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Psychological Stress Exacerbates Development of Inflammatory Bowel Disease

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Abstract
Inflammatory bowel disease (IBD) that considers Crohn's disease (CD) and ulcerative colitis (UC), is a degenerative, reverting, remitting as well as a crippling disorder with unidentified etiology. Recent data demonstrate that the stress stimulated impairment in the gastrointestinal inflammation may be mediated via alterations in luminal bacterial and impairment in hypothalamic-pituitary-adrenal (HPA) axis function and through mucosal mast cells as well as mediator such as corticotrophin releasing factor (CRF). This article reviews the possible mechanisms such as alteration in sensory, motor, and secretory gastrointestinal function, increasing permeability as well as alterations in the immune system that changes stress into IBD. The current knowledge of possible connections of impairment of brain-gut interaction in the pathogenesis of IBD are also reviewed in this article.
Keywords: Inflammatory bowel disease, corticotrophin releasing factor, psychological stress.

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Introduction

Inflammatory bowel disease (IBD) represents a set of agnogenic, incurable inflammatory bowel condition. IBD mainly includes the Crohn's disease (CD) and ulcerative colitis (UC), both having overlapped and distinguishable clinical as well as pathologic characteristics [1]. The CD may occur in any portion of the gastrointestinal tract (GIT) from mouth-anus. However, UC usually involves only the colon and rectum [2, 3]. However, both disorders have different pathologic and clinical features, although their pathological process is not clearly explained [4]. The prevalence of these disorders has raised during the last few decades, equal to 50-200/10^5 and 120-200/10^5 individuals for CD and UC in order given in western countries [5]. The highest report of prevalence values for IBD is in North America (UC, 249/10^5 persons' CD, 319/10^5 persons) and Europe (UC 505/10^5; CD, 332/10^5) [6]. Although the aetiology of IBD is not well-known but immune, environmental and genetic factors are considered to be involved in the pathogenesis [7, 8]. These factors act together, as a result, in genetically susceptible individuals, environmental factors induce bowel symptoms and immune dysfunction [9]. One of these environmental triggers may be psychological factors, especially psychological stress. The objectives of this paper are to review the new development in our understanding of the pathogenic function of psychological stress in IBD as well as to identify the coping strategies applied by IBD patients and to investigate how these strategies are connected to psychological features: anxiety, depression and stress.

1. Possible mechanisms of the effect of psychological stress for the pathogenesis of IBD

1.1 Non-specific effects

Many symptoms of the IBD practiced by individuals can be due to stress-stimulated impairment in the function of gastrointestinal tract (GIT). A generously innervated nerve plexus, called brain-gut axis, exists between the enteric nervous system (ENS) and its autonomic as well as spinal communications to the central nervous system (CNS). GI secretory, sensory as well as motor function and thresholds for the pain perception, may be influenced by emotional and psychological stress directly/indirectly via this gut-brain axis (GBA) [10]. These phenomena are intervened by vasoactive intestinal peptide (VIP), substance P (SP) [11], hormones, neurotransmitters, and several neuropeptides [12]. Stress activates the release of CRF either from central or peripheral parts of the CNS (hypothalamus and adrenal cortex, respectively). CRF stimulates the adrenocorticotropic hormone (ACTH)-cortisol system, while peripheral

CRF regulates mobility of the GI tract. Endogenous CRF conciliates the stress-generated suppression of motility of the upper GI tract and activation motility of the colon [13, 14]. Hence, when features like pain abdomen as well as changes in intestinal function arise in IBD in the absence of remarkable illness behavior, they can be accredited to impairment in motor and sensory function due to psychological stress at least to some extent.

