D. HOLLANDER

INFLAMMATORY BOWEL DISEASES AND BRAIN-GUT AXIS

UCLA School of Medicine and Broad Medical Research Program
The Eli and Edythe L. Broad Foundation, Twelfth Floor,
Los Angeles, California, U.S.A.

The influence of stress on inflammation in inflammatory bowel disease (IBD) is reviewed. In experimental forms of colitis in rats, stress reactivated the disease. A study of stable IBD patients who were followed for over five years explored the influence of stress on exacerbating the disease. Those patients with high prolonged stressful life events were found to have a 90% recurrence rate of their colitis as compared to only 40% recurrence in low stress patients. Some of the mediators of stress include VIP, TNFα, heat shock proteins, glucocorticoid and catecholamines. Stress was shown to increase intestinal permeability to markers such as Cr-EDTA, HRP and dextran 10,000 in rats. In addition, stress increases the permeability of intestinal M-cells. Finally, stress increased the permeability of Paneth cells to HRP. Since Paneth cells synthesize NOD2 mRNA and protein, stress may play a role in the genesis or reactivation of Crohn’s disease involving the terminal ileum. Brain-gut interactions via neural, hormonal and cytokine signals can diminish the mucosal protective factors and increase the permeability of luminal antigens into the intestinal epithelial and immune cells. Stress appears to play a key role in exacerbating and accentuating the intestinal inflammation in IBD through brain-gut interactions.

Key words: inflammatory bowel disease, Crohn’s disease, ulcerative colitis, inflammation, stress, brain-gut axis, psychosomatic
INTRODUCTION

Inflammatory bowel disease - either ulcerative colitis (UC) or Crohn's disease (CD) - was once considered a psychosomatic disorder. The less a disease is understood, the more likely are both the lay and professional public to consider the disease to be psychosomatic. As the knowledge of the pathophysiological basis of IBD has increased, the less emphasis has been placed on psychosomatic factors. Current medical thinking has abandoned the idea that psychosomatic or psychosocial factors cause IBD. Rather, they are now considered to be contributory, but not causative factors, to both the genesis and exacerbation of IBD (1).

IBD does not have a single etiological factor or a single mechanism that could account for its etiology. Instead, research in this group of disorders is uncovering multiple abnormalities in the response of the gut to external factors such as enteric bacteria, food and environmental antigens.

In this brief review, I will summarize some of the more recent studies examining the relationship between psychosocial and psychosomatic factors and IBD. Whenever possible, the mechanisms of interactions will be discussed.

DISCUSSION

Brain-gut interactive pathways

Environmental signals, such as stress, are perceived initially by the central nervous system (CNS) (2). The advent of magnetic resonance imaging and positron emission tomography has enabled us to gain a much better understanding of the specific areas in the brain that are involved in the perception and processing of stress and other signals. Hormonal and neuroendocrine mediators and various neural pathways transmit signals from the CNS to the gut. In addition, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal medullary (SAM) axis also modulate gut secretory, absorptive and defensive factors. This complex, perceptive and directive system transmits environmental signals that are produced by stress to the intestine and could participate in modulating inflammatory bowel disease (3).

Stress, the brain-gut axis and the intestinal immune response

The human gastrointestinal tract contains some 500 or more species of intestinal bacteria. In total, there are over $10^{14}$ bacteria in the human gut. The bacteria secrete both injurious as well as beneficial compounds. One major mechanism that has evolved to protect the intestine against its luminal bacteria is the intestinal immune system. This system includes innate and cell-mediated defense mechanisms that include cytokines, chemokines and antibodies. Under
normal conditions, homeostasis between injury and repair of the gastrointestinal mucosa is tightly regulated by the complex interaction between this wide array of aggressive and defensive factors in the lumen and wall of the intestine.

The complex system that maintains the homeostasis between aggressive luminal factors and defensive mucosal agents is influenced and modulated by many factors, including environmental stress. In animal models of IBD, environmental stresses can re-activate the disease or instigate inflammation. For example, when rats are given dinitrobenzene sulfonic acid (DNBS) at a specific dosage and length of time, they develop colitis. When they are allowed to recover for a few weeks and then are re-challenged with a low dose of DNBS those rats that have not been subjected to environmental stress do not re-develop colitis while those that are subjected to stress develop full-blown colitis. Therefore, the addition of stress can convert quiescent colitis to active colitis with all of its immunological, biochemical, and pathophysiologica l manifestations (4).

