Published in final edited form as:

Curr Gastroenterol Rep. 2009 August ; 11(4): 270–277.

A Role for Corticotropin-releasing Factor in Functional Gastrointestinal Disorders

Yvette Tacheé, PhD, Cornelia Kiank, PhD, and Andreas Stengel, MD

Abstract

Functional gastrointestinal disorders (FGIDs), which include irritable bowel syndrome (IBS), encompass a heterogeneous group of diseases identified by chronic or recurrent symptom-based diagnostic criteria. Psychosocial factors are key components in the outcome of clinical manifestations of IBS symptoms. Anxiogenic and endocrine responses to stress are mediated by the corticotropin-releasing factor (CRF)–CRF₁ receptor pathway. Preclinical studies show that activation of the CRF₁ receptor by exogenous CRF or stress recapitulates many functional symptoms of IBS diarrhea-predominant patients as related to anxiogenic/hypervigilant behavior, autonomic nervous system alterations, induction of diarrhea, visceral hyperalgesia, enhanced colonic motility, mucus secretion, increased permeability, bacterial translocation, and mast cell activation, which are all alleviated by selective CRF₁ receptor antagonists. Clinical studies also support that CRF administration can induce IBS-like symptoms in healthy subjects and heighten colonic sensitivity in IBS patients. Yet to be ascertained is whether CRF₁ receptor antagonists hold promise as a new therapy in IBS treatment.

Introduction

Functional gastrointestinal disorders (FGIDs) are a heterogeneous group of diseases that cannot be explained by structural or biochemical abnormalities or other pathologically based diseases, and are identified by chronic or recurrent symptom-based diagnostic criteria [1]. The Rome III classification system recently regrouped adult FGIDs into six major categories of disorders: esophageal (A), gastroduodenal (B), bowel (C), functional abdominal pain syndrome (D), biliary (E), and anorectal (F) [1]. Each category was divided into subgroups with relatively specific and/or overlapping clinical features. The functional bowel disorders (C) encompass irritable bowel syndrome (IBS; C1), functional bloating (C2), functional constipation (C3), and functional diarrhea (C4), among others [1]. Sub-grouping into symptom profiles was proposed to improve the reliability of diagnosis and treatment outcomes [1]. However, recent reports addressed limitations of the current symptom-based definitions of FGIDs, including the overlap with other conditions such as microscopic colitis, and lack of robustness to generate commonly agreed upon endpoints for clinical trials [2–4]. The exponential growth in experimental and clinical research related to FGIDs has started to unravel structural and biochemical abnormalities, notably in the immune system of IBS patients, challenging the notion of an absence of pathologic or biochemical correlates [5].

Copyright © 2009 by Current Medicine Group LLC

Corresponding author Yvette Taché, PhD Center for Ulcer Research and Education—CURE: Digestive Diseases Research Center, Building 115, Room 117, VA Greater Los Angeles Healthcare System, 11301 Wilshire Boulevard, Los Angeles, CA 90073, USA. ytache@mednet.ucla.edu.

Disclosure No potential conflicts of interest relevant to this article were reported.

A consistent finding across reports is that FGIDs are based on a model that integrates psychosocial factors as key components in the outcome of clinical manifestations of symptoms [6•]. The most-studied FGID in this context is IBS, which is characterized by chronic recurrent symptoms of abdominal pain and bowel dysfunction [1]. Experimental and clinical studies consistently show that acute or chronic stress exposure has plurifunctional impacts on the gut and is a permissive factor in the development and/or exacerbation of IBS symptoms, best exemplified in postinfectious IBS [7,8•,9•]. IBS is one of the most common disorders seen by gastroenterologists and primary care providers, affecting up to 10% of the general adult population, and is associated with significant impairment in quality of life and excessive use of health care resources [2]. Somatic comorbidities and coexisting psychologic conditions are common, primarily anxiety, somatization, and symptom-related fears [6•,10]. Therefore, the impact of stress and psychosocial factors on the predisposition, precipitation, and maintenance of IBS symptoms lends relevance to taking into consideration the underlying molecular mechanisms activated by stress [6•]. Targeting these mechanisms may open new therapeutic venues.

The principal initiator of the stress response is the peptide corticotropin-releasing factor (CRF). Various stressors, including those of immune origin, induce the release of CRF from the hypothalamus. CRF acts as a neuroendocrine hormone to stimulate the pituitary-adrenal (PA) axis and as a neuromodulator of behavior (arousal, anxiety) and autonomic nervous system (ANS) activity that regulates visceral function under stress conditions [7,11]. CRF-related peptides and CRF receptors are expressed not only in the brain but also within the colon, where they activate enteric, endocrine, and immune cells and may be involved in colonic manifestations of IBS [7,12•]. This article addresses the state of knowledge about the CRF system, which encompasses CRF and related peptides acting on two types of CRF receptors, CRF₁ and CRF₂, which are encoded by two distinct genes. The implications of CRF acting in the brain and gut to alter colonic function and stress-induced visceral pain are addressed, along with the relevance to IBS-like symptoms.

The Stress CRF System

The 41-amino acid peptide CRF, isolated in 1981, was originally characterized as a hypothalamic neurohormone involved in the stimulation of the PA axis in response to stress. Axon terminals of CRF neurons originating in the parvocellular part of the paraventricular nucleus of the hypothalamus release CRF into the hypophyseal-portal circulation, which stimulates corticotropin secretion and subsequently leads to increased synthesis and release of circulating cortisol (corticosterone in rodents) from the adrenal cortex [13]. There is also widespread distribution of CRF in extrahypothalamic circuits where it induces central actions that largely recapitulate the disturbances induced by stress [13,14].

