Brain-Gut Axis

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The brain-gut axis represents a complex bi-directional system comprising multiple interconnections between the neuroendocrine pathways, the autonomous nervous system and the gastrointestinal tract. Inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, is a chronic, relapsing-remitting inflammatory disorder of the gastrointestinal tract with a multifactorial etiology.

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1. Introduction

The brain-gut axis represents a complex bi-directional system comprising multiple interconnections between the neuroendocrine pathways, the autonomous nervous system and the gastrointestinal tract[1]. This network is suspected to influence the development of functional gastrointestinal disorders such as inflammatory bowel disease (IBD), gastroesophageal reflux disease and irritable bowel syndrome (IBS) [1][2][3]. Inflammatory bowel disease, comprising Crohn's disease and ulcerative colitis, is a chronic, relapsing-remitting inflammatory disorder[4][5]. IBD most commonly presents with symptoms such as abdominal pain, weight loss, diarrhea, anaemia and fatigue[4][5]. Although the disease is prevalent in areas with high socioeconomic status, such as Europe, North America and Oceania, increased incidence rates are being identified in developing countries [6]. Current evidence shows that the prevalence of IBD increased by one third in the last three decades [7]. Genetic, environmental, immunological and microbial factors are involved in disease pathogenesis, indicating a complex etiology [4][8].

Several studies have suggested that psychological factors may influence the IBD course [9][10][11]. Recently, the bi-directional relationship between psychological morbidity and inflammatory activity has received considerable interest[12]. An increasing number of patients with IBD experience comorbid mental health problems, mainly anxiety and depression, affecting considerably their quality of life (QoL) [13][14][15]. Higher rates of depression and anxiety are reported in patients with IBD as compared to healthy controls[16]. A systematic review reports a prevalence rate of 35% for anxiety and depression in these patients[17]. Despite this evidence, psychological comorbidities remain under-recognized and inadequately treated, increasing the psychological burden of the disease[18][19][20]. Additionally, there is a lack of evidence regarding the exact mechanisms by which depression, anxiety and cognitive dysfunction occur in these patients[20]. Published data have recently proposed the microbiota-gut-brain axis, a communication system comprised of bi-directional interactions between the gut microbiota and the brain, as a key element for explaining the association between psychological distress and IBD[21]. Experimental mouse models of colitis have shown behavioral deviations characterized by new-onset depressive and anxiety symptoms after the induction of gut inflammation, caused by the activation of the hypothalamic-pituitary-adrenal (HPA) axis

and the immune system[22][23]. Evidence from clinical studies indicates that perceived stress and severity of psychiatric symptoms increase the risk for IBD and relapses, and active disease is associated with both depression and anxiety [24][25].

Psychological disorders represent an important aspect of morbidity and impaired QoL in the IBD population; however, depression and anxiety continue to be under-diagnosed in these patients[26]. In this comprehensive review, we summarize the role of the brain-gut axis in the psychological functioning of patients with IBD, and discuss current preclinical and clinical data on the topic and therapeutic strategies potentially useful for the clinical management of these patients.

1.1. Search Strategy

We reviewed and searched MEDLINE and EMBASE using the following terms: “Inflammatory Bowel Diseases”, “Colitis, Ulcerative”, Crohn Disease”, “Depression”, “Anxiety”, “Stress, Physiological”, “Mood Disorders” to identify relevant publications, unrestricted by article type, describing the implication of the brain-gut axis in psychological well-being in patients with IBD in both animal and human studies, the association between mental health disorders and disease course, and therapeutic applications that could potentially be used in the management of the disease. We conducted our search for articles from inception until 21 October 2020, including only articles published in English. Out of 3021 total citations that were identified initially (MEDLINE: 2208; and EMBASE: 813), we selected publications suitable for this review on the basis of importance and emerging concepts in respect to the involvement of the brain-gut axis in the psychological well-being of patients with IBD and translational implications for the disease course.

