

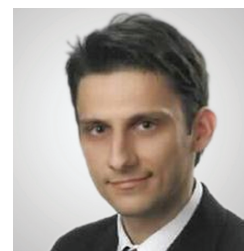
Mechanisms by which Stress Affects the Experimental and Clinical Inflammatory Bowel Disease (IBD): Role of Brain-Gut Axis



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Abstract: Background: Stress of different origin is known to alter so called “brain-gut axis” and contributes to a broad array of gastrointestinal disorders including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and other functional gastrointestinal diseases. The stressful situations and various stressors including psychosocial events, heat, hypo- and hyperthermia may worsen the course of IBD *via* unknown mechanism. The aims of this paper were to provide an overview of experimental and clinical evidences that stress activates the brain-gut axis which results in a mucosal mast cells activation and an increase in the production of proinflammatory cytokines and other endocrine and humoral mediators.



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Methods: Research and online content related to effects of stress on lower bowel disorders are reviewed and most important mechanisms are delineated.

Results: Brain conveys the neural, endocrine and circulatory messages to the gut *via* brain-gut axis reflecting changes in corticotrophin releasing hormone, mast cells activity, neurotransmission at the autonomic nerves system and intestinal barrier function all affecting the pathogenesis of animal colitis and human IBD. Stress triggers the hypothalamus-pituitary axis and the activation of the autonomic nervous system, an increase in cortisol levels and proinflammatory cytokines such as tumor necrosis factor- α , interleukin-8, interleukin-1 β and interleukin-6.

Conclusion: The acute or chronic stress enhances the intestinal permeability weakening of the tight junctions and increasing bacterial translocation into the intestinal wall. An increased microbial load in the colonic tissue, excessive cytokine release and a partially blunted immune reactivity in response to stress result in its negative impact on IBD.

Keywords: Autonomic nervous system, brain-gut axis, cortisol, enteric nervous system, histamine, inflammatory bowel disease, microbiota, proinflammatory cytokines, stress.

INTRODUCTION

A complex set of neural, epigenetic and environmental factors is widely recognized to characterize IBD, which is commonly represented by both ulcerative colitis (UC) and Crohn's disease (CD). These factors lead to severe intestinal disease and long-term discomfort to the patients, sometimes throughout their entire life [1]. An important feature of these diseases is exposure to various degrees of stress and related psychological reactions such as anxiety and depression [2].

Loss of intestinal barrier integrity is a well-recognized medical consequence of a wide range of life-threatening stress conditions, such as heat stroke [3-5], hemorrhagic

shock [6], trauma [7], burn injury [8, 9], pancreatitis [10], and septic shock [11, 12]. Interestingly, even milder stress conditions, such as prolonged endurance exercise [13, 14] and chronic psychological stress [15] can induce intestinal barrier dysfunction. Stress can both evoke damage to the gastric mucosa and perpetuate gastric microcirculation [16]. An increased risk of developing stress-related gastric mucosal lesions and gastrointestinal bleeding has been observed in critically ill patients [16]. Consequently, stress ulcerations are defined as acute gastric mucosal hemorrhagic lesions occurring as complications in severely ill patients after burns, sepsis, major surgery, or trauma to the central nervous system [16-20]. Such upper and lower gut consequences of stress insult depend upon the existence of a complex of psychological factors, long-term depression, psychosis, perceived stress, or brain trauma, which may in turn influence individual vulnerability and bi-directionality of brain pathways known to influence autonomic functions [16-18].