Three novel CRF-related peptides bearing 45% to 26% homology with CRF—a 40-amino acid peptide named urocortin 1 (Ucn 1) and two 38-amino acid peptides named urocortin 2 (Ucn 2) and urocortin 3 (Ucn 3)—were characterized recently and shown to be highly conserved through evolution [15,16]. CRF, Ucn 1, Ucn 2, and Ucn 3 exert their biologic effects by interacting with two highly homologous CRF₁ and CRF₂ receptors that belong to the G-protein-coupled receptor (GPCR) family [13,15]. Studies demonstrated that CRF₁ and CRF₂ receptors differ considerably in their binding characteristics [15,17•]. The CRF₁ receptor displays high affinity to CRF and Ucn 1 but shows no appreciable binding affinity to Ucn 2 and Ucn 3. In contrast, CRF₂ binds to Ucn 1, Ucn 2, and Ucn 3 with greater affinity than CRF, making the family of urocortins the cognate agonists for the CRF₂ receptor subtype [15,17•]. As part of class B1 GPCRs containing exon-intron organization, CRF receptors are subject to extensive alternate splicing. Thus far, 12 CRF receptor splice variants with specific amino acid deletion and distinct agonist binding properties have been

identified in the brain and peripheral tissues including skin, gut, and placenta [17•,18]. The main functional CRF₁ receptor involved in the biologic actions of CRF and Ucn 1 is CRF_{1α}. In humans, the *CRF2* gene consists of 12 exons, and alternate splicing of exon 1 gives rise to three functional membrane isoforms, α (a), β (b), and γ (c), which have a similar pharmacologic profile in binding to urocortin ligands.

The expression of CRF₁ and CRF₂ receptors is tissue specific, regulated by physiologic conditions, and affected by environmental stimuli [17•,18]. CRF receptor variants may have pathophysiologic implications in altering the responsiveness of cells to CRF ligands, leading to attenuation or amplification of the signaling of the two receptors [19]. For instance, the novel CRF_{2a-6} variant identified in the rat upper gut and in the mouse brain corresponds to a soluble form of CRF_{2a}, which displays high binding affinity to CRF and Ucn 1 and therefore may modulate CRF₁-dependent functions by binding peptides without inducing intracellular signaling [20]. However, although CRF, urocortins, and CRF receptors have been identified in the intestine (including myenteric neurons, enterochromaffin and immune cells) in experimental animals and humans, the regulation of CRF receptors and variants during basal or stress conditions or in association with FGIDs is largely unknown [18,21•,22,23•].

The binding of CRF ligands to the functional CRF receptors in the majority of cells is coupled to Gα_s and activates adenylate cyclase, leading to the cyclic adenosine monophosphate second-messenger cascade, including protein kinase A [17•]. In addition, like most G protein-coupled receptors, conformational changes of the CRF receptor after CRF/urocortin binding ligand-CRF receptor interaction can recruit multiple Gα subunits, including G_o, G_{q/11}, G_{i1/2}, and G_z, which modify the activity of several intracellular effector molecules. However, their occurrence is cell type and ligand specific [17•]. CRF receptor signaling cascades also modify the phosphorylation pattern of intracellular proteins and thereby activate mitogen-activated protein kinases (MAPK), such as extracellular signal-regulated kinases 1/2 (ERK1/2) and p38/MAPK pathways [17•,18]. For instance, CRF preferentially activates the ERK pathways in the limbic structures involved in memory, environmental information processing, and behavioral response to stress [24]. Compared with the several described signaling pathways of CRF ligand-receptor interaction targeting several organs, those in the gut are less well known [18].

Activation of CRF₁ Signaling and the Overall Stress Response

A key to establishing the role of endogenous CRF ligands and CRF receptors in the stress response was the development of specific and selective CRF receptor antagonists for CRF₁ or CRF₂ receptors. The first antagonists developed were peptidergic CRF receptor antagonists such as α-helical CRF₉₋₄₁, which was used recently in patients with IBS [25]. Several selective CRF₁ antagonists, which are small, hydrophobic, orally active molecules that readily cross the blood-brain barrier, have been developed [26]. Among the selective CRF₁ antagonists, CP-154,526, antalarmin, DPM696, NBI 30775 (also known as R121919), NBI 35965, and JTC-017 were most commonly used in experimental studies [27•]. These compounds were instrumental in generating substantial data underpinning the key role of the CRF-CRF₁ receptor as a core mediator of the physiologic response to stress as it relates to the activation of the PA axis, anxiogenic behavior, alterations in ANS activity involving the increase in sympathetic and sacral parasympathetic outflow, and a decrease in vagal activity and ANS-related changes in visceral function (cardio vascular, gastrointestinal, and immune) in rodents and primates [7,13,14]. Data generated by this pharmacologic approach have been largely corroborated in studies using a genetic model of deletion of the CRF₁ receptor. A CRF₁ knockout murine model exhibits reduced anxiety-related behavior, impaired stress-induced activation of the PA axis, and visceral hypoalgesia [13,28•,29]. These convergent preclinical studies also have the potential for blocking the CRF₁ system in

the treatment of various human illnesses such as anxiety and depression, eating disorders, inflammatory diseases, substance abuse, preterm parturition, and functional bowel disorders [17,27•,30,31].

Only recently, selective peptide CRF₂ receptor antagonists were developed, namely antisauvagine-30, K41498, and astressin₂-B, which is a more potent, long-acting analog [32]. Emerging evidence supports the potential for the CRF₂ receptor in dampening and/or facilitating the proper recovery of the CRF₁-initiated behavioral, endocrine, cardiovascular, and visceral responses to stress and inhibition of gastrointestinal function [13,33,34].