1.2. Psychological Functioning and the Brain-Gut Axis in IBD

Psychological stress induces a local inflammatory response in the gastrointestinal tract, increases intestinal permeability and modifies visceral hypersensitivity and motility[2][3]. Increased intestinal permeability facilitates the bidirectional link between the brain and the gut by means of neural, endocrine, immune, and humoral links[27]. It is now well assumed that the gut microbiota can modulate the blood–brain barrier permeability [28]. The activation of the HPA axis is considered pivotal in mediating the effect of psychological disorders on gut functioning[1]. Stress acts directly on the hypothalamus, stimulating the secretion of the corticotropin-releasing factor (CRF) and subsequently the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland[3]. In experimental models of colitis, CRF and ACTH increased the intestinal permeability by inducing mast cell degranulation and cytokine secretion[29][30]. Additionally, stress has a dual, opposite influence on the autonomous nervous system by activating the sympathetic nervous system and by inhibiting the vagally mediated anti-inflammatory effects [3]. During stress responses, the sympathetic nervous system, through the secretion of catecholamines from adrenal medulla, exhibits pro-inflammatory effects in the gastrointestinal tract via activation of mast cells, macrophages through the nuclear factor kB signaling pathway and cytokine secretion[31][32][33]. Stress also disrupts the mucosal barrier, allowing gut microbiota to migrate to secondary lymphoid organs and stimulate an innate immune response and interact with the nervous system[1][34]. Animal studies show an amplified HPA axis

response to stress in germ-free mice that is reversed by reformation of the gut microflora, while probiotics lessen behavioral deviations related to alterations of the gut microbiota [35][36][37]. Furthermore, increased intestinal permeability leads to an abnormal enteric nervous system response, i.e., visceral hypersensitivity, with transmission of painful stimuli from gut to brain [1]. A mechanism of visceral hypersensitivity in IBD has not been clearly established yet; however, a possible reason for this is the enteric nervous system activation caused by the exposure to lipopolysaccharides of the local gut bacteria with the subsequent afferent nerve stimulation and activation of the brain–gut axis [1][38]. Comorbid psychologic disorders are also associated with IBS-like symptoms in patients with IBD [39][40].

2. Translational Implications with Therapeutic Applications on the Brain-Gut Axis

2.1. Pharmacologic Management

Currently, the available treatment options for patients with IBD focus mainly on symptomatic improvement and the induction of remission in patients with active disease, whereas scarce attention is given to psychological wellbeing and QoL[41]. Therapeutic regimens based on 5-aminosalicylates, corticosteroids, biologic agents and immunosuppressive drugs are used during the induction and maintenance phase of the disease to attenuate gut and systemic inflammation [42]. The brain-gut axis and its involvement in psychological comorbidity in patients with IBD outlines the need for new management strategies to improve QoL[12][43] [12,138].

Depression and anxiety disorders activate an immune response, increasing the production and secretion of various inflammatory markers, including cytokines, adhesion molecules and chemokines[44][45]. An important marker of inflammatory response in depressed patients is TNF-a[46]. Anti-TNF agents have been shown to improve psychological well-being in patients with psoriasis, cancer and Crohn's disease [46][47][48]. A randomized controlled trial (RCT) for treatment-resistant depression did not show any beneficial effect overall, although patients with high C-reactive protein (CRP) at baseline appeared to have greater improvement in depression scores[49]. Patients with baseline CRP > 5 mg/L, treated with infliximab, had significant improvements in various aspects of depressed mood, such as psychomotor retardation, anhedonia, psychic anxiety and suicidal ideation [49].

Psychological disorders promote a proinflammatory state [50]. Treatment with an anti-TNF agent or an immunomodulator for 1–6 months can improve the depressive state of patients with Crohn's disease regardless of the disease activity[51][52]. Moreover, poor quality of sleep is a frequent extra-intestinal manifestation in patients with IBD[53], which is mainly bi-directional, with the inflammatory state in IBD disrupting the normal sleep patterns of patients[54] [55][149,150]. Abnormal sleep increases disease activity and the risk for possible flare-up of the disease [56]. In a prospective cohort study of 183 enrolled patients with IBD, treatment with anti-TNF agents or vedolizumab resulted in improvement of depression, sleep and anxiety within 6 weeks of initiation of treatment up until one year or more [53].