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Particular stressors were shown to act on both the upper and lower gut *via* bidirectional communication through the brain-gut axis [17, 18]; however, the relationship between the incidence of such brain episodes, gut function, and severity of the disease in response to stress has not been fully explained. Interestingly, stress can influence not only patients with IBD but also those who suffer from irritable bowel syndrome (IBS), which is of clinical relevance for general practitioners (GPs) and the impetus for frequent consultations with gastroenterologists [2, 21, 22]. It is of particular interest that psychosocial factors such as psychological distress, anxiety, and depression have a higher prevalence not only in IBD but also in functional GI-disorders including IBS and functional dyspepsia [19, 20]. Patients suffering from IBS have been recently recognized as carriers of mucosal inflammation throughout the gut that is most likely either initiated or influenced by life-threatening stress. This stress perpetuates changes in mucosal barrier and intestinal microbiome, which have an impact on the patient's quality of life and further contribute to progression of inflammation [20, 21]. Recent studies have documented that the occurrence of these IBS type symptoms results in abdominal pain, bloating, and discomfort associated with changes in bowel habit, which in turn are known to exert a negative influence on both mood and quality of life in patients with various forms of IBD [20-22].

The prevalence of IBS symptoms ranges from 10% to 30% in the general population, with higher prevalence among young adult women. Diet-exacerbated IBS could be mediated by a central brain-oriented mechanism. UC in both humans and experimental animal models is predominantly of local origin and usually developed in the lower bowel, i.e. colon and rectum [23-25]. Stress has been shown to complicate both diseases and worsen the outcomes as manifested by greater incidence of flare ups and index severity of changes in the colon [26].

Neural and Endocrine Aspects of Intestinal Disorders. Focus on Stress

The brain-gut axis is an integrative interaction allowing for a bidirectional communication between central centers. This includes central regulation of appetite, the descending autonomic nerves, the enteric nervous system (ENS) with interneurons, sensory neurons, motor neurons, neurotransmitters, and endocrine pathways [16-18]. The specific centers in the brain including hypothalamus, amygdala, and hippocampus and their interaction with emotional centers localized within limbic system are mainly involved in the control of body reaction in response to stress [27]. The integrative reactions of these centers results in the activation of the hypothalamus-pituitary axis (HPA) and the autonomic nervous system (ANS), a key modulator of the ENS (Fig. 1).

