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Irritable bowel syndrome - An inflammatory disease involving mast cells

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Irritable bowel syndrome (IBS) is traditionally defined as a functional disorder – that is the presence of symptoms in the absence of demonstrable pathological abnormalities. In recent times, low grade inflammatory infiltrates in both the small and large bowel of some patients with IBS – often rich in mast cells, along with serological markers of low grade inflammation have focussed attention on IBS as an inflammatory disease. The observation that mast cells often lie in close association to enteric neurons, and *in-vitro* and *in-vivo* animal studies demonstrating that mast cell mediators may influence enteric motility provides a biologically plausible causal mechanism in IBS. Pilot studies on patients with IBS using the mast cell stabiliser sodium cromoglycate ('proof of concept') have been encouraging. The essential question remains why mast cells infiltrate the bowel of IBS patients. A disturbance of the 'brain – gut axis' is the current favoured hypothesis, whereby childhood stress or psychiatric comorbidity act via neuro-immune mechanisms to modulate low grade inflammation. An alternative hypothesis is that food allergy may be responsible. Serum specific IgE, and skin prick tests are not elevated in IBS patients, suggesting type 1 IgE mediated food allergy is not the cause. However questionnaire based studies indicate IBS patients have higher rates of atopic disease, and increased bronchial reactivity to methacholine has been demonstrated. In this review, we highlight the potential role of mast cells in IBS, and current and future research directions into this intriguing condition.

Key words: IBS; Mast cells; Atopy; Inflammation; Immunology

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders and causes considerable morbidity amongst its sufferers [1]. Long defined as a functional gastrointestinal disorder (implying the lack of demonstrable pathological abnormalities) IBS is increasingly viewed as a low grade inflammatory disorder [2]. Both histological specimens obtained at endoscopy and serological cytokine studies have demonstrated low grade inflammation in IBS [3]. Mast cells (MC) appear to play a particularly important role, and pilot 'intention to treat' studies using MC stabilisers have yielded encouraging results [4]. The observation that mast cells often lie in close association to enteric neurons and *in vitro* and *in vivo* animal studies demonstrating that MC mediators may influence enteric motility provide a biologically plausible mechanism of causation in IBS [5].

Mast cells are normally found in the intestine, but why they

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may be found in higher density and, more importantly, why they are activated in patients with IBS has yet to be determined. One popular current hypothesis is that IBS represents a disturbance of the 'brain-gut axis' whereby stressful early life events and/or psychiatric co-morbidity mediate low level inflammation and mast cell infiltration of the bowel [3]. An alternative hypothesis is that food allergy may be responsible [6]. Traditional measures of type 1 IgE-mediated food allergy, such as serum specific IgE and RAST testing, are usually negative, but questionnaire-based studies indicate an increased prevalence of atopic disease amongst IBS patients and bronchial provocation testing may be abnormal [7, 8]. In this review, the evidence for MC involvement in IBS is discussed, and the need for future collaborative research between gastroenterologists and allergist/immunologist alike is highlighted.

IBS as an inflammatory condition

IBS is a common condition, with a prevalence of 10-20% being reported in Western countries, India, China and Japan [8]. Whilst not life-threatening, IBS causes considerable morbidity and is responsible considerable time off work and an impaired quality of life [9]. Female gender, a family history of IBS, a history of physical or sexual abuse and co-morbid psychiatric disorders are strong risk factors for IBS [10]. Indeed up to 70% of the patients referred to tertiary centres with IBS meet diagnostic criteria for anxiety or depression [10]. While this may represent a minority sub-group where uncontrolled symptoms may be the effect rather than the cause, such patients have focussed interest on the 'brain-gut axis' as the explanatory disease model [3].

IBS has traditionally been defined in terms of a symptom cluster and classed as a functional gastrointestinal disorder – implying an absence of demonstrable anatomical or histological pathology. The advent of gastrointestinal manometry and motility laboratories in the 1970's lead to a focus on disturbances of motility and, later, to heightened sensitivity to luminal distension or 'visceral hyperalgesia or hypersensitivity' [11]. Many patients with IBS manifest abnormal colonic or small bowel motility (slow, fast or incoordinate) and/or hyperalgesia, but such physiological abnormalities have not found a place in routine clinical practice or in diagnosis or classification [11]. The pattern of symptoms remains the cornerstone of diagnosis and classification of functional gut disorders (the Rome III criteria as shown in Table 1) [12]. For patients with IBS, they may then be classified IBS-C (constipation-predominant), IBS-D (diarrhoea-predominant) or IBS-A (alternating) according to their symptom pattern [12].

