Brief Communication

Yonsei Med J 2017 Jul;58(4):872-877
https://doi.org/10.3349/ymj.2017.58.4.872

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

The Effect of Peripheral CRF Peptide and Water Avoidance Stress on Colonic and Gastric Transit in Guinea Pigs

Zahid Hussain, Hae Won Kim, Cheal Wung Huh, Young Ju Lee, and Hyojin Park

Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are common gastrointestinal (GI) diseases; however, there is frequent overlap between FD and IBS patients. Emerging evidence links the activation of corticotropin releasing factor (CRF) receptors with stress-related alterations of gastric and colonic motor function. Therefore, we investigated the effect of peripheral CRF peptide and water avoidance stress (WAS) on upper and lower GI transit in guinea pigs. Dosages 1, 3, and 10 μg/kg of CRF were injected intraperitoneally (IP) in fasted guinea pigs 30 minutes prior to the intragastric administration of charcoal mix to measure upper GI transit. Colonic transits in non-fasted guinea pigs were assessed by fecal pellet output assay after above IP CRF doses. Blockade of CRF receptors by Astressin, and its effect on GI transit was also analyzed. Guinea pigs were subjected to WAS to measure gastrocolonic transit in different sets of experiments. Dose 10 μg/kg of CRF significantly inhibited upper GI transit. In contrast, there was dose dependent acceleration of the colonic transit. Remarkably, pretreatment of astressin significantly reverses the effect of CRF peptide on GI transit. WAS significantly increase colonic transit, but failed to accelerate upper GI transit. Peripheral CRF peptide significantly suppressed upper GI transit and accelerated colon transit, while central CRF involved WAS stimulated only colonic transit. Therefore, peripheral CRF could be utilized to establish the animal model of overlap syndrome.

Key Words: Corticotrophin releasing factor, water avoidance stress, overlap syndrome, GI transit, guinea pig

Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are common gastrointestinal (GI) diseases, comprising 10 to 25% of the general population.[1,2] However, there are several reports regarding frequent overlap between FD and IBS patients.[3-5] Recently, a meta-analysis by Ford, et al.[1] estimated the prevalence of dyspepsia in IBS to be 27%, while the frequency of IBS among patients with FD was predicted to be higher than 37%. According to Rome III criteria, subjects with overlapping FD and IBS show a significant increase in the severity of psychopathology, as well as pathophysiological features.[6-8] Likewise, Tack, et al.[9] also found that patients with FD-IBS overlap had a greater prevalence of hypersensitivity to gastric distention and more severe FD symptoms, compared with patients of FD alone. It is speculated that the overlap syndrome may be a manifestation of generalized GI motor disturbances, altered visceral sensitivity/or brain-gut dysfunction, and stressful early life events.[8-13] Studies in rodents have found that stress enhances gastric contractions, stimulates colonic transit, and causes visceral hyperalgesia. These findings demonstrated that stress might induce abnormalities in GI function.[14-16]

Stress is one of the primary factors associated with the onset, exacerbation, and reactivation of many GI disorders.[10,11] The detail mechanisms by which stress leads to disordered GI functions still remain to be discovered. However, strong experimental evidence suggests that corticotropin releasing factor (CRF) and its receptors in the brain facilitate stress-related alterations in GI motility.[12,13,17,18] Central injection of CRF ligands in experimental animals reproduces stress related alterations

Received: February 10, 2017 **Revised:** April 15, 2017
Accepted: April 18, 2017
Corresponding author: Dr. Hyojin Park, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea.
Tel: 82-2-3463-3882, Fax: 82-2-3463-3882, E-mail: hjpark21@yuhs.ac

•Part of this study was presented in Asian Pacific Digestive Week (APDW) 2016, held on November 2–5, in Kobe, Japan.
•The authors have no financial conflicts of interest.

of gut motor function, whereas CRF antagonist administration prevents the effects of various stressors.[12] In addition to the brain, CRF ligands and receptors are widely expressed in enteric nervous system neurons and other cells of the GI tract in animals and humans.[19-22] Remarkably, peripheral administration of CRF ligands was found to mimic changes similar to that induced by stress, while its antagonists alleviate stress-induced alteration of GI function.[23,24] This indicates the co-existence of a peripheral and central CRF signaling pathway, and together, they might play critical role in stress-related alterations of gut function. Several studies reported differential action of CRF ligands upon interaction with different CRF receptor subtypes on upper and lower GI motility.[25,26]

