Published in final edited form as:
Gastroenterology. 2009 June ; 136(7): 2058–2061. doi:10.1053/j.gastro.2009.04.032.

Evidence for the role of the brain-gut axis in inflammatory bowel disease: Depression as cause and effect?

YVETTE TACHÉ, PhD[*] and **CHARLES N. BERNSTEIN, MD**[**]

[*]CURE: Digestive Diseases Research Center and Center for Neurobiology of Stress, Department of Medicine, Division of Digestive Diseases, David Geffen School of Medicine at UCLA and VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA.

[**]University of Manitoba IBD Clinical and Research Centre and Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

As is the case with most chronic illnesses, there is a higher rate of anxiety and depressive disorders in inflammatory bowel disease (IBD) than in the population at large.[1] Past reviews of IBD and co-occurring psychiatric disorders challenged the long-held belief that IBD was primarily a psychosomatic illness, concluding that there was little support for the role of psychological factors in the development of ulcerative colitis or Crohn's disease. [1,2]

In a recent study using the Manitoba IBD Cohort it was shown that patients with IBD compared to a matched control group were significantly more likely to have a lifetime diagnosis of major depression (27.2% versus 12.3%, odds ratio, OR 2.2, 95% confidence interval, CI 1.64-2.95).[3] The strength of this study and what distinguished it from other past assessments of depression in IBD was that it used population based samples of patients with IBD as well as of age, sex and region matched community controls. It also used a gold standard tool for measuring depression, namely, the Comprehensive International Diagnostic Interview, a structured psychiatric interview. Panic disorder tended to be higher in IBD patients, but agarophobia without panic was not significantly different between groups and social anxiety actually was significantly lower in the IBD group (6% versus 11%, OR 0.52, 95% CI 0.32-0.85). In this study those with depression versus those without a history of depression had earlier age of onset of their IBD symptoms and earlier age at diagnosis of their IBD. For those with a mood disorder over half of mood disorder diagnoses antedated the diagnosis of IBD by more than 2 years and so depression antedating IBD could not be explained simply by IBD symptoms predisposing to depression. Even if mood disorders are in remission prior to the onset of IBD, it has been shown that lifetime experience with anxiety or mood disorders can be important even if not active recently. Previous experience with a mental disorder has been shown to increase the likelihood of a relapse in chronic

Contact information Yvette Taché, Ph.D., Digestive Diseases Division, David Geffen School of Medicine at UCLA and VA Greater Los Angeles Healthcare System 11301 Wilshire Boulevard CURE Building 115, Room 117, Los Angeles, CA 90073 USA, Fax: 310 268 4963; ytache@mednet.ucla.edu Charles N. Bernstein, M.D., Section of Gastroenterology, University of Manitoba 804F-715 McDermot Avenue, Winnipeg, Manitoba, Canada R3E- 3P4; Phone: (204) 789-3369; FAX: (204) 789 3972 cbernst@cc.umanitoba.ca.

Conflicts of interest

Dr Bernstein has served on advisory board or as a consultant to Axcan Pharma, Abbott Canada, Shire Canada and has received research funding support from UCB Canada

conditions, particularly during periods of stress.[4] Cumulatively, these data raise the issue as to whether having depression predisposes to IBD, perhaps by enhancing the intestinal immunoinflammatory response. Evidence has emerged about potential common pathways, particularly between depression and inflammatory conditions such as IBD, related to dysfunctioning immunoregulatory circuits.[5-7] Alternatively, perhaps there is a common genetic predisposition shared by both diseases, or perhaps both diseases are triggered by similar environmental factors with variable lead times to overt presentation.

It is less surprising that there might be a higher rate of depression concurrent with or after the diagnosis of IBD. [8-10] Could having depression adversely impact on the course of the bowel disease? One study of IBD patients enrolled after a flare found that those with clinically significant depressive symptoms at baseline were more likely to relapse sooner. [11] In a prospective study of patients with Crohn's disease major depression was a risk factor for failure to achieve remission with infliximab treatment.[12] Depression is associated with lower adherence to treatment regimens which may also impact on disease course.[13]

A report in this issue of GASTROENTEROLOGY provides preclinical evidence that depression can adversely affect the course of intestinal inflammation. Using two experimental models of colitis: one lymphocyte-dependent (oral dextran sulfate sodium, DSS) and one lymphocyte-independent (intracolonic 2,4 dinitrobenzensulfonic acid, DNBS), Ghia et al. explored the impact of depression on the reactivation of quiescent colitis and underlying mechanisms in mice.[14] Induction of depression triggered by two independent mechanisms including bulbectomy (to induce maladaptive behavioral patterns similar to the symptoms of patients with depression),[15] resulted in colitis reactivation. Conversely, desmethylimipramine that improved the depression also dampened the colitis. An important control experiment was the demonstration that the tricyclic antidepressant treatment that inhibited depression-induced reactivation of colitis, did not influence gut inflammation in the absence of depression. These studies provide novel experimental evidence of a causal relationship between depression and reactivation of colitis and the relevance of antidepressants in stabilizing the impact of depression on quiescent gut inflammation.

