expressed in dorsal raphe nuclei [71].

The mucosal mast cells are important elements in the pathogenesis of IBS [72] (Fig. 1). Barbara et al. [73] identified and quantified immunohistochemically colonic mucosal mast cells in comparison to controls. They demonstrated that mast cells in close proximity to nerves significantly correlated with the severity and frequency of abdominal pain/discomfort. The degranulation of mast cells occurs not only in response to allergens, but also to stress, following the release of NY from sympathetic terminals [51]. Mucosal mast cells can increase mucosal permeability, thus modifying the microbiota with subsequent immune activation of the mucosa. Low grade inflammation-immune activation has been suggested to be one of the most important mechanisms of brain–gut interaction [74]. This effect has been attributed to the influence of interleukins (IL-1β, TNF-α and IL-6) in the development of motor dysfunction, visceral pain and psychological disorders, mediated by the CNS [75, 76].

The strong connection between CNS and ENS is also confirmed by the fact that some neuropeptides and receptors are present both in the CNS and in ENS.

Psychosocial stressors activate the circuits of stress within the EMS and in the peripheral output, through the endocrine response (cortisol, serotonin) and autonomic response (noradrenaline, adrenaline, NY) by moving the mucosal immune system towards a TH2 response (increased activation of mast cells) [53]. The autonomic response may also directly or indirectly modulate gastrointestinal permeability and therefore the access of luminal factors (antigens, bacteria) to the immune system [3, 77]. Luminal factors (interoceptive stressors) modulate the gastrointestinal immune function and cytokines from the gut may modulate the response of the EMS [1, 77].

In conclusion, both exteroceptive stress such as psychosocial stress, and interoceptive stress (Figs. 1, 2) such as gastrointestinal infections, may affect the EMS, which mediates the neuroendocrine and autonomic output to the body, respectively [1, 78]. In fact, alterations at any level of the neural system can alter motility, secretion, immune function, perception and emotional response to visceral stimuli in the gastrointestinal tract.

Acknowledgments The authors thank Mrs. Susan Seeley for her help in editing the manuscript.

Conflict of interest The authors have no conflicts of interest to disclose.

References

1. Mayer EA. The neurobiology of stress and gastrointestinal disease. Gut. 2000;47:861–9.
2. Straub RH, Herfarth H, Falk W, Andus T, Schölmerich J. Uncoupling of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis in inflammatory bowel disease? J Neuroimmunol. 2002;126:116–25.
3. Stasi C, Orlandelli E. Role of the brain–gut axis in the pathophysiology of Crohn's disease. Dig Dis. 2008;26:156–66.
4. Drossman DA. The functional gastrointestinal disorders and the Rome II process. Gut. 1999;45:1–5.
5. Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology. 2006;130:1377–90.
6. Lovallo WR, Thomas TL. Stress hormones in psychophysiological research: emotional, behavioral, and cognitive implications. In: Cacioppo JT, Tassinary LG, Berntson GG, editors. Handbook of psychophysiology. Cambridge: Cambridge University Press; 2000. p. 342–67.
7. Lea R, Whorwell PJ. New insights into the psychosocial aspects of irritable bowel syndrome. Curr Gastroenterol Rep. 2003;5:343–50.
8. Lydiard RB, Fossey MD, Marsh W, Ballenger JC. Prevalence of psychiatric disorders in patients with irritable bowel syndrome. Psychosomatics. 1993;34:229–34.
9. Thijssen AY, Jonkers DM, Leue C, van der Veek PP, Vidakovic-Vukic M, van Rood YR, et al. Dysfunctional cognitions, anxiety and depression in irritable bowel syndrome. J Clin Gastroenterol. 2010;44:e236–41.
10. Delvaux M, Denis P, Allemand H. Sexual abuse is more frequently reported by IBS patients than by patients with organic digestive diseases or controls. Results of a multicentre inquiry. French Club of Digestive Motility. Eur J Gastroenterol Hepatol. 1997;9:345–52.