Apart from CRF induced stress, water avoidance stress (WAS) is also used as a model to study psychological stress.[14-16,27] Enck, et al.[28] reported that WAS delays gastric emptying, while Nozu, et al.[16] demonstrated enhanced gastric contractions are mediated by peripheral CRF1 receptors. However, several studies have shown that WAS augments lower GI transit.[14,15,28] In the colon, WAS stimulates motility mediated by the central CRF pathway.[14,15,28] However, the relationship between stress and impairment of GI motor activity has not been fully elucidated. Therefore, the aim of the present study was to determine the effect of peripheral CRF peptide and water avoidance induced stress on the colonic and the gastric transit in the guinea pig model.

Adult male Hartley guinea pigs (250–350 g, Orient Bio, Inc., Seoul, Korea) were acclimatized to their holding room. A standard guinea pig diet and drinking water were provided *ad libitum*. All experiments were conducted in accordance with the guidelines of animal laboratory Ethics Committees of the Department of Laboratory Animal Medicine, Medical Research Center, Yonsei University College of Medicine. This study was approved by the Institutional Animal Care and Use Committee of Yonsei University College of Medicine with IRB protocol number 2015-0221.

The following chemicals and drugs were used: isotonic sodium chloride solution (Dai Han Pharmaceuticals, Seoul, Korea), charcoal (Sigma, Milwaukee, WI, USA), barium sulfate (Taejoon Pharmaceuticals, Seoul, Korea), r/h CRF (Peptide Institute, Inc., Osaka, Japan) and Astressin (Sigma, St. Louis, MO, USA).

The effect of CRF treatment on upper GI transit was tested by charcoal transit assay in fasted guinea pigs. r/h CRF peptides of different concentrations (1, 3, and 10 μg/kg) and vehicle (saline) were injected intraperitoneal (IP) in guinea pigs. CRF receptor blockade by astressin and the effect of CRF on the upper GI transit was measured by charcoal transit assay. Guinea pigs were IP injected with different doses of astressin (1, 3, and 10 μg/kg) and vehicle (saline) and incubated for 15 minutes. Subsequently, each of these groups was injected with 10 μg/kg of IP CRF. After 30 minutes of stabilization, 3 mL of charcoal mixture was administered via orogastric cannula. 10 minutes after incubation with charcoal mix, guinea pigs were sacrificed to evaluate the charcoal migration. The effect of CRF treatment on lower GI transit was measured by fecal pellet output (FPO) assay in non-fasted guinea pigs. r/h CRF peptides of different concentrations (1, 3, and 10 μg/kg) and vehicle were injected IP in guinea pigs. Guinea pigs were IP injected with different concentrations of astressin (1, 3, and 10 μg/kg), and after 15 minutes of stabilization, 10 μg/kg of CRF was injected IP in each group. Each guinea pig was incubated into an individual experimental cage, and cumulative number and weight of fecal pellets expelled were measured and recorded for 3 hours. WAS was performed as described by Bonaz and Taché[14] and Miwa, et al.[27] Stress model guinea pigs were acclimatized on the platform in a box 1 hour daily for 3 days, and on the next 2 days, were given WAS. Sham stressed group was acclimatized on the platform for 1 hour daily for 5 days. A control group was not subjected to any kind of stress and kept in housing cages only. After WAS exposure for 1 hour on day 5, guinea pigs were administered charcoal mix, incubated for 15 minutes, and then sacrificed and evaluated for upper GI transit. Lower GI transit in stress model was measured by cumulative fecal pellets in the course of the 4th and 5th days of WAS. Statistical analysis was performed using repeated measures ANOVA with post hoc comparison. In all tests, statistical significance was assigned at $p<0.05$. All data were analyzed using SPSS software, version 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

The effect of different doses (1, 3, and 10 μg/kg) of CRF peptide was tested in upper GI transit by charcoal transit assay. As shown in Fig. 1, the percent (%) charcoal migration (cm) in control group (55.6±19.9) was relatively similar to that of CRF 1 μg/kg (64.1±9.2) and 3 μg/kg (57.9±22.7) groups. However, IP CRF 10 μg/kg injected guinea pigs showed significant inhibition of upper GI transit, compared to control (6.4±2.2 vs. 55.6±19.9) (Fig. 1). Similarly, the effect of different doses of CRF