Environmental stress is perceived initially by the CNS, which responds to environmental stimuli by modulating inflammatory or immune response through a complex network of signals that are bi-directional. The CNS communicates with the intestine through the spinal cord, the dorsal root nuclei and intestinal neurons on the one hand and via neurohumoral or neuroendocrine systems on the other hand. Additional pathways of communication of the signals of environmental stress are via the HPA or the SAM axis (5).

Immune cells such as lymphocytes, monocytes, macrophages and granulocytes possess surface receptors for many neuroendocrine products of both the HPA and SAM axes (6). Some of the key mediators of stress that influence the mucosal immune system include substance P, VIP, TNFα, glucocorticoids, nitric oxide, heat shock proteins and others (7). Stressful environmental stimuli appear to produce hypothalamic responses with activation of the brainstem's autonomic nuclei. This type of activation stimulates endocrine and stress responses primarily through sympathetic activation. Undoubtedly, specific neurons within the enteric nervous system are either activated or inhibited by specific circulatory factors and then either stimulate or inhibit the release of specific factors within the intestinal mucosa (7). The specific mechanisms and mediators of stress in individual animal models vary greatly and it is impossible to present a universal model of pathways of activation of the immune system by stress. In fact, the topic becomes extremely complicated the more it is examined by different investigators using different models of stress. Given the enormous number and complexity of the cytokines in the intestinal tract and of the wide variety of the immune cells and immune reactions, one can only summarize a large number of experiments by stating that consistently, environmental stress influences both the systemic and local immune systems of the intestine. The specific mechanisms and pathways vary greatly from one experiment to the next (2).
So far, experiments in laboratory animals have provided most of the data regarding stress and its influence on IBD. However, there are a few prospective controlled observations in patients with IBD that indicate the influence of stress on the course of IBD. In one such study, 62 patients with well-documented, stable ulcerative colitis were enrolled in a prospective five-year observational study. They were evaluated monthly by psychologists using a well-standardized questionnaire called the perceived stress questionnaire (PSQ). Periodically, gastroenterologists performed endoscopy of the colorectal mucosa and biopsied the mucosa for microscopic assessment. Both sets of data were assessed and compared by the two groups of researchers. After five years of follow-up, those patients with consistent low PSQ scores had relapse rates of approximately 40%. In contrast, the patients who had high PSQ scores had relapse rates of closer to 90% by the end of five years of observation. Interestingly, short durations of stress did not trigger an exacerbation of IBD, while long-term stress increased the risk of exacerbation markedly. This prospective controlled study demonstrates that long-term, intense stress contributes to the exacerbation of IBD, but it does not place etiological significance on stress; rather it shifts the role of stress to that of a contributory factor that exacerbates the disease (8). While many individual anecdotal case reports and observations support the conclusions of this prospective study, it is clear that the perception of stress varies from individual to individual and from one culture to another and that we need more studies to understand how and why stress affects the course of IBD. Therefore, as clinicians we must be cognizant of the influence of stress on the clinical course of IBD and reduce stress with psychopharmacological agents or other therapies in order to prevent the recurrence of IBD (9).

**Stress-induced increase in intestinal permeability**

One extensively studied mechanism whereby stress influences the course of IBD is through its influence on intestinal permeability. A major task of the intestine is to form a defensive barrier to prevent the absorption of damaging substances from the external environment of the gut. This protective function of the intestinal mucosa is called **permeability or barrier function**. Investigators use inert, non-metabolized, water-soluble probes, such as rhamnose, mannitol, polyethylene glycol, dextran or lactulose, to measure the permeability barrier or the degree of leakiness of the intestinal mucosa (10). There is ample evidence that permeability is increased in most patients with Crohn's disease and in 10-20% of their clinically healthy relatives (11). The abnormal leakiness of the mucosa in Crohn's patients and their relatives can be greatly amplified by aspirin or NSAID pre-administration (12). Permeability measurements in Crohn's patients can reflect the extent and distribution of the disease and may allow us to predict the likelihood of recurrence of the disease after surgery or medically induced remission (13, 14).
The major determinant of the rate of intestinal permeability is the opening or closure of the tight junctions between enterocytes in the paracellular space (15). Researchers have studied the relationship of stress to jejunal permeability in rats by using probes such as chromium$^{51}$-labeled ethylenediaminetetraacetic acid (Cr-EDTA) and horseradish peroxidase (HRP). Exposure of the rats to stress resulted in a significant increase in the permeability of both probes. The effects of stress could be blocked by the administration of atropine, suggesting that one mediator of the effects of stress is acetylcholine. The major route of permeation of the HRP was found to be the paracellular route. There was also an increase in HRP uptake into Paneth cells in the intestinal crypts (16, 17).