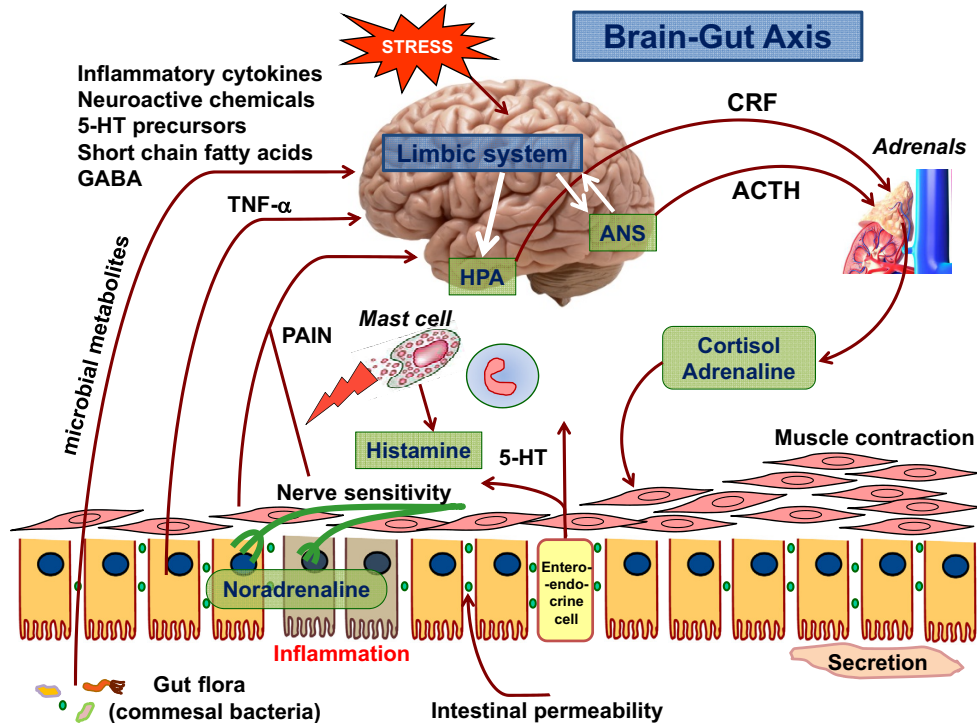


Fig. (1). The complexity of stress affecting the function of brain, gut intestinal mucosa and particular functional components of intestinal *via* brain-gut axis. In response to stress, the inflammatory cytokines (TNF- α), various chemicals, short chain fatty acids (SCFA), and microbial products can alter the autonomic nervous system (ANS) leading to secretion of cortisol and adrenaline from adrenals *via* CRF of and ACTH-dependent pathways. The gut microbiota and neuroactive chemicals including histamine released from mast cells and serotonin (5-hydroxytryptamine) are known to impair the intestinal secretion and intestinal mucosa in response to stress. Various stressors render the intestinal mucosa more permeable, more absorbable to bacterial cytotoxins and neurotransmitters (norepinephrine), and contribute to the development of local inflammation. In conditions associated with stress, bacteria can undergo translocation from intestinal lumen into systemic circulation affecting the central and peripheral organs.

The efferent communication between the CNS and the gut mucosa include the vagal nerve and pelvic parasympathetic efferents and postganglionic sympathetic neurons [28]. The stress-induced activation of the HPA, widely accepted as a marker of stress response, results in an enhanced secretion of glucocorticosteroids and mineralocorticosteroids from the *zona fasciculata* and *zona glomerulosa* of the adrenal cortex, respectively [29, 30]. Another remaining part of ANS, namely, the sympathetic autonomic system becomes also activated. This leads to an increase in the secretion of major *adrenal medulla* hormones -- mainly catecholamines such as epinephrine and norepinephrine [31]. All these self-perpetuating downstream signals act *via* neural connections of brain-gut pathway together with reactive oxygen metabolites (ROM), local inflammatory factors, and circulating cytokines such as IL-1 β , TNF- α , and IL-6 affecting gut homeostatic functions. Changes in the ecology of gut lumen flora and secretory activities of these microorganisms can also alter the gut function *via* mechanisms involving change in the local environment and the signaling molecules including catecholamines and neuromediators of ENS (Fig. 1). The gut sends off the visceral signals of pain to the brain *via* ascending pathways involving the spinothalamic, spinoreticular, and spinomesencephalic tracts [27, 28].

Brain-gut Signals in Stress-induced Functional GI Disorders

Stress-induced release of HPA hormones including adrenocorticotrophic hormone (ACTH), corticotropin-releasing factor (CRF), and major catecholamine hormone noradrenalin is inhibited by substance P (SP) [29, 32]. The release of CRF from the hypothalamus in response to activation of the HPA has been shown to stimulate the synthesis of corticotropin in the pituitary gland, which stimulates the adrenal cortex to release cortisol, the major corticosteroid hormone released to the blood stream [31, 32]. Finally, circulating cortisol in the blood stream is made available to every tissue. This facilitates the cooperation between the brain and peripheral effectors known to govern specific GI-functions including motility, secretion, and defense of the gut [34]. The interaction between CRH and its receptor CRF₁R is the most important in mediating the behavioral, neuroendocrine, and vasomotor responses to stress. On the other hand, SP is considered to play an important role in the modulation of inflammation during stress: previous studies have convincingly shown that the activity of SP in the central nervous system is increased in response to stress [30, 32]. The comprehensive interplay between nerve endings releasing neurotransmitters and mast cells releasing histamine, white blood elements including eosinophils, or plasma cells has been proposed based on the observation that mast cells identified in the GI-tract as enterochromatoffin-like (ECL) cells are structurally innervated within the intestinal mucosa [28, 29, 33, 34]. Mast cells are known to release histamine which is responsible for blood vessel permeability, secretory functions, and reciprocal release of other peptides observed upon neural stimulation [28, 29]. For instance, calcitonin gene-related peptide (CGRP)-immunoreactivity co-localizes with SP, and both neurotransmitters were found adjacent to mucosal mast cells [32]. This suggests a complex relationship between neural

