Painful Functional Bowel Disorders: Psychological Factors

Painful functional bowel syndromes such as irritable bowel syndrome and functional dyspepsia (FD) are characterized by unexplained persistent or recurrent pain in the abdomen. These syndromes are common across the world, affecting up to 15–20% of the population [3,10,12,15]. A number of mechanisms have been suggested to explain this syndrome, with two major themes dominating the clinical literature [10]. First, visceral hypersensitivity to mechanical distension is found in a significant subset of patients and appears to correlate with postprandial pain [14,18,22]. Second, psychological and psychiatric problems are very common and are widely held to have a pathogenic role, given that patients with FD are more anxious and depressed than healthy controls [3,12,15,21]. In a clinical study that included structured psychiatric interviews, the investigators found that 87% of patients with FD, compared to 25% of patients with organic dyspepsia, had a psychiatric diagnosis [15]. Psychological factors related to FD patients included major depressive disorders, anxiety disorders, and somatization [10,12].

Psychological Factors as Drivers of Gastrointestinal Symptoms

Anybody who has experienced “butterflies in the stomach” or stress-related changes in bowel habits can attest to the fact that the brain can influence gut function and sensation. Several clinical studies have suggested that psychosocial comorbidity is a major contributor to the severity of functional dyspepsia and its impact on quality of life [19]. These findings are reinforced by a considerable volume of experimental research that links stress and depression to altered gastrointestinal sensory and motor function [1,5,6,9,17]. Together, these findings have led to the widespread belief that the physical symptoms of FD reflect either somatization or stress-induced disturbance of upper-gastrointestinal physiology. Indeed, successful management of patients with functional bowel disorders requires careful attention to these psychosocial factors, often in consultation with mental health professionals.

Gastrointestinal Problems as Drivers of Psychological Symptoms

Despite the studies reviewed above, it is still unclear whether the association between functional bowel disorders and psychological symptoms represents a cause or effect. This question will require rigorously conducted longitudinal studies that document the onset of psychosocial dysfunction in relationship to visceral symptoms. Indeed, recent studies indicate that the relationship may be bidirectional—symptoms in the gut can lead to psychological issues, and vice versa. For example, investigators in Australia followed a cohort of patients prospectively for 12 years and found that among people free of a functional gastrointestinal disorder (FGID) at baseline, higher levels of anxiety at baseline represented a significant independent predictor of developing new-onset FGIDs 12 years later. Conversely, among people who did not have elevated levels of anxiety and depression at baseline, those with a FGID at baseline had significantly higher levels of anxiety and depression at follow-up [7]. These results are reinforced by experimental findings that suggest that minor, transient irritation of the gut in neonatal animals can lead to features of depression and anxiety that persist into adulthood [11].

The Brain-Gut Axis and Underlying Biological and Neural Circuits

The biological basis of these phenomena is only just beginning to be understood. The gut and brain communicate with each other by multiple means, including hormonal and neural mechanisms. An important example of hormonal involvement is CRF (corticotropin-releasing factor), a hormone secreted by the hypothalamus. Experimental alterations in secretion of CRF and expression of its receptor, CRF1, have been implicated in the pathophysiology of stress-related phenomena as well as anxiety, depression, and changes in in gastrointestinal motility and visceral sensation [16,20]. A variety of CRF-receptor antagonists have also demonstrated the ability to block increased colonic activity and painful sensations induced by acute or chronic stress [13].

The gut also relays information to various important nuclei in the brain via ascending fibers in the vagus nerve, with potentially far-reaching consequences. The central amygdala, for instance, transforms noxious and stressful signals into behavioral and autonomic responses that include anxiety and depression. A recent report showed that a probiotic (*Lactobacillus rhamnosus*) can reduce stress-induced corticosterone and anxiety- and depression-related behavior in mice, but this beneficial effect can be prevented by vagotomy [2,8]. Electrical modulation of the vagus nerve has been approved by the U.S. Food and Drug Administration for the treatment of depression [4]. Thus, the vagus nerve can modulate emotional responses to gastrointestinal stimulation.

Facts and Fallacies

It is clear that psychological morbidity is common in patients with functional visceral pain conditions, and an understanding of this issue is crucial to the optimal management of these disorders. What is not clear is how much of this comorbidity is cause and effect. Nevertheless, recognition of this association has led to many unintended consequences, including the stigmatization of this syndrome as being “all in the head,” dismissal of patients’ suffering, and a lack of an organized approach to drug development. Much remains to be learned about the complex relationship between the “big brain” in the head and the “little brain” in the gut and how pathology in one can lead to changes in the other. Research in this area could significantly alter our clinical approach and treatment of these disorders.

