J Gastroenterol 2007; 42[Suppl XVII]:48–51
DOI 10.1007/s00535-006-1942-7

Journal of Gastroenterology

Role of corticotropin-releasing hormone in irritable bowel syndrome and intestinal inflammation

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Corticotropin-releasing hormone (CRH) is a major mediator of stress response in the brain-gut axis. Irritable bowel syndrome (IBS) is presumed to be a disorder of the brain–gut link associated with exaggerated response to stress. We first showed that peripheral administration of CRH aggravated visceral sensorimotor function as well as adrenocorticotropic hormone (ACTH) response in IBS patients. We then administered α-helical CRH (αhCRH), a non-selective CRH receptor antagonist among IBS patients. Electrical stimulation of the rectum induced significantly higher motility indices of the colon in IBS patients than in the controls. This response was significantly suppressed in IBS patients but not in the controls after administration of αhCRH. Administration of αhCRH induced a significant increase in the barostat bag volume of the controls but not in that of IBS patients. αhCRH significantly reduced the ordinate scale of abdominal pain and anxiety evoked by electrical stimulation in IBS patients. Plasma ACTH and serum cortisol were generally not suppressed by αhCRH. Last, administration of CRH1-receptor (CRH-R1) specific antagonist blocked colorectal distention-induced sensitization of the visceral perception in rats. Moreover, pretreatment with CRH-R1 antagonist blocked colorectal distention-induced anxiety, which was measured with elevated plus-maze, in rats. Evidence supporting the concept that peripheral CRH and CRH-R1 play important roles in brain-gut sensitization is increasing. Several studies have identified immunoreactive CRH and urocortin as well as CRH-R1 and CRH-R2 mRNAs in human colonic mucosa. In addition, reverse transcription-polymerase chain reaction has revealed the expression of CRH-R1 mRNA in both the myenteric and submucosal plexus in the guinea pig. Application of CRH has been shown to evoke depolarizing responses associated with elevated excitability in both myenteric and submucosal neurons. On the other hand, peripheral injection of CRH has been reported to induce discrete effects on colonic secretory and motor function, and permeability. There are functional differences between CRH-R1 and CRH-R2. For instance, activation of CRH-R1 causes a proinflammatory response, whereas stimulation of CRH-R2 provokes anti-inflammatory changes. In addition, there is evidence of the contrasting roles of CRH-R1 and CRH-R2 in visceral nociception. While CRH-R1 is involved in the pro-nociceptive effects of visceral pain, CRH-R2 mediates an anti-nociceptive response. These findings suggest the major role of CRH in stress-related pathophysiology of IBS and possibly in inflammation of the intestinal mucosa.

Key words: corticotropin-releasing hormone (CRH), brain-gut axis, irritable bowel syndrome (IBS), CRH1-receptor (CRH-R1), CRH2-receptor (CRH-R2)

Introduction

Irritable bowel syndrome (IBS) is a disorder of chronic abdominal pain and abnormal bowel movements.[1] IBS is common and important in developed countries.[2] IBS has a great impact on quality of life of the patients and on medical economy.[3,4] Recent advances in neurogastroenterological research clearly demonstrate that mutual and reciprocal interactions between the brain and the gut play a major role in the pathophysiology of IBS.[5] IBS is known as one of stress-related disorders.[6] IBS patients have a higher incidence of sexual or physical abuse than patients with organic gastrointestinal disorders.[7] Traumatic stress may trigger sensitization of the neuroenteric circuits in IBS-prone individuals.

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Corticotropin-releasing hormone (CRH)

Identification of the key molecule which forms or maintains IBS status is important. There are several candidate substances which regulate changes in colonic motility, changes in visceral perception, and changes in autonomic function under stress. Corticotropin-releasing hormone (CRH) is a plausible molecule of the key mediator.[8–10] The *CRH* gene is located at region 13 of the long arm of chromosome 8.[11] The promoter area and coding region of the gene are well analyzed, and transcription, translation, and processing are clarified.

Stress is processed in the brain and the signal is conducted to the paraventricular nucleus (PVN) of the hypothalamus.[12] CRH is released in the PVN and stimulates adrenocorticotropic hormone (ACTH) secretion from the pituitary gland.[8] ACTH stimulates the adrenocortex and releases cortisol. At the same time, CRH activates sympathetic nervous system and stimulates cardiovascular system.[13] CRH also activates sacral parasympathetic outflow and stimulates colonic motility.[9] Recently, distention of the colon is known to activate the CRH system in the brain.[14] Therefore, visceral stimulation is interpreted as interoceptive stress.

