Supplementary Box 1: Other clinical gastrointestinal inflammatory disorders causing gut dysfunction

There are numerous other gastrointestinal disorders in which inflammation contributes to disordered motility, secretion and sensation, which are likely to be underlined by inflammation-induced neuropathy. There are relatively few studies of neuropathy in animal models of these inflammatory digestive diseases.

Chronic oesophagitis

Chronic oesophagitis occurs in patients with eosinophilic oesophagitis, erosive GERD, and columnar-lined or Barrett oesophagus. Patients with eosinophilic oesophagitis present with symptoms of dysphagia and chest pain that are refractory to acid reduction therapies. Many studies have found abnormal oesophageal motility in eosinophilic oesophagitis that may involve fibrosis-mediated reduced compliance and longitudinal muscle dysfunction. Enhanced oesophageal sensitivity to distension occurs in symptomatic, but not asymptomatic gastro-oesophageal reflux disease. Notably, Barrett oesophagus patients demonstrate reduced sensitivity to mechanical and chemical stimuli. In both gastro-oesophageal reflux disease and Barrett oesophagus there are defective lower oesophageal sphincter relaxations and reduced oesophageal peristalsis. Interestingly, following argon plasma coagulation thermoablation treatment for Barrett oesophagus, oesophageal sensitivity returns to normal, but dysmotility remains.

Genetic mouse models of eosinophilic oesophagitis develop oesophageal strictures as assessed by barium-swallow that do not resolve after reduction of eosinophilia. Smooth muscle contractility is increased in these models.

Hypersensitivity assessed in animal models of oesophagitis are discussed in the text.

Chronic gastritis, peptic ulcer disease, and functional dyspepsia

Chronic gastritis and peptic ulcer disease are associated with reduced antroduodenal motility, an increased sensitivity to acid and usually present with anaemia, non-cardiac chest pain or dyspeptic symptoms. By contrast, functional dyspepsia is defined as the presence of dyspeptic symptoms in the absence of an organic cause that readily explains them and its clinical manifestations are excellently reviewed elsewhere.

Nearly 80% of patients with gastritis can be successfully treated by Helicobacter pylori eradication. Gastritis can also arise from a CD4+ T-cell-mediated autoimmune response and use of non-steroidal anti-inflammatory drugs (NSAIDs). Collagenous gastritis is rare, but may be aetiologically similar to microscopic colitis. It appears that inflammation rather than H. pylori infection itself causes the symptoms of gastritis. Eradication therapy does not eliminate dysmotility or sensitivity in patients with functional dyspepsia, whilst gastro-oesophageal reflux disease and gastritis is common in H. pylori-negative patients. Among H. pylori-positive patients with gastritis and in patients who have been endoscopically defined remission, the degree of histological gastritis correlates with the degree of motor dysfunction. Gastritis is associated with numerous changes in the structure of extrinsic and enteric nerves including increased TRPV1, CGRP, substance P, VIP and NPY-immunoreactive nerve fibres in the gastric mucosa that persist following H. pylori eradication and is also present in H. pylori-negative gastritis.

It is of interest to note that plexitis may also play an important role in idiopathic as well as diabetic gastroparesis.

Coeliac disease

Coeliac disease is a chronic intestinal inflammation induced by dietary gluten in genetically predisposed individuals. The autoimmune-targeted destruction of absorptive epithelial cells by CD8+ intraepithelial lymphocytes causes enhanced permeability and nutrient malabsorption. Electrochemical chloride secretion is unaffected during active coeliac disease, which suggests normal secretory epithelial cells and ENS circuits. There are numerous motility disorders associated with active celiac disease including nutracker oesophagus, delayed gastric emptying, reduced oro-cecal transit, and reduced antral and duodenal motility. Additionally, patients with coeliac disease have higher internal anal sphincter pressures and lower rectal distension thresholds for sensation and pain. While permeability is only partially restored by a gluten-free diet motor dysfunction is resolved. Recently it has become clear that a proportion of patients with IBS have gluten sensitivity where symptoms can be improved by a gluten-free diet. Conversely, there are a proportion of patients for whom a gluten-free diet resolves inflammation, but have persistent gastrointestinal symptoms.

Microscopic colitis

Microscopic colitis consists of both lymphocytic colitis and collagenous colitis, presents clinically as chronic or recurring watery diarrhea without bleeding where the mucosa appears normal under endoscopic inspection, but histology reveals increased intraepithelial lymphocytes or a subepithelial collagen band, respectively. First described in the 1970s, the colonic mucosa demonstrates poor sodium, chloride and water absorption and increased electrogenic chloride secretion that may, in some patients, be due to bile acid malabsorption.

Plexitis

Lymphocytic ganglionitis and intestinal lymphocytic epithelioganglionitis, the latter having plexitis concurrent with increased intraepithelial lymphocytes, are considered distinct pathologically defined clinical entities. Plexitis-induced neuropathy is causative for approximately 25% of cases of chronic intestinal pseudo-obstruction, a condition that may reflect the extreme end of a spectrum of plexitis-related disorders.

