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Review Article

New insights into the pathogenesis and pathophysiology of irritable bowel syndrome

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Abstract

The pathogenesis and pathophysiology of irritable bowel syndrome is complex and still incompletely known. Potential pathogenetic factors include genes, infectious events, psychological symptoms and other loosely defined environmental factors. Both alterations at the central and peripheral level are thought to contribute to the symptoms of irritable bowel syndrome, including psychosocial factors, abnormal gastrointestinal motility and secretion, and visceral hypersensitivity. Today irritable bowel syndrome is viewed upon as a disorder of dysregulation of the so-called brain–gut axis, involving abnormal function in the enteric, autonomic and/or central nervous systems, with peripheral abnormalities probably dominating in some patients and disturbed central processing of signals from the periphery in others. Lines of evidence also suggest that inflammation within the gastrointestinal tract may be of great importance in at least subgroups of irritable bowel syndrome patients. To conclude, a complex picture of the pathogenesis and pathophysiology of irritable bowel syndrome is emerging, with interactions between several different alterations resulting in the divergent symptom pattern in these patients.

Keywords: Brain–gut axis; Gastrointestinal motility; Inflammation; Irritable bowel syndrome; Serotonin; Visceral hypersensitivity

1. Introduction

Irritable bowel syndrome (IBS) is characterized by abdominal pain and/or discomfort together with disturbed bowel habits [1]. It is one of the most common gastrointestinal disorders [2] and patients suffering from IBS constitute a great deal of the work load for gastroenterologists and primary care physicians [3–6]. Unfortunately, the available treatment options for IBS patients are limited, which is partly due to the fact that pathogenetic and pathophysiologal factors of importance for IBS are incompletely known. However, the interest in this topic has steadily increased during the last years and this has substantially improved our current understanding of IBS. Traditionally IBS has been viewed upon as a disorder where altered gastrointestinal motility, visceral hypersensitivity and psychosocial factors are the most important pathophysiological factors. However, recent studies have provided evidence that IBS is due to a dysregulation of the brain–gut axis. This involves abnormal function and interplay between the enteric, autonomic and/or central nervous systems (ENS, ANS and CNS), with peripheral alterations probably dominating in some patients and disturbed central processing of signals from the periphery dominating in others. A major problem however is the lack of understanding about the relationship between the different pathophysiological alterations and the various symptoms experienced by the patients (Fig. 1).

This paper will focus on studies published in the last 5 years, providing evidence for altered interplay between different parts of our nervous system along the brain–gut axis in patients with IBS, as well as presence of low-grade inflammation, immunological changes, abnormal levels of gastrointestinal (GI) neuropeptides and hormones leading to disturbed GI function and the involvement of genetic factors in IBS. It will also shed light on new findings regard-

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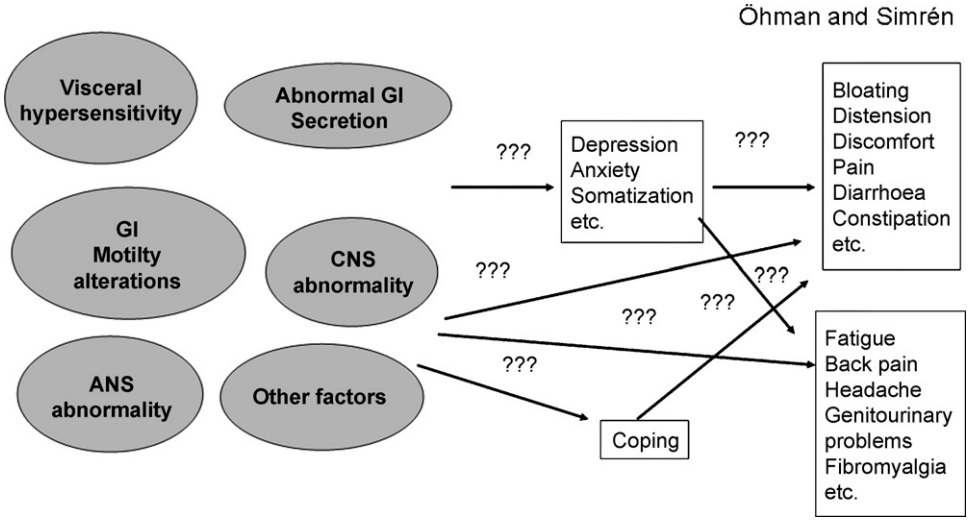

Fig. 1. The relationship between the different pathophysiological alterations described in IBS and the specific symptom pattern of the patient is unclear.

ing 'classical' pathophysiological factors, such as visceral hypersensitivity, altered GI motility and psychological abnormalities. Hopefully this new knowledge will help us to understand this enigmatic disorder better in the future to be able to develop more effective treatment options.

2. Genetic factors

IBS patients often report that family members have similar symptoms and recent studies support that IBS clusters in families [7–9]. Twin studies to evaluate the importance of genetic versus environmental factors in the familial aggregation of IBS have been performed with somewhat discrepant results, but taken together they suggest a strong environmental basis for IBS, and if there is a genetic contribution it seems to be a modest one [10–12]. Moreover, a number of recently published investigations have examined the DNA sequences of IBS subjects directly, looking for genetic variants increasing the risk for having IBS. The strongest evidence for a link between a specific polymorphism and IBS has been found for the serotonin transporter gene. More specifically, available studies suggest that serotonin-transporter polymorphisms may be of importance for which subtype of IBS the patients belong to [13–15], as well as for the response to treatment [16]. Also polymorphisms of alpha$_2$-adrenergic receptors have been found to be related to the bowel habit of IBS patients in one study, as well as to more severe somatic symptoms [13], whereas no association was found between polymorphisms of the beta$_3$ subunit of the G-protein and IBS [17], contrary to what has been found in functional dyspepsia [18]. Other studies have found cytokine gene polymorphisms to be more common in IBS patients, thereby providing some evidence that genetically determined immune activity plays a role in the pathophysiology of IBS [19,20]. However, none of the cytokine gene polymorphisms could predict the development of post-infectious IBS.

To summarize, recent investigations support a genetic susceptibility to IBS, even though it seems to be rather modest. Future studies in larger samples are needed to define clinically relevant subgroups, characterize inheritance, identify genes and to better define the environmental contributors to IBS [21].

3. Psychological factors

3.1. Related to IBS per se or just a consequence of symptom severity?

Rather than being a cause of IBS, psychosocial factors have since the late eighties been looked upon largely as factors related to the severity of the disease, affecting fluctuations in the symptom pattern and determining the health care seeking behaviour of the patients. This has been based on studies supporting an association between psychosocial factors and patient status rather than with IBS *per se* [22,23]. However, recent studies have challenged this view to some extent. Two population-based studies found an association between psychosocial factors and IBS, which was not explained by health care seeking, but was also seen in IBS subjects who had not sought health care for their symptoms [24,25]. Moreover another prospective population-based study from the UK looked at factors predicting the onset of new abdominal pain over 12 months. The main findings from that study were that in subjects free of abdominal pain, psychological distress, fatigue, health anxiety and illness behaviour were predictors of future onset rather than merely a consequence of symptoms [26]. Another Australian community-based investigation demonstrated that psychological distress levels do not seem to be important in explaining GI symptom change over a 1-year period, but was linked to having persistent GI symptoms and frequently seeking health care for them over time [27]. Taken together, these results suggest that psy-