Pathophysiology of irritable bowel syndrome

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Traditionally, irritable bowel syndrome has been considered to be a disorder with no known underlying structural or biochemical explanation, but this concept is likely to be outdated. In this Review we challenge the widely accepted view that irritable bowel syndrome is an unexplained brain–gut disorder. There is epidemiological evidence that, in a major subset of patients, gastrointestinal symptoms arise first and only later do incident mood disorders occur. Additionally, possible mechanisms for gut–brain dysfunction have been identified, suggesting primary gut disturbances might be the underlying cause in a subgroup. Underlying mechanisms that could lead to irritable bowel syndrome include genetic factors (most notably an identified mutation of *SCN5A*); post-infectious changes, chronic infections and disturbances in the intestinal microbiota; low-grade mucosal inflammation, immune activation, and altered intestinal permeability; disordered bile salt metabolism (in 10–20% of cases with diarrhoea); abnormalities in serotonin metabolism; and alterations in brain function, which could be primary or secondary factors. Identical irritable bowel syndrome symptoms are probably due to different disease processes; grouping patients with this disorder into either diarrhoea-predominant or constipation-predominant subtypes promotes heterogeneity. An approach based on the underlying pathophysiology could help to develop therapies that target causes and ultimately provide a cure for patients with irritable bowel syndrome.

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Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder characterised by chronic or recurrent abdominal pain associated with either relief or exacerbation by defecation, or a change in bowel habit.[1] Most patients can be classified, according to the predominant stool pattern they have, into IBS with diarrhoea, IBS with constipation, and those who have both diarrhoea and constipation, known as mixed-stool-pattern IBS.

IBS is one of the most widely recognised functional bowel disorders, with more than 10% of the global adult population reporting symptoms compatible with the condition in population-based surveys.[2] In routine clinical practice, a diagnosis of IBS is made on the basis of typical symptoms.[3] The use of investigations is often restricted to a selected panel of tests that help to exclude known organic diseases that present with similar symptoms, such as inflammatory bowel disease or coeliac disease.

In the past, IBS has been considered to have no underlying structural or biochemical basis, although in this review we will challenge this accepted model. As a result, unlike other organic gastrointestinal diseases, treatment of IBS is often targeted towards the predominant, or most troublesome, symptom the patient experiences, rather than being based on the underlying pathophysiology.[4] As a consequence, treatments are not sufficiently effective and the natural history of the disorder in the long term is unchanged by most therapeutic interventions.[5] The prevalence and the poor response to established therapies for IBS has resulted in a substantial economic impact.[6] Although there is no excess mortality associated with IBS,[7] this disorder has a considerable effect on quality of life, and IBS can induce serious disability.[8] As a consequence, a better understanding of the potential underlying mechanisms involved in the generation of symptoms is crucial for improving effectiveness of future treatments.

We would propose that these emerging disease concepts should form the basis of a future categorisation of IBS subject to pathophysiological symptoms (table 1); to support therapeutic decision making that targets specific disease mechanisms with appropriate treatments. The current therapeutic approach, aiming to improve individual IBS symptoms, is not sufficiently effective since similar symptoms could be due to several causes.

Defining IBS: one disorder, or many?

Although IBS is traditionally considered to be a disorder with no known underlying pathological explanation for the symptoms that patients report, this concept is probably outdated. Conventionally, IBS is divided into subgroups according to the predominant stool pattern because this categorisation defines treatment options and so, by definition, it is a heterogeneous disorder. We propose that there are, in fact, several different underlying disease mechanisms underlying these subtypes. This concept is strongly supported by the observation that IBS symptoms can occur in the setting of established structural—but clinically inactive—gastrointestinal diseases, including inflammatory bowel disease,[9] coeliac disease,[10] idiopathic bile acid diarrhoea,[11] and microscopic colitis.[12] Similarly, patients with duodenal ulcers might not have gastrointestinal symptoms until a complication occurs, and other patients could continue to have symptoms even after healing of the ulcer.[13] Thus, factors other than just the structural lesion are probably responsible for the manifestation of symptoms.

