Inflammatory bowel disease

The putative role of endogenous and exogenous opiates in inflammatory bowel disease

S Collins, M Verma-Gandhu

The mu opioid receptor (MOR) is upregulated in inflammatory bowel disease, prompting consideration of the development of selective MOR agonists for the treatment of inflammatory bowel disease

The paper by Philippe and colleagues[1] in this issue of *Gut* provides new insight into the pathophysiology of inflammatory bowel disease (IBD) ***(see page 815)***. It also offers a new line of potential therapy for these diseases. The paper demonstrates the upregulation of μ opioid receptors (MOR) in inflamed tissue from patients with Crohn's disease and ulcerative colitis, and localises the upregulation, at least in part, to lamina propria mononuclear cells, including CD4+ and CD8+ lymphocytes. The paper also shows that a MOR agonist DALDA reduced the secretion of the important proinflammatory cytokine tumour necrosis factor α (TNF-α) from colonic tissue from IBD and control subjects. The study was a logical extension of previous work by the same authors showing that the MOR agonist DALDA reduced inflammation in two murine models of experimental colitis and that mice genetically deficient in the MOR were highly susceptible to induction of inflammation in the gut.[2] Taken together, these findings not only demonstrate the therapeutic potential of drugs that target the MOR in IBD, but also that endogenous opiate may confer a measure of protection against inflammation. Both findings have important clinical implications.

The findings that proinflammatory cytokines such as TNF-α upregulate the MOR in T cells and monocytes, together with the ability of the MOR agonist DALDA to suppress cytokine production and inflammation, suggest an opiate mediated feedback loop to regulate inflammatory responses. Disruption of this feedback, as shown for example in MOR deficient mice, increases susceptibility to inflammation.[2] β-Endorphin is the endogenous ligand for MOR and immunoreactive β-endorphin increases in active IBD, particularly ulcerative colitis; expression decreases during remission.[3] This temporal association between MOR expression, β-endorphin, and active inflammation further supports the notion of an inducible opiate mediated feedback mechanism for containing the inflammatory response in IBD. The fact that upregulation of MOR was restricted to inflamed sites in IBD tissue[1] further supports the notion of a local control mechanism rather than part of a generalised remodelling that occurs, for example, in neural tissue in IBD.[4]

Could such an important circuit be vulnerable to interference? Recent studies have shown that antagonism of mu opioid receptors may be useful in conditions associated with thermal dysregulation[5] and may protect against circulatory shock and cerebral ischaemia during heatstroke.[6] Clearly, if such drugs become available, they should be used cautiously in IBD patients. Interference could also come from dietary sources. There is also growing interest in opiate ligands (including antagonists) that are present in the diet. Opioid peptide precursors, for example in milk proteins,[7] can be released during food processing or digestion and alter host physiology.[8] Beta-sacomorphin is an example of a milk derived opiate which is absorbed in the gut and alters immune function.[9] Perhaps we should view reported intolerance to dairy products in IBD patients in a different light?[10 11]

The main source of β-endorphin in the gut is the enteric nervous system. A recent study showed a statistically significant close apposition between axonal varicosities of enteric nerves and lymphocytes in the gut associated lymphoid structures of the murine intestine.[12] The findings of Philippe and colleagues,[1] taken in conjunction with these findings, raises the possibility that the nervous system modulates intestinal inflammation via MOR regulation of cytokine production by lymphocytes.

It is of interest to note that the findings in the study of Phillipe and colleagues[1] were substantially more prominent in patients with ulcerative colitis than Crohn's disease. This is unlikely to reflect the distribution of MORs which are found in greater abundance in the small intestine compared with the colon.[13] The role of behavioural factors in the natural history of IBD remains controversial but in general, greater attention has always been paid to the role of behaviour in ulcerative colitis than Crohn's disease[14 15]; it is possible that there is a more prominent neuromodulatory component to ulcerative colitis to account for the findings of Phillipe and colleagues.[1]

Immune cells also produce endorphin and its release is controlled by neuroendocrine factors.[16–18] A role for lymphocyte derived endorphin has been described in somatic[19] and visceral nociception.[20] These studies identify an antinociceptive role for lymphocytes during chronic inflammation, and upregulation of the opiate receptor system in the gut may account for the observation that while acute colitis is accompanied by hyperalgesia,[21] chronic inflammation is associated with raised thresholds for pain in patients with ulcerative colitis[22] or Crohn's disease.[23]