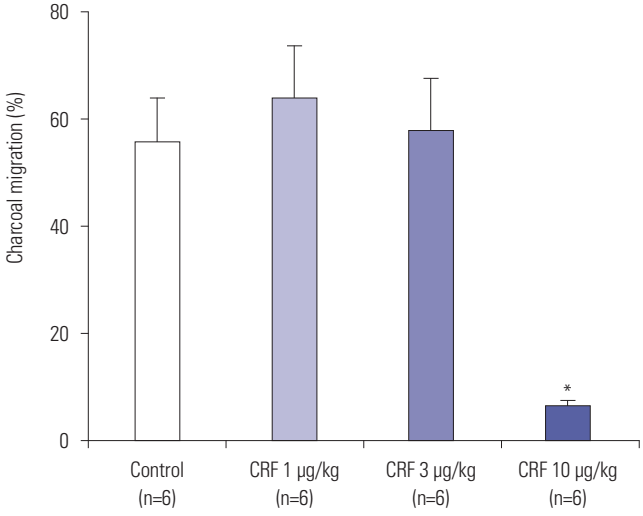

Fig. 1. The effect of different doses of CRF peptide on upper GI transit in guinea pig. Values are mean±SEM. *$p<0.05$ in comparison to control. CRF, corticotropin releasing factor; GI, gastrointestinal.

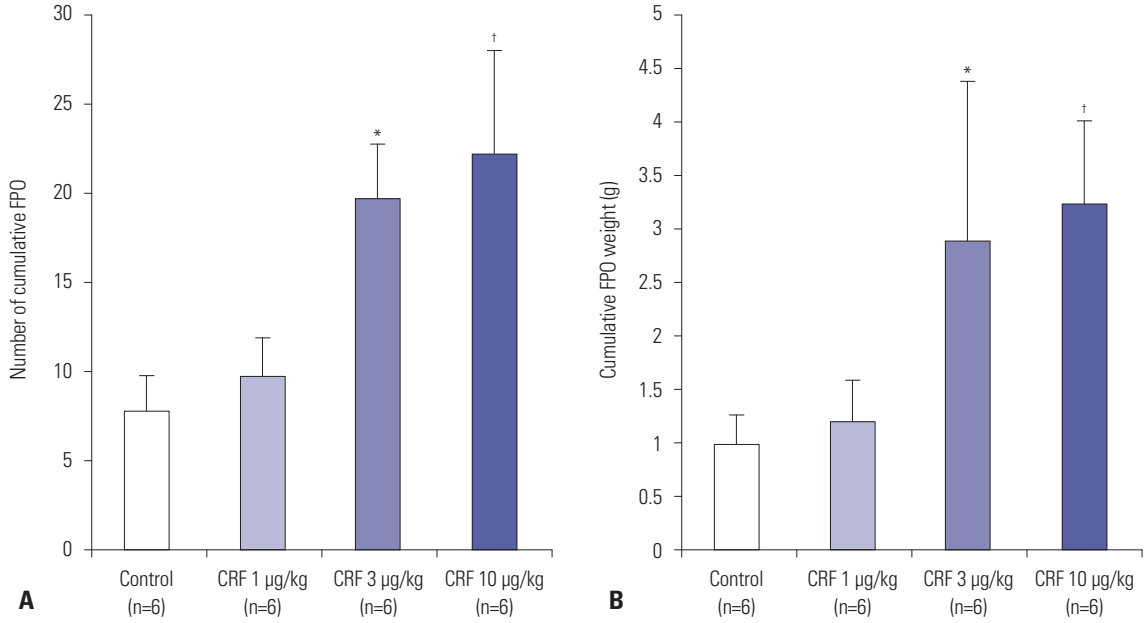

Fig. 2. Effect of different doses of CRF peptide on the lower GI transit in guinea pig. (A) The effect of different concentrations of CRF on the number of cumulative fecal pellets. (B) The effect of different concentrations of CRF on the cumulative FPO weight (g). Values are mean±SEM. *p<0.05, †p<0.01 in comparison to control. CRF, corticotropin releasing factor; GI, gastrointestinal; FPO, fecal pellet output.