Antidepressants (SSRIs and TCAs) are frequently prescribed to patients with IBD [57]. It is estimated that about one fourth of them use antidepressants and anxiolytics/sedatives respectively[58]. Factors associated with the increased use of psychotropic medications in patients with IBD include Crohn's disease, middle age, history of gastrointestinal surgery and increasing number of inpatient and outpatient events [58]. Antidepressants exert their anti-inflammatory properties by reducing the production of proinflammatory cytokines (IL-1β, IL-10, IL-4 and TNF-a) and downregulating the expression of nuclear factor kB, which are hypothesized to play a key role in IBD pathogenesis [59]. Another proposed mechanism of the possible beneficial role of antidepressants on the course of IBD is the enhancement of the vagal anti-inflammatory function, which has been observed in an animal model of colitis after treatment with amitriptyline[60].

A systematic review of 15 studies demonstrated a beneficial effect of antidepressants on IBD course, as well as on the decrease of depression and anxiety levels in most included studies, highlighting the possibility of their implication in the current management plans of patients. In an observational study of 67 patients with IBD with increased baseline anxiety, treatment with antidepressants for 6 months resulted in a significant improvement of depression, anxiety, QoL and sexual dysfunction; however, most participants were in remission before the initiation of antidepressant treatment [61]. Frolkis et al. detected that depression and anxiety increased the risk of IBD development, an association that was attenuated by the use of SSRIs and TCAs[62]. Moreover, in a retrospective cohort study including patients with IBD in remission reporting abnormal anxiety/depression baseline levels, use of SSRIs at baseline resulted in lower rates of therapy escalation as compared to those not receiving them (HR: 0.47; 95% CI: 0.24–0.93) [63]. Similar results were observed for any class of antidepressants (HR: 0.59; 95% CI: 0.35–1.00); however, the association disappeared after adjusting for confounding[63]. Two RCTs that evaluated the influence of antidepressant use on IBD courses have shown contradictory results[64][65]. In the first one, the authors observed that treatment with duloxetine for 12 months significantly reduced depression and anxiety levels, as well as the mean score of symptom severity as compared to placebo[64]. However, a pilot RCT failed to identify any benefit of treatment with fluoxetine in QoL and symptoms of anxiety and depression of patients with IBD [65].

Gastrointestinal symptoms, such as diarrhea and abdominal pain, are highly prevalent among patients with IBD even without active disease, mimicking the clinical presentation of individuals with IBS and impairing their QoL [66][67]. According to previous meta-analyses, TCAs show beneficial effects in patients with IBS, inducing a significant clinical improvement and decrease in abdominal pain scores[68][69]. The role of TCAs in the management of IBS-related symptoms in patients with IBD was investigated by a retrospective cohort study comprising 81 IBD and 77 IBS patients [70]. A moderate improvement of symptoms was observed in both the IBD and IBS cohorts. A significantly better clinical response of patients with ulcerative colitis was noted as compared to those with Crohn's disease (83% vs. 50%, respectively; $p = 0.01$) [70]. These findings indicate a promising use of TCAs in patients with IBD with accompanying gastrointestinal symptoms [70].

2.2. Psychological Therapies

Besides the use of antidepressants and conventional pharmacologic therapy, a recent clinical practice update recommends psychological interventions, such as cognitive-behavioral therapy, hypnotherapy and mindfulness

therapy, for the management of IBD individuals with functional gastrointestinal symptoms[71]. A systematic review with meta-analysis of 32 RCTs has detected a beneficial effect of specific psychological treatments in patients with IBS, mainly cognitive-behavioral therapy, hypnotherapy, dynamic psychotherapy and multi-component psychotherapy either in person or by telephone[72].

Evidence from a previous systematic review regarding the efficacy and methodological challenges of psychotherapy in patients with IBD suggest that cognitive-behavioral therapy can be used as an adjunctive treatment for depression and anxiety in IBD individuals, while hypnotherapy may improve the physical symptoms of the disease and stress coping strategies need more evidence [73]. However, an RCT with weekly 2 h cognitive-behavioral therapy sessions delivered either face-to-face or online did not have a significant effect on disease activity of IBD participants after 24 months of follow-up, and did not improve their mental health state[74]. A similar finding was seen in another RCT evaluating the impact of multi-convergent therapy (cognitive-behavioral therapy techniques with mindfulness-meditation) on the IBDQ scores, in which the improvement was not statistically significant in the intention-to-treat population; however, after a subgroup analysis involving patients with IBD with IBS-related symptoms, a statistically significant improvement in QoL was observed [75].

