The gut-brain axis in IBD: An investigator's perspective

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SM COLLINS, HP WEINGARTEN, K MCHUGH. The gut-brain axis in IBD: An investigator's perspective. Can J Gastroenterol 1995;9(5):257-260. Three clinical observations in inflammatory bowel disease (IBD) prompt an examination of the role of gut-brain interactions in the pathophysiology of IBD. The first is the recognition that anorexia is among several factors that lead to malnutrition in IBD patients. The second is the suspicion that stressful life events may precipitate exacerbations of IBD. The third is that IBD and irritable bowel syndrome (IBS) seem to be related. Recent work in animal models has provided insights into these clinical observations. Animal models of colitis exhibit a marked reduction in feeding during the acute phase of inflammation. Interestingly, thirst mechanisms are preserved and meal pattern analysis reveals that meal frequency is unchanged while meal size is reduced. These observations suggest that the anorexia does not reflect a general debility or malaise phenomenon. The anorexia is mediated in part by prostaglandins and interleukin-10. In another set of experiments, the authors evaluated the effect of stress on colitis induced by trinitrobenzene (TNB) in rats. Mild restraint stress had no effect on the histology or activity of myeloperoxidase in rats that had not previously had colitis. In contrast, stress caused an acute exacerbation of colitis, reflected histologically and by myeloperoxidase activity, in rats with TNB colitis six weeks previously. These results provide new evidence in support of a causal relationship between stress and reactivation of intestinal inflammation. The apparent relationship between IBD and IBS has prompted speculation of a causal relationship between inflammation and gut 'irritability'. Studies in animal models of colitis and jejunitis have shown that mucosal injury and inflammation are associated with neuromuscular dysfunction and abnormal motility. Neuromuscular dysfunction often persists after the mucosa has healed. More recent studies indicate that cells in the muscularis externa, which includes smooth muscle, are capable of cytokine and other inflammatory mediator production. Thus, one may speculate that the local production of mediators outlasts the mucosal injury and maintains a state of persistent dysfunction in the tissue. This may contribute to postinflammatory irritability in the gut. In summary, recent studies provide a tangible basis for further investigation of the inter-relationships between behaviour and inflammation in the clinical expression of IBD. (*Pour le résumé, voir page 258*)

Key Words: *Anorexia, Colitis, Cytokines, Inflammation, Stress*

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THE GUT-BRAIN AXIS IS A neurohumoral bidirectional communication network that integrates behaviour and intestinal function. Brain to gut communication is evident in many demonstrations of central nervous system (CNS) control of intestinal physiology including motility and acid secretion. This may be relevant to the pathogenesis of functional bowel disease and stress-induced peptic ulceration. Gut to brain communication is reflected in studies on feeding behaviour that have identified satiety signals originating from the upper and lower gut that influence appetitive behaviour. With growing acceptance of neuroimmune interactions, it is possible to extrapolate our knowledge of brain-gut interactions to increase our understanding of the pathophysiology of inflammatory bowel disease (IBD).

INFLAMMATION AND FEEDING BEHAVIOUR

Weight loss and growth retardation in children with IBD (1) are multifactorial and likely reflect impaired nutrient absorbtion, increased metabolic demands and decreased food intake (anorexia) (2). Weight loss may be so severe that Crohn's disease patients have been used as a body weight control in studies of anorexia nervosa (3). However, the mechanisms whereby inflammation produces anorexia are unknown, but may reflect perturbation of satiety signals that originate in the gut (4) or the effects of inflammatory mediators on feeding control centres in the brain.