The results of the study of Philippe and colleagues[1] prompt consideration of the development of selective MOR agonists for the treatment of IBD. Clearly, suppression of inflammation and attenuation of pain via MOR would be beneficial but are there concerns? A study showed that motility in the colon is altered in patients with ulcerative colitis,[24] and that the colon is particularly sensitive to the effects of opiates during active colitis, with a propensity for the generation of non-segmenting contractions.[25] It was believed that the accompanying increase in intracolonic pressure accounted for the reported temporal association between opiate administration and toxic megacolon.[25]

An interesting concept emerges from the two studies of Philippe and colleagues.[1] The human and animal studies show quite clearly that MOR agonists can attenuate inflammation through inhibition of proinflammatory cytokine release. The animal work shows that in the absence of MOR, there is a marked susceptibility to inflammatory stimuli. Taken together, these observations suggest tonic inhibition of inflammation mediated via the MOR. Long term opiate use in IBD patients is not uncommon and constitutes an important management problem.[26] If indeed exogenous opiates provide a protective anti-inflammatory influence acting via the MOR dependent mechanism described by Philippe and colleagues,[1] then discontinuation of the narcotic could, theoretically, precipitate a relapse of IBD.

The work of Philippe and colleagues[1] provides new insights into the regulation of intestinal inflammation. It raises the possibility of exciting new therapeutic options but also prompts questions regarding the relationship of narcotic use and the natural history of IBD.

Gut 2006;**55**:756–757.
doi: 10.1136/gut.2005.084418

Authors' affiliations
S Collins, M Verma-Gandhu, Intestinal Diseases Research Program, and Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada

Correspondence to: Professor S M Collins, Room 4W8, McMaster University Medical Centre, 1200 Main St West, Hamilton, Ontario L8N 3Z5, Canada; scolins@mcmaster.ca

Conflict of interest: None declared.

REFERENCES

1 **Philippe D**, Chakass D, Thuru X, *et al*. Mu opioid receptor expression is increased in inflammatory bowel diseases: implications for homeostatic intestinal inflammation. *Gut* 2006;**55**:815–23.
2 **Philippe D**, Dubuquoy L, Groux H, *et al*. Anti-inflammatory properties of the mu opioid receptor support its use in the treatment of colon inflammation. *J Clin Invest* 2003;**111**:1329–38.
3 **Yamamoto H**, Morise K, Kusugami K, *et al*. Abnormal neuropeptide concentration in rectal mucosa of patients with inflammatory bowel disease. *J Gastroenterol* 1996;**31**:525–32.
4 **Neunlist M**, Aubert P, Toquet C, *et al*. Changes in chemical coding of myenteric neurones in ulcerative colitis. *Gut* 2003;**52**:84–90.
5 **Chen X**, McClatchy DB, Geller EB, *et al*. The dynamic relationship between mu and kappa opioid receptors in body temperature regulation. *Life Sci* 2005;**78**:329–33.
6 **Chen ZC**, Kuo JR, Huang YP, *et al*. mu-Opioid receptor blockade protects against circulatory shock and cerebral ischemia during heatstroke. *J Cardiovasc Pharmacol* 2005;**46**:754–60.
7 **Meisel H**, FitzGerald RJ. Opioid peptides encrypted in intact milk protein sequences. *Br J Nutr* 2000;**84**(suppl 1):S27–31.
8 **Teschemacher H**. Opioid receptor ligands derived from food proteins. *Curr Pharm Des* 2003;**9**:1331–44.
9 **Elitsur Y**, Luk GD. Beta-casomorphin (BCM) and human colonic lamina propria lymphocyte proliferation. *Clin Exp Immunol* 1991;**85**:493–7.
10 **Cashman KD**, Shanahan F. Is nutrition an aetiological factor for inflammatory bowel disease? *Eur J Gastroenterol Hepatol* 2003;**15**:607–13.
11 **Mishkin S**. Dairy sensitivity, lactose malabsorption, and elimination diets in inflammatory bowel disease. *Am J Clin Nutr* 1997;**65**:564–7.
12 **Crivellato E**, Soldano F, Travan L. A light and electron microscopic quantitative analysis of nerve-immune cell contacts in the gut-associated lymphoid tissue of the mouse colon. *J Submicrosc Cytol Pathol* 2002;**34**:55–66.
13 **Sternini C**, Patierno S, Selmer IS, *et al*. The opioid system in the gastrointestinal tract. *Neurogastroenterol Motil* 2004;**16**(suppl 2):3–16.
14 **Engel GL**. Studies of ulcerative colitis. II. The nature of the somatic processes and the adequacy of psychosomatic hypotheses. *Am J Med* 1954;**16**:416–33.
15 **Sim M**, Brooke BN. Ulcerative colitis; a test of psychosomatic hypotheses. *Lancet* 1958;**2**:125–6.
16 **Kavelaars A**, Ballieux RE, Heijnen CJ. In vitro beta-adrenergic stimulation of lymphocytes induces the release of immunoreactive beta-endorphin. *Endocrinology* 1990;**126**:3028–32.
17 **Kavelaars A**, Berkenbosch F, Croiset G, *et al*. Induction of beta-endorphin secretion by lymphocytes after subcutaneous administration of corticotropin-releasing factor. *Endocrinology* 1990;**126**:759–64.
18 **Kavelaars A**, Ballieux RE, Heijnen CJ. Beta-endorphin secretion by human peripheral blood mononuclear cells: regulation by glucocorticoids. *Life Sci* 1990;**46**:1233–40.
19 **Stein C**, Hassan AH, Przewocki R, *et al*. Opioids from immunocytes interact with receptors on sensory nerves to inhibit nociception in inflammation. *Proc Natl Acad Sci U S A* 1990;**87**:5935–9.
20 **Verma-Gandhu M**, Bercik P, Motomura Y, *et al*. Immune cells modulate visceral pain by endogenous opioid production. *Gastroenterology* 2005;**128**(suppl 2):A225.
21 **Farthing MJ**, Lennard-Jones JE. Sensibility of the rectum to distension and the anorectal distension reflex in ulcerative colitis. *Gut* 1978;**19**:64–9.
22 **Mayer EA**, Berman S, Suyenobu B, *et al*. Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis. *Pain* 2005;**115**:398–409.
23 **Bernstein CN**, Niazi N, Robert M, *et al*. Rectal afferent function in patients with inflammatory and functional intestinal disorders. *Pain* 1996;**66**:151–61.
24 **Kern F Jr**, Almy TP, Abbot FK, *et al*. The motility of the distal colon in non specific ulcerative colitis. *Gastroenterology* 1951;**19**:492–503.
25 **Garrett JM**, Sauer WG, Moertel CG. Colonic motility in ulcerative colitis after opiate administration. *Gastroenterology* 1967;**53**:93–100.
26 **Edwards JT**, Radford-Smith GL, Florin TH. Chronic narcotic use in inflammatory bowel disease patients: prevalence and clinical characteristics. *J Gastroenterol Hepatol* 2001;**16**:1235–8.

