UNDERSTANDING THE PATHOPHYSIOLOGY OF IBS

Giovanni Barbara, Marco Dolci, Cesare Cremon, Maria Raffaella Barbaro, Lara Bellacosa, Anita Fucili, Vincenzo Stanghellini

Department of Clinical Medicine and Center for Applied Biomedical Research (CRBA), University of Bologna, Italy

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ABSTRACT

While irritable bowel syndrome (IBS) is still considered a ‘disorder of gut function’ and is diagnosed on the basis of symptoms, evidence is growing to indicate the existence of biochemical, molecular, immune, and microbiological abnormalities in large subsets of patients. According to the current view, luminal factors (e.g. derived from food, microbiota, and bile acids) permeate into the mucosa through a leaky epithelial barrier. These substances elicit abnormal responses, partly related to the activation of the immune system, which evoke altered neuro-muscular responses and stimulation of pain pathways. This research is providing a new way of thinking about the pathophysiology of IBS and will potentially lead to the development of novel treatments for these common disorders.

Keywords: Irritable bowel syndrome, pathophysiology, intestinal motility, visceral hypersensitivity, post-infectious irritable bowel syndrome, serotonin, microbiota, mucosal permeability, neuro-immune interactions.

INTRODUCTION

The irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder (FGID) affecting between 10-20% of the population. IBS is defined on the basis of symptoms reported by the patients as recurrent abdominal pain or discomfort at least 3 days a month in the previous 3 months, associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in form (appearance) of stool. IBS is further classified according to the predominant bowel habit into diarrhoea predominant IBS (IBS-D), constipation predominant IBS (IBS-C) and mixed bowel pattern IBS (IBS-M). Traditionally IBS has been considered a disorder characterised by a dysfunction in the brain-gut axis, associated with: 1) psychosocial factors; 2) changes in intestinal motility; and 3) increased perception of stimuli arising from the intestine. More recently, several molecular and biochemical abnormalities have been identified. These include genetic polymorphisms, transient gastrointestinal infections, neuro-immune interactions, increased mucosal permeability, altered serotonin metabolism, and the participation of luminal factors, including gut microbiota and dietary factors. These new findings have fuelled the interest in IBS pathophysiology and opened new avenues for the development of specific treatments for this common condition.

PSYCHOSOCIAL FACTORS

In the collective imagination, IBS is a disturbance of young, anxious, otherwise healthy subjects. At the end of the 19th century Sir William Osler wrote that patients with ‘mucous colitis’ (what we would consider IBS nowadays) have a normal colonic epithelium and that many of them are hysterical, hypochondriac, self-centred, neurasthenic, and suffered from colicky abdominal pains. Indeed, compared with the general population, IBS patients have a higher prevalence of psychological comorbidity (e.g. affective disorders such as anxiety, hostility and phobia,
history of emotional, physical, and sexual abuse). In addition, substantial evidence supports a key role for stress in the pathophysiology of gut motor dysfunction and increased sensitivity in patients with IBS. Nonetheless, it is obvious that psychological factors alone are insufficient to explain the complex, multifaceted manifestations of IBS. Certainly, not all subjects with disturbances of the psychological sphere develop IBS and the prevalence of anxiety, paranoid ideation, hostility, depression, and obsessive-compulsive disorders in patients in community samples is only slightly higher compared with those found in the general population without IBS. In a recent study, a large group of community subjects was followed-up for 12 years in the attempt to detect the relative weight of psychological versus peripheral factors in the pathogenesis of FGID. As expected, the presence of psychological impairment at the beginning of the observational period represented a predictive factor for the development of IBS at the end of follow-up. However, FGID diagnosis at baseline was significantly associated with higher levels of subsequent anxiety and depression at follow-up. Taken together, these data provide support to the notion that long-lasting gut dysfunction may well contribute to the stress, anxiety, and depression experienced by at least a subgroup of patients with IBS.