Effect of CRH is mediated via CRH receptors in the cell membrane of effecter organs.[15] CRH receptor is a seven transmembrane G-protein coupled receptor.[15] Activated G-protein stimulates adenylate cyclase and increases intracelluar cyclic AMP. CRH receptors are expressed in the various brain regions.[16,17] They are the cerebral cortex, cerebellum, hypothalamus, anterior pituitary, amygdala, hippocampus, locus ceruleus, lateral septum, and others. CRH receptors are also expressed in the peripheral organs.[18] They are heart, arterial smooth muscle, lung, spleen, stomach, intestine, adrenal glands, kidney, skin, skeletal muscle, testis, ovary, and uterus, and others.

CRH: clinical evidence

We injected CRH in normal men.[10] Segmental contractions of the colon were induced by CRH. In IBS patients, exogenous administration of CRH induced robust colonic motility.[10] Exogenous administration of CRH also induced exaggeration of colonic motility indices in IBS patients. Besides, exogenous administration of CRH induced exaggeration of ACHT secretion in IBS patients. This finding was replicated by Dinan et al.[19]

If CRH is a key molecule in pathophysiology of IBS, CRH antagonist will produce some favorable change in IBS patients. α-Helical CRH is a 33 amino acids-peptide which has the action of antagonizing CRH receptors.[20] The electrical stimulation of the rectum induced an increase in motility indices in IBS patients but not in controls. This response was inhibited by administration of α-helical CRH.[20] The electrical stimulation of the rectum induced decrease in the colonic volume in IBS patients but not in controls.[20] Administration of α-helical CRH significantly increased the colonic volume in controls but not in IBS patients. Besides, the electrical stimulation of the rectum significantly induced an intensity-dependent increase in the ordinate scale of abdominal pain in both groups. Administration of α-helical CRH significantly decreased the pain ordinate scale at electrical stimulation in IBS patients.[20] IBS patients reported more anxiety in response to the visceral stimulation. Administration of α-helical CRH clearly reversed this change.[20]

CRH: animal evidence

Data from animal experiments also support the concept of a role of CRH in IBS pathophysiology.[21] Colorectal distention significantly induced noradrenaline release in the rat hippocampus.[22] Noradrenalinergic neurons originated from the locus ceruleus are known to have a positive feedback loop with CRH neurons. Administration of α-helical CRH significantly suppressed hippocampal noradrenaline release induced by colorectal distention.[14] This finding indicates that colorectal distention-induced firing of the locus ceruleus forms a positive feedback loop with CRH neurons and that blockade of CRH receptors is a key to suppressing noradrenalinergic neurons. Moreover, colorectal distention significantly increased plasma ACTH.[14] Experiments were performed single acute distention for 10 min and 20 min and repetitive distention once per day for 7 days. Administration of specific CRH-R1 antagonist JTC017 significantly suppressed plasma ACTH release by colorectal distention for 10 min at acute experiments. In chronic experiments, HPA axis was habituated and CRH-R1 antagonist was less effective than in acute 10-min distention. In acute experiments, colorectal distention induced anxiety-like behaviors measured by elevated plus-maze. Pretreatment with CRH-R1 antagonist reversed the colorectal distention-induced anxiety. In chronic experiments, in contrast, neither colorectal distention nor administration of CRH-R1 antagonist significantly changed anxiety-like behaviors in rats. In chronic distention, colorectal distention significantly increased fecal pellet output. Pretreatment with CRH-R1 antagonist reversed the colorectal distention-induced colonic hypermotility. In contrast, neither colorectal distention nor administration of CRH-R1 antagonist significantly changed colonic motility in rats.[14]