1.2 Intestinal permeability

The intestinal barrier is made of enterocyte membranes, secreted mucus, tight junctions, as well as immunologic factors, such as intraepithelial lymphocytes, neutrophils, mast cells and macrophages. This barrier dysfunction can be stimulated by various kinds of stress (e.g., psychological, physiological, pathological, pharmacological) and increase the permeability of the intestine. Enhanced permeability to endotoxin, a constituent of the walls of luminal bacteria, influences local or systemic inflammatory responses. The immune responses can then lead to more severe conditions such as exertional heat stroke. During intense exercise-heat stress, possibly combined with other stresses, decreases in blood flow to the intestine, and straight thermic damage to the intestinal mucosa, can result in disruption of the barrier and endo-toxemia. The resulting inflammatory response is considered to be associated with impaired thermoregulation and multiple-organ dysfunction [15, 16]. Probable factors for avoiding various stress-related intestinal barrier problems consist environmental, nutritional, or pharmaceutical approaches, or a combination of these [16].

1.3 Psychoneuroimmunology

It is more likely that bidirectional relationships exist among nervous system, immune system, and psychological processes, since IBD is not only affected by stress, but also it increases the risk of psychological difficulty [17]. Moreover, it is thought that a poorly restrained response in the gut mucosa promotes inflammation in genetically susceptible IBD patients. Immune dysfunction and cross-reactivity of immune-cells against host epithelial cells is seen to be involved as important processes by which the inflammatory reactions arise [9, 18].

It is progressively acknowledged that the enteric nervous system (ENS), autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis can act together directly with the immune system in the gut [19]. ENS include 10^8 neurons and determines the motility, the passage of the blood in the smallest vessels of the GI tract, as well as exocrine and endocrine functions [20]. It transmits through efferent and afferent neurons of the sympathetic and parasympathetic ANS (the 'brain–gut' axis). Unlike the other nervous systems in the body, it is capable of working in the absence of central input from the brain (the 'brain-in-the-gut') [20]. Nerve fibers of the ANS create confidential effector junctions with macrophages as well as lymphocytes in the lymph glands, spleen, thymus, bone marrow, and mucosa-related lymphoid tissue [19]. Neurons of ANS and ENS include different kinds of neurotransmitters such as catecholamines, neurotensin, somatostatin, vasoactive intestinal peptide, SP and angiotensin II. These neurotransmitters have the capacity to affect neutrophils, macrophages, lymphocytes as well as other unhealthy cells at the Neuro-immune cell interchange [19, 21, 22]. Lymphocytes along with other unhealthy cells also contain receptors for the hormones and neuropeptides of the HPA axis i.e., corticosteroids, CRF, adrenocorticotrophic hormone (ACTH), and growth hormone [19, 21, 22].

1.4 Role of CRF in IBD

CRF is an important mediator in the induction of psychological stress-related disorder. CRF signaling pathway is engaged in the endocrine, behavioral and visceral responses to stress [23, 24], also stimulates the changes in motility, which is generally observed because of stress, with inhibited gastric drainage but enhanced motility of the colon. The usage of exclusive CRF antagonists has established that central CRF enhances colonic mobility through activation of CRF1 receptor and inhibits gastric drainage through regulation of CRF2 receptor [25].

Recent studies have indicated that peripheral CRF-associated processes also promote stress-elicited alterations in in motility of the gut and function of bowel mucosal. Peripheral CRF injection decreases gastric drainage and motility by interacting with CRF-R2 and increases motility, transit of the colon, as well as defecation via CRF-R2 stimulation [24]. Furthermore, intraperitoneal CRF injection causes colonic mast cell activation and degranulation through CRF-R1 and CRF-R2 and raises ion secretion as well as the permeability of mucosal barrier to macromolecules. Thus, as a result, stimulates bowel inflammation and changes visceral sensitivity [26].