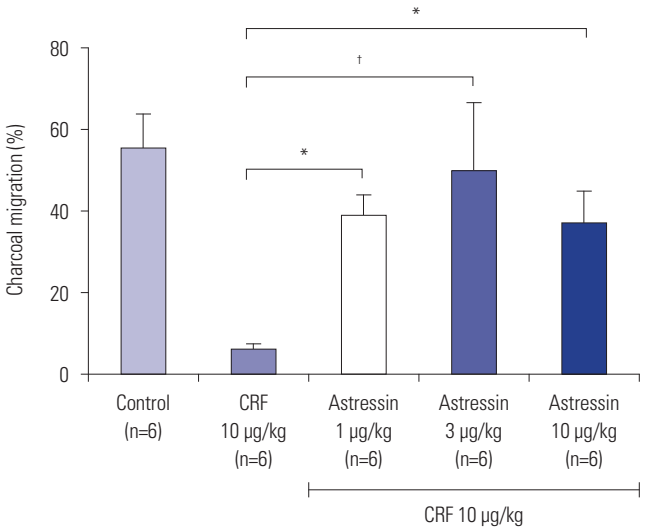

Fig. 3. The effect of astressin on upper GI transit in comparison to only CRF 10 μg/kg. Values are mean±SEM. *p<0.01, †p<0.001. CRF, corticotropin releasing factor; GI, gastrointestinal.

peptide on lower GI transit was analyzed by FPO assay. As shown in Fig. 2A, the number of fecal pellets expelled in the control group was 7.8±4.4, whereas those in the CRF (1, 3, and 10 μg/kg) IP injected groups were 9.8±4.5, 19.6±1.8, and 22.1±13.8, respectively. The data clearly showed a dose dependent increase in the FPO in CRF injected guinea pigs. As compared to controls, CRF 3 and 10 μg/kg treated guinea pigs significantly increased the cumulative fecal pellets and weight (Fig. 2). Upper and lower GI transit experiments in this study confirmed 10 μg/kg of IP CRF was the most effective dose that can impact both upper and lower GI transit in the experimental model of guinea pig. Next, the effect of astressin was tested on this model. As shown in Fig. 3, pretreated guinea pigs with different doses (1, 3, and 10 μg/kg) of astressin significantly increases the upper GI transit, compared to only CRF 10 μg/kg treated model. In contrast, the effects of different doses (1, 3, and 10 μg/kg) of astressin on lower GI transit significantly reduced FPO, compared to only the CRF 10 μg/kg treated model (Fig. 4). WAS experiment was divided into three different groups: control, sham stress, and stress model. Charcoal migration assay showed that WAS had an insignificant effect on upper GI transit among different groups (Fig. 5). In contrast, WAS significantly accelerated lower GI transit (Fig. 6). The cumulative FPO of the stress model was more than 3 fold compared to sham stress and control groups (p<0.05) (Fig. 6).

Several studies demonstrated that patients with one of the GI diseases often suffer from a second overlapping disease.[29-32] A recent population based study from China based on Rome III criteria showed 33% overlap of patients of IBS in FD patients and 45.9% of FD in IBS patients.[30] Again a study from Japanese general population showed the prevalence of overlap of FD and/or IBS in gastroesophageal reflux disease (GERD), GERD, and/or IBS in FD, and GERD and/or FD in IBS were 46.9, 47.6, and 34.4% respectively.[2] Apart from high prevalence, our previous study, as well as several other reports, have suggested a health related decline in quality of life and higher severity symptom score among patients of FD-IBS overlap.[2,29-33] Despite higher incidence, there is no successful animal model with face and construct validity for human syndrome. Therefore, it was imperative to develop an animal model that could mimic more than one symptom of the human overlap syndrome and could be used for the identification of molecular targets in drug development.

https://doi.org/10.3349/ymj.2017.58.4.872

Emerging evidence links the activation of CRF receptors with stress-related alterations of gastric and colonic motor function.[34-37] In order to establish an experimental animal model of overlap syndrome, the present study targeted CRF receptors to analyze its effects on upper and lower GI transit in conscious guinea pigs. This study showed that 10 μg/kg IP CRF significantly inhibited upper GI transit, compared to controls. In contrast, IP CRF led to dose dependent acceleration of lower GI transit, compared to controls. Therefore, our data clearly indicated that peripheral administration of CRF simultaneously exerts an inhibitory effect on upper gastric transit and stimulatory effect on colonic propulsive activity. Our findings support earlier observations that central or peripheral CRF suppresses gastric emptying and stimulates colonic transit.[24-26,34-37]