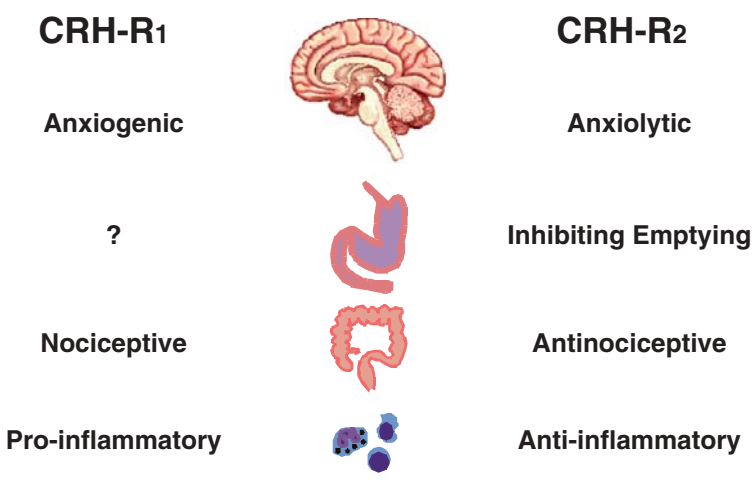

Fig. 1. Functional differences between CRH-R1 and CRH-R2. In the brain, R1 stimulation causes anxiety whereas R2 stimulation induces anxiolysis. In the gut motility, R1 stimulation evokes colonic motility whereas R2 stimulation inhibits gastric emptying. R1 mediates visceral nociception whereas R2 may reduce visceral perception. Activation of CRH-R1 causes proinflammatory response, whereas stimulation of CRH-R2 provokes anti-inflammatory changes

Inflammation of the gut and CRH

Chronic low-grade inflammation or discrete inflammation of the gut mucosa combined with psychosocial stress may trigger the sensitization of the lower gastrointestinal tract in IBS.[23,24] Several reports indicated that there is low-grade inflammation of the colonic mucosa in IBS patients.[25,26] Increase in intraepithelial lymphocytes, CD3 positive cells, and CD25 positive cells was found in the colonic mucosa of IBS patients.[26]

Activated immune system may result in elevated plasma cytokines in the peripheral blood in IBS patients. Dinan et al.[19] reported increase in plasma interleukin-6 level in IBS patients. There was no abnormality in the plasma level of TNF-α. Interestingly, the plasma level of interleukin-6 positively correlated with the CRH-stimulated ACTH level. Some links between macrophage and colonic function may be present. Studies by Muramatsu et al.[27] proved mRNA of the CRH family peptide urocortin and CRH receptors in the human colonic mucosa. The major source of urocortin in the human colonic mucosa is macrophages. Furthermore, Wood's group recently proved the existence of CRH immunoreactivity and CRH receptors in the myenteric plexus of the guinea pig.[28] There are abundant CRH-R1 positive cells in the myenteric neurons. Most of them are excitatory neurons which enhance colonic and intestinal motility. Besides, there is some evidence that peripheral CRH induces inflammation via an increase in intestinal permeability.[29] Degranulated mast cells may play a role in the proinflammatory action of CRH.

On the other hand, CRH-R2 has been proven to have an anti-inflammatory action.[30] CRH-R2-deficient mice showed increased paw edema after the exposure to the heat stimuli. Besides, CRH-R2 has anti-nociceptive action.[31] Administration of CRH-R2 agonist human urocortin2 inhibited spinal expression of immunoreactivity of the extracelluar signal-regulated kinase 1/2 evoked by the colorectal distention in rats. There are functional differences between CRH-R1 and CRH-R2.[32] In the brain, R1 stimulation causes anxiety whereas R2 stimulation induces anxiolysis. In the gut motility, R1 stimulation evokes colonic motility whereas R2 stimulation inhibits gastric emptying. R1 mediates visceral nociception whereas R2 may reduce visceral perception. Finally, activation of CRH-R1 causes proinflammatory response, whereas stimulation of CRH-R2 provokes anti-inflammatory changes (Fig. 1).

Conclusion

In IBS patients, psychosocial or interoceptive stress is likely to induce CRH release and ACTH release. Stress increases colonic motility, visceral perception, and anxiety. Many reports proved that exogenous administration of CRH increased colonic motility, visceral perception, and anxiety. Administration of CRH receptor antagonist blocks increased colonic motility, visceral perception, and anxiety induced by stress. There is some evidence that low-grade inflammation in the colonic mucosa of IBS. CRH family peptides and/or receptors may interact with immune cells. Therefore, in the near future, the role of CRH family peptides and/or receptors in the intestinal inflammation should be addressed.

Acknowledgments. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a Grant-in-Aid for Scientific Research from the Ministry of Health, Labour, and Welfare of Japan.

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