In recent studies, we have investi-

Axe tractus digestif-cerveau dans les MII : point de vue d'un chercheur

RÉSUMÉ : Trois observations cliniques typiques de la maladie inflammatoire de l'intestin (MII) justifient que l'on se penche sur le rôle des interactions entre le tractus digestif et le cerveau dans sa physiopathologie. La première est la reconnaissance du fait que l'anorexie fait partie des nombreux facteurs qui entraînent la malnutrition chez les patients atteints de MII. La deuxième est la théorie selon laquelle les événements stressants de la vie peuvent déclencher des exacerbations de MII. La troisième est que les MII et le syndrome du côlon irritable (SCI) semblent apparentés. De récents travaux effectués à partir de modèles animaux ont fourni des renseignements sur ces observations cliniques. Les modèles animaux de colite démontrent une réduction marquée de l'alimentation durant la phase aiguë de l'inflammation. Il est intéressant de noter que le mécanisme de la soif est préservé et l'analyse des modes alimentaires révèle que la fréquence des repas reste inchangée, mais que les portions diminuent. Ces observations suggèrent que l'anorexie ne reflète pas une faiblesse générale ni un phénomène de malaise. L'anorexie est amenée en partie par les prostaglandines et l'interleukine-10. Dans une autre série d'expériences, les auteurs ont mesuré l'effet du stress sur la colite induite par du trinitrobenzène (TNB) chez des rats. Un léger stress par contention n'a produit aucun effet sur l'histologie ou l'activité de la myéloperoxidase chez des rats qui n'avaient jamais fait de colite. Par contre, le stress a provoqué une exacerbation aiguë de la colite, manifestée histologiquement par l'activité myéloperoxidase chez des rats atteints de colite induite par TNB six semaines auparavant. Les résultats fournissent de nouvelles preuves à l'appui d'un lien de cause à effet entre le stress et la réactivation de l'inflammation intestinale. Le lien apparent entre MII et SCI a pavé la voie à certaines spéculations quant à un lien causal entre l'inflammation et l'irritabilité intestinale. Les études dans des modèles animaux de colite et de jéjunite ont révélé que les lésions muqueuses et l'inflammation sont associées à une dysfonction neuromusculaire et à une motilité anormale. La dysfonction neuromusculaire persiste souvent après la cicatrisation de la muqueuse. Des études plus récentes indiquent que les cellules de la musculaire externe, qui comprend le muscle lisse, peuvent produire des cytokines et autres médiateurs de l'inflammation. Ainsi, il est possible de supposer que la production locale de médiateurs dure plus que la lésion de la muqueuse et maintient un état de dysfonction tissulaire persistante. Cela peut contribuer à l'irritabilité post-inflammatoire de l'intestin. En résumé, les études récentes offrent une base tangible pour poursuivre la recherche sur les liens entre comportement et inflammation dans l'expression clinique des MII.

gated food intake in rats with colitis induced by trinitrobenzene (TNB) sulphonic acid (5). Intrarectal administration of TNB resulted in a significant increase in myeloperoxidase (MPO) activity in the colon during the first five days, and this was accompanied by a substantial decrease in feeding that was maximal during the first 48 h and was reversible after four days. Changes in food intake were accompanied by a significant decrease in body weight. The suppression of feeding was independent of the manner in which colitis was induced because a similar response was observed in rats with colitis induced by acetic acid. Anorexia also occurred regardless of whether nutrient was presented as a solid or liquid, and was evident with the ingestion of an elemental diet (6). Because neither water intake nor sham feeding was suppressed, it is unlikely that the reduction in feeding reflects a general malaise phenomenon. Moreover, meal pattern analysis revealed that rats exhibited a normal frequency of meal initiation but simply consumed less at each meal; this pattern is not consistent with a general malaise effect (7).

Subsequent study revealed that the anorexia is sensitive to cyclooxygenase inhibitors (6) and an interleukin (IL)-1 receptor antagonist delivered either into the peritoneal cavity or, more effectively, into the CNS (8). Because several actions of IL-1 are prostaglandin-mediated these results suggest that IL-1 plays a pivotal role in mediating the anorexia associated with TNB colitis. Studies examining the contributions of IL-6 and tumour necrosis factor (TNF)-α to the anorexia observed in this model are ongoing.

These observations illustrate that inflammation induces gut to brain signalling, resulting in the expression of anorexia in a model of experimental colitis.

STRESS AND IBD

The impact of stress on organic disease has been examined in several organ systems, such as the cardiovascular system, and in the context of disease processes including neoplasia and type I diabetes (9). However, in relation to IBD, the contribution of stress remains controversial. Earlier investigators postulated that some physiological consequences to stress, such as sustained intestinal muscle spasm, might actually cause mucosal inflammation that could not be attributed to ischemia (10). While stress is not generally considered to be a causal factor in the pathogenesis of IBD, there are some studies that support that stress may exacerbate IBD. There are two lines of evidence in this regard. First, a temporal association between stressful life events and exacerbations of IBD has been demonstrated (11,12), although this has not be confirmed by some other studies (13,14). Second, lifestyle adjustments, including stress management, have been reported to improve the course of IBD, resulting in fewer exacerbations (15).

