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COMMENTARY

Colitis: it is not just for the colon anymore

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Abbreviations: DNBS, dinitrobenzene sulfonic acid; GI, gastrointestinal; GMC, giant migrating complex; IBD, inflammatory bowel disease; MMC, migrating motor complex; TNBS, trinitrobenzene sulfonic acid

Ulcerative colitis and Crohn's colitis are two forms of idiopathic inflammatory bowel disease (IBD) that manifest clinically with rectal bleeding, diarrhea, abdominal pain, and weight loss associated with inflammation of the colon (Phillips, 2000). Alterations in the function of the gastrointestinal (GI) tract in IBD are not restricted to the colon. Since nutrient absorption occurs in the small intestine, and individuals with IBD often suffer from malnutrition and weight loss, it is clear that reduced small intestinal function contributes to the symptoms of these diseases. Given the importance of the autonomic nervous system in the control of the GI tract, any widespread disturbance of the gut function is potentially mediated through an alteration in the innervation of the gut; however, the mechanisms that underlie the phenomenon of altered small bowel function during colitis are not understood. An article in this issue (Blandizzi *et al*., 2003) presents convincing evidence that colitis leads to distinct changes in the neural circuitry of noninflamed regions of the bowel, and suggests that this may underlie the changes in small bowel function that accompany colitis.

It has been 65 years since Mackie (1938) first described a delay in small bowel barium transit in a large proportion of patients with ulcerative colitis. These observations lead him to declare that the concept of the pathophysiological restriction of colitis to the colon was 'no longer tenable'. Since this initial observation, several studies have described reduced small bowel transit associated with colitis, and found the phenomenon the result of decreased intraluminal pressures and a lower rate of intestinal propulsion, irrespective of remission status of the disease (Manousos & Salem, 1965; Ritchie & Salem, 1965; Rao *et al*., 1987). Although well described, an understanding of the mechanisms that underlie this phenomenon remain unclear.

The use of animal models of colitis has greatly advanced our understanding of the pathophysiology of IBD (see Farrell *et al*., 2001). For instance, these models have demonstrated the involvement of specific immune factors and led to the development of novel therapeutics that have significant promise in the treatment of IBD. Little attention, however, has been devoted to understanding the mechanisms that underlie altered small bowel motility during colitis. Two previous studies have demonstrated altered function in the small bowel during experimental colitis. In TNBS-induced colitis in rats, Jacobson *et al*. (1995) described reduced evoked noradrenaline release from enteric nerves in the distal colon, where inflammation existed, as well as in the proximal colon and ileum where inflammation was not present. Aube *et al*. (1999) have described an increased frequency, with unaltered velocity, of the interdigestive migrating motor complexes in the noninflamed ileum of rats with trinitrobenzene sulfonic acid (TNBS) induced colitis. Although a mechanism was not discovered for this phenomenon, it was not mediated by nitric oxide, prostaglandins or muscarinic acetylcholine receptors. In addition, they found no evidence of altered frequency of giant migrating complexes associated with colitis.

The paper presented by Blandizzi *et al*. (2003) in this issue corroborate and extend these previous studies by revealing a mechanism that is likely to contribute to altered small bowel motility in colitis. The authors convincingly show that

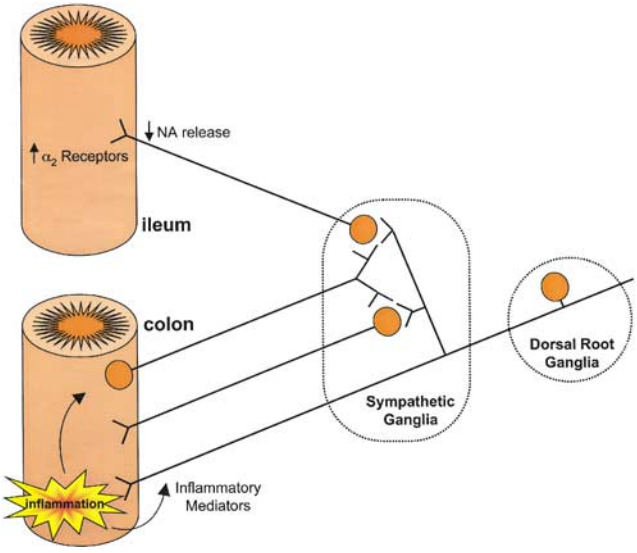

Figure 1 Schematic illustration of a neural pathway that may underlie widespread bowel dysfunction during colitis. Intestinofugal and dorsal root ganglion neurons likely respond to inflammatory signals in the inflamed colon and transmit this information to the sympathetic ganglia. Sympathetic neurons that innervate the small bowel are altered by this input, causing a reduction in noradrenalin release and an increase in α_2 adrenoceptors in the target tissue.

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increased α_2 adrenoceptors in the inflamed colon of dinitrobenzene sulfonic (DNBS) acid treated rats occur on prejunctional receptors located on cholinergic and adrenergic neurons. Importantly, they describe that this phenomenon occurs in both the inflamed colon, as well as the noninflamed ileum. They go on to show that autoinhibition of adrenergic neurons probably contributes to decreased small bowel transit, as antagonism of α_2 adrenoceptors restores normal transit in intact inflamed rats but not sympathectomized rats. This result alone suggests inhibition of α_2 adrenoceptors as a potential therapeutic target for the treatment of altered small bowel motility in colitis.

As with most autoreceptor systems, it is difficult to dissect which is cause or effect, altered release of neurotransmitter, or altered autoreceptor function. It is possible that increased α_2 adrenoceptor expression is an effect of decreased sympathetic outflow (Jacobson *et al*., 1995). Changes clearly take place in sympathetic neurons that innervate the inflamed colon (Swain *et al*., 1991; Sharkey *et al*., 1999). If concurrent alterations occur in sympathetic neurons that innervate the small bowel (as suggested by Jacobson *et al*., 1995), the sympathetic nervous system may be the conduit that distributes inflammation-induced changes to distant, noninflamed sites (Figure 1). Is this an effect of altered communication between sympathetic ganglia that innervate distant regions, or are changes in sympathetic neurons that innervate the small bowel altered via a spinal reflex? With a reinvigoration of the study of altered small bowel function during colitis, expected as a result of the data presented by Blandizzi *et al*. (2003), it is likely an answer will be forthcoming.

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