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Review

Corticotropin releasing factor receptors in functional and inflammatory gastrointestinal disorders

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INTRODUCTION

The influence of emotion on gastric motor function was first described as anecdotal clinical observations by Cabanis and Beaumont followed by Pavlov's and Cannon's pioneering experimental studies in cats and dogs at the beginning of the 1900s. Alterations of the gastrointestinal (GI) motility pattern and transit by various stressors were thereafter well documented with the development of quantitative techniques to monitor GI motility pattern and transit in experimental animals and humans.[1]

Experimental studies have convincingly established peripheral stimulatory actions of CRF on colonic secretory and motor function and permeability. A direct action of CRF at the enteric nervous system was established by the presence of CRF1 receptors on colonic myenteric neurons.[2] However, it was only during the past two decades that attempts were made to unravel these mechanisms.

In this review we analyze current evidence of the role of corticotropin releasing hormone receptors of the GI tract in the expression of functional and inflammatory bowel disorders.

Key words: irritable bowel syndrome, corticotropin releasing factor, corticotropin releasing factor receptors, enteric nervous system, inflammatory bowel disorders, stress

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Stress and the brain-gut axis

Various forms of physical or psychological stress may alter gastrointestinal functions in humans and animals. Some of these stress conditions may cause, or at least be associated with, diseases such as peptic ulcer or the irritable bowel syndrome.[3]

Humans experience stress of various types during daily life, and adequate responses to these stressors are necessary for survival. If the severity or the chronicity of the stressful experience exceeds the adaptive capacity, the individual will be predisposed to illness and disease in multiple organ systems.

Early-life experience plays an important role in stress responsiveness throughout life. In animal models, neonatal adversity can result in permanent functional changes in the stress-mediating systems of the central nervous system. For example, newborn rats subjected to maternal separation demonstrate increased release of corticotrophin-releasing factor (CRF), altered expression of glucocorticoid receptors, as well as changes in the norepinephrine and GABA systems. It was also shown in humans that adverse early –life events are associated with hyperresponsiveness to stress and alterations in the hypothalamic-pituitary adrenal axis. There is evidence that early-life trauma and ongoing psychological stress can affect the clinical course of intestinal disorders and also reactivate inflammation in experimental colitis.[4] The mechanisms underlying stress-induced exacerbations of intestinal diseases are, however, largely unknown.

Studies in human subjects with gastric fistulas demonstrated that fear, anger and stress may alter gastroin-

Abbreviations used in the text

CRF= Corticotropin Releasing Factor, CRF1= Corticotropin Releasing Factor receptor 1, GI= Gastro-Intestinal, ENS= Enteric Nervous System

testinal functions, resulting in decreased gastric secretion, blood flow, and emptying. An endogenous mediator regulating and coordinating gastrointestinal secretory and motor responses following stress is the corticotropin releasing factor (CRF).[4]

CRF and other neuropeptides

Gastrointestinal tract (GI) response to stress is regulated by a brain-gut axis with centrally located mechanisms as well as by GI local mechanisms. These central and GI local mechanisms include special types of receptors as well as interactions of these receptors with the enteric nervous system (ENS). These interactions are also regulated by central and local (autocrine and paracrine) mechanisms.[5]

Several ENS agonists (corticotropin releasing factor-CRF, neuropeptide Y-NPY, neostigmine) and antagonists (cholecystokinin, bombesin, lidocaine, tetradotoxin) have so far been described and their anatomical area of action has been more or less identified at the level of GI myenteric plexus (mucosal and muscularis). On the contrary, very little is known about the endocrine type of receptors during brain-gut axis response to stress. In addition, other stress hormones activated by CRF, such as the propiomelanocortin-derived a-melanocyte-stimulating hormone (a-MSH), or catecholamines, which have complex interactions with the cytokine network, may also contribute to finely orchestrate the inflammatory process.[6]