Research conducted in the past decade has demonstrated the biological plausibility of a relationship between stressful stimuli and immune function in animals (16,17) and in humans (18). A dominant theme of this research concerns the interplay among neuropeptides, hormones and cytokines (19). Cytokines such as IL-1 and TNF-α share certain physiological properties with the stress-associated hormone corticotrophin-releasing factor (20), and are co-produced in the hypothalamus and released in response to stress

(21). In addition to contributing to the stress response, cytokine production by immunocytes may be modulated as a result of the stress response. For example, stress alters IL-2 gene expression and protein production by T lymphocytes and leukocytes in animals and humans (17,18). The existence of neuropeptide receptors on immune cells, including those in the gut (22, 23), is thus important, and it should be noted that the expression of these receptors is, in turn, susceptible to the effects of stress (24). Conversely it has been shown that cytokines may profoundly influence neurotransmitter content and release in nerves, including those in the enteric nervous system (25). These findings provide the basis for the existence of dynamic bidirectional interactions between the immune system and both the central and enteric nervous systems. Because cytokines such as IL-1 play an important role in the initiation, maintenance and control of intestinal inflammatory processes (26-28), stress may alter intestinal inflammatory conditions by influencing cytokine profiles.

Preliminary data from our laboratory provide evidence in support of the hypothesis that there is a causal relationship between stress and the exacerbation of intestinal inflammation (29). In these studies, acute colitis was induced in rats by intrarectal administration of TNB. The animals were allowed to recover for six weeks before being subjected to mild restraint stress. The stress per se did not induce inflammation in rats without colitis, but caused a significant increase in inflammatory activity, as reflected by the activity of MPO in the colon, in rats with previous colitis. Interestingly, the stress-induced reactivation of colitis was accompanied by a reduction in the expression of IL-1β MRNA in the colon. We speculate that IL-1 plays a protective role at this late stage of colitis (26) and that the expression of the cytokine in the gut was downregulated by corticosteroids released as part of the stress response.

These data provide evidence in favour of a causal link between stress and intestinal inflammation, and prompt further exploration of the relationship between stress and IBD activity in humans.

RELATIONSHIP BETWEEN IBD AND IRRITABLE BOWEL SYNDROME

There has been debate over the existence of a special relationship between IBD and irritable bowel syndrome (IBS) (30). The observations upon which a relationship is suspected are as follows. Patients in remission from IBD often complain of symptoms suggestive of an irritable bowel (31). This could reflect the coexistence of IBD with a highly prevalent disorder or could represent the fact that inflammation in the gut leads to irritability of the gut, a notion derived from the now well-established fact that active mucosal inflammation causes changes in neuromuscular function not only at the site of inflammation (32,33) but also at noninflamed remote sites (34,35). Our data also indicate that changes in nerve and muscle function persist after the mucosal inflammation has subsided, as reflected by a normal level of activity of MPO activity and normal histology (36,37). These persistent changes in tissue function may correspond to changes in sensory-motor function observed in animals and humans following inflammatory episodes. MacPherson and co-workers (38) showed that colitis induced in cats caused colonic motor changes that persisted long after changes in mucosal inflammation had subsided. Similar observations were made by Sethi and Sarna (39,40) in dogs with pan colitis induced by acetic acid. Others have shown that, in patients with a previous history of *Salmonella enteritidis* there is persistent IBS-like symptomatology and evidence of changes in rectal sensitivity and motor responsiveness (41). These findings are similar to those obtained in IBD patients in histologically proven remission (42,43). Based on the animal studies and the study on salmonella patients postinfection, the present authors conclude that mucosal inflammation results in persistent neuromotor dysfunction, and thus a basis for ongoing symptoms, once the inflammatory changes have subsided.

Based on recent studies from our laboratory, one may speculate that the following sequence of events occurs. Mucosal injury and subsequent inflammation lead to changes in function of the deeper neuromuscular tissues. In addition to changing physiological function in these tissues, the inflammatory process leads to a phenotypic shift in the neuromuscular tissues allowing them to express genes for cytokines (44). The locally produced cytokines are therefore in a position to maintain the altered physiological function of these tissues. The underlying assumption is that the inflammatory process in the mucosa is subject to tighter control and is more rapidly downregulated whereas the changes in the deeper neuromuscular tissues lack the presence of an equivalent control mechanism, thereby permitting changes to persist through autostimulation (44).

Thus, the emerging hypothesis is that IBD produces IBS by virtue of the inflammatory response to involve the neuromuscular tissues to the extent that they maintain a state of dysfunction that persists after resolution of the mucosal inflammation.

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