Colonic diverticulitis

Colonic diverticulitis is common especially in the elderly. Usually asymptomatic, diverticulitis becomes diverticular disease as symptoms of abdominal pain arise, and becomes diverticulitis when the diverticula become inflamed. The latter patients may present with fever and leukocytosis or in more complicated cases with fistula, obstruction or peritonitis. Diverticular disease without diverticulitis may indicate colonic hypersensitivity that may or may not be related to diverticula. While commonly held that stasis in diverticula leads to bacterial overgrowth and diverticulitis, there is little direct evidence for this. Microscopic colitis, usually increased lymphoid aggregates, has been observed in patients with diverticulitis, suggesting both that inflammation may contribute to diverticula and that microscopic colitis may in fact precede diverticulitis. Acute diverticulitis is a risk factor for recurrent diverticular disease and microscopic colitis is common in these patients. Segmentation of the colon, responsible for abnormally high colonic pressures and created by highly contracted hastra, occurs more frequently in patients with diverticulitis and is exacerbated by prostaglin, an inhibitor of acetylcholine esterase. There is also evidence of structural neuroplasticy of enteric neurons in diverticulosis that may involve plexitis.


Supplementary Box 2: Non-neuronal influences on gastrointestinal function

Although the focus of this Review is on neuroplasticity, it is important to keep in mind that neurons are only one contributor to gastrointestinal function. There are significant impairments of smooth muscle, interstitial cells of Cajal and secretory and absorptive epithelial cells that probably contribute to dysfunction. Specific examples are listed below for patients with IBD.

**Smooth muscle**

Resected smooth muscle cells from patients with IBD have a reduced ability to contract compared to resected muscle from patients with cancer.1-8 In Crohn’s disease there is marked smooth muscle hypertrophy9,7 and these cells contribute to fibrogenesis, wound healing and stricture formation.10-12 In ulcerative colitis, hypertrophy with a lack of fibrosis occurs in benign strictures and contributes to bowel shortening.13-15

**ICCs**

Interstitial cells of Cajal (ICC) are pacemaking cells that create the bioelectrical slow wave potential that leads to phasic contractions of the smooth muscle13 and are key contributors to digestive disease.14 In Crohn’s disease overall ICC numbers are greatly reduced15-17 and show signs of cellular damage.6,18,20 In ulcerative colitis, some studies identify a loss of ICC,21 although others do not,16,18 whilst cellular damage to ICC is also apparent.20

**Epithelium**

Colonic water and sodium absorption are reduced, but potassium excretion is increased in patients with IBD.5,22-27 Malabsorption of sodium and water28 and nutrients29 occurs even in the non-involved segments of the small intestine, and prostaglandin-induced chloride secretion is reduced in the ileum of patients with ulcerative colitis.30 suggesting that changes in epithelial transport may be independent of the local inflammatory milieu. Patients with IBD demonstrate malabsorption of fat, vitamin B12,29 carbohydrates and amino acids,31 with malnourishment a particular concern in subsets of patients, especially children with IBD. Upregulation of the cystic fibrosis transmembrane regulator (CFTR),32 decreased expression of the down-regulated in adenoma (DRA) chloride transporter33 and reduced activity of SLC26A334 or the basolateral sodium/potassium pump35 might also contribute to IBD-related secretory changes independently of the enteric nervous system. In addition, reduced barrier function and enhanced paracellular permeability might contribute to loss of electrochemical gradients required for secretory and absorptive processes.26 In remitted ulcerative colitis, sodium and water absorption36-38 and muscarinic acetylcholine receptor-mediated chloride secretion remains reduced.39 Interestingly, in remitted disease, cAMP-mediated chloride secretion is enhanced.40 The enteric nervous system might also contribute to secretory changes as anionic chloride secretion is reduced in the colonic mucosa of patients with ulcerative colitis,22,40 although increased submucosal resistance might partially contribute to this observation.41 Furthermore, secretory reflexes of the enteric nervous system, which involves prostaglandins, acetylcholine and vasoactive intestinal peptide, might contribute to these changes as inflammatory cytokines41 and histamine42 alter short circuit currents.


<table>
<thead>
<tr>
<th>Animal Models</th>
<th>Model class</th>
<th>Species</th>
<th>Inflammatory response</th>
<th>Ref #</th>
<th>Neuroplasticity/ alterations</th>
<th>Ref #</th>
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<td>Chemical</td>
<td>Ferret</td>
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<td>1</td>
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<td>Ovalbumin sensitization/challenge</td>
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<td>3–5</td>
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<td>3–5</td>
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<tr>
<td>CD2-IL-5 and rTA-CC10-IL-13</td>
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<td>Mouse</td>
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<td>6,7 NA</td>
<td></td>
<td>6</td>
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<td><strong>Gastritis</strong></td>
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<td>Iodoacetamide</td>
<td>Chemical</td>
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<td>Acetic acid</td>
<td>Chemical</td>
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<td>Chemical</td>
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<tr>
<td>DSS</td>
<td>Chemical</td>
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<td>16</td>
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<td>Schistosoma mansoni</td>
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<tr>
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<td>Chemical</td>
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<tr>
<td><strong>TNBS and/or DNBS</strong></td>
<td>Chemical</td>
<td>Mouse, rat and guinea-pig</td>
<td>Combines with endogenous proteins and antigens to evoke a transmural Th1-mediated inflammation</td>
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<td><strong>Mustard oil</strong></td>
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<tr>
<td><strong>Trichuris muris</strong></td>
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<td>116</td>
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Abbreviations: Ach, acetylcholine; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglia; DSS, dextran sodium sulphate; ENS, enteric nervous system; 5-HT, serotonin; MPO, myeloperoxidase; NA, not available; PAR2, protease activated receptor 2; Th1, type 1 T helper cells; Th2, type 2 T helper cells; TLR, Toll-like receptor; TNBS, trinitrobenzene sulphonic acid; TRPA1, transient receptor potential cation channel member A1.

16. Ilic, N., Gruden, M., Gebhart, G. F. Gastric inflammation t