components consisting of the extrinsic afferents (vagal and/or spinal), epithelial component, and immune cells of the gut mucosa [34]. Moreover, the activity of various stressors is directly linked with SP-mediated inflammatory activity in peripheral tissues including the gut [29-32]. The over-expression of SP in the gut potentiates inflammation by several independent mechanisms, including facilitation of leukocyte (mainly white polymorphs) recruitment and subsequent tissue infiltration and stimulation of ROM generation, known to augment tissue damage [33-35]. Interestingly, the activated neutrophils were shown to exert antimicrobial activities and to act as a source of proinflammatory cytokines including IL-17A, IL-23 and IL-6 identified in patients with IBD at the site of inflammation [36]. Under stress conditions, O₂^{•-} concentrations rise leading to excessive production of deleterious oxygen metabolite, hydroxyl radical (OH[•]) through the Haber-Weiss reaction. The excessive formation of OH[•] is known to inactivate an essential mitochondrial enzyme pyruvate dehydrogenase identified in mitochondria, which depolymerizes enzymatic activity of mucin in the GI-tract. This mechanism can lead to mitochondrial RNA and DNA damage [35]. Apart from influencing mitochondrial metabolism, ROM was shown to influence progression through the cell cycle. ROM in human colon adenocarcinoma cells stimulated expression of p53 which, among other functions, has been shown to play the role of an oxidative response transcription factor, therefore causing S phase arrest [37]. This excessive ROM production undoubtedly contributes to development of mucosal inflammation in IBD patients. These oxygen cytotoxic products generated by phagocytes, neutrophils, and macrophages have been implicated in the formation of direct epithelial colonic damage in IBD [38]. Several commonly used IBD therapeutics such as immunosuppressants, corticosteroids and anti-TNF- α antibodies could also affect the IBD progression by interfering with cellular oxidative stress and cytokine production [38]. For instance, targeting ROM by mesalazine (5-ASA), a metabolite of sulfasalazine widely used in the treatment of UC in humans, led to the reduction of oxidative stress by inhibiting O₂^{•-} and H₂O₂ production as well as preventing mucosal GAPDH inhibition [39].

It is accepted that psychological status and physiological stimuli play an important role in the development of functional GI disorders (FGIDs) such as IBD and IBS [18]. The relationship between adverse symptoms, anxiety, and depression, as well as individual visceral hypersensitivity is critical for the regulation of psychological mood which can influence the generation and perception of regulatory physiological signals [40]. Stress-induced adrenal corticosteroid release is known in turn to impair the cortical function (i.e. hippocampus) leading to depression which can reactivate IBD [41]. This psychological manifestation is associated with a decrease in the synaptic levels of 5-hydroxytryptamine (serotonin) and norepinephrine in various brain region as well as reduced production and release of brain-derived neurotrophic factor (BDNF) in the hippocampus [40, 42].

A recent large prospective population-based study in more than 700 patients with IBD identified perceived stress, negative affect or mood, and major life events to be associated with symptomatic flares [43-45]. Longitudinal

follow-up studies have suggested that there is a higher risk of developing anxiety or depression among people without mood disorders who report GI symptoms compatible with IBS at baseline [21, 46]. These studies have also suggested an increased likelihood of developing GI symptoms *de novo* among people who, at baseline, demonstrate anxiety or depression but not GI symptoms [47]. This bidirectional effect of the brain-gut pathway seen in FGIDs supports the notion that the relationship between the brain and the gut may also be bidirectional in UC, and that coexistent anxiety or depression, if unrecognized or untreated, may have a role in the generation of symptoms compatible with IBS in UC patients. In addition, chronic stress can modify many functions in the gut. These include permeability of intestinal wall, motility, and visceral pain changing also the central circuit of pain signals. The transmission of pain sensations and pain perception are influenced by the gut microbiota supporting the view that stress can interact with intestinal flora *via* gut-brain axis in complementary or opposing fashion, finally affecting behavior of visceral nociception [48]. Psychosocial stress and depression have been reported as essential factors affecting disease activity index in the pathogenesis of CD and UC [48, 49]. The mechanism of adverse effect of depression could involve the increasing risk of immune-mediated diseases through its effect on the HPA axis and ANS, systemic inflammatory cytokines, or immune cell function [50-52]. The understanding of brain-gut axis in psychosocial stress patients with IBD remains unexplored because studies examining the role of depression in IBD have primarily focused on those with established disease [52]. As mentioned above, patients with IBD are known to experience an increased risk of anxiety and depression [53, 54]. Moreover, patients with IBD can inadequately cope with psychosocial mechanisms: when they are exposed to additional stressful life events and depression, these factors would contribute to risk of disease relapse [49, 55]. Previous studies in humans revealed that depression is associated with elevated levels of C-reactive protein and tumor necrosis factor- α (TNF- α), both key mediators of inflammation in patients with IBD [55, 56].