11. Bennett EJ, Tennant CC, Piesse C, Badcock CA, Kellow JE. Level of chronic life stress predicts clinical outcome in irritable bowel syndrome. Gut. 1998;43:256–61.
12. O'Mahony SM, Hyland NP, Dinan TG, Cryan JF. Maternal separation as a model of brain–gut axis dysfunction. Psychopharmacology (Berl). 2011;214:71–88.
13. Irwin C, Falsetti SA, Lydiard RB, Ballenger JC, Brock CD, Brener W. Comorbidity of posttraumatic stress disorder and irritable bowel syndrome. J Clin Psychiatry. 1996;57:576–8.
14. Prior A, Colgan SM, Whorwell PJ. Changes in rectal sensitivity after hypnotherapy with irritable bowel syndrome. Gut. 1990;31:896–8.
15. Poitras P, Riberdy Poitras M, Boivin M, Verrier P. Evolution of visceral sensitivity in patients with irritable bowel syndrome. Dig Dis Sci. 2002;47:914–20.
16. Houghton LA, Calvert EL, Jackson NA, Cooper P, Whorwell PJ. Visceral sensation and emotion: a study using hypnosis. Gut. 2002;51:701–4.
17. Mulak A, Bonaz B. Irritable bowel syndrome: a model of the brain–gut interactions. Med Sci Monit. 2004;10:RA55–62.
18. Silverman DH, Munakata JA, Ennes H, Mandelkern MA, Hoh CK, Mayer EA. Regional cerebral activity in normal and pathological perception of visceral pain. Gastroenterology. 1997;112:64–72.
19. Drossman DA, Ringel Y, Vogt BA, Leserman J, Lin W, Smith JK, et al. Alterations of brain activity associated with resolution of emotional distress and pain in a case of severe irritable bowel syndrome. Gastroenterology. 2003;124:754–61.
20. Mertz H, Morgan V, Tanner G, Pichens D, Price R, Shyr Y, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. Gastroenterology. 2000;118:842–8.
21. Baciu MV, Bonaz BL, Papillon E, Bost RA, Le Bas JF, Fournet J, et al. Central processing of rectal pain: a functional MR imaging study. Am J Neuroradiol. 1999;20:1920–4.
22. Bonaz B, Baciu M, Papillon E, Bost R, Gueddah N, Le Bas JF, et al. Central processing of rectal pain in patients with irritable bowel syndrome: an fMRI study. Am J Gastroenterol. 2002;97:654–61.
23. Sternberg EM, Chrousos GP, Wilder RL, Gold PW. The stress response and the regulation of inflammatory disease. Ann Intern Med. 1992;117:854–66.
24. Gue M, Tekamp A, Tabis N, Junien JL, Buéno L. Cholecystokinin blockade of emotional stress- and CRF-induced colonic motor alterations in rats: role of the amygdala. Brain Res. 1994;658:232–8.
25. Sajdyk TJ, Shekhar A, Gehlert DR. Interactions between NPY and CRF in the amygdala to regulate emotionality. Neuropeptides. 2004;38:225–34.
26. Swanson LW, Sawchenko PE, Rivier J, Vale WW. Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. Neuroendocrinology. 1983;36:165–86.
27. Taché Y, Monnikes H, Bonaz B, Rivier J. Role of CRF in stress-related alterations of gastric and colonic motor function. Ann NY Acad Sci. 1993;697:233–43.
28. Taché Y, Martinez V, Million M, Rivier J. Corticotropin-releasing factor and the brain–gut motor response to stress. Can J Gastroenterol. 1999;13:18A–25A.
29. Smith GW, Aubry JM, Dellu F, Contarino A, Bilezikjian LM, Gold LH, et al. Corticotropin releasing factor receptor 1-deficient mice display decreased anxiety, impaired stress response, and aberrant neuroendocrine development. Neuron. 1998;20:1093–102.
