Stress, inflammation and the irritable bowel syndrome

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SM Collins, G Barbara, B Vallance. Stress, inflammation and the irritable bowel syndrome. *Can J Gastroenterol* 1999;13 (Suppl A):47A-49A. Studies in animals have shown that inflammation of the mucosa of the gastrointestinal tract is accompanied by changes in enteric nerve and smooth muscle function, and in gut motility and sensation. In some instances, these changes persist long after resolution of the mucosal inflammation. Some of these observations have been made in human studies of irritable bowel syndrome (IBS) in patients after an enteric infection or in patients in remission from ulcerative colitis. Stress has also been implicated as a modulator of gastrointestinal inflammation in both animal and human studies. In animals, stress causes a reactivation of previous enteric inflammation and induces the attendant physiological changes. Prior stress also enhances the response to subsequent inflammatory stimuli. In humans, postinfectious IBS tends to occur in patients with psychological profiles similar to those observed in IBS patients and in whom there is a higher incidence of stressful life events just before exposure to the infection. Taken together, these observations link stress and inflammation as a putative pathogenetic mechanism in at least a subset of IBS patients.

Key Words: Gut inflammation, Irritable bowel syndrome, Stress

Stress, inflammation et syndrome du côlon irritable

RÉSUMÉ : Des études menées chez l'animal ont démontré que l'inflammation de la muqueuse des voies gastro-intestinales s'accompagne d'altérations de la fonction des muscles lisses et des nerfs entériques et d'une atteinte de la motilité et de la sensibilité intestinales. Dans certains cas, les altérations persistent longtemps après la résolution de l'inflammation muqueuse. Certaines de ces observations ont été faites lors d'études menées chez l'être humain auprès de patients atteints du syndrome du côlon irritable, après une infection entérique ou chez les patients présentant une récurrence de colite ulcéreuse. Le stress a également été mentionné comme modulateur de l'inflammation gastro-intestinale tant chez l'animal que chez l'être humain. Chez l'animal, le stress provoque une réactivation de l'inflammation entérique antérieure et s'accompagne des anomalies physiologiques correspondantes. Un stress antérieur rehausse également la réaction à des stimuli inflammatoires subséquents. Chez l'être humain, le syndrome du côlon irritable post-infectieux a tendance à survenir chez les patients dont le profil psychologique est semblable à ceux des patients qui souffrent de SCI et chez qui on note une fréquence plus élevée d'événements stressants dans la vie, juste avant l'exposition à l'infection. Ensemble, ces observations permettent d'établir un lien entre stress et inflammation, comme mécanisme pathogénique potentiel chez au moins une sous-série de patients victimes de SCI.

The irritable bowel syndrome (IBS) is a clinical descriptor for a number of chronic abdominal symptom complexes, but the term does not provide insight into the underlying pathophysiological and pathogenetic mechanisms. IBS is heterogeneous not only in terms of its clinical presentation but also in terms of its pathophysiology and

pathogenesis. Indeed, there is little congruency between the clinical presentation, and the underlying pathophysiology and pathogenesis. A possible exception is a subgroup of IBS patients who develop chronic symptoms after an enteric infection. This occurs in about 30% of patients with salmonella gastroenteritis (1), and this subgroup comprises

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one-third of the IBS patient population (2). Recent studies have provided insights into factors that predispose patients to the development of postinfectious IBS (PI-IBS). PI-IBS is more common in females than males, and is associated with a higher incidence of stressful life events in the six months preceding the infection (3). Patients with PI-IBS have been shown to have abnormal sensory-motor function in the anorectum (4). These observations prompt consideration of a model in which stress and possibly other psychological factors converge with infection to produce a state of intestinal dysfunction that persists long after recovery from the infection.

Another pertinent observation is the increased prevalence of gastrointestinal symptoms in patients in remission from inflammatory bowel disease (IBD), as demonstrated previously by Isgar et al (5). That study showed that patients with endoscopically proven ulcerative colitis in remission had a higher than expected prevalence of IBS-like symptoms. Moreover, these symptoms, which included constipation, could not be easily explained on the basis of ongoing inflammatory activity. Again, this finding suggests that inflammation per se leads to persistent dysfunction of the motility apparatus of the gut. This is supported by the demonstration of altered anorectal function in patients with histologically proven ulcerative colitis in remission (6). These results are important in that the inflammatory process in ulcerative colitis is restricted to the mucosa and lamina propria, and does not usually penetrate the deeper neuromuscular tissues that are implicated in the abnormal anorectal function.

What, therefore, is the mechanism whereby mucosal inflammation causes dysfunction in the neuromuscular tissues? Are these changes restricted to the site of infection and inflammation? Can they persist after recovery from the infection? What is the role of stress? To address these questions, one needs to turn to basic research.

DOES MUCOSAL INFLAMMATION ALTER FUNCTION IN THE DEEPER NEUROMUSCULAR TISSUES?

