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Pathophysiology of Irritable Bowel Syndrome: A Review

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Abstract

Introduction: Irritable Bowel Syndrome (IBS) affects up to 1 in 5 individuals with morbidity similar to that for individuals with diabetes. It is defined by symptoms (rather than signs) and is classified as a functional somatic disorder by the psychiatric manuals DSM-5 and ICI-10. It is also associated with several psychiatric disorders. Despite this, there is a growing understanding and appreciation of how genetics, the gut and gut microorganisms contribute to the symptoms that define IBS. This paper critically reviews the known pathophysiology of IBS.

Method: Literature review on the pathophysiology of IBS.

Results: IBS is the result of central and gut dysfunction, both of which can affect the development and response of each other. Dysregulation of the communication between the two is also important. Gut microorganisms also appear to have an important role.

Conclusion: More research is needed to better understand how the brain and gut develop, and how they interact with each other and their environment. This will help better target the treatment for patients with IBS.

Introduction

Irritable Bowel Syndrome (IBS) is a chronic condition that causes recurrent abdominal pain and discomfort. It was traditionally regarded to be a psychological disease. However, after the introduction of somatoform disorders in the early 1980s, it is now classified as a functional somatic disorder in the DSM-5 and ICD-10 [1,2]. The most widely used criteria to diagnose IBS are the Rome III criteria [3], which are based on symptoms rather than signs or biomarkers. This has added to the complexity of the study of the underlying pathophysiology of IBS [4-6].

It is generally accepted that a biopsychosocial model is best for describing IBS [7]. This model includes genetics, altered gastrointestinal functioning and sensitivity, infection, gut microorganisms, an exaggerated stress response, behavioral responses and dysregulation between the communication between the brain and gut [6,8-13]. The management and study of IBS overlaps many disciplines.

The prevalence of IBS varies geographically with the prevalence in South East Asia being 7%, 12% in northern Europe and North America, and 21% in South America [14]. It is more common in younger people and in females [15]. While IBS does not affect mortality [16], the quality of life has been reported to be lower than in patients with diabetes [17]. Patients with IBS form the largest subgroup seen in gastroenterology clinics and account for 12% of patients seen in general practice [18].

Method

Review papers were initially acquired by searching PubMed using combinations of the keywords: Irritable Bowel Syndrome (IBS), pathophysiology, brain gut axis, brain and axis. From these reviews, relevant and key papers were attained.

Pathophysiology

It has been recognized for over 150 years that there is a bidirectional interaction between the brain and gut. Communication between the two occurs through the Brain-Gut-Axis (BGA). The BGA regulates satiety, nausea, sensation of visceral pain, sphincter operation and peristalsis [19,20]. It consists of the Central Nervous System (CNS), the Autonomic Nervous System (ANS) and the Enteric Nervous System (ENS). All 3 systems have a common embryological origin and share several neurotransmitters and neuromodulators, including serotonin [21,22]. Parasympathetic efferents from the brain to the gastrointestinal system include the vagus nerve, which innervate the proximal two thirds of the gastrointestinal tract, and sacral nerves that innervate the distal one third.

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They receive projections from regions of the brain that are important in the regulation of arousal, fear, emotions and behavior [23]. Parasympathetic stimulation increases gut secretion and motility. In contrast, sympathetic stimulation reduces gut motility and secretion [24]. Gastrointestinal symptoms occur with fear, anxiety, stress and emotional state and eating [8,25-27].

Wall tension, osmolality, acidity and macronutrient composition are sensed by mechanosensory and chemosensory receptors and are transmitted *via* parasympathetic and sympathetic afferents to the hypothalamus [28-30], locus coeruleus, amygdala and periaqueductal grey via the nucleus tractus solitarii [31-33]. Neurons from these regions project to areas involved in regulating arousal and fear [30,34], emotional functioning [23,35], eating behavior and in coordinating emesis [29,36,37]. These regions of the brain show abnormal activation patterns in psychiatric disorders, especially mood and anxiety disorders [38,39].