The mucosal changes and motility generated by peripheral CRF cope with those produced by acute stress. Additionally, peripheral CRF antagonists avert acute restraint as well as water avoidance stress-induced inhibited gastric evacuation, promotion of mucosal permeability, and colonic motor function. Furthermore, early trauma induced dysfunction of gut mucosal in adult rats. Peripheral administration of CRF antagonist prevents this response. Chronic psychological stress decreases host defense and induces bowel inflammation via mast cell-dependent processes. Above evidences demonstrate that stimulation of mast cells and peripheral CRF receptors are major mechanisms concerned in stress-induced impairment of bowel physiology [24].

1.5 Anxiety and Depression in IBD

Awareness of the patients regarding their incurability, unpredictable course, the development of cancer or fear of surgery and prognosis are the contributing factors to risk of anxiety in IBD patients [27, 28]. When people develop IBD, they adjust themselves to the disease and accept the condition. Sometimes because of the weak social support or coping skill, patient may avoid social events, feel unhappy and frustrated. Seligman's theory says, incurability and uncertain course of disease impair patient's faith regarding self-control [29] and self-effectiveness [30-32] and so lead to helplessness and an individual becomes susceptible to depression.

Though IBD has long been associated with depression and anxiety, the relationship of depression and anxiety with disease activity in IBD has been controversial, it is not clear if these conditions preceed or confirm diagnosis, or if these are constituents of IBD. An England research team performed a study, using a database of related hospital record abstract to conclude if anxiety and depression co-occur with CD or UC more frequently than expected by chance, and to observe the relationship that exists. From previous studies, it has been found that more anxiety and depression preceded UC (but not the CD) than expected by chance; and more anxiety five or more years followed UC. For CD, anxiety and depression were more common in the year following diagnosis [33].

1.6 Physiological stress and coping in IBD

In recent years, both doctors and patients have found that psychological stress deteriorate the course of IBD. Bitton et al. [34] reported that the coping way of some patients raises the risk of CD relapse after 1 year. Once IBD occurs, uncertainty and long term course of the disease may lead to a broad extent of psychological as well as interpersonal concerns of the individual. These comprise impairment of body image, loss of bowel control, fatigue, fear of sexual insufficiency, feeling dirty, social isolation of dependency and concerns regarding achieving one's full potential [10, 31]. Indeed, clinical characteristics, such as involuntary defecation or soiling and absence bowel control, results in a loss of self-disgracefulness or influence stigmatization in IBD individuals [29, 35].

1.7 Stress and Coping

Stress is explained as a threat, either physical or psychological, to the homeostasis of an organism [36]. Similarly, coping is defined as the thoughts and behaviours applied to fulfill the intrinsic and extrinsic requirements of the situation perceived as taxing [37]. Coping theory says the patient's capacity of dealing with stress relies on his /her coping resources as well as approaches; he/she applies when stressed. These resources comprise the social support a patient gets as well as their constant personality traits: Optimistic individuals not only cope well, but also have a powerful sense of self-esteem and self-control [38].

There are different coping strategies and may change with passing time. Some common categories of coping strategies include emotion-oriented, problem solving, supportant and avoidance-oriented approach. Among most of the gastroenterologist who have experienced questionnaires regarding patients' psychological states and perceived stress level, only fewer will be with those devised to identify people's coping strategies [34].

There is an increasing evidence that psychological stress can affect the natural history of IBD[39]. To date, most reports have been cross-sectional, indicating that patients use strategies ranging from passive as well as escape-avoidance methods [40, 41], to optimistic, confrontive and self-reliant approaches [42]. Some [40, 43, 44] but not all [42, 45] experiments demonstrate that a positive coping approach upgrade health-associated quality of life. Bitton et al. [46] reported that coping strategy, like stress, may change disease activity in IBD. Thus, as in quiescent UC [47], variable study proved that perceived stress raised the relapsing chance in individuals with latent CD. Conversely, patients with a low stress level and using low avoidance behaviour (i.e., keeping themselves to themselves) had

sustained remission (85% at 1 year). The authors imply that such patients help maintain low stress levels by limiting their activities, thereby avoid potentially awkward conditions and overextending their limits.