In a different study, stress was shown to increase colonic permeability to fluorescein-labeled high molecular weight dextran 10,000. The stress-related increase in colonic permeability was shown to be mediated by adrenal corticosteroids. Pharmacological administration of dexamethasone to control animals reproduced the influence of stress on colonic permeability (18).

Additional mechanisms by which stress may affect the permeability of the intestine were studied in mice subjected to restraint and acoustic stress. Permeability was measured with the Cr-EDTA probe. Stress was found to increase colonic IFN $\gamma$ levels. IFN $\gamma$ knockout mice did not have stress-related increase in their colonic permeability. The findings suggest that IFN $\gamma$ production is also required for stress-mediated increase in colonic permeability (19).

Severe combined immune deficient (SCID) mice that lack CD4$^+$ T cells were also resistant to the influence of stress on intestinal permeability. Another factor that modified the influence of stress on permeability was the myosin light chain (MLC), which, when phosphorylated by its kinase, increased the influence of stress on colonic permeability. Inhibition of the MLC kinase decreased the influence of stress on colonic permeability (19). All of these data suggest that the effects of stress on colonic permeability require the presence of CD4$^+$/CD8$^+$ T cells, IFN $\gamma$ and MLC phosphorylation. Some of these mechanisms may become effective targets for pharmacological interventions that are designed to minimize the effects of stress on permeability of the intestine in patients with IBD.

**ADDITIONAL MECHANISMS AND MEDIATORS OF THE EFFECT OF STRESS ON IBD**

**Corticotropin-releasing factor (CRF)**

CRF mediates the influence of stress both centrally and peripherally. Centrally, environmental stress causes CRF to be produced and secreted by the para-ventricular nucleus of the hypothalamus. When released it activates the HPA, resulting in the secretion of both adrenal steroid and catecholamines. CRF is also produced in the colonic crypts, probably by enterochromaffin cells (20). CRF from both central and peripheral sources does increase permeability of the
intestine both directly and through mediators such as corticosteroids. In addition, increased CRF secretion affects other endocrine secretions and, as a consequence, mediates stress effects on targets other than the intestine.

**Autonomic nervous system**

Both sympathetic and parasympathetic pathways are involved in transmission of the influence of stress to the intestine. For example, cholinergic antagonists have been shown to inhibit stress-related increase in intestinal permeability of the colon (16). Since atropine sulphate does not cross the blood-brain barrier, the inhibitory effect of atropine must take place peripherally, rather than in the central nervous system.

**The enteric nervous system**

The enteric nervous system (ENS) is one of the largest components of the peripheral nervous system. Its structural support is provided through unique glial cells (21). The intrinsic nerves may participate in mediating stress signals to the bowel through mediators such as substance P (22). At the same time, glial cells also participate in mediating stress effects by acting as antigen-presenting cells and by producing pro- and anti-inflammatory cytokines (21).

**CONCLUSIONS**

The interactions between the brain and the gut are illustrated by the role of stress in IBD. This interaction has been demonstrated in many animal experiments and in some controlled observations in patients with IBD. No longer is stress considered to be an etiological factor in causing the disease, but, rather, stress appears to be a factor contributing to the exacerbation of the disease. Stress is perceived by the CNS in very specific locations, such as the hypothalamus. The CNS is then able to modulate the degree of inflammation of the bowel through multiple routes including neural and neuroendocrine pathways, the HPA axis, the release of CRF and its effects on adrenal-corticoid secretion, the autonomic nervous system and systemic stimulation or suppression of immune functions. The multiplicity of pathways by which the brain affects the gut makes it very difficult to study and to modulate the system pharmacologically. Until recently, it has been difficult to assay the influence of stress on the intestine, but techniques that enable us to measure the permeability of the gut in both laboratory animals and humans increasingly provide us with non-invasive ways to measure a key intestinal defensive function. Recent studies have disclosed that environmental stress does affect intestinal permeability through multiple independent pathways and mechanisms. Perhaps in the future, sequential measurements of intestinal permeability in patients with IBD may prove to be both a useful research
instrument and a clinical tool to assess the influence of therapeutic attempts to decrease the effects of stress on intestinal inflammation.

REFERENCES


Received: November 15, 2003
Accepted: December 18, 2003

Authors address: Daniel Hollander, M.D., UCLA School of Medicine and Broad Medical Research Program, The Eli and Edythe L. Broad Foundation, 10900 Wilshire Boulevard, Twelfth Floor, Los Angeles, California 90024-6532, USA, Phone (310)954-5090; fax (310) 954-5092
E-mail: dhollander@broadmedical.org