Activation of CRF₁ Receptors: Role in IBS Symptoms and Pathophysiology

Comorbidity with anxiety/depression

The CRF-CRF₁ pathway is well positioned to be part of the underlying mechanisms in the pathophysiology of IBS related to stressful life events (including major traumatic childhood events in the medical history), which are risk factors influencing the onset and severity of symptoms [1,6•,35]. Investigations in IBS patients indicate that there is overactivity of the PA axis and enhanced plasma corticotropin and cortisol response to exogenous CRF [36]. In a phase 1, randomized, double-blind, placebo-controlled clinical trial, the CRF₁ antagonist NBI-34041 attenuated the neuroendocrine response to psychosocial stress in healthy male subjects [37].

Between 29% and 92% of IBS patients in tertiary care centers have symptoms of coexisting psychiatric disorders, predominantly anxiety/depression [6•,38]. Many preclinical studies substantiate that the activation of brain CRF₁ receptors recapitulates depression-like symptoms in experimental animals [39] and show the efficacy of CRF₁ antagonists in curtailing behavioral symptoms associated with experimental models of anxiety/depression (Table 1) [27•,30]. However, the few clinical studies that tested CRF₁ antagonists in anxiety/depression reported equivocal results. The first small, open-label clinical study in patients with severe anxiety and depression treated with the CRF₁ receptor antagonist NBI-30775/RS121919 showed an improvement in symptoms [27•]. This contrasts with a recent double-blind, randomized, placebo-controlled clinical report using the CRF₁ receptor antagonist CP-316311, which failed to demonstrate efficacy in an interim analysis in male patients with depression, whereas treatment with a positive control, sertraline, had beneficial effects [40]. Therefore, these data call for additional studies with structurally diverse CRF₁ antagonists and controlled clinical trials to establish their therapeutic use. This is further supported by the fact that stress-coping behavioral techniques and psychotropic agents, including tricyclic antidepressants known to reduce CRF levels [41], are increasingly recognized as therapeutic options in treating FGIDs [6•]. These interventions exert beneficial effects on abdominal pain and bowel symptoms in IBS (the effects are best observed in patients in whom diarrhea and abdominal pain predominate) [6•]. Taken together, these findings support a potential role for brain CRF₁ pathway dysregulation as part of the mechanisms that may underlie the comorbidity involving depression and IBS symptoms.

Changes in autonomic activity

Autonomic dysfunction was recognized early as a possible relevant pathway leading to or modulating IBS symptoms. The most consistent changes found are an increase in sympathetic activity and a decrease in vagal activity in IBS patients compared with healthy controls, as reflected by changes in heart rate variability and skin conductance [42]. The altered autonomic nervous system activity in IBS patients is similar to that induced by stress and observed in depressed patients [43]. In experimental animals, the activation of central CRF₁ receptors leads to increased sympathetic nerve activity, plasma catecholamine release, and sacral parasympathetic tone, but decreases vagal activity [31]. Conversely, CRF₁

receptor antagonists prevent autonomic dysfunction linked with stress [14]. These convergent data are consistent with overactivity of the CRF-CRF₁ system in the brain, which may contribute to behavioral and autonomic alterations in patients with IBS and coexisting psychiatric disorders (eg, anxiety/depression).

Altered bowel movements

A cardinal symptom of IBS is altered bowel movements in a subgroup of patients experiencing diarrhea-predominant manifestations [1]. Activation of CRF₁ receptors expressed in the brain and colon have been convincingly implicated in the stress-induced activation of colonic secretory and motor function leading to a diarrhea response in experimental animals [34]. Acute activation of CRF₁ receptors in the brain or periphery induces stress-like stimulation of propulsive colonic motor function and diarrhea in rodents [34,44]. Conversely, centrally or peripherally administered CRF₁ receptor antagonists (ie, CP-154,526, CRA 1000, NBI 27914, NBI 35965, antalarmin, and JTC-017) alleviate exogenous CRF and stressor (restraint, water-avoidance stress, elevated plus maze, social intruder)-induced stimulation of colonic secretomotor function in rodents and abolish the diarrhea [34]. The pathway through which acute central injection of CRF stimulates colonic motor function and diarrhea does not involve the concomitant stimulation of the PA axis but brain activation of autonomic nuclei regulating the sacral parasympathetic outflow to the pelvic organs [34,45]. Effector mechanisms of autonomic alterations involve the parasympathetic cholinergic-mediated increase of colonic serotonin (5-HT) release acting on 5-HT₃ and 5-HT₄ receptors. This was shown by the blockade of colonic motor stimulation in response to central injection of CRF by atropine and subcutaneous or intracolonic administration of the 5-HT₃ antagonists granisetron, ramosteron, ondansetron, and azasetron, and the 5-HT₄ antagonist SB-204070 in rats [45]. In addition, central injection of CRF increases the 5-HT content in the rat colon, consistent with enhanced luminal release of serotonin, most likely originating from enterochromaffin cells [34,45].

In contrast to the ANS-mediated central action of CRF, the colonic stimulation induced by peripheral injection of CRF and Ucn 1 involves direct action on CRF₁ receptors expressed on colonic enteric neurons [22,23•]. Peripheral injection of CRF or the selective CRF₁ agonist stressin₁-A activates cholinergic and nitrergic myenteric neurons in the proximal and distal colon, which are involved in the peristaltic reflex [23•]. The activation takes place in colonic myenteric neurons bearing CRF₁ receptors and is blocked by CRF₁ receptor antagonists [22,23•]. Moreover, CRF and Ucn 1 also increase contractility in vitro in rat colonic preparations, and the response is blocked by a CRF₁ antagonist but not by a CRF₂ antagonist [22]. Lastly, the in vitro colonic contractile response induced by CRF or Ucn 1 is blocked by tetrodotoxin consistent with a direct action on myenteric neurons [22].