CRF and bowel inflammatory conditions

Several convergent findings implicate the activation of brain corticotrophin releasing factor (CRF) receptors in mediating the delayed gastric emptying and stimulation of colonic motor function resulting not only from acute exposure to psychological, physical or chemical stress but also from activation of the immune system.[1]

The development of an inflammatory response triggers the activation of the neuroendocrine system via hypothalamic corticotropin-releasing factor (CRF). A growing body of evidence indicates that immune activation of the neuroendocrine system provides a counter-regulatory mechanism that critically modulates inflammatory events. CRF-mediated activation of the pituitary adrenal axis and the consequent hypersecretion of glucocorticoids provide a major anti-inflammatory mechanism at multiple levels.[7]

It has also been shown that longer exposure to stress induces bacterial internalization into the epithelium and inflammatory cell infiltration in the lamina propria suggesting that stress can be important in the initiation of intestinal inflammation.[4] Thus stress-induced mucosal abnormalities may have implications for pathogenesis as well as symptoms in intestinal diseases. An increased tendency for intestinal ion and fluid secretion would make stress-susceptible individuals more prone to diarrhea, and a more vulnerable intestinal barrier would predispose stress-susceptible individuals to inflammation because of uptake of proinflammatory luminal antigens.

The physiology of CRF

The 41-amino acid peptide corticotropin releasing factor (CRF) was isolated from ovine hypothalamus and structurally characterized in 1981 as a novel hypothalamic releasing factor stimulating the release of pituitary propiomelanocortin peptides. CRF is a brain-produced protein, which stimulates the production of adrenocorticotropic hormone (ACTH), β-endorphin and the pro-melaninotropic stimulating hormone. The final outcome of this cascade is the increase of c-AMP production in all target tissues.[5]

CRF has a broad range of effects on the nervous, endocrine, reproductive, cardiovascular, gastrointestinal, and immune systems. Various kinds of stressors or stress related conditions can induce CRF production in the brain (*Figure*). These stressors can be categorized as pscycho/physiological, immunological, visceral and chemical and exert their actions on the brain in a largely unknown way.

CRF-receptors: distribution and function

CRF acts through central and peripheral receptors. Central CRF receptors are called type 1 receptors (CRF1) and are located at the circumventricular organs-the paraventricular nucleus and the locus ceruleus complex. When stimulated by CRF, central CRF1 receptors regulate many of the autonomic, behavioral, endocrine and visceral responses, which occur during acute and chronic stress conditions.[8] This has also been proved experimentally as intravenous or intracerebroventricular administration of the CRF non-specific antagonist (astressin, a-helical-CRF 10μg/Kg) alleviated anxiety, depression or spontaneous waking produced by CRF exogenous administration.[9]

A non-selective brain-blood barrier transporter system for CRF exists, thus peripheral (intravenous, subcutaneous, intraperitoneal) or central (intracerebroventricular) administration of various CRF agonists and antagonists may produce central or peripheral actions depending on the degree of brain-blood barrier penetrating capacity.[1]