Coping strategies may play an essential role, especially in adolescent IBD patients. Adolescents with IBD usually employ more avoidance-oriented coping strategies than their healthy peers [40]. In adolescents, IBD interferes with growth, education and employment as well as sexual and psychological development. It is therefore not surprising that adolescents IBD have increased prevalence of psychological distress, especially depression [48]. Health related quality of life is better if adolescents with IBD use coping strategy that includes more positive expectations and less depressive aspects regarding their disease [40, 45]. This patient group would seem to be particularly worthy of management, focusing on coping as well as drug strategies.

1.8 Brain-gut interactions

The gut is capable of working as an autonomous organ. Even so, in normal condition, the gut and CNS interact together via ANS, comprised by the sympathetic (i.e., the spanchnic nerves) as well as the parasympathetic nervous system (i.e., the sacral parasympathetic pelvic nerves the vagus nerve) [49]. The brain has the ability of integrating inputs arriving from the GI tract within a central autonomic network unionized around the cerebral cortex, limbic system and hypothalamus and in return to update the ANS and HPA axis [49, 50]. A dysfunction of these brain-gut interactions is demonstrated in irritable bowel syndrome (IBS) traditionally observed as a bio-psychosocial model in which stress perform encouraging role [49, 50]. IBD develops as a result of an improper inflammatory reaction to gut micro-organisms in a genetically predisposed host [49]. A Study performed in animal demonstrate that the cholinergic anti-inflammatory pathway via an antitumor necrosis factor effect of the efferent vagus nerve could be a curative aim in IBD via nutritional, pharmacologic, or neuro-stimulation approach. Furthermore, the psychophysiological vulnerability of IBD patients, secondary to the possible existence of any mood disorders, non-adaptive coping strategies, distress, raised perceived stress emphasize the psychological requirements of individuals with IBD [51].

Stress and animal models of IBD

Psychological and physical stresses are broadly considered as inducers and/or modifiers of the clinical course of different GI diseases such as IBS, IBD or peptic ulcer [52]. Growing research evidences from different models such as early maternal separation, immobilization or thermal injury in experimental animals uniformly promotes the capacity of stress to initiate the growth of gastric ulcers, impaired motility of the digestive tract, ion secretion, as well as enhanced mucosal permeability showing the way of antigens to the lamina propria and bacterial translocation. Stress may also co-operate with other pathological agents such as non-steroidal anti-inflammatory drugs, *Helicobacter pylori* or colitis-triggering chemicals to develop GI disorder. The brain-gut axis gives the anatomical ground via environmental influences and emotions to modulate the GI function via the activation of mucosal inflammation and digestive immune system. Under this condition, mucosal mast cells – at a cellular level - and CRF –at a molecular level - seem to perform an important role [52].

2. Chronic psychological stress and animal models of IBD

Like human, some animals when exposed to chronic stress may grow intestinal inflammation. Cotton top tamarins have higher chance to develop a colitis similar to UC when exposed to prolonged stress of imprisonment, though remission occurs after returning to the natural living atmosphere [53]. Similarly, fatal colitis may also be seen in Siamese gibbons when kept in captivity [54].

As in humans, experimental models of psychological stress have been established to explain the function of psychological stress in animal models of IBD. A period restraint stress, where movement of animals is limited by binding gently, is the commonest method used to produce acute stress in the rodent. This may be combined with either partial immersion in water or a cold environment. The water avoidance stress, is another model employed for acute stress, in which an experimental animal is set on a smaller floor encircled by water [55]. Chronic maternal separation is applied for inducing chronic stress and depression. An unsupportive factor, that involves the application of suitable control groups in all animal experiments, is that regular handling is inherently stressful.