The potential physiologic relevance of the CRF₁ receptor activation within the colon is inferred by the blunting of acute wrap restraint, water-avoidance stress, or novel environment-induced defecation and diarrhea by the peripheral injection of peptide CRF antagonists with poor access to the brain [34]. The data suggest that psychologic stressors activate the CRF system first in the brain to induce autonomic-related alterations of colonic function, and these autonomic changes then recruit the local CRF-CRF₁ system in the colon as part of the effector component of this response. Consistent with the preclinical studies in rodents, peripheral administration of the CRF antagonist α -helical CRF₉₋₄₁ was reported to suppress a rectal electrical stimulation-induced increase of sigmoid colonic motility in IBS compared with control subjects [46]. However, a recent, randomized, double-blind, placebo-controlled study indicated that oral administration of two doses of the CRF₁ antagonist BMS-562086 did not lead to significant changes in stool frequency or colonic transit in a small number of IBS-D patients compared with placebo (Table 2) [47]. Therefore, further studies are required to establish the therapeutic transferability of preclinical and phase 1

clinical studies that consistently showed a blunting of colonic response to stress by the administration of CRF peptide antagonists or selective CRF₁ antagonists.

Visceral hypersensitivity

Visceral hypersensitivity and abdominal pain are cardinal features in IBS [1]. Several convergent studies using acute or chronic injection of CRF₁ antagonists in rats or CRF₁ receptor knockout mice established that the activation of CRF₁ receptors is involved in visceral hyperalgesia to colorectal distention (CRD) in various acute or chronic experimental models of visceral pain (Table 1) [28•,44,48•]. A recent report showed that chronic treatment with the CRF₁ antagonist CP-154,526 alleviated the development and maintenance of visceral hyperalgesia induced in a model of repeated intermittent psychologic stress [49] or repeated CRD 6 weeks after the development of colitis [50]. Similarly, the visceral motor response to phasic CRD was inhibited in wild-type mice pretreated with the CRF₁ antagonist NBI 30775 or in CRF₁ knockout mice [28•]. In healthy human subjects, the administration of CRF decreased the visceral pain threshold to repetitive rectal distentions, and enhanced the intensity of discomfort sensation to CRD as observed in rodents [31,44,51•]. Further clinical evidence supporting translational aspects of CRF receptors in the pathophysiology of IBS comes from recent reports that the peripheral injection of α -helical CRF₉₋₄₁ prevented the rectal electrical stimulation-induced increase of visceral perception and anxiety in IBS patients compared with healthy controls and almost normalized the altered electroencephalographic activities in IBS patients under basal conditions and in response to CRD (Table 2) [25].

Hypervigilance

Hypervigilance has been discussed as a contributor to visceral hypersensitivity in IBS patients [52]. Experimental studies show that CRD induces CRF₁-mediated activation of noradrenergic neurons in the locus coeruleus projecting to the forebrain areas associated with arousal, hypervigilance, and anxiety [53]. These observations may have relevance to the CRF₁-mediated circuitries in IBS patients who display hypersensitivity to CRD and hypervigilance to rectal stimuli [52]. The altered pain threshold to CRD may cause a more pronounced and frequent CRF-CRF₁ receptor-mediated activation of locus coeruleus noradrenergic neurons and thereby provide a mechanism underlying visceral hypervigilance [31].

Altered intestinal barrier function

The status of intestinal barrier integrity in IBS has led to controversial data [54]; however, emerging evidence supports that small intestinal and colonic paracellular permeability in IBS patients is altered, as is the intestinal barrier's ability to withstand noxious agents [55•]. A recent study also showed a positive correlation between increased colonic permeability of IBS patients and abdominal pain severity [55•]. Vast and convincing preclinical study literature established that acute or chronic stress linked with early maternal separation or repeated water-avoidance stress increases short-circuit current, macromolecule flux, paracellular and transcellular permeability, and mucus secretion in the rodent colonic mucosa through activation of mucosal mast cells [8•,56,57•]. A role of the peripheral CRF₁ signaling pathway in such responses was substantiated by the ability of systemic or intraperitoneal injection of CRF to reproduce the changes induced by stress and the blockade of acute or chronic stress-induced colonic barrier dysfunction by peripheral injection of peptide CRF antagonists in rodents and pigs (Table 1) [8•,44,56,57•]. The observation that mast cell-deficient rodents exposed to stress no longer displayed increased intestinal permeability and the reversibility of these effects by mast cell reconstitution, as reflected by increased permeability, underlines the importance of mast cells in stress-related colonic barrier dysfunction under stress conditions [56,57•]. Likewise, in colonic mucosal biopsies

of healthy subjects, CRF activates subepithelial mast cells and induces a CRF receptor-mediated mast cell-dependent increase in transcellular uptake of protein antigens (Table 2) [21•]. Moreover, clinical studies showed the localization of activated mast cells in proximity to colonic nerves, which is correlated with abdominal pain in IBS. These studies also show a high correlation among the severity of abdominal pain, mast cell number, and mast cell activation in colonic mucosal biopsies of IBS patients, consistent with a possible role of the CRF receptors on mast cells in this process [58].