To validate whether CRF indeed alters gastric and colonic transits through modulation of peripheral CRF receptors, different doses of CRF receptor antagonist astressin were injected IP in conscious guinea pigs. Our data showed that even the lowest dose (1 μg/kg) of astressin significantly blocks exogenous CRF-induced alterations of gastric and colonic transits. Hence, our study confirms that CRF acts through peripheral CRF pathways and corroborated earlier findings indicating the differential role of non-selective CRF peptide on the gastric emptying and colonic transit.[34-37] Several studies demonstrated

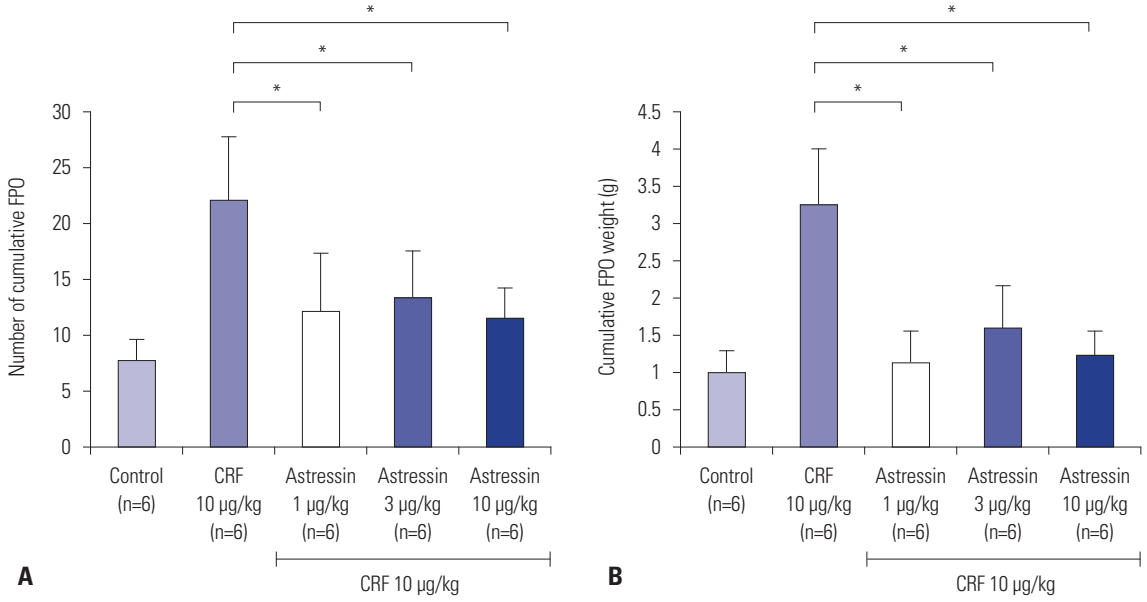

Fig. 4. The effect of astressin on (A) the number of cumulative fecal pellets and (B) cumulative fecal weight in comparison to only CRF 10 μg/kg. Mean±SEM (n=6/group). *p<0.01. CRF, corticotropin releasing factor; FPO, fecal pellet output.

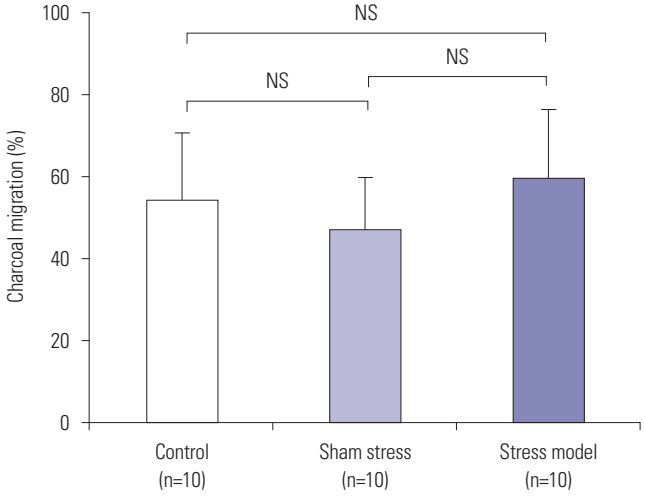

Fig. 5. The effect of water avoidance stress on upper GI charcoal transit (%) in guinea pigs. Values are mean±SEM. NS, not significant; GI, gastrointestinal.