30. Timpl P, Spanagel R, Sillaber I, Kresse A, Reul JM, Stalla GK, et al. Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor. Nat Genet. 1998;19:162–6.
31. Cole MA, Kalman BA, Pace TW, Topczewski F, Lowrey MJ, Spencer RL. Selective blockade of the mineralocorticoid receptor impairs hypothalamic–pituitary–adrenal axis expression of habituation. J Neuroendocrinol. 2000;12:1034–42.
32. Munakata J, Mayer EA, Chang L, Schmulson M, Liu M, Tougas G, et al. Autonomic and neuroendocrine responses to recto-sigmoid stimulation. Gastroenterology. 1998;114:A808.
33. Heitkemper M, Jarrett M, Cain K, Shaver J, Bond E, Woods NF, et al. Increased urine catecholamines and cortisol in women with irritable bowel syndrome. Am J Gastroenterol. 1996;91:906–13.
34. Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB. Altered pituitary–adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry. 2001;158:575–81.
35. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology. 2000;25:1–35.
36. Stratakis CA, Chrousos GP. Neuroendocrinology and pathophysiology of the stress system. Ann N Y Acad Sci. 1995;771:1–18.
37. Spiller RC, Jenkis D, Thornley JP, Hebden JM, Wright T, Skinner M, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute *Campylobacter enteritis* and in post-dysenteric irritable bowel syndrome. Gut. 2000;47:804–11.
38. Creed F. The relationship between psychosocial parameters and outcome in the irritable bowel syndrome. Am J Med. 1999;107:74–80.
39. Gwee KA, Leong YL, Graham C, McKendrick MW, Collins SM, Walters SJ, et al. The role of psychological and biological factors in postinfective gut dysfunction. Gut. 1999;44:400–6.
40. Aggarwal A, Cutts TF, Abell AL, Cardoso S, Familoni B, Bremer J, et al. Predominant symptoms in irritable bowel syndrome correlate with specific autonomic nervous system abnormalities. Gastroenterology. 1994;106:945–50.
41. Tougas G. The autonomic nervous system in functional bowel disorders. Gut. 2000;47:iv78–80.
42. Heitkemper M, Jarret M, Cain KC, Burr R, Levy RL, Feld A, et al. Autonomic nervous system in women with irritable bowel syndrome. Dig Dis Sci. 2001;46:1276–84.
43. Elsenbruch S, Orr WC. Diarrhea and constipation-predominant IBS patients in postprandrial autonomic and cortisol responses. Am J Gastroenterol. 2001;96:460–6.
44. Azpiroz F. Hypersensitivity in functional gastrointestinal disorders. Gut. 2002;51:i25–8.
45. Gupta V, Sheffield D, Verne GN. Evidence for autonomic dysregulation in irritable bowel syndrome. Dig Dis Sci. 2002;47:1716–22.
46. Chang L, Berman S, Mayer EA, Suyenobu B, Derbyshire S, Naliboff B, et al. Brain responses to visceral and somatic stimuli in patients with irritable bowel syndrome with and without fibromyalgia. Am J Gastroenterol. 2003;98:1354–61.
47. Jarret ME, Burr RL, Cain KC, Hertig V, Weisman P, Heitkemper MM. Anxiety and depression are related to autonomic nervous system function in women with irritable bowel syndrome. Dig Dis Sci. 2003;48:386–94.
48. Isgar B, Harman M, Kaye MD, Whorwel PJ. Symptoms of irritable bowel syndrome in ulcerative colitis in remission. Gut. 1983;24:190–2.
49. Park JH, Rhee PL, Kim HS, Lee JH, Kim YH, Kim JJ, et al. Mucosal mast cell counts correlate with visceral hypersensitivity in patients with diarrhea predominant irritable bowel syndrome. Gut. 2000;47:804–11.