Low-grade inflammation

Several recent clinical studies provide evidence that in a subset of patients, IBS is associated with low-grade inflammation in the intestinal mucosa as shown by cellular infiltration of CD3⁺, CD25⁺ lymphocytes, and/or mast cells and enhanced proinflammatory cytokine release [5,58,59]. In addition, the small intestine of patients with diarrhea-predominant IBS shows bacterial overgrowth associated with increased mast cell activation and hyperplasia [60]. Prospective studies also established a 4% to 31% incidence of IBS following bacterial gastroenteritis and that stressful life events increase the risk to develop postinfectious IBS [9•,58]. A recent clinical study revealed heightened baseline levels of tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6 after a 24-hour ex vivo culture of peripheral blood mononuclear cells of IBS patients and increased IL-6 inducibility after LPS stimulation [61]. The proinflammatory response was exaggerated in diarrhea-predominant IBS patients [61]. Moreover, production of TNF- α from stimulated monocytes and IL-5 and IL-10 from stimulated lymphocytes was higher in blood from IBS patients than from control subjects, and correlated positively with anxiety and depression scores [5,61]. A local paracrine/autocrine proinflammatory action by CRF₁ receptor activation was reported in several models of intestinal inflammation in vitro and in vivo as well as the up-regulation of CRF expression in immune cells of the human colonic lamina propria in response to inflammation. [62]. However, further studies are required in IBS patients with low-grade inflammation to assess whether the up-regulation of CRF ligands and alterations of CRF receptors are involved in low-grade inflammation.

Conclusions

The CRF/Ucn 1–CRF₁ receptor system, identified in the brain and colon, has been implicated as one of the most important mediators coordinating the response to stress. In particular, the activation of CRF₁ receptors plays a core role in the PA axis stimulation and in the development of anxiogenic and visceral responses independently from the PA axis. In addition, preclinical reports established that the activation of CRF₁ receptors by CRF and Ucn 1 recapitulates key features of IBS diarrhea-predominant patients as it relates to induction of diarrhea and visceral hyperalgesia, increase in colonic motility, permeability, bacterial translocation, mucus secretion, mast cell activation, and anxiogenic/hypervigilance, which are alleviated by various selective CRF₁ receptor antagonists (Table 1). Clinical studies support that CRF administration can induce IBS-like symptoms and colonic alterations in healthy subjects and heighten sensitivity in IBS patients, and that these symptoms are dampened by a peptide CRF antagonist (Table 2) [12•]. Evidence also supports that the CRF₁ signaling system offers a strong basis for understanding the mechanistic processes involved in stress-related exacerbation of functional bowel disorders. However, whether the CRF₁ receptor signaling system at a central or peripheral level (or a combination of both) plays a major role in the neurobiologic common denominator of IBS symptoms requires additional clinical studies [12•,31,48•]. It remains to be ascertained whether the current CRF₁ receptor antagonists hold promise as a new therapeutic venue in the treatment of stress-related IBS symptoms. So far, the impressive basic science data contrast with the equivocal clinical reports of CRF₁ antagonists.

Acknowledgments

Dt. Taché is supported by VA Research Career Scientist Award and National Institutes of Health R01 grants. Dr. Stengel is supported by the German Research Foundation Grant STE 1765/1-1.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology*. 2006; 130:1377–1390. [PubMed: 16678553]
2. Talley NJ. Functional gastrointestinal disorders as a public health problem. *Neurogastroenterol Motil*. 2008; 20(Suppl 1):121–129. [PubMed: 18402649]
3. Mayer EA. The challenge of studying the biology of complex, symptom-based GI disorders. *Gastroenterology*. 2008; 134:1826–1827. [PubMed: 18477481]
4. Limsui D, Pardi DS, Camilleri M, et al. Symptomatic overlap between irritable bowel syndrome and microscopic colitis. *Inflamm Bowel Dis*. 2007; 13:175–181. [PubMed: 17206699]
5. Kindt S, Van Oudenhove L, Broekaert D, et al. Immune dysfunction in patients with functional gastrointestinal disorders. *Neurogastroenterol Motil*. 2009; 21:389–398. [PubMed: 19126184]
- 6•. Grover M, Drossman DA. Psychotropic agents in functional gastrointestinal disorders. *Curr Opin Pharmacol*. 2008; 8:715–723. [PubMed: 18760380] This excellent review describes the rationale for using psychotropic agents in FGIDs, along with the vital role of psychosocial factors and when and how to prescribe psychotropic antidepressants. The authors also note the recent studies using serotonin norepinephrine reuptake inhibitors and potential new targets, including CRF receptor antagonists.
7. Taché Y, Bonaz B. Corticotropin-releasing factor receptors and stress-related alterations of gut motor function. *J Clin Invest*. 2007; 117:33–40. [PubMed: 17200704]
- 8•. Gareau MG, Silva MA, Perdue MH. Pathophysiological mechanisms of stress-induced intestinal damage. *Curr Mol Med*. 2008; 8:274–281. [PubMed: 18537635] This review thoroughly covers alterations of intestinal barrier function induced by acute and chronic stressors in humans and in rodents along with the mechanisms responsible for barrier dysfunction, including the role of mast cells and CRF. The impacts of a defective mucosal barrier on the development of low-grade inflammation and hyperalgesia are noted.
- 9•. Grover M, Herfarth H, Drossman DA. The functional-organic dichotomy: postinfectious irritable bowel syndrome and inflammatory bowel disease-irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2009; 7:48–53. [PubMed: 18848909] This review reported the clinical evidence for postinfectious IBS with persistent gut inflammation, and the influence of stress and psychologic distress. A rationale for the concept of inflammatory bowel disease–IBS is elaborated along with a unified understanding of postinfectious IBS and inflammatory bowel disease.
10. Riedl A, Schmidtman M, Stengel A, et al. Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *J Psychosom Res*. 2008; 64:573–582. [PubMed: 18501257]
11. Bale TL. Sensitivity to stress: dysregulation of CRF pathways and disease development. *Horm Behav*. 2005; 48:1–10. [PubMed: 15919381]
- 12•. Fukudo S. Role of corticotropin-releasing hormone in irritable bowel syndrome and intestinal inflammation. *J Gastroenterol*. 2007; 42(Suppl 17):48–51. [PubMed: 17238026] This review highlights the importance of the CRF signaling system in patients with IBS, particularly underlined by clinical studies showing the induction by peripheral administration of CRF and reduction by CRF receptor antagonists of IBS symptoms.
13. Bale TL, Vale WW. CRF and CRF receptor: role in stress responsivity and other behaviors. *Annu Rev Pharmacol Toxicol*. 2004; 44:525–557. [PubMed: 14744257]