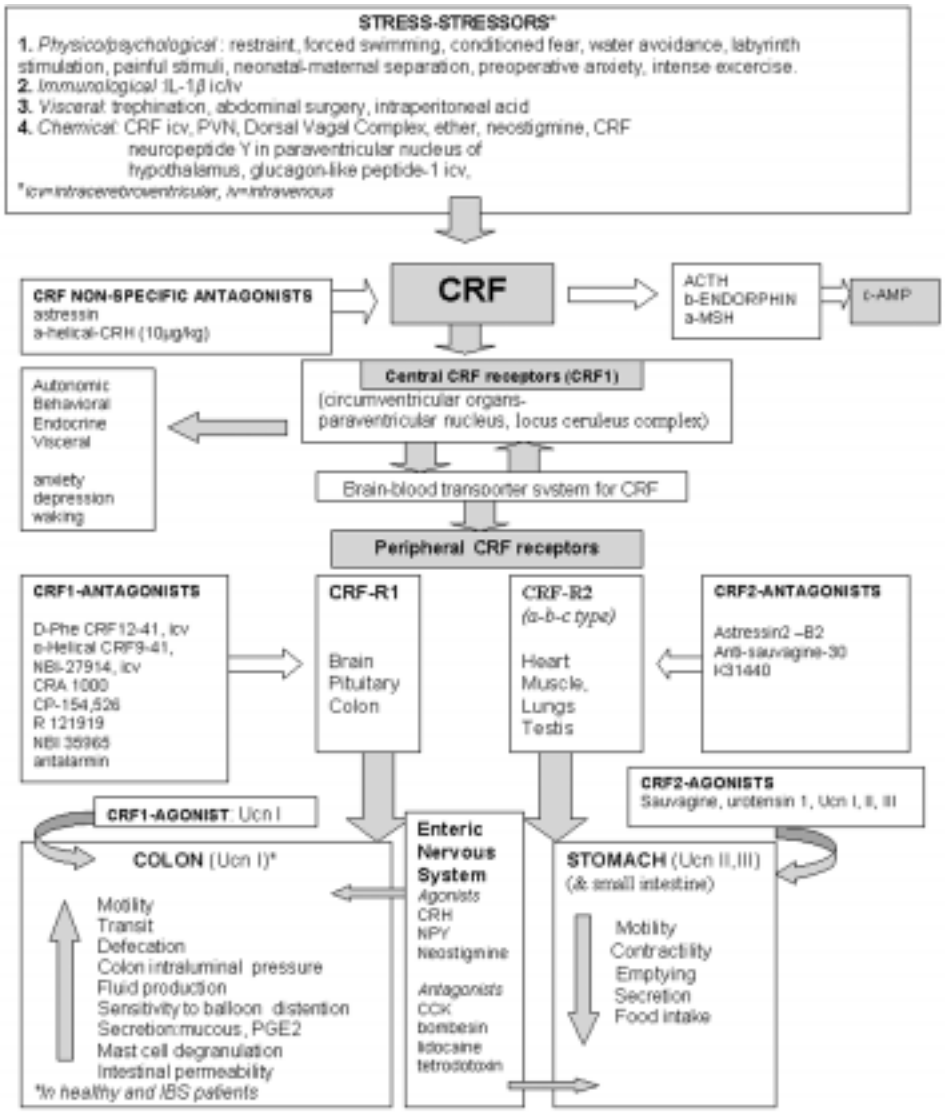

Figure. The CRF system role in irritable or inflamed gut

In the periphery CRF1 receptors are found in the colon, while CRF type 2 receptors (CRF2), are mainly located at the stomach, small intestine, heart, lungs and reproductive tissues such as testis and epididymis. Three CRF2 subtypes a-b-c are recognized in humans while only subtype b exists in rats. The cloning of CRF1 and CRF2 receptors revealed receptor proteins with a similar size (40-45 Kda) as deducted by the cDNA sequence. Either absence of significant translation or, more likely, species variation could explain the differences of CRF receptor expression in human and rat colon. It could be also postulated that varying degrees of maturation may account for differential receptor expression by inflammatory cells. CRF binds preferably to CRF1 receptors (higher affinity) than to CRF2 receptors.[10]

When peripheral CRF1 is stimulated by CRF it induces colonic responses mimicking stress condition.[11-12] Thus, CRF1 activation in colon increases all of the following: motility, colon transit, defecation, intraluminal pressure, fluid production and secretion (mucous, prostaglandin E2), mast cell degranulation, intestinal permeability and sensitivity or abdominal pain during balloon distention.[13] Those effects of CRF1 colonic receptor activation have been noticed in irritable bowel syndrome (IBS) patients as well as in healthy controls. The colonic response to central CRF-CRF1 pathway activation is unrelated to pituitary-adrenal hormone release and is mediated by modulation of the autonomic nervous system, particularly stimulation of sacral parasympathetic activity in rodents.[7]