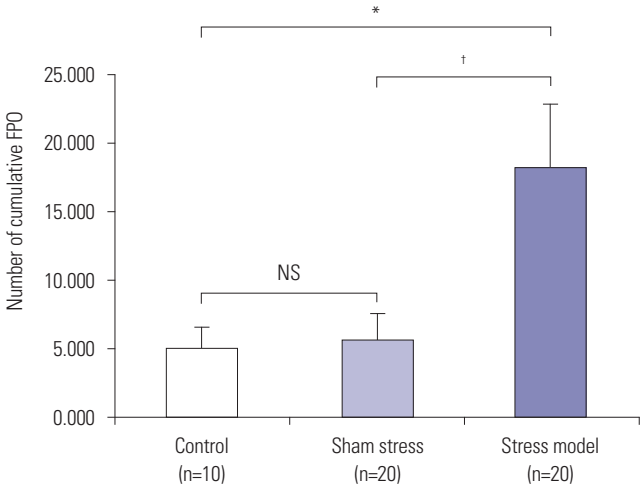

Fig. 6. Effect of water avoidance stress (WAS) on lower GI transit in guinea pigs. The number of cumulative fecal pellets in control, sham stress and stress groups due to WAS. Values are mean±SEM. *p<0.01, †p<0.05 is significant. GI, gastrointestinal; FPO, fecal pellet output; NS, not significant.

the selective CRF action on the activation of CRF2 receptors in the inhibition of gastric emptying and CRF1 receptors in the stimulation of colonic transit.[34,38,39] Thus, these results strongly suggest that CRF receptor subtypes 2 and 1 may be activated simultaneously during stress or during central and peripheral administration of CRF.[34-37]

The WAS model was applied to analyze the role of central CRF pathways in GI motility. The WAS model represents psychological stress condition in guinea pigs.[27] Our study clearly showed an increase in cumulative FPO in stress model, compare to sham stress and control groups. This corroborates earlier findings that WAS stimulates colonic motility mediated by the central CRF pathway.[14,27,28,40] Surprisingly, there was an insignificant difference in upper GI transit among the control, sham stress, and stress models. This is in contrast to earlier findings that indicated delayed gastric emptying due to WAS.[28] We speculate that acute WAS may fail to produce a certain high threshold level of CRF to modulate the upper GI motility. Our peripheral CRF data (Fig. 1) precisely indicated high dose (10 μg/kg) and inhibition of upper GI transit. In addition to vital threshold dose, the distribution of CRF receptor subtypes (1 and 2) may induce opposite actions on upper and lower GI transit.[25,34]

In conclusion, peripheral r/h CRF was found to induce opposite actions on upper and lower gut transit in conscious guinea pigs. WAS involved central CRF signaling pathway stimulated colonic propulsive activity, but failed to inhibit upper GI transit. CRF peptides were shown to mediate through interactions with peripheral CRF receptors that have physiologic relevance in acute psychological stress-induced overlap syndrome. This overlap syndrome model may provide new venues and construct validity for the identification of molecular targets/biomarkers under stress-related activation of CRF pathways.

ACKNOWLEDGMENTS

This study was supported by a Faculty Research Grant, Department of Internal Medicine, Yonsei University College of Medicine, 2015.