Another psychological intervention that has been evaluated and implicated mainly in the treatment of IBS, is gut-directed hypnotherapy [76]. The mechanisms by which hypnotherapy exerts its beneficial effects in gut diseases include anti-inflammatory properties, alterations in central processing of peripheral visceral signs and effects on the autonomous nervous system [76]. A systematic review of seven RCTs reported a significant improvement in gastrointestinal symptoms of IBS patients in six studies; the effect remained long-term in four studies. In this review, only one RCT discussed the role of gut-directed hypnotherapy in IBD individuals[76]. Patients with ulcerative colitis remained in remission for significantly more time as compared to controls, and this difference was still significant after one year[76][77].

Stress coping strategies, and especially mindfulness-based stress reduction, are used as supplemental treatments for anxiety disorders and have been shown to induce physical and psychological benefits in chronically ill patients and patients suffering from chronic pain and fibromyalgia [78][79][80]. A trial including patients with ulcerative colitis in remission examined the influence of mindfulness-based stress reduction therapy on disease course, psychological well-being and QoL [174]. No effect of the psychological intervention was observed on disease course and inflammatory markers, whereas it improved QoL in patients who experienced a relapse[81]. Two other RCTs examining the effect of mindfulness-based stress reduction therapy have detected an improvement in QoL and depression scores; however, no change was observed on disease course, disease activity, and various inflammatory markers of the disease[82][83].

The most recent study that evaluated the influence of psychological therapies on disease course, QoL, mental health and perceived stress of patients with IBD is a systematic review and meta-analysis by Gracie et al., including 14 RCTs and 1196 patients. Most patients were in remission (only two RCTs included patients with active disease) and received cognitive-behavioral therapy, psychodynamic psychotherapy, stress-reduction treatments or hypnotherapy. The results showed that psychological therapy did not have beneficial effects on disease course and

mental health scores (anxiety, depression, perceived stress) of patients with IBD. However, psychological interventions induced a significant improvement in disease-related QoL at the end of therapy that was lost at the end of the follow-up. This effect was more prominent with cognitive-behavioral therapy treatment, while no significant benefit was observed in study outcomes according to IBD subtype. To determine the effect of psychological interventions on IBD course, as well as psychological functioning of patients with IBD, further, adequately powered RCTs should be conducted, which should take into account baseline disease activity status and consider the frequent drop-outs that occur in psychological treatments [73].

2.3. Potential Therapies Targeting the Microbiome

Among the different therapeutics that can potentially be used to target the microbiome, probiotics is the most commonly studied in the literature. Probiotics exert anti-inflammatory properties in murine models of colitis and maintain the integrity of the gut barrier, rendering them as potential agents in the treatment of IBD[84]. According to experimental studies, consumption of probiotics can be helpful in the management of depression by downregulating the HPA-axis that is highly activated in depressed patients and by increasing the production of GABA and serotonin, neurotransmitters with antidepressant properties[85][86][87]. Although more evidence exists regarding the management of IBS (psychological interventions, diet, probiotics)[88], a recent meta-analysis of 22 RCTs evaluated the role of probiotics in the management of IBD individuals[89]. The results showed no additional benefit of probiotics as compared to placebo in inducing remission in patients with active ulcerative colitis and equivalent action to ASAs in preventing relapse of the disease[89]. When the studies examining the probiotic VSL#3 were analyzed separately, there was a significant benefit for patients with active ulcerative colitis (RR: 0.74; 95% CI: 0.63–0.87)[89]. However, in patients with Crohn's disease, probiotics did not exert a beneficial effect in preventing relapse of the disease, even after surgically inducible remission, or bringing the disease to a quiescent state[89].