The observation that a percentage of patients who suffer from acute gastroenteritis go on to develop IBS renewed interest in IBS as an inflammatory condition [13]. Follow-up of these patients in multiple centres and cohorts has revealed a tendency to develop IBS-D and have low grade inflammatory infiltrates (often containing MCs) at endoscopy [3]. Subsequent endoscopic comparisons of patients with IBS-D who did not describe a pre-existing acute infectious gastroenteritis found similar low grade inflammatory changes, allowing the 'inflammatory hypothesis' to be applied more generally [3].

Mast cell infiltrates in IBS

Many but not all human endoscopic biopsy studies of patients with IBS have found increased numbers of MCs in the luminal mucosa (Table 2) [14-19]. The density of MCs in both small and large bowel may be increased in patients with IBS, but the results are somewhat contradictory. Some studies demonstrate increased density in the small and not the large bowel and others vice-versa. Increased density of MCs has been found in both male and female patients and in all subtypes of IBS. The presence of MCs per se does not necessarily imply they are pathogenically important unless they are activated. Indeed, Barbara et al demonstrated an increased number of degranulating MCs in patients with IBS compared to that in healthy controls [17]. Tryptase release from duodenal biopsies was elevated; arguably increased MC numbers should naturally cause increased tryptase following laboratory manipulation of biopsy specimens.

There have been some attempts to correlate the density of MCs to clinical symptoms [17]. Several studies have shown

Table 1. Rome III diagnostic criteria for irritable bowel syndrome

At least 3 months, with onset at least 6 months previously of recurrent abdominal pain or discomfort* associated with 2 or more of the following:

- Improvement with defecation; *and/or*
- Onset associated with a change in frequency of stool; *and/or*
- Onset associated with a change in form (appearance) of stool

*Discomfort means an uncomfortable sensation not described as pain.

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Table 2. Studies of intestinal mast cell infiltration in irritable bowel syndrome

Reference	No. of IBS	No. of control	Duodenum	Jejunum	Ileum	Colon	Significance
[14]	48	24	N/A	N/A	N/A	+	yes
[15]	50	21	N/A	N/A	N/A	+	yes
[16]	41	48	+	N/A	N/A	N/A	yes
[17]	44	22	N/A	N/A	N/A	+	yes
[18]	20	14	N/A	+	N/A	N/A	yes
[19]	42	12	N/A	N/A	N/A	+	yes

an association with the severity of abdominal pain [5, 17]. Two groups have examined the associations with psychiatric co-morbidity, particularly anxiety and depression which are commonly described in IBS [14, 15]. In only one was the density of MCs in the intestine significantly correlated with the severity of anxiety and depression [15] .

A rationale for mast cells as a causative factor for IBS symptomatology

There are several layers of evidence in support of a major role of MCs in the genesis of symptoms in IBS.