**INTESTINAL MOTILITY**

In the past, IBS was termed ‘spastic colon’ and ‘spastic colitis’ in support of the concept that IBS is characterised by changes in colonic motor function and mild mucosal irritation. Manometry studies showed altered patterns of colonic and small intestinal motor function, including a higher number of high amplitude contractions (HAPCs), and enhanced responses to meal ingestion, cholecystokinin, or the stress hormone corticotrophin releasing factor. Compared with healthy subjects, IBS-D patients show accelerated colonic transit. Conversely, IBS-C patients showed fewer HAPC, reduced motility, and delayed colonic transit. Although in the majority of studies the relationship between motility changes and symptoms was rather poor, one study showed that >90% of HAPC were correlated with the occurrence of abdominal pain. More robust correlations have been described between bowel habit and transit time changes as detected with radiopaque markers or scintigraphy.

**VISCERAL HYPERSENSITIVITY**

A reduced threshold for perception of visceral stimuli (i.e. visceral hypersensitivity) is a common finding in FGID, including non-cardiac chest pain, functional dyspepsia, and IBS. Visceral hypersensitivity is considered a key element in the pathogenesis of pain perception in patients with IBS. Hypersensitivity to balloon distension of the rectum was initially detected in 95% of IBS patients but subsequently shown to be present only in about half of patients, particularly those with IBS-D. The correlation of visceral hypersensitivity with abdominal pain, quality-of-life, and psychological impairment has been reported to be poor. However, large sample studies showed that, compared with normosensitive IBS patients, those with rectal hypersensitivity had more pain, bloating, and diarrhoea. The pathophysiology of visceral hypersensitivity remains incompletely understood, but likely, involving both peripheral and central (i.e. central nervous system) mechanisms. Among peripheral factors, sensitisation of afferent nerve fibres by serotonin or immune activation has been the focus of recent studies (see below, paragraph on serotonin and neuro-immune interactions). Brain imaging studies (e.g. functional magnetic resonance imaging, positron emission tomography) showed that, in response to experimental rectal distension, compared with healthy controls, IBS patients display enhanced activation of areas involved in pain processing (thalamus, insula, anterior circulate cortex). Nonetheless, results of brain activation and reported pain to peripheral stimuli should be considered with caution as they are highly influenced by the patient’s emotional status, including anxiety, anticipation of pain, and hypervigilance.

**INTESTINAL GAS**

Bloating is extremely common in patients with FGID and occurs in up to 96% of patients with IBS. Most patients consider this symptom extremely distressing and about two-thirds of them consider it the worst of their symptoms. Bloating is more frequent in patients with IBS-C (75%), than in those with IBS-D (41%), and in IBS-C bloating correlated with abdominal distension.
There is no evidence that bloating is caused by an increased amount of gas in the intestine.  
On the other hand Serra et al.  
showed that 18 out of 20 IBS patients, compared with only 4 of 20 healthy subjects, developed gas retention, gastrointestinal symptoms or abdominal distension (>3 mm girth increment) after an infusion of a gas mixture in the jejunum. These data suggest that impaired handling rather than increased gas plays a role in the development of bloating in patients with IBS.

**LUMINAL FACTORS AND MICROBIOTA**

Food ingestion often aggravates symptoms in patients with IBS. Attention has been recently directed on fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), which are poorly absorbed in the small intestine and reach the colon where they are fermented by bacteria with consequent production of gas and stimulation of colonic motor activity. Diets containing low-FODMAPs have been shown to be beneficial in IBS, although the exact role of these diets in IBS and their applicability in everyday practice remains unclear. Non-coeliac gluten sensitivity is another area of great interest as it is potentially involved in symptom development in a subgroup of IBS patients.

Bile acid malabsorption has been identified in a subgroup of IBS-D patients. Excessive colonic bile acids stimulate secretion and colonic motility and stimulate pain pathways, hence contributing to diarrhoea and abdominal pain. According to a recent study, about 25% of patients with IBS-D had increased levels of intracolonic bile acids as the result of bile acid malabsorption or excessive bile acids biosynthesis in the liver. Among the potential mechanisms involved in this effect, of mention are the mutation of bile acids transporter in ileum and the decreased expression fibroblast growth factor 19 (FGF19), which is produced by ileal enterocytes and regulates bile acids synthesis in the hepatocyte through a negative feedback.