A specific CRF1 endogenous agonist called urocortin I (Ucn I), results in the same phenomena when it interacts with CRF1 receptors during endogenous production or exogenous administration. On the other hand all specific CRF1 antagonists (a-helical CRF9-41, CP-154,526, antalarmin, NBI-27914, NBI-35695, R-121919, CRA-1000) when administered exogenously result in the opposite to CRF or Ucn I induced phenomena.[14] Consequently exogenous CRF1 antagonist administration is mimicking bowel relaxation conditions, which parallel a central nervous system relaxing pattern due to simultaneous CRF1 antagonist binding to central CRF1 receptors through the brain blood barrier transporter system.[15]

Peripheral CRF2 receptors when stimulated by CRF produce similar to stress-induced upper GI tract reactions such as decrease in gastric motility, contractility, emptying, and secretion. In addition food intake is also decreased. Specific CRF2 agonists such as urocortin I,II and III (Ucn I, II,III), sauvagine and urotensin 1, result in the same phenomena when they interact with CRF2 receptors during endogenous production (Ucn) or exogenous administration (sauvagine).[16] On the other hand all specific CRF2 antagonists (astressin2-B2, anti-sauvagine-30, K31440) when administered exogenously result in the opposite to CRF or CRF-2 agonists induced phenomena.[17-18] Consequently exogenous CRF2 antagonist administration mimicks upper GI relaxation conditions.

Functional and inflammatory GI tract disorders and CRF

Human studies

Irritable bowel syndrome is presumed to be a disorder of the brain-gut link. Psychological stress induces colonic segmental contractions, which are exaggerated in IBS patients.

In one study,[9] peripheral administration of alpha-helical-CRF (10μg/kg), which is a non-selective CRF receptor antagonist, improved gastrointestinal motility, visceral perception, and negative mood in response to gut stimulation, without affecting the hypothalamo-pituitary-adrenal axis (plasma ACTH and serum cortisol) in IBS patients. There have been recently, several interesting trials with CRF receptor antagonists (CRF1 type) in order to produce effective drugs for IBS induced GI tract symptoms but also for other GI tract impaired motility and inflammatory states such as postoperative gastric ileus, cyclic vomiting syndrome and enterotoxin-mediated intestinal inflammation.[1]

The presence of CRF1 and CRF2 mRNA transcripts in human intestinal biopsies has been described[19] although the CRF protein molecule exact localization has been not identified. In addition to the mapping of CRF ligands and receptors in the brain and gut, the development of potent selective CRF1 and CRF2 antagonists and generation of transgenic mouse models has provided useful information.

However, there is a paucity of information regarding the localization of CRF receptor protein in the periphery mainly due to the limitations of existing methodologies to directly detect the receptor molecule expressed on the cell surface in its native state and reveal any detail about its anatomical localization.

Animal studies

A study[20] in mice showed the efficacy of subcutaneous injection of the CRF1 antagonist CP-154,526 to block abdominal surgery induced delayed gastric emptying (GE). Moreover, CRF1-deficient mice subjected to laparotomy and cecal manipulation had normal GE.

Rats exposed to chronic stress develop a prolonged barrier defect to macromolecules and epithelial mitochondial damage. Neonatal trauma can induce phenotypic changes in adulthood, including enhanced vulnerability of the gut mucosa to stress (increased paracellular leakage via tight junctions and increased endocytosis of macromolecules) via mechanisms involving peripherally located CRF receptors.[4]

In another study,[21] it has been shown that brain CRF1 and vagal pathways are essential for gastric ulceration to occur in response to stress and that peripheral CRF1 antagonists may therefore be prophylactic against stress ulcer in the critically ill. There are functional receptors for CRH that mediate relaxation of ceacal circular smooth muscle cells of guinea pig[22] and peripheral CRF has been shown to activate myenteric cholinergic neurons in the proximal colon through CRF1 receptor.[23]