- MCs are present in the appropriate microenvironment of the gastrointestinal tract. They are found in both the mucosa and serosal layers and express high affinity (FcRγ) receptors to IgE [3]. MCs in humans lie in close proximity to neural endings and may form membrane-membrane interactions [20]. The factors regulating the close apposition of MCs to enteric neural cells are incompletely understood, but may involve a two-way communication by which MCs produce neurotrophic growth factors, and MCs are in turn attracted by neuropeptides Further research into this complex interplay is clearly needed if the 'brain-gut' axis is to be understood (see above) [21].
- Mediators released from MCs are capable of inducing sensorimotor dysfunction. Degranulation of MCs is associated with release of mediators such as histamine, tryptase and prostaglandins which may influence enteric efferents via proteinase-activated receptors [22]. Furthermore, a study using mucosal mediators of IBS patients on rat jejunal sensory nerve firing found that the stimulatory effect of the mucosal mediators released from the mucosal biopsies of IBS patients could be inhibited by histamine receptor blockade [5].
- MC activation may cause abdominal symptoms consistent with IBS. Patients with clear IgE-mediated allergic reactions to food often complain of functional abdominal symptoms [23]. More strikingly, patients with systemic mastocytosis who have an enteric infiltrate often complain of a pattern of abdominal symptoms that fulfil criteria for IBS [24].
- Apparent efficacy of treatments aimed at decreasing MC mediator release and/or infiltration. Sodium cromoglycate is classified as a 'mast cell stabiliser' and has shown promise in pilot 'proof-of-concept' studies to improve the symptoms of IBS patients [25]. The oral anti-inflammatory 5ASA has been found in one small randomised controlled study to decrease the symptoms of IBS, and this corresponded with a decrease in the density of the MC infiltrate within the colon. Furthermore the mast cell stabiliser and antihistamine (H-1 receptor blocker) ketotifen was found to decrease the symptoms of IBS in a recent placebo controlled trial involving 60 patients (30 in each arm) [26]. Curiously, the patients who received ketotifen and improved symptomatically at 8 weeks were not less likely than controls to manifest mast cell degranulation (as defined by tryptase or histamine release on endoscopic biopsy specimens) and the intestinal infiltration of mast cells was unchanged following the treatment course [26]. This led the authors to suggest that H-1 receptor blockade, and not mast cell stabilisation was the likely therapeutic mechanism [26]. Cleary further research is required.

IBS and the brain-gut axis

As outlined above, the term 'brain-gut axis' refers to the bi-directional communication between the gut (enteric nervous system, luminal wall) and the central nervous system (including the hypothalamopituitary axis) [27]. More recently, the complex neuro-immune interactions between the intestinal microflora and the host has been incorporated into this model (Fig. 1). The brain-gut-axis model attempts to explain the complex interplay of factors potentially responsible for the precipitation and perpetuation of

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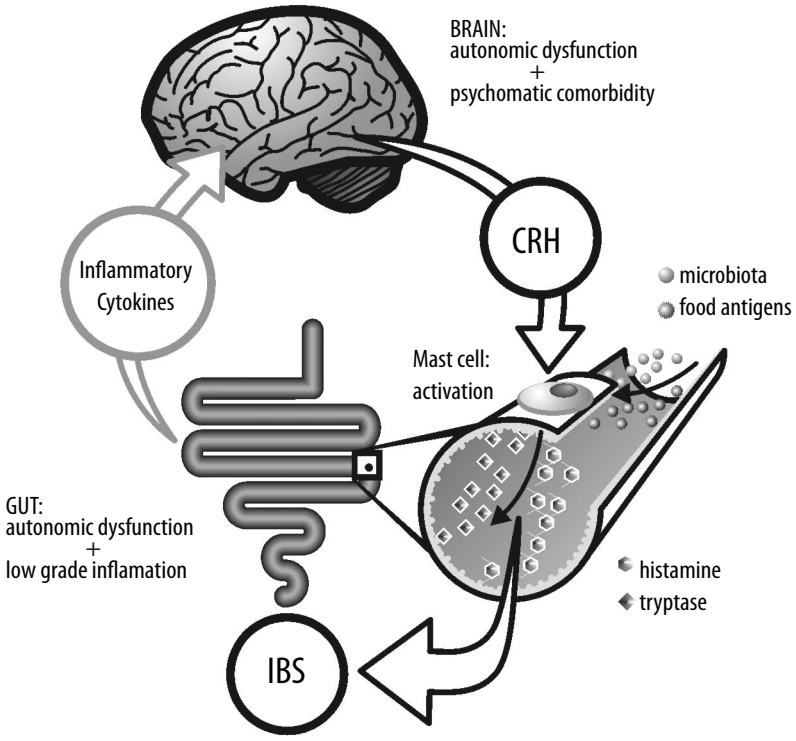

Fig. 1. The Brain – Gut axis in irritable bowel syndrome (IBS).

IBS and other gastrointestinal conditions. Animal studies have shown that maternal deprivation may result in later sensitivity to manometric gastrointestinal stimuli, whilst stressing an adult rodent can result in increased cortisol releasing hormone (CRH), and colonic MC infiltration and degranulation [28]. The interplay between stress and the disturbed gastrointestinal motility and sensory function is particularly pertinent given the association between childhood physical and sexual abuse, psychiatric illness, life stress and IBS. Indeed, human studies reveal abnormal colonic motility mimicking IBS in subjects injected with CRH [29].