50. Church MK, Lowman MA, Robinson C, Holgate ST, Benyon RC. Interaction of neuropeptides with human mast cells. Int Arch Allergy Appl Immunol. 1989;88:70–8.
51. Arzubiaga C, Morrow J, Roberts LJ, Biaggioni I. Neuropeptide Y, a putative cotransmitter in noradrenergic neurons, induces mast cell degranulation but not prostaglandin D2 release. J Allergy Clin Immunol. 1991;87:88–93.
52. Gui XY. Mast cells: a possible link between psychological stress, enteric infection, food allergy and gut hypersensitivity in the irritable bowel syndrome. J Gastroenterol Hepatol. 1998;13:980–9.
53. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve-an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev. 2000;52:595–638.
54. Gershon MD. Serotonin and its implication for the management of irritable bowel syndrome. Rev Gastroenterol Disord. 2003;3: S25–34.
55. Mertz H. Role of the brain and sensory pathways in gastrointestinal sensory disorders in humans. Gastroenterology. 2002;51:i29–33.
56. Mayer EA, Naliboff BD, Chang L. Basic pathophysiologic mechanisms in irritable bowel syndrome. Dig Dis. 2001;19:212–8.
57. Kim DY, Camilleri M. Serotonin: a mediator of the brain–gut connection. Am J Gastroenterol. 2000;95:2698–709.
58. Kim HJ, Camilleri M, Carlson PJ, Cremonini F, Ferber I, Stephens D, et al. Association of distinct $\alpha 2$ adrenoceptor and serotonin transporter polymorphisms with constipation and somatic symptoms in functional gastrointestinal disorders. Gut. 2004;53:829–37.
59. Whitehead WE, Engel BT, Schuster MM. Irritable bowel syndrome: physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. Dig Dis Sci. 1980;25:404–13.
60. Simrén M, Abrahamsson H, Bjornsson ES. An exaggerated sensory component of the gastrocolonic response in patients with irritable bowel syndrome. Gut. 2001;48:20–7.
61. Slater BJ, Plusa SM, Smith AN, Varma JS. Rectal hypersensitivity in the irritable bowel syndrome. Int J Colorectal Dis. 1997;12:29–32.
62. Harraf F, Schmulson M, Saba L, Varma JS. Subtypes of constipation predominant irritable bowel syndrome based on rectal perception. Gut. 1998;43:388–94.
63. Steens J, Van Der Schaar PJ, Penning C, Brussee J, Masclee AA. Compliance, tone and sensitivity of the rectum in different subtypes of irritable bowel syndrome. Neurogastroenterol Motil. 2002;14:241–7.
64. Tam FSF, Hiller K, Bunce K. Investigation of the 5-HT receptor type involved in inhibition of spontaneous activity of human colonic circular muscle. Br J Pharmacol. 1992;106:25P.
65. Evangelista S. Involvement of tachykinins in intestinal inflammation. Curr Pharm Des. 2001;7:19–30.
66. Holzer P, Holzer-Petsche U. Tachykinins in the gut. Part II. Roles in neural excitation, secretion and inflammation. Pharmacol Ther. 1997;73:219–63.
67. Holzer P, Holzer-Petsche U. Tachykinins in the gut. Part I. Expression, release and motor function. Pharmacol Ther. 1997; 73:173–217.
68. Leng YX, Wei YY, Chen H, Zhou SP, Yang YL, Duan LP. Alteration of cholinergic and peptidergic neurotransmitters in rat ileum induced by acute stress following transient intestinal infection is mast cell dependent. Chin Med J. 2010;123:227–33.
69. Stead RH, Tomioka M, Quinonez G, Simon GT, Felten SY, Bienenstock J. Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. Proc Natl Acad Sci USA. 1987;84:2975–9.
70. Palsson OS, Morteau O, Bozymski EM, Woosley JT, Sartor RB, Davies MJ, et al. Elevated vasoactive intestinal peptide concentrations in patients with irritable bowel syndrome. Dig Dis Sci. 2004;49:1236–43.
71. Salio C, Lossi L, Ferrini F, Merighi A. Neuropeptides as synaptic transmitters. Cell Tissue Res. 2006;326:583–98.
72. Farhadi A, Fields JZ, Keshavarzian A. Mucosal mast cells are pivotal elements in inflammatory bowel disease that connect the dots: stress, intestinal hyperpermeability and inflammation. World J Gastroenterol. 2007;13:3027–30.
73. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology. 2004;126:693–702.
74. Rodríguez-Fandiño O, Hernández-Ruiz J, Schmulson M. From cytokines to Toll-like receptors and beyond—current knowledge and future research needs in irritable bowel syndrome. J Neurogastroenterol Motil. 2010;16:363–73.
75. Liebregts T, Adam B, Bredack C, Röth A, Heinzel S, Lester S, et al. Immune activation in patients with irritable bowel syndrome. Gastroenterology. 2007;132:913–20.
76. Dinan TG, Quigley EM, Ahmed SM, Scully P, O'Brien S, O'Mahony L, et al. Hypothalamic–pituitary–gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? Gastroenterology. 2006;130:304–11.
77. Wood JD. Neuropathophysiology of irritable bowel syndrome. J Clin Gastroenterol. 2002;35:S11–22.
78. Stasi C, Zignego AL, Laffi G, Rosselli M. The liver–cytokine–brain circuit in interferon-based treatment of patients with chronic viral hepatitis. J Viral Hepatitis. 2011;18:525–32.