Castro et al (7) and Schanbacher et al (8) first showed that enteric infection is accompanied by changes in gut motility. Farmer et al (9) demonstrated that enteric infection was accompanied by changes in the contractility of intestinal muscle. Studies have subsequently been extended to show that enteric infection is accompanied not only by changes in smooth muscle contraction (10) but also by changes in muscle growth (11), and in neurotransmitter release and content in the myenteric plexus (12-14). These changes are a consequence of the inflammatory response rather than a direct effect of the infective organism and involve T lymphocytes (15) and cytokines including interleukin-1-beta (16,17). Subsequent work has been extended to the colon and has shown clearly that changes in smooth muscle and enteric nerves occur even with very mild and superficial inflammation (18). Taken together, these observations demonstrate that nonpenetrating mucosal inflammation causes changes

in enteric nerve and muscle function, and alters motility. Mild inflammation is, therefore, a candidate process to account for gut dysfunction in a subset of IBS patients.

ARE THESE CHANGES RESTRICTED TO THE SITE OF INFLAMMATION?

It is observed clinically that an infection of the proximal intestine (salmonella gastroenteritis) produces changes in neuromotor function in the anorectum in patients with PI-IBS. Studies in animal models have demonstrated that inflammation at one site produces changes in smooth muscle contraction and in neurotransmitter release at noninflamed sites (19,20).

CAN CHANGES IN NEUROMUSCULAR FUNCTION PERSIST AFTER RECOVERY FROM THE INFECTION?

Studies in animal models support the concept that acute transient inflammation of the gut may result in motor disturbances that persist after resolution of the mucosal inflammation. In a cat model of colitis induced by local installation of acetic acid, motor abnormalities occurred not only during the acute inflammation, but also after the inflammation had resolved (21). Studies in nematode-infected mice have shown that acute inflammation induces changes in enteric nerve and smooth muscle function that persist long after the inflammatory response has resolved (22,23).

WHAT IS THE ROLE OF STRESS?

Previous studies have shown not only that stress alters motility in vivo, but also that repeated stress causes sustained changes in smooth muscle contractility in vitro (24). Stress also influences the inflammatory response. Gue et al (25) showed that prior stress enhanced the inflammatory response of rats to subsequent exposure to trinitrobenzene sulphonic acid. This suggests that stress may play a role in priming the gut for inflammatory stimuli, which may have clinical bearing in the context of postinfectious IBS (3,4).

Studies in animal models have also shown that stress may reactivate previous colitis (26). In one study, animals were allowed to recover for six weeks after acute colitis was induced with trinitrobenzene sulphonic acid, with no chemical or histological evidence of residual inflammation. Animals that were then exposed to three days of mild restraint stress developed a reactivation of the inflammatory process, with an attendant deterioration of colonic physiology. Thus, stress may precipitate functional disturbances in a previously inflamed gut, such as in quiescent IBD (5).

LINKS TO HUMAN DATA

At least two clinical scenarios in IBS are relevant to the present article. One is the relationship between IBS and IBD. Isgar et al (5) showed that IBS-like symptoms occur with a higher than expected prevalence in patients with ulcerative colitis. Patients in the study were in remission from their IBD, as reflected by normal biopsies from the rectosigmoid. Rao et al (6) studied sensory-motor changes in patients with

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ulcerative colitis and found abnormalities in motility as well as an increase in sensory perception following rectal distension. These changes were evident not only in patients with active disease, but also in those with quiescent colitis. While it is theoretically possible that these changes are independent of the colitis, when these observations are taken in conjunction with results emerging from the animal studies cited above, it is more likely that the physiology of the colon is altered by the active colitis and that these changes persist after resolution of the mucosal inflammation, thereby providing a basis for IBS-like symptom generation.

This notion may be taken one step further in the context of PI-IBS. This term was first coined by Chaudhary and Truelove (2) in their 1962 review of a large IBS population in Oxford, United Kingdom. They found that as many as one-third of their patients developed IBS following what appeared to have been an episode of food poisoning or some other acute episode. McKendrick and Read (27) followed an outbreak of salmonella food poisoning in Sheffield, United Kingdom, and their prospective analysis indicated that almost one-third of individuals with food poisoning went on to develop an IBS-like syndrome in the subsequent three

months. Studies of anorectal motility in these patients demonstrated perturbed sensory and motor function (1), and biopsies indicated an increased cellularity, but not overt inflammation, in the rectal mucosa (4). Interestingly these patients had no prior history of IBS but exhibited a psychological profile similar to that previously associated with IBS, with high scores for anxiety and depression (3). The authors also found that those who went on to develop IBS had a higher incidence of stressful life events in the six months before infection (3). These data may be interpreted in a number of ways, but it is clear that the Sheffield study has provided the first prospective data supporting a link between enteric infection and IBS (27). The concept that stress and behaviour may have been predisposing factors is tantalizing and is supported by scientific data from recent work on animals. Taken together, a number of clinical applied and basic scientific observations support a model of IBS which, in at least a subset of patients, involves a triangular relationship among stress, inflammation and disturbed gut physiology.

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