References

[1] Aro P, Talley NJ, Ronkainen J, Storskrubb T, Vieth M, Johansson SE, Bolling-Sternevald E, Agreus L. Anxiety is associated with uninvestigated and functional dyspepsia (Rome III criteria) in a Swedish population-based study. Gastroenterology 2009;137:94–100.

[2] Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci USA 2011;108:16050–5.

[3] Choung RS, Talley NJ. Novel mechanisms in functional dyspepsia. World J Gastroenterol 2006;12:673–7.

[4] Grimm S, Bajbouj M. Efficacy of vagus nerve stimulation in the treatment of depression. Expert Rev Neurother 2010;10:87–92.

[5] Hsu YC, Liou JM, Liao SC, Yang TH, Wu HT, Hsu WL, Lin HJ, Wang HP, Wu MS. Psychopathology and personality trait in subgroups of functional dyspepsia based on Rome III criteria. Am J Gastroenterol 2009;104:2534–42.

[6] Kellow JE, Azpiroz F, Delvaux M, Gebhart GF, Mertz HR, Quigley EM, Smout AJ. Applied principles of neurogastroenterology: physiology/motility sensation. Gastroenterology 2006;130:1412–20.

[7] Koloski NA, Jones M, Kalantar J, Weltman M, Zaguirre J, Talley NJ. The brain-gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study. Gut 2012;61:1284–90.

[8] Konsman JP, Luheshi GN, Bluthe RM, Dantzer R. The vagus nerve mediates behavioural depression, but not fever, in response to peripheral immune signals; a functional anatomical analysis. Eur J Neurosci 2000;12:4434–46.

[9] Langeluddecke P, Goulston K, Tennant C. Psychological factors in dyspepsia of unknown cause: a comparison with peptic ulcer disease. J Psychosom Res 1990;34:215–22.

[10] Lee KJ, Kindt S, Tack J. Pathophysiology of functional dyspepsia. Best Pract Res Clin Gastroenterol 2004;18:707–16.

[11] Liu L, Li Q, Sapolsky R, Liao M, Mehta K, Bhargava A, Pasricha PJ. Transient gastric irritation in the neonatal rats leads to changes in hypothalamic CRF expression, depression- and anxiety-like behavior as adults. PLoS One 2011;6:e19498.

[12] Magni G, di Mario F, Bernasconi G, Mastropaolo G. DSM-III diagnoses associated with dyspepsia of unknown cause. Am J Psychiatry 1987;144:1222–3.

[13] Martinez V, Tache Y. CRF1 receptors as a therapeutic target for irritable bowel syndrome. Curr Pharm Des 2006;12:4071–88.

[14] Mertz H, Fullerton S, Naliboff B, Mayer EA. Symptoms and visceral perception in severe functional and organic dyspepsia. Gut 1998;42:814–22.

[15] Mimidis K, Tack J. Pathogenesis of dyspepsia. Dig Dis 2008;26:194–202.

[16] Tache Y, Kiank C, Stengel A. A role for corticotropin-releasing factor in functional gastrointestinal disorders. Curr Gastroenterol Rep 2009;11:270–7.

[17] Tache 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.

[18] Tack J, Caenepeel P, Fischler B, Piessevaux H, Janssens J. Symptoms associated with hypersensitivity to gastric distention in functional dyspepsia. Gastroenterology 2001;121:526–35.

[19] Tack J, Masaoka T, Janssen P. Functional dyspepsia. Curr Opin Gastroenterol 2011;27:549–57.

[20] 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;19:754–60.

[21] Van Oudenhove L, Vandenberghe J, Geeraerts B, Vos R, Persoons P, Fischler B, Demyttenaere K, Tack J. Determinants of symptoms in functional dyspepsia: gastric sensorimotor function, psychosocial factors or somatisation? Gut 2008;57:1666–73.

[22] Vandenberghe J, Vos R, Persoons P, Demyttenaere K, Janssens J, Tack J. Dyspeptic patients with visceral hypersensitivity: sensitisation of pain specific or multimodal pathways? Gut 2005;54:914–9.