The intestinal microbiota may play an additional modulating role in the brain-gut axis and are the subject of current intense research interest. It is not known why some patients with IBS demonstrate abnormalities in their microbiota, but it is proposed that the spectrum of flora in these patients favours a pro-inflammatory mucosal reaction [30]. Encouragingly, a few studies suggest a role for probiotics in successfully alleviating the symptoms of IBS [30].

IBS and food allergy

Patients frequently attribute their symptoms to food intake and there is little doubt that food is an important trigger for those symptoms [23]. There are many mechanisms by which this can occur and these include luminal distension and osmotic effects, direct stimulation of the MCs or enteric nervous system by bioactive chemicals such as salicylates, and food hypersensitivity (non-IgE-mediated) reactions [31]. However, there is no direct evidence to suggest that classical IgE mediated type 1 allergic reactions to food antigens play a role in the symptoms of IBS [23]. Skin prick and serum specific IgE antibody testing to common food antigens are generally identical to healthy controls [31].

Few studies have examined responses to foods in the gut-associated immune compartment, which may be very different to those in the systemic immune compartment. One approach is to perform the equivalent of skin prick tests via the colonoscope and to look for wheal reactions after the mucosal injection of food antigens. This test, the colonoscopic allergen provocation test (COLAP), showed positive responses to specific food antigens in a significant majority of patients with functional gut symptoms

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and suspected food hypersensitivity who had normal skin prick and serum specific IgE to common food antigens [32]. Hence it is conceivable that a percentage of IBS patients have an IgE or other immune-mediated food hypersensitivity that is being 'missed'. There have been no subsequent reports of the further application of the COLAP test or on findings in patients with IBS. This deserves further study.

IgG antibodies to common food antigens may be detected in the serum of healthy children and adults [6]. Patients with IBS have elevated titres of these antibodies in some studies, although no correlation between the degree of elevation in IgG and the severity of the symptoms has been demonstrated [33, 34]. A randomised controlled trial involving only patients with IBS who were allocated either a sham diet or elimination diet to culprit foods to which the IgG antibodies were elevated demonstrated symptomatic benefit at 12 weeks, but only after data were corrected for adherence [6]. Healthy controls were not included in this study and IgG antibodies were not measured at the conclusion of the study. Sustained benefit from this food-specific IgG approach has been claimed by another group, but the concurrent use of probiotics reduced the clarity of the findings [34]. Further studies are warranted. Until a cause-effect relationship is clearly established, the quantitative (and not qualitative difference) in serum IgG to food antigens could conceivably be an epiphenomenon, perhaps related to an inflamed or 'leaky' gut [35].

IBS and atopic diseases

IBS patients are no more likely than the background population to record positive skin prick or serum specific IgE tests to common environmental antigens. Curiously however, there is an increased prevalence of IBS amongst patients with other 'atopic' conditions, according to some studies [7]. For example, an association was found between allergy patients attending a tertiary hospital clinic and a high proportion of IBS symptoms meeting Rome criteria using a self-report questionnaire [7]. In a retrospective case control study of more than 7,000 patients attending a general practise setting in the UK, an increased prevalence of allergic rhinitis and asthma amongst patients with lower gastrointestinal symptoms was reported [36]. It should be pointed out that questionnaire-based studies potentially introduce responder bias; IBS patients may, for example, display a 'learned illness' behaviour and be expected to complain of symptoms without organic cause. Several more objective papers have linked asthma with IBS and have demonstrated increased airway responsiveness to inhaled methacholine and/or reversibility with bronchodilators in IBS patients who do not give a history of asthma or other atopic conditions [8]. In a study of 133 IBS patients and matched healthy controls, asthma was diagnosed in 15% of the IBS group compared to 1.5% of controls [8]. By contrast, another group failed to demonstrate an increased prevalence of asthma amongst IBS patients in a study of 42 IBS patients and 42 matched healthy controls [37].

Hence it would appear that the association between IBS and atopic conditions is controversial, and that traditional measures of 'atopy' are negative [7]. Rather the association is based on self reported symptom clusters and/or the objective finding of bronchial hyper-reactivity. As many cases of asthma, particularly of adult onset are apparently unrelated to allergy, other shared cofactors may be responsible for the association, including alterations in sympathetic/ parasympathetic tone [38]. Further study is needed, perhaps examining the mucosa of both the bronchi and gut of the putative 'asthmatic' IBS subgroup, and correlating the IBS symptoms with respiratory function tests over time.

