of the CCL5 chemokine, which recruits neutrophils and manifests as IBD.7

The identity of the activating trigger for the NLRP6 inflammasome in epithelial cells is unknown. The trigger might be a damage-induced molecular pattern, which is one mechanism by which the host could distinguish harmless commensals from pathogens, both of which express similar molecular patterns as ligands for TLRs. However, in some instances, the pathogen and commensal dichotomy might simply relate to the context of their encounter with the immune system. Thus, a commensal in the wrong place will be treated as a pathogen; likewise, the handling of commensals in certain genetically susceptible individuals might be similar to that of pathogens. Another explanation for immunologic discrimination between pathogens and commensals could involve recognition of symbiotic bacterial molecules in a process that favors colonization with commensals.8 An immunomodulatory polysaccharide produced by the prominent gut commensal, Bacteroides fragilis, has been reported to suppress T,17 effector cells by signaling through TLR2 on regulatory T cells, thereby enabling the commensal to avoid an adverse immune response and successfully colonize the host. The response to polysaccharide is distinct from that seen with other TLR2 ligands that promote clearance of pathogens. The immunomodulatory properties of polysaccharide also have efficacy in an animal model of IBD, confirming the potential for mining the microbiota for drug discovery (Figure 1).

Other examples of bacterial-derived metabolites with therapeutic potential include the production of a soluble protein ligand for the epidermal growth factor receptor by Lactobacillus rhamnosus GG (which attenuates intestinal inflammation by inhibiting cytokine-induced apoptosis in intestinal epithelial cells), and the discovery of an antimicrobial agent with narrow-spectrum activity against Clostridium difficile.9,10 The latter was uncovered by an extensive screen of fecal colonies for antimicrobial producers and resulted in the identification of a strain of B. thuringiensis that produces a heterodimeric bacteriocin, thuricin CD, which has potent activity against C. difficile. Using a distal colon model, thuricin CD was shown to be as effective as vancomycin and metronidazole but exhibited a narrower spectrum of activity without causing ‘collateral damage’ to the dominant phyla within the surrounding commensal microbiota.

What can we expect from this field in the immediate future? Microbial enterotypes are likely to be refined and correlated with human genotypes with respect to disease risk, and longitudinal studies will shed light on the impact of lifestyle variables over time. However, as molecular profiling continues apace, studies of the microbiota should be complemented with a return to culture-based in vitro studies to fulfill the promise of mining the microbiota and to understand the molecular basis of host–microbe interactions in health and disease.

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Acknowledgments
F. Shanahan is supported, in part, by Science Foundation Ireland.

Competing interests
The author declares associations with the following companies: Alimentary Health Ltd, GlaxoSmithKline, Procter & Gamble. See the article online for full details of the relationships.


Emerging concepts in neurogastroenterology and motility
Keith A. Sharkey and Gary M. Mawe

Neurogastroenterology encompasses intrinsic and extrinsic neural processes that regulate gut functions, sensation and related behaviors such as ingestion. In 2011, key advances were made in understanding gut–brain interactions, visceral sensation, serotonin signaling, neurogenesis and neuromuscular transmission.


Neural control of the gastrointestinal tract in both health and disease is a rapidly evolving and intriguing subject area. Key advances have been made on several fronts in neurogastroenterology in 2011. Here, we highlight a breadth of studies that represent major milestones in our understanding of the effect of nutrients and gut microbiota on emotion and food intake; the role of stress in visceral hypersensitivity; the concept that enteric glia can serve as neuronal precursors; and the roles of serotonin signaling in the gut. In addition, we discuss the identification of a novel class of cells that could mediate inhibitory neuromuscular signaling in the gastrointestinal tract.

It is becoming increasingly clear that signals arising in the lumen of the gastrointestinal tract can lead to changes in emotional state and behaviors such as food intake. The notion that foods with a high fat content are ‘comfort foods’ was substantiated this year by MRI studies demonstrating that intragastric infusion of fatty acid positively enhanced emotional states, decreased hunger scores and increased neural activity in the regions of the brain that process emotions.1 These findings indicate that
luminal nutrients can have acute effects on mood as well as satiety. Evidence indicates that endocannabinoid signaling in the gut regulates fat consumption. Thus, the capacity to regulate fat intake exists within the gut, and this process could, in turn, have an effect on emotional state and long-term energy balance.

In addition to nutrients, gut–brain communication can also be influenced by enteric microflora, including resident microbes and ingested probiotics. A recent study has shown that probiotic bacteria influence emotional behavior by modulating the subunits of receptors of the neurotransmitter γ-aminobutyric acid, and attenuate anxiety via activation of vagal pathways. Probiotic treatment strategies might, therefore, prove to be beneficial in stress-related disorders (such as anxiety and depression), which are common comorbidities of functional and inflammatory bowel disorders.

