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Targeting the Gut Brain Axis: A Recent Concept in Treatment of IBS

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Abstract

Irritable bowel syndrome (IBS) is the most prevalent Functional gastrointenstinal disorders (FGIDs) prevalence estimated at 12%. IBS is an important health care concern as it greatly affects patient's quality of life and imposes a significant economic burden to health care system.Cardinal symptoms of IBS include abdominal pain and altered bowel habits. The diagnosis of IBS can be made by performing a careful review of the patients's symptoms, taking a thoughtful history (e.g diet,medication,medical,surgical and psychological history), evaluating patients for the presence of warning signs (e.g red flag of anemia,hematochezia, Unintentional weight loss) and using the Rome IV criteria. Different pathophysiological mechanisms like psychosocial factors, altered motility and altered sensations are associated with IBS. The objectives of this review is to focus on the relation of gut brain axis in treatment of IBS.

Keywords: Irritable Bowel Syndrome, IBS, Gut Brain Axis, Abdominal Pain

1. Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder in which recurrent abdominal pain and/or discomfort is associated with a change in bowel habbit [1]. The pathogenesis of IBS is multifactorial,includes genetic,physiological,psychological and environmental factors.The clinical characteristics of IBS present as persistant or intermittent episodes, including abdominal pain, abdominal distention, bowel habits and changes in stool behavior, thus severely affecting the quality of life [2,3]. The etiology of IBS remains unclear. Theories have ranged from purely psychologic to more recent proposals about postinfectious alterations in GI tract neuromuscular function's may best be viewed as a biopsychosocial disorder in which altered GI motility, GI hypersensitivity and psychosocial factors all interact to predispose someone to the syndrome. Patients with IBS have an exaggerated gastrocolic reflex, altered gastric emptying, increased small bowel contractions and increased small intestinal transit, all of which are exacerbated by food intake or stress [4]. Revised Roman standard IV defines irritable bowel syndrome as: In the past three months abdominal pain occurred on average at least one day per week accompanied by two or more of the following symptoms: I)Related to a change in defecation frequency ii) associated with defecation iii) related to a change in stool consistency (symptoms should last for at least six months) [5]. According to clinical manifestations can be classified into the following subtypes: unclassified (IBS-U),mixed type (IBS-M),constipation predominant (IBS-C) and diarrhea predominant (IBS-D) among which diarrhea type is most prevalent [6].

2. Role of Gut Brain Axis in IBS

The BGA constitutes the enteric nervous system (ENS) and the gut wall in the periphery, the CNS and the hypothalamus-pituitary-adrenal (HPA) axis [7]. The main pain signaling pathways in the BGA are the spinothalamic tracts and dorsal columns with descending supraspinal afferents originating from the rostral ventral medulla [8]. The signals from the GI tract influence the brain, which in turn can exert changes in motility, secretion and immune function [9]. Recent studies have reported that IBS-related mental disorders (including schizophrenia, anxiety disorders and depression) are related to or regulated by changes in microbiota, while probiotics and antibiotics, exogenous probiotics and microbial substrates have a certain therapeutic effect on these symptoms [10,11]. Microbiota may become a potential indicator or

a therapeutic target of many mental diseases, such as depression, Parkinsonism and IBS [11].

Signals from the GI tract influence the brain, which in turn can exert changes in motility, secretion and immune function [9]. Visceral hypersensitivity is a key mechanism underlying abdominal pain, one of the main symptoms of IBS [12]. There is one structural magnetic resonance imaging(MRI) study, in which the thinning in the anterior mid-cingulate and insular cortex, structures important for perception of internal body states were observed in the IBS patients [13,14]. Although the underlying cause of cortical thinning was not elucidated, factors like decreased cell size, apoptosis of neural cells, death of glia and astrocytes, fewer dendritic spines, reduced synaptic density and excitotoxicity related to enhanced glutamate signaling were suggested as possible contributors [15]. Significant upregulation of BDNF (Brain Derived neurotrophic factor) in colonic mucosa and structural alterations of mucosal innervation in biopsies are observed in patients with Ascendance expression of BDNF was closely correlated with the degree of abdominal pain in IBS. Endogenous BDNF released in response to inflammation contributes to the development of central sensitization and thus plays a pathophysiological role in the altered gut sensation in IBS [16]. Inhibition of the BDNF system could therefore be beneficial for the alleviation of symptoms in the IBS patients. Toll like receptors(TLRs) have been localized on mucosal surfaces, including the colonic epithelial CellStar's are activated by various bacterial and viral components which stimulate transcription of inflammatory cytokines like IL-1b,IL-6 and TN alfa and affect transmission in the spinal cord, resulting in central sensitization and hyperalgesia [17,18]. There is beneficiary role of cholinergic, dopaminergic and noradrenergic pathways in regulating immunity and cytokine production in IBS, suggesting a positive influence of acetylcholine and catecholamines on the IBS symptoms [19]. The bi-directional communication between the brain and the gut opens up new treatment possibilities and directs us to newer anti-IBS drugs. IBS patients get benefit from centrally acting treatments like stress coping strategies, both at cognitive and behavioral level or psychotropic agents. Some of the TCAs, SSRIs, SNRIs or BZDs proved to be effective in symptom relief via mood stabilization, modulation of pain perception and amelioration of GI motility and secretion [20].

3. Drugs Targeting Gut Brain Axis in IBS

Tegaserod a selective and partial 5-HT4 receptor agonist that increase the peristaltic reflex and decreases visceral sensitivity and provide relief of IBS-C symptoms [21,22]. Alosetron a selective 5-HT3 antagonist that impedes intestinal transit and prolongs colonic transit time was first drug to demonstrate global symptom efficacy in non-constipated IBS patients [23]. Ramosetron inhibited stress or corticotrophin releasing factor-induced water secretion, accelerated colonic transit and reduced stress-induced colonic nociception [24]. Low-dose tricyclic antidepressants (TCAs) have been used for severe abdominal pain and their anticholinergic properties may have a beneficial effect on diarrhea [25]. Guanylate cyclase-C receptors are located on the luminal aspect of the enterocytes. Endogenous ligands such as guanylin and uroguanylin secreted from goblet cells stimulate GC-C receptor, which is also the receptor responsible for the diarrheagenic effects of the E.Coli heat stable enterotoxin [26]. Linaclotide, GC-C agonist has been shown to accelerate colonic transit and improve stool consistency in patients with IBS-C [27]. Pregabalin is an α2δ ligand that is approved for treatment of somatic pain due fibromyalgia and painful diabetic neuropathy. It binds voltage gated calcium channels, reducing depolarization associated with calcium influx at the nerve terminals and reducing effects of transmitters such as glutamate, noradrenaline, substance P and calcitonin gene related peptide. It is shown to reduce gas and pain sensation with no significant on colonic compliance, suggesting a direct effect on visceral sensory pathway [28]. The bile acid sequestrant, colesevelam slowed colonic transit in patients with IBS-D [29]. The mast cell stabilizer ketotifen decreased visceral hypersensitivity and improved intestinal symptoms and health related quality of life in patients with IBS who had evidence of visceral hypersensitivity [30].

4. Conclusion

A number of different therapeutic interventions are available for the management of patients with IBS, including approved pharmacological agents and other interventions like dietary modification, psychological interventions. Treatment of patients with IBS should be personalized taking into consideration of the symptoms, symptom intensity and patient preference regarding treatment goals. In this review it is focused on the disturbances in the Gut Brain interaction as a cause of IBS and drugs modulating it.

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