Stress as a precipitating factor for food allergy – towards a unifying conceptual framework with treatment implications

Two opposing models of IBS causation have been outlined:

- The 'head-down' hypothesis: psychological or physical stress activates the hypothalamic-pituitary axis, central and enteric nervous system to release CRH and neuropeptides to attract MCs to the bowel wall [39]; and
- The 'bottom-up' hypothesis: Food allergens/antigens incite the inflammatory infiltrate [7].

There is no reason why both forces can't be operating (Fig. 1). This is supported by studies of patients with post-infectious IBS, in which patients with a history of physical or sexual abuse or depression (head-down) are more likely to develop IBS following a self limited episode of acute infectious diarrhoea (bottom-up) [13, 40].

Animal models provide a clue as to how stress may 'prime' a patient to develop a localised inflammatory response to food antigens. Rats that were subjected to stress prior to consumption of a labelled oral antigen (horse-radish peroxidase - HRP) were not only more likely to absorb the HRP, but also more likely to form circulating HRP-specific IgE and develop a denser inflammatory infiltrate containing MCs in the intestinal wall [28]. While this

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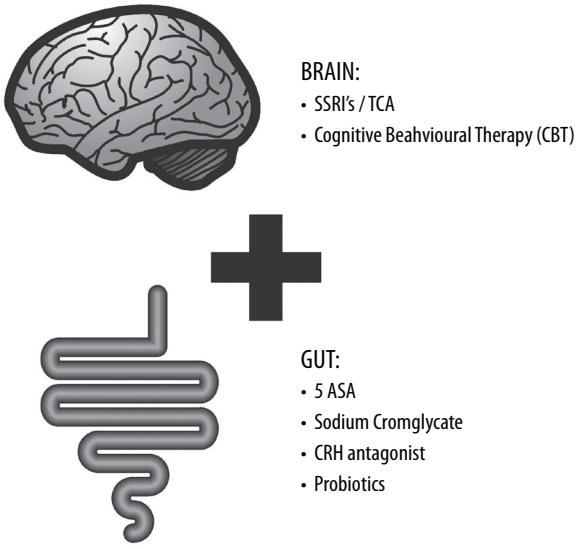

Fig. 2. Proposed dualistic treatment model of irritable bowel syndrome.

model is not directly applicable to IBS in humans in that these patients have a normal serum IgE to food antigens, the concept of stress modulating intestinal permeability, antigen presentation and inflammatory cell recruitment may guide future research. Promising avenues of inquiry may include the study of toll-like receptors on enterocytes as well as cytokine and microarray analysis.

Recent advances in dietary therapy directed at food intolerance (specifically short-chain poorly absorbed carbohydrates) have improved the ability to achieve symptomatic control in the majority of patients with IBS, but this therapy is purely symptomatic and does not address the potential causes of IBS [41]. In light of the above unifying hypothesis, more pathogenically-related therapy can be proposed. Potential 'head-down' therapies such as the use of antidepressant medication, hypnotherapy and cognitive behavioural therapy, which show benefit in some patients, may be combined with 'bottom-up' therapies such as excluding validly identified food antigens form the diet or pharmacological agents such as mast cell stabilisers, antihistamines and mesalazine, which also have some evidence for efficacy [1, 25]. Thus, a dualistic treatment approach based upon the unifying hypothesis may improve therapy in the future (Fig. 2).

Summary

IBS is one of the most common gastroenterological disorders, yet its aetiology remains elusive. Recent interest has focussed on low grade inflammation, particularly involving MCs in its pathogenesis. The most compelling overall hypothesis to explain the MC infiltrate is of a disturbance of the brain-gut axis, whereby MCs may be attracted to the bowel via neuropeptides – although only animal models support this assertion. While current evidence suggests type 1 IgE-mediated food allergy is an unlikely cause of the MC infiltrate, patients with IBS appear to describe more frequent atopic symptoms and studies of the gut immune compartment have produced some signals that immune-mediated reactions to food antigens may indeed be causally related to symptom genesis. Cleary, IBS represents a fertile soil for research for both gastroenterologists and allergy/immunologists alike.

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