14. Wood SK, Woods JH. Corticotropin-releasing factor receptor-1: a therapeutic target for cardiac autonomic disturbances. *Expert Opin Ther Targets*. 2007; 11:1401–1413. [PubMed: 18028006]
15. Hauger RL, Grigoriadis DE, Dallman MF, et al. International Union of Pharmacology. XXXVI. Current status of the nomenclature for receptors for corticotropin-releasing factor and their ligands. *Pharmacol Rev*. 2003; 55:21–26. [PubMed: 12615952]
16. Fekete EM, Zorrilla EP. Physiology, pharmacology, and therapeutic relevance of urocortins in mammals: Ancient CRF paralogs. *Front Neuroendocrinol*. 2007; 28:1–27. [PubMed: 17083971]
- 17•. Hillhouse EW, Grammatopoulos DK. The molecular mechanisms underlying the regulation of the biological activity of corticotropin-releasing hormone receptors: implications for physiology and pathophysiology. *Endocr Rev*. 2006; 27:260–286. [PubMed: 16484629] This review describes the regulation of CRF receptors and their variants under physiologic as well as pathophysiologic conditions and the cell specificity of multiple signaling cascades activated by CRF receptors. It also highlights the importance based on the involvement of the CRF signaling system in various regulatory functions, such as the cardiovascular system and energy balance.
18. Wu SV, Yuan P-Q, Wang L, et al. Identification and characterization of multiple corticotropin-releasing factor type 2 receptor isoforms in the rat esophagus. *Endocrinology*. 2007; 148:1675–1687. [PubMed: 17218420]
19. Markovic D, Lehnert H, Levine MA, Grammatopoulos DK. Structural determinants critical for localization and signaling within the seventh transmembrane domain of the type 1 corticotropin releasing hormone receptor: lessons from the receptor variant R1d. *Mol Endocrinol*. 2008; 22:2505–2519. [PubMed: 18772229]
20. Chen AM, Perrin MH, Digruccio MR, et al. A soluble mouse brain splice variant of type 2alpha corticotropin-releasing factor (CRF) receptor binds ligands and modulates their activity. *Proc Natl Acad Sci U S A*. 2005; 102:2620–2625. [PubMed: 15701705]
- 21•. Wallon C, Yang PC, Keita AV, et al. Corticotropin-releasing hormone (CRH) regulates macromolecular permeability via mast cells in normal human colonic biopsies in vitro. *Gut*. 2008; 57:50–58. [PubMed: 17525093] This is the first study investigating the effects of CRF on colonic biopsies from healthy human subjects providing proof of the concept that CRF induces a CRF receptor–mediated rapid-onset increase in macromolecular mucosal permeability and bacterial translocation through activation of mucosal mast cells that are endowed with both CRF receptor subtypes.
22. Kimura T, Amano T, Uehara H, et al. Urocortin I is present in the enteric nervous system and exerts an excitatory effect via cholinergic and serotonergic pathways in the rat colon. *Am J Physiol Gastrointest Liver Physiol*. 2007; 293:G903–G910. [PubMed: 17717045]
- 23•. Yuan PQ, Million M, Wu SV, et al. Peripheral corticotropin releasing factor (CRF) and a novel CRF1 receptor agonist, stressin1-A activate CRF1 receptor expressing cholinergic and nitrergic myenteric neurons selectively in the colon of conscious rats. *Neurogastroenterol Motil*. 2007; 19:923–936. [PubMed: 17973638] This experimental study anchored the peripheral CRF signaling in the colon by showing the expression of functional CRF₁ receptors in rat colon myenteric neurons at the gene and protein levels and their activation in response to peripheral injection of CRF linked with the stimulation of propulsive colonic motor function and diarrhea in rats.
24. Silberstein S, Vogl AM, Bonfiglio JJ, et al. Immunology, signal transduction, and behavior in hypothalamic-pituitary-adrenal axis-related genetic mouse models. *Ann N Y Acad Sci*. 2009; 1153:120–130. [PubMed: 19236335]
25. Tayama J, Sagami Y, Shimada Y, et al. Effect of alpha-helical CRH on quantitative electroencephalogram in patients with irritable bowel syndrome. *Neurogastroenterol Mot*. 2007; 19:471–483.
26. Tellew JE, Luo Z. Small molecule antagonists of the corticotropin releasing factor (CRF) receptor: recent medicinal chemistry developments. *Curr Top Med Chem*. 2008; 8:506–520. [PubMed: 18397172]
- 27•. Holsboer F, Ising M. Central CRH system in depression and anxiety—evidence from clinical studies with CRH1 receptor antagonists. *Eur J Pharmacol*. 2008; 583:350–357. [PubMed: 18272149] This review describes the results of two clinical trials using CRF₁ antagonists showing the effectiveness of the treatment in patients with major depression and in healthy

subjects after a psychologic stressor. The authors conclude that CRF₁ antagonists are a promising option in the drug treatment of patients with depression and/or anxiety.