Key to the mapping of CRF receptor protein expression is the development of specific antibodies selective for type 1 and 2 receptors. The presence of CRF receptors on parietal cells may play a role in the inhibition of gastric acid secretion induced by peripheral CRF administration of sauvagine, a high-affinity ligand of the CRF2. Interesingly, no CRF receptors were observed in the antrum.[24]

By using specific CRF antisera both CRF receptors were found[25] in the mucosal layer of the proximal colon, CRF1 being more widely expressed through the intesti-

nal crypts and submucosal and myenteric nervous plexus. Using CRF1 antisera CRF1 immunostaining was detected in the goblet cells of the crypts of the colonic mucosal, as well as in scattered cells on the absorptive surface epithelium and in isolated cells in the lamina propria suggesting that labeling could in part be localized to cells of an inflammatory nature. The submucosal and muscularis layers were basically negative except for some cells shown to be of neuronal origin. CRF2 expression was demonstrated in the blood vessels of submucosal layer whereas no immunoreactivity was found in the externa muscularis and cells of the myenteric plexus. The described pattern of immunostaining was observed in proximal colon preparations, while in the distal colon staining was less intense suggesting a possible difference in the number of expressed binding sites in the region.

Future perspectives for CRF antagonists in Gastroenterology

Extensive preclinical research effort has solidified the concept that overactivity in the brain corticotrophin releasing factor (CRF) signaling system contributes to the onset of anxiety disorders and depression.[2]

Existing preclinical and clinical data, support the testing of new CRF antagonists, particularly more potent CRF-R1 antagonists, in IBS and the view that CRF-R1 are a promising target for the treatment of IBS.

Recent findings in monkeys and humans indicate that the CRF-R1 antagonists antalarmine and R-121919 alleviate manifestations of anxiety and depression.[6] Also reports on the beneficial effect of CRF-R1 antagonist treatment on depressive symptoms in patients with major depression suggests a therapeutic potential for CRF-R1 antagonists, particularly in subsets of IBS patients who have psychiatric illness and gastrointestinal symptoms of enhanced bowel motor function.

Clinical studies in patients with major depression and post-traumatic disorders showed that CRF levels are elevated in the cerebrospinal fluid and lowered by effective antidepressants. In patients treated with interferon a for chronic hepatitis C, activation of the brain CRF pathways induced by interferon a is frequently associated with psychiatric side effects that have overlapping features with major depression. In mice synthetic recomninant type I interferon a induced a depressive-like behavior that is abolished by pretreatment with the CRF1 receptor antagonist CP-154,526. In the upper gut, other potential clinical relevance of targeting CRF1 receptors has been recently reviewed in the context of cyclic vomiting syndrome and postoperative gastric ileus.[2]

In addition, CRF receptor antagonists may also have value in some forms of gut inflammation. A number of studies in rodents and humans established that CRF, acting through CRF1 receptors exerts an autocrine-paracrine proinflammatory action in peripheral tissues undergoing an inflammatory process. CRF, Urocortin 1, and CRF1 receptors have been detected at both the gene and the protein levels at sites of inflammation in the rodent and human intestine. Peripheral administration of CRF1 receptor antagonists significantly inhibits the degree of inflammation associated with an acute enterotoxic response, as monitored by the reduction in toxin A induced ileal secretion, epithelial cell damage, mucosal edema, neutrophil infiltration, and mucosal content of interleukin 1b and tumor necrosis factor a.[2] This points to the potential use of specific CRF1 receptor antagonists in intestinal inflammatory conditions. In conclusion, peripheral CRF receptors may be a useful target for treatment of stress-related symptoms in patients with irritable bowel syndrome or/and inflammatory bowel disease.

Although a lot of progress has so far been made, the exact GI tract localization and GI physiological function of these CRF receptors has not been clearly identified and described during functional and inflammatory bowel disorders.[26]

In addition, the exact relationship of these receptors to other inflammation or motility indices has not yet been described.

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