**MUCOSAL PERMEABILITY**

Several structures contribute to the intestinal mucosal barrier, hence regulating intestinal permeability. These include the mucus layer, the enterocytes, and intercellular tight junctions (TJs) positioned between epithelial cells. Disruption of the mucosal barrier leads to mucosal immune activation and stimulation of sensory pain pathways, leading to visceral hypersensitivity and pain perception. Increased mucosal permeability has been first shown in patients with post-infectious IBS (PI-IBS) by means of the lactulose/mannitol method and subsequently confirmed in patients who developed IBS after a waterborne outbreak of gastroenteritis in Walkerton, Ontario. Increased intestinal permeability has been documented also in patients with non-specific IBS. Electron microscopy studies showed enlarged paracellular spaces and cytoskeleton condensation suggestive of TJ dysfunction in the jejunum of IBS-D patients. Piche et al. demonstrated that colonic biopsies had significantly higher permeability...
compared with controls. Increased permeability was associated with significantly lower expression of tissue zonula occludens mRNA (one of the main TJ components) compared to asymptomatic controls. In addition, mucosal supernatants of patients with IBS, but not from healthy controls, markedly increased permeability of epithelial cell monolayers. Although the origin of these mediators remains unknown, proteases, which are produced in excess by intestinal mast cells or by luminal bacteria, are likely participant in increased mucosal permeability. The trigger factors involved in the increased intestinal permeability of IBS remain elusive. Recent studies suggest the participation of stress, food allergy or gluten.

GASTROINTESTINAL INFECTIONS

Up to now, acute infectious gastroenteritis is the strongest known risk factor for the development of IBS, with a relative risk around 12. PI-IBS may develop after bacterial infection (e.g. Shigella, Salmonella, and Campylobacter) or viral gastroenteritis. Risk factors for PI-IBS comprise the virulence of the pathogen, younger age, female sex, the long duration of the initial gastroenteritis, the use of antibiotics, and psychological factors. Genetic factors, including polymorphisms for genes involved in the control of pro-inflammatory cytokine production (IL-6), host-bacteria interactions and epithelial paracellular permeability, have been demonstrated in patients with PI-IBS. More than half of these patients also have a mild immune activation including higher numbers of mast cells, intraepithelial lymphocytes, lamina propria T cells, calprotectin-positive macrophages, and enteroendocrine cells likely contributing to pain and abdominal pain perception (see below).

NEURO-IMMUNE INTERACTIONS

The development of IBS after infectious gastroenteritis and the higher prevalence of IBS-like symptoms in patients with inflammatory bowel diseases in remission, microscopic colitis or coeliac disease on a gluten free diet, support the potential involvement of immune activation in the pathogenesis of IBS. While there is no evidence of elements typical of acute inflammation or mucosal architecture distortion, a high proportion of these patients has higher mucosal counts of mast cells, T cells and B cells along with increased release of immune mediators (e.g. cytokines, prostanoids, histamine, and proteases). In our laboratory we have introduced the use of mucosal biopsy supernatants in the assessment of the impact of the mucosal milieu on bowel physiology. This is obtained by applying colonic supernatants obtained from IBS patients or controls to intestinal tissues of laboratory animals or human colon specimens obtained from the disease-free margins of surgical resections for colon carcinoma.