Existing evidence in UC patients who were exposed to acute psychological stress revealed that stress insult enhanced serum and colonic mucosa levels of proinflammatory cytokines [57]. The effect of psychological counseling or treatment with antidepressants has been explored in patients with UC who acted as their own controls before and after receiving institutional consultation or other interventions [58]. In these patients, lower incidence of disease relapse as manifested by greater values of disease activity as well as less frequent utilization of glucocorticosteroids following their introduction has been observed [58, 59]. Additionally, improvement in overall depression scores were found for UC patients in a recent study following treatment with immunosuppressive therapy with or without probiotics *via* the brain-gut axis [60]. The use of probiotics in UC patients with IBS-type symptoms may therefore be a viable therapeutic option [61, 62]. However, the efficacy and mechanism of the potential beneficial action of probiotics in IBD patients should be further elucidated. The use of probiotics have been examined in numerous randomized controlled trials concerning human UC; however, there is no satisfactory

conclusions due to the large variety of species and strains that had been employed. Therefore, more convincing data are required using additional randomized trials in humans. Interestingly, however, the probiotic bacterial strain of *Escherichia coli* Nissle 1917 was found beneficial in preventing relapse of disease activity in quiescent UC [61]. The probiotic *Escherichia coli* Nissle 1917 exerted protective activity in experimental rodent models of cold-stress induced gastric lesions due to an increase in the gastric microcirculation mediated by protective prostaglandins and nitric oxide-related mechanisms [63]. Unfortunately, none of the studies discussed so far addressed the efficacy of probiotics in the treatment of IBS-type symptoms in patients with UC with or without acute or chronic stress background and history.

Relationship between Stress, Intestinal Inflammation and Gut Microbiota in Experimental Colitis and the Course of IBD in Humans

Evidence to support the role of brain-gut axis in IBD -- including UC in humans that would depend upon a bidirectional relationship between the brain and gut -- comes mainly from studies in animal models with experimental colitis. Chronic GI inflammation involves behavioral changes that mimic alterations in mood disorders in humans [64]. It has been demonstrated that the induction of depression can reactivate inflammation of the colonic mucosa in murine models of quiescent colitis [41, 65]. Since this effect can be attenuated by the administration of antidepressant drugs, interference with the inhibition of proinflammatory macrophage activity by the vagus nerve has been proposed to explain the therapeutic efficacy of these drugs in experimental colitis [41, 62, 65].

Although animal models such as dextran sulfate sodium (DSS)-induced colitis do not represent the complexity of the human disease, recent attempts prompting the determination of intestinal inflammation in animal models of IBD have further uncovered signaling pathways during colon inflammation, thus suggesting the potential for novel advancements in the therapy of these intestinal disorders. In a DDS murine model of colitis, induction of depression by olfactory bulbectomy or intracerebroventricular injection of reserpine was associated with reactivation of inflammation in mice with previously established quiescent chronic inflammation [41]. Moreover, this effect was mediated in part by an increase in proinflammatory cytokine secretion by macrophages [41]. Interestingly, administration of tricyclic antidepressants prevented reactivation of colitis among depressed mice but not non-depressed mice [38, 41]. The mechanism of deleterious influence of stress on intestinal disorders may involve the activation of interleukin (IL)-6, IL-10, IL-1 β , and tumor necrosis factor- α (TNF- α) production in response to stimulation by bacterial lipopolysaccharide [41, 44]. In addition, acute experimental stress in animals and stressful life events in humans can also alter the number and function of CD4 and CD8 lymphocytes and natural killer as well as modulate platelet function and their activation [41, 44, 66]. The higher number of important stress events was recorded in a period preceding exacerbation of ulcerative colitis in patients with clinically and endoscopically inactive