Crohn's disease

Probiotics for Crohn's disease: what have we learned?

C Prantera

Probiotics do not seem to be a therapeutic option for patients with Crohn's disease, either in the acute phase or for maintenance

A causative role of bacteria in Crohn's disease (CD) has been surmised for a long time. Only in recent years however has there been a large body of evidence from genetic and bacteriological studies indicating that the intestinal flora is the essential factor in driving the Crohn's inflammatory process in genetically susceptible individuals.[1–5]

The therapeutic arsenal for treating CD assumes the correctness of the above hypothesis. Thus immunosuppressors are used to reduce the host response and antibiotics are used to suppress the bacterial flora, with a consequent decreased activation of the gut immune system.[6] Between the two strategies it should theoretically be better to remove the harmful cause instead of reducing the host defences by inducing a form of immunodeficiency that is susceptible to opportunistic infections.

If the intervention on the gut flora works, substituting antibiotics (which are heavily burdened by side effects) with probiotics is an appealing alternative. Probiotics are defined as a living microbial food ingredient with a beneficial effect on human health[7]; however, the concept that probiotics are a type of long life elixir useful in many pathological conditions needs to be viewed with caution.

In a world medical scenario, where new science develops new drugs and the financial cost increases, natural remedies, relatively cheap and potentially free from side effects, catch the consumer's attention, thereby possibly biasing medical judgement.

To date, diverse probiotics, containing different strains and quantities of bacteria, are sold on the market.[8] Their therapeutic effects may include a competitive action with commensal and pathogenic flora and an influence on the immune response through various mechanisms.[9] Probiotics have been successfully employed in the treatment of antibiotic associated and *Clostridium difficile* diarrhoea,[10–11] traveller's diarrhoea,[12] and rotavirus infection.[13] For inflammatory bowel diseases (IBD), some researchers have reported success with different strains of probiotics in the treatment of ulcerative colitis,[14 15] CD,[16–18] and in pouchitis treatment and prevention.[19 20] *E coli* Nissle 1917, the yeast *Saccharomyces boulardii*, *Lactobacillus rhamnosus* strain GG (LGG), and VSL#3, a cocktail of eight different strains, are the various probiotics employed in these studies. Several significant flaws however limit the importance of many of the