Our studies showed that IBS supernatants, infused through a mesenteric artery of the isolated intestinal rat loop, elicited higher sensory fibre activation compared to control supernatants. These effects were significantly inhibited by antagonists of the histamine receptor type-1, proteases inhibitors and serotonin type-3 receptor antagonists, suggesting the participation of mast cells and enterochromaffin cells releasing serotonin in the sensory activation in IBS. Cenac et al. showed that intracolonic injection of IBS supernatants in mice evoked visceral hypersensitivity. This effect was blunted in proteinase activated-2 receptor knock-out mice implying the participation of proteases acting on PAR-2 receptors on sensory nerves. Using sophisticated computerised optical techniques, Bühner et al. showed a rapid histamine, serotonin, and protease-dependent hyper-activation of human enteric nerves in response to IBS supernatants. Although most of these effects could be reduced by inhibitors/antagonists of immune mediators or serotonin, a potential implication of factors derived from luminal bacteria has also been proposed. In addition, the severity and frequency of perceived abdominal painful sensations in IBS patients were directly correlated with the number of activated mast cells in proximity of nerve endings. Thus, taken together, these studies provide not only evidence of infiltration of immune cells in subgroups of patients with IBS, but also implications of immune activation for disturbed intestinal function.

SEROTONIN

Serotonin, or 5-hydroxytryptamine (5-HT), is released by enterochromaffin cells in response to mechanical and chemical stimuli (food, short chain fatty acids produced by intestinal microbiota). 5-HT regulates and generally stimulates secretory, motor, and sensory functions.
of the gastrointestinal tract acting on receptors spread all over the gut. 5-HT biological activity is terminated by the serotonin reuptake transporter (SERT) located on enterocytes. The potential role of 5-HT in IBS is supported by the therapeutic efficacy of 5-HT 3 receptor antagonists and 5-HT 4 receptor agonists on IBS symptoms. Decreased postprandial 5-HT platelet-depleted plasma levels have been detected in patients with IBS-C, suggesting a problem with 5-HT release to physiological stimuli. Increased plasma levels of 5-HT have been shown under fasting and fed conditions in patients with IBS-D or PI-IBS, suggesting a reduced 5-HT reuptake and/or metabolism. Although several studies demonstrated a reduced SERT expression in the colon of patients with IBS, conflicting data have been reported. We showed that the spontaneous release of 5-HT was significantly increased in patients with IBS irrespective of bowel habit and correlated with the severity of abdominal pain.

### GENETIC FACTORS

Overall, IBS exhibits typical features of a complex disorder with interactions between environmental and genetic factors. Epidemiological studies of familial aggregation and twins suggest a role of genetic predisposition in the incidence of IBS, although social learning is probably at least as important. Several studies assessed the risk effects of single nucleotide polymorphisms (SNPs) in IBS candidate genes. However, at present, our knowledge on genetic predisposition to IBS remains limited. Previous small studies identified polymorphisms in serotonergic and inflammatory genes as susceptibility SNPs for IBS. As previously mentioned in this review, SNPs in genes involved in immune activation, epithelial barrier and host-microbiota interaction (TLR9, IL-6, and CDH1) were associated with PI-IBS. Another study correlated colonic transit and pain sensation with polymorphisms in the neuropeptide S receptor gene (NPSR1), a gene involved in inflammation, anxiety and nociception. A functional Klotho gene variant regulating hepatic bile acid synthesis was associated with colonic transit in IBS-D. In the largest genetic study of IBS, Zucchelli et al. demonstrated in two independent cohorts from Sweden and USA a strong association between rs4263839 in TNFSF15 and IBS, particularly IBS-C. The association between this gene which is involved in Th17 immune response and IBS (although in this case with a different subtype, i.e. IBS-D) was recently replicated in UK individuals. In this study, polymorphisms in TNF were also associated with PI-IBS.

### CONCLUSIONS

Biochemical, genetic, metabolic, microbiological, molecular, and genetic factors can be now identified in large subgroups of patients with FGID in general and IBS in particular. These findings will likely influence the way we consider and classify these disorders and provide the basis for the development of novel pharmacological and non-pharmacological approaches. These have been recently reviewed elsewhere and include, new 5-HT4 agonists, and 5-HT3 antagonists, 5-HT synthesis inhibitors, m-opioid antagonists, chloride channel openers, guanylate cyclase-c agonists, inhibitor of ileal bile acid transporter, spherical carbon adsorbers, new probiotics and non-absorbable antibiotics, mast cell stabilisers, and 5-aminosalicylates.

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