ulcerative colitis evaluated prospectively for one year [67]. Duffy *et al.* [68] have also shown that there is a positive temporal relationship between incidence of stress and exacerbation of IBD. Disease activity stratified by an increased risk of clinical exacerbation was higher among stress-exposed patients compared with unexposed patients [68].

Stress and inflammation are interacting together as clearly demonstrated in animal studies; however, it is less clear whether stress is directly associated with inflammation in IBD patients. Recently, Targownik *et al.* [69] demonstrated that perceived stress was strongly associated with symptomatic based disease activity both in CD patients and those with UC. However, there was no correlation between symptom scores and the degree of inflammation for participants with CD, and only a weak correlation for those with UC. Furthermore, perceived stress was not inversely correlated with intestinal inflammation as measured in their study by fecal calprotectin [69]. They concluded that the association between perceived stress and IBD symptoms may occur independently of inflammatory activity associated with IBD [69].

Even the accumulated evidence on relationship between stress and IBD in human is controversial and not fully explained. Several studies have implicated stress as an important factor in both predisposition and reactivation of colitis in hapten-induced animal models [70, 71]. Indeed, both acute and chronic stress applied to laboratory animals have been shown to increase ion and water secretion and intestinal permeability in the jejunum and the colon of laboratory animals. These changes were paralleled by a marked increase in epithelial macromolecular permeability, and were mimicked by the intraperitoneal injection of CRF through mast cells and neural pathways [70, 71]. For instance, mild restraint stress has been found to exaggerate the inflammatory response and disease activity when TNBS was administered [67]. Interestingly, when animals were exposed to stress which had been applied after administration of TNBS, this also resulted in an aggravation of colitis in these species [71]. Therefore, stress may predispose the organism to organ injury such as intestinal damage by either an increase in mucosal susceptibility to an inflammatory stimulus through altering intestinal physiological processes (for example, epithelial permeability) or by affecting the balance between mucosal oxidant and antioxidant mechanisms [72]. In another study, the mild restraint stress reactivated the inflammatory process in rats which have recovered from TNBS-induced colitis: this effect was reflected in increases in both MPO activity and inflammatory infiltrates in animals exposed to stress without accompanying structural damage [73]. The increased mucosal infiltration of neutrophils and mononuclear cells in the colonic mucosa and increased MPO activity observed in animals exposed to stress seem to suggest that white blood cells may be an initiating factor in intestinal inflammation and impairment of the mucosal defense mechanisms [73]. The relation between inflammation and cancer involves key inflammatory mediators, such as NF- κ B-targeted gene products including TNF- α and COX-2 [52, 74]. The interaction of microbe-gene-inflammation involves an excessive production of TNF- α which has been implicated in both animals with experimental anxiety and depressive

human subjects [75]. Interestingly, gut bacteria can also influence the change in behavior of animals [75]. This is supported by the theory of dysbiosis originating from observations in germ-free mice or pathogen-free mice [76]. Gut bacteria are hypothesized to act directly on lower bowel motility, sensitivity, and inflammation causing overgrowth and changes in the relative population of detrimental phyla such as *Firmicutes* and *Bacteroides* [76]. The most severe consequences of damage to the intestinal barrier involve translocation of bacteria or bacterial wall products into the circulation. These bacterial products can activate the innate immune system, leukocyte activation and CD4⁺ lymphocytes that were reported to induce pro- and anti-inflammatory cascades [77]. In agreement with the leukocyte and microbial concept in IBD, Qui *et al.* [77] reported that mechanism of the stress-induced reactivation of colitis could involve a transfer of information on the increased intestinal susceptibility by a CD-4-enriched population of lymphocytes from the spleen and the lymph nodes. When inflammation is sufficiently severe, shock -- and ultimately, multiple organ dysfunction syndrome (MODS) -- can occur [78]. In line with these evidences, a high incidence of bacteremia and/or endotoxemia was observed in patients who suffer from hemorrhagic shock or burn injury [79, 80].