In this study, the authors also pursued mechanistic investigations based on their previous work indicating that depressive-like behaviors increased the severity of acute DSS and DNBS colitis in mice by interfering with the counter-inflammatory action of the vagus nerve exerted by nicotine receptors on gut macrophages. [16] They also previously reported that tricyclic antidepressants act by restoring parasympathetic anti-inflammatory function.[16] Using pharmacologic and surgical approaches along with genetically modified mice, in the current study Ghia et al. similarly implicated impairment of the vagal cholinergic pathway regulating cytokine secretion in depression-induced reactivation of dormant colonic inflammation. [14] Desmethylimipramine treatment normalized these changes.[14] In addition, they identified a critical role of the α-7 subunit of the nicotinic acetylcholine receptor in inhibiting proinflammatory cytokine release from gut macrophages.[14] These studies expand the growing evidence for the “cholinergic anti-inflammatory pathway” coined by Tracey and the involvement of α-7 subunit of the nicotinic acetylcholine receptor. [17, 18] Of interest was the demonstration that the colonic barrier function was not altered as monitored five days after reactivation of colitis in depressed mice regardless of treatment with desmethylimipramine. However, additional time points would be required to strengthen the conclusion that “the reactivation seen here is not due to the changes in intestinal barrier function”.

Gastroenterologists are generally ill equipped to treat depression and perhaps even to diagnose it in its mild form. Inquiry into mood disorders by gastroenterologists might be limited by time constraints, reported as the main barrier to inquiring of patients with irritable

bowel syndrome about sexual abuse.[19] Alternatively, they may simply feel they lack the experience to deal with a newly uncovered mental illness. It might just be time for gastroenterologists to become equipped with brief surveys that can screen for depression.[20,21] It would help to have access to mental health professionals who can consult on their patients expeditiously if depression is diagnosed. Recent European consensus guidelines for Crohn's disease management include recommendations to assess for anxiety and depression and identify appropriate treatment if needed.[22] Both pharmacological and behavioral therapies commonly used in depression have found some success in managing irritable bowel syndrome.[23] Could these therapies become important adjuncts in IBD treatment? Based on both human and animal model data it seems warranted to consider clinical trials of antidepressant therapy in IBD both for those who are depressed but possibly also in those without depression. A review of the literature of antidepressant therapy in IBD underscored how limited the data are in this area.[24] Even if antidepressant therapy does not impact on intestinal inflammation it may impact on quality of life.[25] In view of the clinical evidence of dysregulation of the autonomic nervous system and lower parasympathetic function in IBD patients much like in depressed patients,[26,27] the preclinical findings of Ghia et al. highlight the potential relevance in assessing whether antidepressants can improve the autonomic dysfunction in IBD patients and thereby restore the vagal anti-inflammatory pathways.

Acknowledgments

Dr. Bernstein is supported in part by a Crohn's and Colitis Foundation of Canada Research Scientist Award and the Bingham Chair in Gastroenterology and Dr. Taché by Veterans Administration Research Career Scientist Award and NIHDDK.