Flatulence, bloating, diarrhea, constipation and abdominal pain are common symptoms in patients with IBS, functional GI disorders and IBD that impair their QoL [90]. Even patients with IBD in remission experience gastro-intestinal symptoms that fulfill the criteria for concurrent diagnosis of IBS[90][91]. New evidence suggests that a diet high in FODMAPs (Fermentable, Oligosaccharides, Disaccharides, Monosaccharides and Polyols) is responsible for generating abdominal symptoms in patients with IBS-like symptoms and IBD[92][93]. FODMAPs are poorly absorbed short-chain carbohydrates that stay in the gut lumen and are fermented by colonic bacteria in gas products that trigger the abdominal IBS-like symptoms[94][95]. Clinical evidence suggests that a low FODMAP diet exerts a beneficial effect in the symptoms of patients with IBS and currently is indicated in the management of the disease[96][97][98]. In a RCT of 78 patients with IBD with IBS-like symptoms in remission or with mild-to-moderate disease, a low FODMAP diet for 6 weeks resulted in significant reduction of IBS symptoms and improvement of QoL as compared to patients that followed a normal diet[99]. Following a subgroup analysis, the results showed greater benefit in symptoms improvement in patients with Crohn's disease with a history of bowel surgery and in those with quiescent disease, while a trend toward reduction of disease activity was seen in patients with ulcerative colitis[99]. An RCT of 88 patients investigating the efficacy of low FODMAP diet in IBD individuals with functional gastro-intestinal symptoms noted a significant control of symptoms in the majority of patients and a reduction in

reported symptoms of any severity, such as abdominal pain, flatulence, bloating, incomplete evacuation or heartburn, as well as improvement in stool consistency in most patients [100]. In a randomized, double-blinded, placebo-controlled, cross-over, re-challenge trial, 32 patients with IBD followed a low FODMAP diet with adequate relief of their symptoms [101]. Patients were randomly assigned to 3-day FODMAP challenges with subsequent assessment of stool output and symptom severity[101]. There was a significant increase in incidence and severity of IBS-related symptoms in the fructan challenge group as compared to the placebo group (glucose), findings that were not observable in sorbitol and galacto-oligosaccharides challenge groups[101]. Two other studies have shown an improvement on symptoms of abdominal pain, bloating and diarrhea in IBD individuals, but not on constipation in which the response was inadequate[102][103]. Even though there are clinical studies, and especially RCTs showing a beneficial effect of low FODMAP diet in IBS-related symptoms in patients with IBD, larger studies should be conducted in order to introduce this novel strategy in patient management.

Given the role of fecal microbiota in the pathogenesis of IBD, another management strategy that has gained ground recently is fecal microbiota transplantation [104]. Fecal microbiota transplantation has demonstrated high efficacy in the treatment of recurrent Clostridium difficile infection with inadequate response to standard treatment [105]. In a meta-analysis of patients with active ulcerative colitis, a higher proportion of patients receiving fecal microbiota transplantation achieved combined clinical/endoscopic remission as compared to those receiving placebo with a good safety profile [106]. However, the effect was short-term and further studies are needed to prove the efficacy of fecal microbiota transplantation as a maintenance treatment and establish the safety of the procedure in order to be introduced in the treatment of patients with IBD[107].

2.4. Environmental Factors Affecting the Brain-Gut Axis

The epidemiology of IBD has been evolving over the last few years with an increasing adoption of the Western lifestyle[107]. Other than for predisposing genetic factors, dysbiosis, diet changes and environmental risk factors from the early life period play a pivotal role on the onset of this spectrum of diseases[8][107]. Especially, the phenomenon of “urbanization”, which includes behavioral changes, diet alterations and exposure to environmental pollution, which might affect the development of IBD in the Western world, and evidence has shown an increased incidence of Crohn’s disease and ulcerative colitis in urban societies [108][109]. In the last few decades, urban environments are characterized by high levels of ambient air pollution which has serious health effects in residents of these areas. From the perspective of the effects in the gut microenvironment, air pollution activates the innate immune system and increases the secretion of pro-inflammatory cytokines, while concurrently disrupting the gut barrier, creating an inflammatory state that alters gut microbiota [110]. Additionally, high concentrations of NO_2 and SO_2 in ambient air has been associated with earlier development of Crohn’s disease and ulcerative colitis respectively[111]. An ecological analysis has demonstrated a direct correlation between air pollutant emissions and IBD hospitalizations in the state of Wisconsin, an effect that was also observable in other immune-mediated diseases, such as multiple sclerosis and asthma [112]. This evidence suggests the hypothesis that environmental conditions and gut inflammation are associated with each other, creating new pathways and environmental interventions in prevention strategies of IBD [109].

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