- 28*. Trimble N, Johnson AC, Foster A, Greenwood-Van Meerveld B. Corticotropin-releasing factor receptor 1-deficient mice show decreased anxiety and colonic sensitivity. *Neurogastroenterol Motil.* 2007; 19:754–760. [PubMed: 17539891] This study showed the prevention of viscerosensitivity following colorectal distention in CRF₁ knock-out mice, which was also observed after treatment with a CRF₁ antagonist in CRF₁ receptor-bearing mice. This study translates existing pharmacologic evidence of the involvement of the CRF₁ signaling system in viscerosensitivity following stress in a genetic model, allowing the study of chronic stress under conditions of depleted CRF₁ receptor activation.
29. Keck ME, Ohl F, Holsboer F, Muller MB. Listening to mutant mice: a spotlight on the role of CRF/CRF receptor systems in affective disorders. *Neurosci Biobehav Rev.* 2005; 29:867–889. [PubMed: 15899517]
30. Stahl SM, Wise DD. The potential role of a corticotropin-releasing factor receptor-1 antagonist in psychiatric disorders. *CNS Spectr.* 2008; 13:467–483. [PubMed: 18567971]
31. Taché Y, Brunnhuber S. From Hans Selye's discovery of biological stress to the identification of corticotropin-releasing factor signaling pathways: implication in stress-related functional bowel diseases. *Ann N Y Acad Sci.* 2008; 1148:29–41. [PubMed: 19120089]
32. Rivier J, Gulyas J, Kirby D, et al. Potent and long-acting corticotropin releasing factor (CRF) receptor 2 selective peptide competitive antagonists. *J Med Chem.* 2002; 45:4737–4747. [PubMed: 12361401]
33. Nazarloo HP, Buttrick PM, Saadat H, Dunn AJ. The roles of corticotropin-releasing factor-related peptides and their receptors in the cardiovascular system. *Curr Protein Pept Sci.* 2006; 7:229–239. [PubMed: 16787262]
34. Stengel A, Taché Y. Neuroendocrine control of the gut during stress: corticotropin-releasing factor signaling pathways in the spotlight. *Annu Rev Physiol.* 2009; 71:219–239. [PubMed: 18928406]
35. Fujii Y, Nomura S. A prospective study of the psychobehavioral factors responsible for a change from non-patient irritable bowel syndrome to IBS patient status. *Biopsychosoc Med.* 2008; 2:16. [PubMed: 18817571]
36. Dinan TG, Quigley EM, Ahmed SM, et al. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? *Gastroenterology.* 2006; 130:304–311. [PubMed: 16472586]
37. Ising M, Zimmermann US, Kunzel HE, et al. High-affinity CRF1 receptor antagonist NBI-34041: preclinical and clinical data suggest safety and efficacy in attenuating elevated stress response. *Neuropsychopharmacology.* 2007; 32:1941–1949. [PubMed: 17287823]
38. North CS, Hong BA, Alpers DH. Relationship of functional gastrointestinal disorders and psychiatric disorders: implications for treatment. *World J Gastroenterol.* 2007; 13:2020–2027. [PubMed: 17465442]
39. Ising M, Holsboer F. CRH-sub-1 receptor antagonists for the treatment of depression and anxiety. *Exp Clin Psycho-pharmacol.* 2007; 15:519–528.
40. Binneman B, Feltner D, Kolluri S, et al. A 6-week randomized, placebo-controlled trial of CP-316,311 (a selective CRH1 antagonist) in the treatment of major depression. *Am J Psychiatry.* 2008; 165:617–620. [PubMed: 18413705]
41. Holsboer F, Barden N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. *Endocr Rev.* 1996; 17:187–205. [PubMed: 8706631]
42. Tillisch K, Mayer EA, Labus JS, et al. Sex specific alterations in autonomic function among patients with irritable bowel syndrome. *Gut.* 2005; 54:1396–1401. [PubMed: 15923667]
43. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. *Psychosom Med.* 2005; 67(Suppl 1):S29–S33. [PubMed: 15953797]
44. Larauche M, Gourcerol G, Wang L, et al. Cortagine, a CRF1 agonist, induces stress-like alterations of colonic function and visceral hypersensitivity in rodents primarily through peripheral pathways. *Am J Physiol Gastrointest Liver Physiol.* 2009 Epub ahead of print.