This microbe-gut-brain communication helps to understand the pathogenesis of FGIDs and concept of the feedback loop linking the gut-brain to the brain-gut as shown in Fig. 2. In a study by Zwolinska-Wcislo *et al.*, [74], TNBS-induced colitis in rats was associated with inflammation and upregulation of gene expression for proinflammatory COX-2. Treatment with antibiotics such as amoxicillin and probiotics such as Lacidofil accelerated healing of these colonic lesions during the time course of experimental colitis, and subsequently down-regulated the expression of COX-2 mRNA in colonic mucosa [74]. Moreover, administration of aspirin (ASA), the most potent NSAID, significantly increased the area of colonic damage, produced an increase in colonic tissue weight, and elevated the stress-related plasma cytokine IL-1 β and TNF- α levels as well as the mRNA expression of these proinflammatory cytokines in the colonic mucosa in comparison with rats not treated with ASA [74]. It was, therefore, proposed that the inhibition of COX-2 enzyme by therapeutic agents such as celecoxib to prevent colonic damage by ROM and/or proinflammatory stimuli such as TNF- α and IL-1 β in rodent model of colitis [74] could be at least in part translated to IBD patients and considered as an alternative strategy for treatment of human UC as well as intestinal cancer chemoprevention in humans.

The predominant negative consequence of acute injury to the intestinal mucosa induced by bacteria, stressors such as endotoxins, heat stroke, hemorrhagic shock, or NSAID ingestion is the translocation of bacteria or bacterial wall fragments into the bloodstream [81-83]. However, recent studies have demonstrated that other inflammatory mediators besides endotoxin (*e.g.* proteases) can translocate by crossing the intestinal barrier. Such translocations from the intestine may be equally -- if not more -- important in initiating proinflammatory cascades responsible for cytokine activation and release as well as behavioral alterations and MODS [81, 84-86].