REFERENCES

1. Ford AC, Marwaha A, Lim A, Moayyedi P. Systematic review and meta-analysis of the prevalence of irritable bowel syndrome in individuals with dyspepsia. Clin Gastroenterol Hepatol 2010;8:401-9.
2. Kaji M, Fujiwara Y, Shiba M, Kohata Y, Yamagami H, Tanigawa T, et al. Prevalence of overlaps between GERD, FD and IBS and impact on health-related quality of life. J Gastroenterol Hepatol 2010;25:1151-6.
3. Talley NJ, Dennis EH, Schettler-Duncan VA, Lacy BE, Olden KW, Crowell MD. Overlapping upper and lower gastrointestinal symptoms in irritable bowel syndrome patients with constipation or diarrhea. Am J Gastroenterol 2003;98:2454-9.
4. Agréus L, Svärdsudd K, Nyrén O, Tibblin G. Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. Gastroenterology 1995;109:671-80.
5. Caballero-Plasencia AM, Sofos-Kontoyannis S, Valenzuela-Barranco M, Martín-Ruiz JL, Casado-Caballero FJ, López-Mañas JG. Irritable bowel syndrome in patients with dyspepsia: a community-based study in southern Europe. Eur J Gastroenterol Hepatol 1999;11:517-22.
6. Mayer EA, Craske M, Naliboff BD. Depression, anxiety, and the gastrointestinal system. J Clin Psychiatry 2001;62 Suppl 8:28-36.
7. Levy RL, Olden KW, Naliboff BD, Bradley LA, Francisconi C, Drossman DA, et al. Psychosocial aspects of the functional gastrointestinal disorders. Gastroenterology 2006;130:1447-58.
8. Corsetti M, Caenepeel P, Fischler B, Janssens J, Tack J. Impact of coexisting irritable bowel syndrome on symptoms and pathophysiological mechanisms in functional dyspepsia. Am J Gastroenterol 2004;99:1152-9.
9. Tack J, Demedts I, Dehondt G, Caenepeel P, Fischler B, Zandecki M, et al. Cinical and pathophysiological characteristics of acute-onset functional dyspepsia. Gastroenterology 2002;122:1738-47.
10. Chang L. The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome. Gastroenterology 2011;140:761-5.
11. Caso JR, Leza JC, Menchén L. The effects of physical and psychological stress on the gastro-intestinal tract: lessons from animal models. Curr Mol Med 2008;8:299-312.
12. Taché Y, Martinez V, Million M, Wang L. Stress and the gastrointestinal tract III. Stress-related alterations of gut motor function: role of brain corticotropin-releasing factor receptors. Am J Physiol Gastrointest Liver Physiol 2001;280:G173-7.
13. Taché Y, Martinez V, Wang L, Million M. CRF1 receptor signaling pathways are involved in stress-related alterations of colonic function and viscerosensitivity: implications for irritable bowel syndrome. Br J Pharmacol 2004;141:1321-30.
14. Bonaz B, Taché Y. Water-avoidance stress-induced c-fos expression in the rat brain and stimulation of fecal output: role of corticotropin-releasing factor. Brain Res 1994;641:21-8.
15. Bradesi S, Schwetz I, Ennes HS, Lamy CM, Ohning G, Fanselow M, et al. Repeated exposure to water avoidance stress in rats: a new model for sustained visceral hyperalgesia. Am J Physiol Gastrointest Liver Physiol 2005;289:G42-53.
16. Nozu T, Kumei S, Takakusaki K, Okumura T. Water-avoidance stress enhances gastric contractions in freely moving conscious rats: role of peripheral CRF receptors. J Gastroenterol 2014;49:799-805.
17. Bale TL, Vale WW. CRF and CRF receptors: role in stress responsivity and other behaviors. Annu Rev Pharmacol Toxicol 2004;44:525-57.
18. Taché Y, Million M. Central corticotropin-releasing factor and the hypothalamic-pituitary-adrenal axis in gastrointestinal physiology. In: Johnson LR, Barrett KE, Merchant JL, Ghishan FK, Said HM, Wood JD, editors. Physiology of the gastrointestinal tract. 4th ed. Burlington: Elsevier Academic Press; 2006. p.791-816.
19. Kawahito Y, Sano H, Mukai S, Asai K, Kimura S, Yamamura Y, et al. Corticotropin releasing hormone in colonic mucosa in patients with ulcerative colitis. Gut 1995;37:544-51.
20. Liu S, Gao X, Gao N, Wang X, Fang X, Hu HZ, et al. Expression of type 1 corticotropin-releasing factor receptor in the guinea pig enteric nervous system. J Comp Neurol 2005;481:284-98.
21. Porcher C, Juhem A, Peinnequin A, Sinniger V, Bonaz B. Expression and effects of metabotropic CRF1 and CRF2 receptors in rat small intestine. Am J Physiol Gastrointest Liver Physiol 2005;288:G1091-103.
22. Chatzaki E, Crowe PD, Wang L, Million M, Taché Y, Grigoriadis DE. CRF receptor type 1 and 2 expression and anatomical distribution in the rat colon. J Neurochem 2004;90:309-16.
23. Taché Y, Perdue MH. Role of peripheral CRF signalling pathways