45. Nakade Y, Fukuda H, Iwa M, et al. Restraint stress stimulates colonic motility via central corticotropin-releasing factor and peripheral 5-HT₃ receptors in conscious rats. *Am J Physiol Gastrointest Liver Physiol*. 2007; 292:G1037–G1044. [PubMed: 17158256]
46. Sagami Y, Shimada Y, Tayama J, et al. Effect of a corticotropin releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome. *Gut*. 2004; 53:958–964. [PubMed: 15194643]
47. Sweetser S, Camilleri M, Linker Nord SJ, et al. Do corticotropin releasing factor-1 receptors influence colonic transit and bowel function in females with irritable bowel syndrome? *Am J Physiol Gastrointest Liver Physiol*. 2009 Epub ahead of print.
48. Martinez V, Taché Y. CRF₁ receptors as a therapeutic target for irritable bowel syndrome. *Curr Pharm Des*. 2006; 12:1–18. This article reviewed CRF₁ receptor antagonists tested in the preclinical setting for their ability to block acute or chronic stress-induced increased propulsive colonic motor function and visceral hyperalgesia. The possible beneficial effects of CRF₁ antagonists in improving IBS symptoms, the frequent association with psychologic comorbidities, and related mechanisms of action of CRF₁ antagonists to curtail IBS-like symptoms are also discussed.
49. Larauche M, Bradesi S, Million M, et al. Corticotropin-releasing factor type 1 receptors mediate the visceral hyperalgesia induced by repeated psychological stress in rats. *Am J Physiol Gastrointest Liver Physiol*. 2008; 294:G1033–G1040. [PubMed: 18308857]
50. Saito-Nakaya K, Hasegawa R, Nagura Y, et al. Corticotropin-releasing hormone receptor 1 antagonist blocks colonic hypersensitivity induced by a combination of inflammation and repetitive colorectal distension. *Neurogastroenterol Motil*. 2008; 20:1147–1156. [PubMed: 18761632]
51. Nozu T, Kudaira M. Corticotropin-releasing factor induces rectal hypersensitivity after repetitive painful rectal distention in healthy humans. *J Gastroenterol*. 2006; 41:740–744. [PubMed: 16988761] This clinical trial shows a reduction of the pain threshold in healthy human subjects to colorectal distention following intravenous injection of CRF. This reduction reflects the visceral hypersensitivity to colorectal distention observed in IBS patients and therefore provides proof of concept that endogenous CRF may participate in the development of visceral pain in IBS.
52. Naliboff BD, Berman S, Suyenobu B, et al. Longitudinal change in perceptual and brain activation response to visceral stimuli in irritable bowel syndrome patients. *Gastroenterology*. 2006; 131:352–365. [PubMed: 16890589]
53. Kosoyan H, Grigoriadis D, Taché Y. The CRF₁ antagonist, NBI-35965 abolished the activation of locus coeruleus by colorectal distention and intracisternal CRF in rats. *Brain Res*. 2005; 1056:85–96. [PubMed: 16095571]
54. Camilleri M, Gorman H. Intestinal permeability and irritable bowel syndrome. *Neurogastroenterol Motil*. 2007; 19:545–552. [PubMed: 17593135]
55. Piche T, Barbara G, Aubert P, et al. Impaired intestinal barrier integrity in the colon of patients with irritable bowel syndrome: involvement of soluble mediators. *Gut*. 2009; 58:196–201. [PubMed: 18824556] Using colonic biopsies, the authors showed an increase in paracellular permeability in IBS patients compared with healthy controls. The biopsy supernatant was investigated to identify possible biomarkers to facilitate the still very complex and therefore time- and resource-consuming diagnosis of IBS.
56. Teitelbaum AA, Gareau MG, Jury J, et al. Chronic peripheral administration of corticotropin-releasing factor causes colonic barrier dysfunction similar to psychological stress. *Am J Physiol Gastrointest Liver Physiol*. 2008; 295:G452–G459. [PubMed: 18635602]
57. Santos J, Yates D, Guilarte M, et al. Stress neuropeptides evoke epithelial responses via mast cell activation in the rat colon. *Psychoneuroendocrinology*. 2008; 33:1248–1256. [PubMed: 18691825] This in vitro study using colonic tissue of the stress-susceptible Wistar-Kyoto rat strain shows increased paracellular permeability following CRF application, which is blocked by CRF receptor antagonists. The CRF response was also reduced in mast cell-deficient rats, indicating that the CRF-induced induction of colonic permeability is mast cell-mediated.
58. De Giorgio R, Barbara G. Is irritable bowel syndrome an inflammatory disorder? *Curr Gastroenterol Rep*. 2008; 10:385–390. [PubMed: 18627650]

59. Santos J, Alonso C, Vicario M, et al. Neuropharmacology of stress-induced mucosal inflammation: implications for inflammatory bowel disease and irritable bowel syndrome. *Curr Mol Med*. 2008; 8:258–273. [PubMed: 18537634]
60. Posserud I, Stotzer PO, Bjornsson ES, et al. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. *Gut*. 2007; 56:802–808. [PubMed: 17148502]
61. Liebrechts T, Adam B, Bredack C, et al. Immune activation in patients with irritable bowel syndrome. *Gastroenterology*. 2007; 132:913–920. [PubMed: 17383420]
62. Gross KJ, Pothoulakis C. Role of neuropeptides in inflammatory bowel disease. *Inflamm Bowel Dis*. 2007; 13:918–932. [PubMed: 17343284]

Table 1

Preclinical studies highlighting the relevance of corticotropin-releasing factor-1–receptor blockade to reduce irritable bowel syndrome–like symptoms

Characteristics in patients with IBS (diarrhea-predominant):	In experimental animals, CRF₁ antagonists block stress-related:
Anxiety and/or depression	Anxiety/depression
Hypervigilance	Hypervigilance/locus coeruleus activation
Changes in autonomic functions (decreased vagal, increased sympathetic activity)	Autonomic responses(decreased vagal, increased sympathetic activity)
Increased bowel movements/diarrhea	Stimulation of colonic motility/defecation/diarrhea
Ion transport dysfunction	Colonic mucosal barrier dysfunction (increased secretion)
Mast cell changes (number, activation)	Activation of mast cells
Increased barrier permeability	Increased colonic permeability/antigen translocation
Lower pain threshold to colorectal distention	Hypersensitivity to colorectal distention

CRF—corticotropin-releasing factor; IBS—irritable bowel syndrome.

(Data from Grover and Drossman [6•], Fukudo [12•], Taché and Brunnhuber [31], and Santos et al. [59].)

Table 2

Mimicry between activation of the corticotropin-releasing factor signaling system and irritable bowel syndrome–related symptoms in humans

Study	Symptoms
CRF agonists stimulate/activate/increase in healthy humans or IBS patients:	
Fukudo [12•]	Hypothalamic-pituitary-adrenal axis
Fukudo [12•]	Motility
Wallon et al. [21•]	Permeability/bacterial translocation
Nozu and Kudaira [51•]	Viscerosensitivity
Wallon et al. [21•]	Mast cells
Holsboer and Ising [27•]	Anxiety/depression
Gross and Pothoulakis [62]	Inflammation
CRF antagonists reverse IBS-associated increase of:	
Ising and Holsboer [39], Binneman et al. [40], Sagami et al. [46]	Anxiety (may or may not influence)
Fukudo [12•]	Motility (may or may not influence)
Wallon et al. [21•]	Permeability
Fukudo [12•]	Viscerosensitivity
Gross and Pothoulakis [62]	Inflammation

CRF—corticotropin-releasing factor; IBS—irritable bowel syndrome.