References

1. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: A review of comorbidity and management. Inflamm Bowel Dis. Jan 22.2009 epub ahead of print.
2. North CS, Alpers DH. A review of studies of psychiatric factors in Crohn's disease: Etiologic implications. Ann Clin Psychiatry. 1994; 6:117–24. [PubMed: 7804387]
3. Walker JR, Ediger JP, Graff LA, et al. The Manitoba IBD Cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. Am J Gastroenterol. 2008; 103:1989–1997. [PubMed: 18796096]
4. Kessler RC, Merikangas KR, Berglund P, et al. Mild disorders should not be eliminated from the DSM-V. Arch Gen Psych. 2003; 60:1117–22.
5. Rosenkranz MA. Substance P at the nexus of mind and body in chronic inflammation and affective disorders. Psychol Bull. 2007; 133:1007–1037. [PubMed: 17967092]
6. Rook GAW, Lowry CA. The hygiene hypothesis and psychiatric disorders. Trends Immun. 2008; 29:150–158.
7. Ghia J, Blennerhassett P, Collins SM. Impaired parasympathetic function increases susceptibility to inflammatory bowel disease in a mouse model of depression. J Clin Invest. 2008; 188:2209–2218. [PubMed: 18451995]
8. Kurina LM, Goldacre MJ, Yeates D, et al. Depression and anxiety in people with inflammatory bowel disease. J Epidemiol Community Health. 2001; 55:716–720. [PubMed: 11553654]
9. Lerebours E, Gower-Rousseau C, Merle V, et al. Stress life events as a risk factor for inflammatory bowel disease onset: a population-based case-control study. Am J Gastroenterol. 2007; 102:122–131. [PubMed: 17100973]
10. Fuller-Thomson E, Sulman J. Depression and inflammatory bowel disease: findings from two nationally representative Canadian surveys. Inflamm Bowel Dis. 2006; 12:697–707. [PubMed: 16917224]

11. Mittermaier C, Dejaco C, Waldhoer T, et al. Impact of depressive mood on relapse in patients with inflammatory bowel disease: A prospective 18-month follow-up study. Psychosom Med. 2004; 66:79–84. [PubMed: 14747641]
12. Persoons P, Vermeire S, Demyttenaere K, et al. The impact of major depressive disorder on the short- and long term outcome of Crohn's disease treatment with infliximab. Aliment Pharmacol Therap. 2005; 22:101–10. [PubMed: 16011668]
13. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: Meta analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000; 160:2101–7. [PubMed: 10904452]
14. Ghia JE, Blennerhassett P, Deng Y, Verdu EF, et al. Re-activation of inflammatory bowel disease in a mouse model of depression. Gastroenterology. 2009
15. Takahashi K, Saitoh A, Yamada M, Maruyama Y, Hirose N, Kamei J, Yamada M. Gene expression profiling reveals complex changes in the olfactory bulbectomy model of depression after chronic treatment with antidepressants. J Pharmacol Sci. 2008; 108:320–334. [PubMed: 19023179]
16. Ghia JE, Blennerhassett P, Collins SM. Impaired parasympathetic function increases susceptibility to inflammatory bowel disease in a mouse model of depression. J Clin Invest. 2008; 118:2209–18. [PubMed: 18451995]
17. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest. 2007; 117:289–296. [PubMed: 17273548]
18. Van Der Zanden EP, Boeckxstaens GE, de Jonge WJ. The vagus nerve as a modulator of intestinal inflammation. Neurogastroenterol Motil. 2009; 21:6–17. [PubMed: 19140954]
19. Ilnyckyj A, Bernstein CN. Sexual abuse in irritable bowel syndrome: To ask or not to ask, that is the question. Can J Gastroenterol. 2002; 16:801–806. [PubMed: 12464974]
20. Mulrow CD, Williams JW Jr, Gerety MB, et al. Case-finding instruments for depression in primary care settings. Ann Intern Med. 1995; 123:913–921. [PubMed: 7755226]
21. Means-Christensen AJ, Sherbourne CD, Roy-Byrne PP, et al. Using five questions to screen for five common mental disorders in primary care: diagnostic accuracy of the Anxiety and Depression Detector. Gen Hosp Psychiatry. 2006; 28:108–118. [PubMed: 16516060]
22. Caprilli R, Gassull MA, Escher JC, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. Gut. 2006; 55(suppl. 1):36–58.
23. Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut. 2009; 58:367–78. [PubMed: 19001059]
24. Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Andrews JM, Holtmann GJ. Antidepressants and inflammatory bowel disease: a systematic review. Clin Pract Epidemol Ment Health. 2006; 2:1–9.
25. Sareen J, Jacobi F, Cox BJ, et al. Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions. Arch Intern Med. 2006; 166:2109–16. [PubMed: 17060541]
26. Sharma P, Makharia GK, Ahuja V, Dwivedi SN, Deepak KK. Autonomic dysfunctions in patients with inflammatory bowel disease in clinical remission. Dig Dis Sci. 2009; 54:853–61. [PubMed: 18712478]
27. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. Psychosom Med. May-Jun;2005 67(Suppl 1):S29–33. [PubMed: 15953797] Arch Intern Med. 2006:2109–16. [PubMed: 17060541]