Psychological stress generated during an experiment seems to be capable to contribute in both induction and re-stimulation of GI inflammation in animal

models of colitis. Rats exposed to restraint stress for four days before induction of colitis by 2,4,6-trinitrobenzenesulfonic acid (TNBS) [56]. Restraint stress, when no other stimuli exist, induces partial re-stimulation of mucosal inflammation in rats, which, had recovered from TNBS colitis six weeks earlier; though no inflammatory changes were detected on the microscope, rise in colonic myeloperoxidase was seen. [57]. A period of restraint stress decreased TNBS dose needed to re-stimulate colitis in mice, which had recovered from TNBS colitis eight weeks previously [58]. Though recipient mice did not induce IBD soon, they needed a smaller TNBS dose in the presence of restraint stress to develop mucosal ulceration than did controls.

Chronic stress seems to make an animal with colitis more susceptible to the effects of acute stress. Also, an adult rat that experienced prolonged maternal separation previously and which were then exposed to many unescapable foot shocks, experienced more severe dextran sodium sulphate induced colitis than did controls [59].

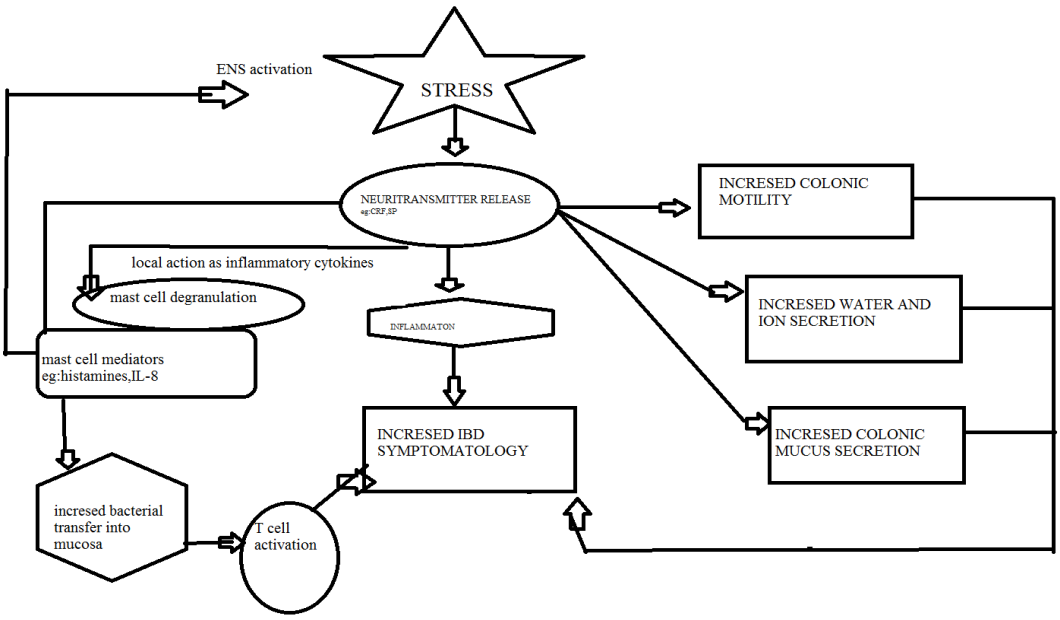

Figure 1: Pathways by which ENS is likely to mediate stress induced increases in IBD symptomatology and disease activity. CRF, SP, IL.

Conclusion

In recent years, many current evidences demonstrate that psychological factors perform an essential role in the course of IBD as well as in their pathophysiology and in how patient manage with these chronic and disabling disorders. In more than last two decades, advancements in the scientific method along with development, in psychoneuroimmunology and psycho-neuroendocrinology, have made better, if still not complete, the concept of pathophysiological mechanism. Additionally, laboratory experiment has emphasized on different mechanism in which both systemic as well as gastrointestinal immune and inflammatory responses are affected by stress.

Transforming these results in therapeutic interventions focused on stress deduction still exists as a challenge; their solution is not only beneficial for patients but also gives further ideas about the pathogenesis of IBD.

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