Although stress is known to potentiate visceral pain and discomfort, a lack of adequate animal models has meant that the mechanisms that underlie this form of visceral hypersensitivity have not been resolved. Advances in the past year have provided insights into peripheral and central mechanisms and have helped to explain how stress exacerbates visceral pain. Following the resolution of infectious colitis in mice, induction of stress resulted in exaggerated peripheral nociceptive signaling—which is analogous to postinfectious IBS. The hyperexcitability of primary afferent neurons in this model is associated with enhanced expression of β-adrenergic and glucocorticoid receptors in these cells. Interestingly, the effects of stress are mimicked by agonists of these receptors, thus providing potential new therapeutic targets. In addition to changes in primary afferent neurons, stress-induced activation of astroglial cells in the spinal cord also seems to contribute to visceral hypersensitivity through the modulation of glutaminergic signaling. These novel observations highlight the importance of spinal glia and glutamate metabolism in the sensation of pain.

Glia in the brain and gut serve a wide array of functions beyond their original definition as the ‘glue’ that holds neurons together. In the gut, these functions are known to include metabolic regulation, neurotransmission and support of barrier integrity. Two independent studies published during the past year provide compelling evidence that enteric glia have the potential to give rise to neurons in adult gut or in culture under certain restricted conditions. Laranjera and colleagues used genetic lineage tracing to confirm previous results showing that neurogenesis does not seem to occur in the enteric nervous system under steady state conditions. This observation was corroborated by Joseph and colleagues who used incorporation of a thymidine analogue to investigate cell division. Remarkably, after injury to the myenteric plexus, glia were shown to generate new neurons in vivo. However, the conditions under which neurons can be replaced seem to be limited to injury to the plexus. Gliogenesis was observed both in steady-state conditions and in response to injury, but the function of new glial cells remains to be determined. In culture conditions, enteric glia could readily form new neurons, which indicates that endogenous precursors exist within a patient’s own bowel and could be used for transplantation to replace neurons lost or damaged as a result of idiopathic or acquired enteric neuropathies.

Serotonin (5-hydroxytryptamine; 5-HT) in the gastrointestinal tract can trigger motor, secretory and vasodilator reflexes under physiological conditions, and acts as a proinflammatory mediator and stimulator of emesis, pain and discomfort in pathophysiological conditions. Changes in serotonin signaling have been reported in patients with functional gastrointestinal disorders; however, the causative role of serotonin in the symptoms of these conditions is not yet fully established. A report suggests that mucosal serotonin could contribute to visceral pain in these individuals. In patients with IBS, spontaneous serotonin release from the mucosa is increased, which correlates with the severity of abdominal pain. Moreover, biopsy supernatants from these individuals activate discharge of extrinsic afferent fibers in an ex vivo rat preparation, and this response is inhibited by griseofulvin—an antagonist of the 5-HT3 receptor.

The majority of serotonin is synthesized, stored and released by enterochromaffin cells in the gastrointestinal mucosa; serotonin also serves as an enteric neurotransmitter, but the physiological role of enterochromaffin cell and neuronal serotonin signaling has not been fully determined. Li and colleagues addressed this issue using mice that lack the genes for tryptophan hydroxylase 1 or 2 (enzymes required for serotonin biosynthesis in enterochromaffin cells and neurons, respectively). Although mice lacking mucosal serotonin did not exhibit a clear phenotype with regard to gut function, mice deficient in neuronal serotonin exhibited lower neuronal density, slower intestinal transit and accelerated gastric emptying when compared with healthy mice. These findings indicate that neuronal serotonin protects the integrity of the enteric nervous system and contributes to normal gastrointestinal motility. Mucosal serotonin can act as a proinflammatory mediator, but Tsujita et al. demonstrated that activation of 5-HT3 receptors on enteric nerve terminals triggers an anti-inflammatory effect. 5-HT3 agonists facilitate acetylcholine release, which, in turn, can dampen proinflammatory cytokine induction via α7 nicotinic receptors on macrophages. This finding suggests that 5-HT3 agonists might, by inhibiting the inflammatory response and promoting propulsive motility, have a beneficial effect in certain conditions, such as postoperative ileus.

One of the ongoing controversies in neurogastroenterology over the past decade has been the mechanism by which smooth muscle cells receive inhibitory purinergic signals from enteric motor neurons. These signals do not seem to be mediated either directly by smooth muscle or indirectly by interstitial cells of Cajal because mice lacking interstitial cells of Cajal still exhibit purinergic inhibitory junction potentials, and isolated smooth muscle cells exhibit mixed excitatory and inhibitory responses to ATP. Kurahashi and colleagues shed light on this dilemma in a report demonstrating that a novel class of excitatory cells (referred to as ‘fibroblast-like cells’), which express platelet-derived growth factor receptor α, exhibit all of the properties necessary to detect and transmit purinergic
signals from nerve terminals to smooth muscle. These interstitial cells should be investigated for potential contributions to gastrointestinal motor disorders.

The gastrointestinal dysfunctions that fit under the umbrella of neurogastroenterology represent a considerable burden to society with limited treatment options. Continued efforts, such as those highlighted here, will provide a better understanding of these enigmatic disorders and open new avenues for therapies of the future.

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**Competing interests**
The authors declare no competing interests.