https://doi.org/10.3349/ymj.2017.58.4.872

in stress-related alterations of gut motility and mucosal function. Neurogastroenterol Motil 2004;16 Suppl 1:137-42.
24. Williams CL, Peterson JM, Villar RG, Burks TF. Corticotropin-releasing factor directly mediates colonic responses to stress. Am J Physiol 1987;253(4 Pt 1):G582-6.
25. Martínez V, Wang L, Rivier JE, Vale W, Taché Y. Differential actions of peripheral corticotropin-releasing factor (CRF), urocortin II, and urocortin III on gastric emptying and colonic transit in mice: role of CRF receptor subtypes 1 and 2. J Pharmacol Exp Ther 2002;301:611-7.
26. Maillot C, Million M, Wei JY, Gauthier A, Taché Y. Peripheral corticotropin-releasing factor and stress-stimulated colonic motor activity involve type 1 receptor in rats. Gastroenterology 2000;119:1569-79.
27. Miwa H, Koseki J, Oshima T, Hattori T, Kase Y, Kondo T, et al. Impairment of gastric accommodation induced by water-avoidance stress is mediated by 5-HT2B receptors. Neurogastroenterol Motil 2016;28:765-78.
28. Enck P, Merlin V, Erckenbrecht JF, Wienbeck M. Stress effects on gastrointestinal transit in the rat. Gut 1989;30:455-9.
29. Nastaskin I, Mehdikhani E, Conklin J, Park S, Pimentel M. Studying the overlap between IBS and GERD: a systematic review of the literature. Dig Dis Sci 2006;51:2113-20.
30. Wang A, Liao X, Xiong L, Peng S, Xiao Y, Liu S, et al. The clinical overlap between functional dyspepsia and irritable bowel syndrome based on Rome III criteria. BMC Gastroenterol 2008;8:43.
31. Lee HJ, Lee SY, Kim JH, Sung IK, Park HS, Jin CJ, et al. Depressive mood and quality of life in functional gastrointestinal disorders: differences between functional dyspepsia, irritable bowel syndrome and overlap syndrome. Gen Hosp Psychiatry 2010;32:499-502.
32. Park JM, Choi MG, Cho YK, Lee IS, Kim JI, Kim SW, et al. Functional gastrointestinal disorders diagnosed by Rome III questionnaire in Korea. J Neurogastroenterol Motil 2011;17:279-86.
33. Park H. Functional gastrointestinal disorders and overlap syndrome in Korea. J Gastroenterol Hepatol 2011;26 Suppl 3:12-4.
34. Martínez V, Wang L, Rivier J, Grigoriadis D, Taché Y. Central CRF, urocortins and stress increase colonic transit via CRF1 receptors while activation of CRF2 receptors delays gastric transit in mice. J Physiol 2004;556(Pt 1):221-34.
35. Taché Y, Bonaz B. Corticotropin-releasing factor receptors and stress-related alterations of gut motor function. J Clin Invest 2007;117:33-40.
36. Martínez V, Rivier J, Taché Y. Peripheral injection of a new corticotropin-releasing factor (CRF) antagonist, astressin, blocks peripheral CRF- and abdominal surgery-induced delayed gastric emptying in rats. J Pharmacol Exp Ther 1999;290:629-34.
37. Gourcerol G, Wu SV, Yuan PQ, Pham H, Miampamba M, Larauche M, et al. Activation of corticotropin-releasing factor receptor 2 mediates the colonic motor coping response to acute stress in rodents. Gastroenterology 2011;140:1586-96.
38. Nozu T, Tsuchiya Y, Kumei S, Takakusaki K, Okumura T. Peripheral corticotropin-releasing factor (CRF) induces stimulation of gastric contractions in freely moving conscious rats: role of CRF receptor types 1 and 2. Neurogastroenterol Motil 2013;25:190-7.
39. Stengel A, Taché Y. Neuroendocrine control of the gut during stress: corticotropin-releasing factor signaling pathways in the spotlight. Annu Rev Physiol 2009;71:219-39.
40. Mönnikes H, Schmidt BG, Taché Y. Psychological stress-induced accelerated colonic transit in rats involves hypothalamic corticotropin-releasing factor. Gastroenterology 1993;104:716-23.