Initial research that aimed to explore the underlying disease mechanisms of IBS centred on alterations of gastrointestinal motility[14] and visceral sensory function.[15] However, despite the fact that alterations in both motor and sensory function are likely to be relevant for the manifestation of symptoms, the focus of subsequent research has shifted towards possible explanations for these abnormalities. The role of several mechanisms has

	Mechanism	Causes	Prevalence in patient cohorts	Relevance in clinical setting
Central processing of afferent stimuli	Alteration of the central processing of afferent stimuli (including visceral afferents)	Minimal systemic inflammation, or effects of early childhood trauma, may alter the central processing of afferent stimuli	10% to 20%	Lowered sensory thresholds may be a key driver for symptom manifestation
Anxiety and depression	Alteration of the central processing of afferents (including visceral)	Multifactorial, activation of immune systems seems to aggravate underlying disturbances	Up to 75%	Influences health care-seeking behaviour, can be targeted with antidepressants
Post-infectious IBS	Post-inflammatory neuroplastic changes, visceral hyperalgesia	Exposure to pathogens causing alterations of gut permeability, inflammation	10% to 20%	Prevention of infections, early intervention in affected patients (eg, antibiotics), potentially primary prevention with probiotics
Post-inflammatory IBS	As for post-infectious	A chronic or transient immune process (ie, controlled by appropriate immune modulation) has triggered the same or similar events that cause symptoms in post-infectious IBS	10% to 30% of patient with inflammatory bowel disorders in remission	Post-inflammatory IBS symptoms need to be distinguished from symptoms that are due to occult activity of inflammatory bowel disease
Bile acid malabsorption	Most likely genetically determined alteration of the function of the apical ileal bile acid transporter	Type 2, or idiopathic, likely due to a genetic defect in the apical ileal bile acid transporter	Up to 20% of patients with severe IBS-D symptoms	Targeted treatment (binding of bile acids) available
Visceral hyperalgesia	Central and peripheral mechanisms implicated	Can occur after infections or inflammation (post-inflammatory visceral hyperalgesia), or CNS-mediated visceral hyperalgesia after psychological trauma can occur	30% to 40%	Can be assessed in specialised laboratories. Treatment effects with psychotropic drugs may be explained by alterations of visceral sensory function
Mutations in *SCN5A*	*SCN5A* encodes the α-subunit of the voltage-gated sodium channel NaV1.5	Genetically determined	2% of all IBS patients, but only 31% of patients with *SCN5A* mutations have IBS symptoms	Relevant for constipation predominant IBS. The anti-arrhythmic mexiletine has the potential to "cure" symptoms in these patients

Table 1: **Factors relevant for the manifestation of IBS symptoms and frequency of these features in patients populations**

been explored, including disorders of the gut–brain axis; diet; genetic factors; infections and disturbances in the intestinal microbiota; low-grade mucosal inflammation, immune activation, and altered intestinal permeability; disordered bile salt metabolism; abnormalities in serotonin metabolism; and alterations in brain function.

Evidence that IBS is a gut–brain disorder

IBS symptoms that do not relate to the gastrointestinal tract, most notably anxiety and depression, are highly prevalent in outpatient and community samples,[16,17] and these associations are not explained by health-care-seeking behaviour alone. Such observations have led many to conceptualise IBS as a primary disorder of brain–gut function,[18] or even primary somatisation,[19] with the brain driving the gut manifestations, fatigue, and other complaints. However, there is now emerging epidemiological evidence from three prospective studies[20–22] in two different countries that in about half of patients, functional gastrointestinal symptoms arise first and that mood disorders develop later, suggesting that primary gut disturbances might be the underlying driver of the mood disorder in at least a subgroup of patients. In an independent study[23] of IBS and psychiatric disorders, the use of structured interviews showed that 40% of patients with a mood disorder and 23% of patients with anxiety developed these diagnoses after the onset of IBS. Other evidence implicates intestinal inflammation,[24] the cytokine response,[24] and the gut microbiome[25] in precipitating such gut to brain alterations in IBS. If correct, the implications of these findings are potentially profound, because they suggest that by reversing this gastrointestinal dysfunction (which is achievable since the gut is more accessible than the brain) there is the potential to improve or even reverse mood and gut dysfunction.

The role of diet in IBS

Many patients with IBS report dietary triggers, although often these are not reproduced when re-challenge occurs with the offending food in a double-blind manner.[26] Nevertheless, some foods appear to be implicated in the generation of IBS symptoms, and a change in diet can rapidly alter the microbiome.[27] High amounts of insoluble fibre were reported[28] to exacerbate symptoms among patients with IBS more than 20 years ago, but in recent years there has been a resurgence of interest in the role of diet in IBS. Fermentable oligosaccharides, monosaccharides, and disaccharides and polyols (FODMAPs), which are present in stone fruits, legumes, lactose-containing foods, and artificial sweeteners, might exacerbate symptoms in a subgroup of patients due to their fermentation and osmotic effects.[29] MRI studies[30] show that when FODMAPs such as fructose are administered to healthy volunteers, small bowel distension occurs because of increased small bowel water content.

A proportion of patients with IBS, who have no genetic, serological, or mucosal markers of coeliac disease, also seem to have improvement in symptoms after the withdrawal of gluten from their diet. These patients are often labelled as having non-coeliac gluten sensitivity. In one multicentre double-blind trial,[31] 140 patients with