The Hypothalamic Pituitary Adrenal (HPA) axis also allows communication between the brain and the gut. The perception or experience of stress results in the activation of the HPA axis. The hypothalamus releases peptides (including Corticotropin-Releasing Hormone (CRH)) that act on the pituitary, which in turn, releases hormones (including Adrenocorticotropic Hormone (ACTH)) that controls the release of hormones (including cortisol) from the adrenal cortex of the adrenal glands. Cortisol stimulates the production of Norepinephrine (NE) and epinephrine in the adrenal medulla. CRH and NE are the main regulators of the HPA axis, through negative and positive feedback, respectively. Dysregulation of the HPA axis produces symptoms of anxiety and depression [40-44], abdominal symptoms [45], and in animal models cause intestinal inflammation and mucosal barrier dysfunction [46-50]. Patients with IBS have an overactive HPA axis, the activity of which appears to be different from other psychiatric illnesses [51].

Systemic inflammation (including inflammatory bowel disease [52], hepatitis and gastric inflammation is linked to anxiety, depression and fear [53,54]. These responses are modulated by visceral (vagal) afferents [34]. Animal studies have shown that when this inflammation occurs during the neonatal period, the results are long lasting, with increased sensitivity of the HPA axis to stress [55]. Gastric sleeve operations appear to alter eating behavior *via* the stomach-brain axis through changes in neuropeptide Y and ghrelin [56-58]. Interestingly, neurological complications are seen in 15% of gastric surgery cases [59].

In the ENS, serotonin is important for gastrointestinal secretion, motility and sensation [60], and to transmit information to the CNS. Altered serotonin signaling results in intestinal and extra intestinal symptoms in IBS. Diarrhoea is due to reduced serotonin reuptake, while constipation is due to impaired serotonin release [61].

A growing field of study is the effect of gut microorganisms on physical and mental health. A number of studies have shown that the composition or certain microorganisms are linked to, and can influence, psychiatric disorders including depression, anxiety [62,63], autism [64], schizophrenia and IBS [65-70]. One theory in how microorganisms can influence mental health is through the release of metabolites (such as NE, dopamine, serotonin, Gamma-Aminobutyric Acid (GABA), histamine, gastrin, n-butyrate and fatty acids) directly into the blood and lymph [20,71]. Other metabolites are dependent on microorganisms for their synthesis [72]. These metabolites have the potential to alter inflammation, gut motility and secretion, visceral sensation, the stress response, brain development, attenuation, learning, memory, behavior and mood [73-80]. In animal models, differences in microorganism composition after birth has been shown to lead to lower serotonin levels [72], behavioral and brain structural differences [81,82], long-term effects on the HPA axis [83,84], and lower BMIs [85-87].

Another theory of how gut microorganisms can alter mental health (or how mental health can alter gut microorganisms) comes from the observations that patients with IBS have altered expression of Toll-Like Receptors (TLR) [88,89], and that tryptophan (the precursor for serotonin) can be degraded after TLRs are activated [90]. Microorganism lipopolysaccharides can also act on TLRs to cause the release of cytokines that can result in a neuroinflammatory processes [91]. Some microorganisms can also alter the expression of cannabinoid and opioid receptors, resulting in altered visceral pain [92].

Post-infective IBS may be due to the destruction of ENS motor neurons [93], bile malabsorption [94], an increase in serotonin-containing enteroendocrine cells and T lymphocytes [95], and antibiotic use [96,97].