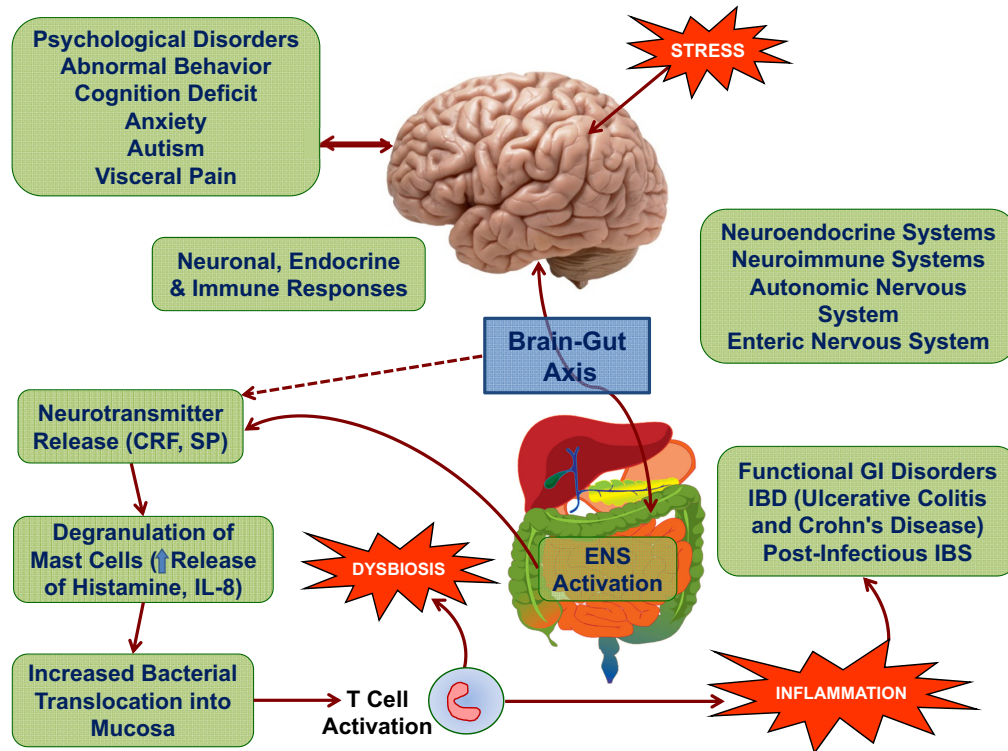


Fig. (2). Schematic presentation of psychoneurological, endocrine, and immune responses to stress leading to intestinal inflammation, dysbiosis, and functional gastrointestinal disorders (FGIDs) including inflammatory bowel disease (IBD). Stress-induced activation of brain-gut axis and both autonomic and enteric systems (ANS and ENS) causes intestinal inflammation mediated by degranulation of mast cells releasing histamine and proinflammatory cytokines, T lymphocyte cell activation and bacterial translocation from mucosa to blood stream and peripheral organs.

Animal studies revealed that the chronic exposure to stress contributes to changes in the expression pattern of intestinal hexose and lipid transporters because the coordinated and site-specific increase in expression of glucose transporters SLC5A1 and SLC2A2 may correlate with pathological changes induced by stress [87]. These clearly indicates that chronic stress not only promotes intestinal inflammation, but also may promote metabolic alterations including sugar uptake and glycaemia. This is corroborative with the observation that hyperglycemia and the development of metabolic syndrome have been implicated in some human phenotypes of IBD [87]. Moderate exercise can also influence the course of experimental colitis in rodents both with standard diet and in those fed with diet-induced obesity [88, 89]. Lipid-rich diet augmented the severity of experimental colitis, while the beneficial effects of physical exercise accelerated healing of colitis by modifying muscle-adipose tissue crosstalk -- including the release by skeletal muscle of a newly discovered protein named irisin [88]. Exercise can also affect the development of IBD since Elsenbruch *et al.* [90] recently reported significantly higher mental and physical health scores and significantly greater improvements on the IBD Questionnaire (IBDQ) for subjects in an exercise group than controls post-intervention. Further studies are needed to confirm these interesting findings in terms of the benefits of moderate vs strenuous exercise (perceived as stressor) in large scale patient population with functional GI disorders.

In summary, the interaction between the predisposition of the host due to genetic and environmental factors, and an inappropriate immune response to bacterial flora in the intestinal lumen are the major factors in pathogenesis of IBD including Crohn's disease and ulcerative colitis. The role of stress-induced gut mucosal pathophysiology has not been fully clarified but recent evidence indicates that chronic stress may be implicated in the development of disease. The scientific evidence for an epidemiologic connection between IBD and stress is conflicting. In this review we provided existing evidence that persistent stress and life events increase the risk for exacerbations of both ulcerative colitis and, to a lesser extent, CD; however, the epidemiological as well as mechanical evidence is less convincing. The brain conveys neural, endocrine and circulatory messages to the gut *via* brain-gut axis. These messages reflect changes in CRH, mast cells activity, neurotransmission at the ANS nerve endings, and intestinal barrier function determined so far in both stress animal models and human IBD. Such signals are transduced from the CNS to the gut mucosa and in opposite direction from gut to the brain *via* vagal afferent pathways, thus constituting a loop between central and peripheral GI organs. The mechanism through which stress from different origin can affect multiple aspects of functional GI disorders -- including on the emerging role of microbiome and probiotic bacteria -- should be further explored under both experimental conditions and human clinical trials.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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