Discussion

Our understanding of functional bowel disorders has evolved from the belief that they originated purely from psychological stress to our current, albeit still limited, understanding that includes the recognition of the importance of the interaction within and between the brain and the gut. It is tempting to postulate that effective blood tests and treatments will emerge as the pathophysiology is further elicited. Indeed biomarkers are being studied [98], and the FDA has approved a blood screening test for IBS based on biomarkers [99]. However, such tests and related treatments are likely to be limited to a subset of patients whose symptoms are mainly due to bowel dysfunction and may have limited use in patients who have a more central aetiology of their symptoms. Although, given the bi-directional interaction between the brain and gut; and how they have the potential to affect the development of each other; one must be cautious in studying one without the other [5]. Nevertheless, it is interesting to reflect that gastritis was once considered to be a largely functional disorder until the discovery of a causative agent (H. pylori), test and cure [13,100].

IBS crosses many fields, making its definition and management a political issue [4]. By definition, IBS is a somatic/functional disease as defined by the ICD-10 and up to 48% have the most severe somatisation disorder as defined in the DSM-5 [2,101]. The high rate of psychiatric co-morbidities seen in patients with IBS and the fact that anti-depressants are one of the most effective, comprehensive and common treatments for IBS, give support for psychiatry to lead the management of patients with IBS. Gastroenterologists also have a claim as IBS patients are the most common subgroup of patients that they see in their clinics [18]. Furthermore, studies on gut microorganisms and its effect on the gut and brain are very topical and promising. By sheer number of consultations, general practitioners are very important in the management of patients with IBS [18]. Psychologyis also important has given the history of functional bowel disorders and the very high effectiveness of the placebo in the treatment of IBS, despite the marginal efficacy of psychotherapies. The argument for each of these specialties obviously promotes the benefit of multi-disciplinary teams and integrated services in the management and study of IBS [102]. Also, given that there are many other somatisation disorders that include other fields (for example,

fibromyalgia is the second most common diagnosis in rheumatology clinics [103], there is a strong argument for the creation of a new specialty (or subspecialty) for medical-psychiatric interface disorders that are both somatic and mental [4,104, 105].

It is not surprising that the brain and gut communicate with each other given they evolved together and are dependent on each other for survival. There is strong evolutionary pressure for the brain to detect the health of the gut and to modify behavior; and for the gut to react appropriately to the needs of the rest of the body. Additionally, evolutionary pressure has resulted in a symbiotic relationship between the host and gut microorganisms. While this field of study is still in its infancy, it is established that microorganisms can communicate with its host *via* nerves, through metabolites in the blood and lymph, and through the immune system. The brain is able to alter the gut environment through nervous innervations, hormones and behaviors that encourage or hinder different populations of microorganisms. Dysfunction of the communication between the gut and brain may be one reason for IBS. Another may be a difference in, or limited ability for, adaption to a changing environment. Exposure to gut microorganisms is important in the developing brain [80,81], and presumably establishes the host for life. Similarly, psychological stresses can alter gut microorganisms. The benefit of the co-adaption that formed in younger life may be less effective in later life if the environment changes. This may be a growing issue in the modern world as we are living longer and are exposed to a more diverse set of foods, chemicals, antibiotics, stressors and environments. There are also social, cultural and religious factors that affect things such as what we eat, when we eat, defecation, and flatulence.

Conclusion

Our understanding of IBS is still very limited with ambiguity about the most appropriate treating specialty; limited treatment options that focus on symptoms; and an emerging knowledge of the pathophysiology. More research is needed into the pathophysiology and relative importance of the brain, gut, gut microorganisms, and their interaction. This will help identify which patients may be more amenable to psychological or pharmacological treatment. It will also lead to more effective drug targets for the treatment of IBS and guidelines that could enhance the development of the brain, gut and microorganism populations. Moreover, it will contribute to the field of psychiatry through a better understanding of how the brain interacts with itself and its environment.

Finally, it is important to educate doctors that IBS is more than just a diagnosis of exclusion, and that a patient's symptoms are the result of the interaction between the brain and the body, and the contribution of each varies between patients. Appreciation of this will help doctors validate the suffering experienced by patients and help guide the management of the illness.

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