EDITORIAL

Neurohormonal signalling in the gastrointestinal tract: new frontiers

Keith A. Sharkey[1] and Gary M. Mawe[2]
[1]*Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary, Alberta, Canada*
[2]*Department of Neurological Sciences, University of Vermont, Burlington, VT, USA*

Email: ksharkey@ucalgary.ca

It was over a century ago that Bayliss and Starling, in *Journal of Physiology* articles (Bayliss & Starling, 1899, 1900, 1902), paved the way for our appreciation of the unique neurohormonal features of gastrointestinal (GI) function. They defined the Law of the Intestine, which states: 'Local stimulation of the gut produces excitation above and inhibition below the excited spot. These effects are dependent on the activity of the local nervous mechanism' (Bayliss & Starling, 1899). In other words, they demonstrated that the nervous system of the intestine contains intrinsic neural circuitry necessary and sufficient for generating and coordinating intestinal motility. Their contemporary, John Newport Langley, commented that 'It is from the cells of the enteric nervous system that the best case can be made out for the existence of a peripheral nerve-cell reflex' (Langley, 1903). Bayliss and Starling's observations also led to the creation of the field of endocrinology by establishing that factors released from the gut enter the circulation to ultimately elicit pancreatic secretion (Bayliss & Starling, 1902). Over the ensuing hundred years or so, 'enteric neuroscience' developed independently, as did the field of 'gut hormones'.

Recently, the fields of enteric neuroscience and gut hormones have converged, as it has become increasingly clear that nerves in the gut are important targets of many of the hormones and paracrine factors also found in the GI tract. During the past decade, we have witnessed a veritable explosion of new information about neurohormonal signalling in the gut. This area of investigation has expanded even further with the recognition of the importance of the gut microbiota in digestive system physiology and in gut–brain communication, extending the notion of the gut–brain axis to that of the microbiota–gut–brain axis (Rhee *et al.* 2009; Bercik *et al.* 2012; Mayer *et al.* 2014).

In this special issue of *The Journal of Physiology*, leading experts discuss some of the latest advances in neurohumoral signalling in the GI tract. These papers highlight the complex interplay between the neural elements of the gut and humoral mediators that are released in response to a meal or to the microbial content of the gut lumen. Nerves and hormones work together to shape digestive processes that ensure the efficient assimilation of nutrients from food, but the effects of these regulatory systems are not limited to the gut wall. Neurohumoral mechanisms serve to protect the host from harm (real or perceived), and they contribute to central homeostatic control of food intake and energy balance. However, as we shall see, these mechanisms may also be 'hijacked' and contribute to the dysfunction of the gut under pathophysiological conditions, leading to the symptoms of functional GI disorders, such as irritable bowel syndrome.

The goal of this special issue of *The Journal of Physiology* is to highlight some of the key new findings in gut neurohormonal signalling, with a focus on the integrative physiological context of these signalling mechanisms in health and disease. The issue begins with an overview of the subject presented by Graham Dockray, the recipient of the 2013 Bayliss–Starling Lecture. This article is focused around the actions of the regulatory peptide cholecystokinin (CCK) (Dockray, 2014). CCK was the second of the gut hormones to be discovered (in 1928) and the first to be directly shown to signal to the brain via the vagus nerve. Dockray's group has championed the notion that vagal afferent neurons are more than simple sensors of the gut *milieu*, but are in fact integrative centres, with the phenotype of the vagal afferent neurons reflecting the nutrient status of the animal. CCK serves as a humoral 'switch' regulating the expression of vagal afferent neurotransmitters and their receptors, working in concert with the adipocyte-derived hormone leptin to set the gain of the vagal system to balance nutrient and energy status (Dockray, 2014).

In the six articles that follow, three themes are developed that build upon the concepts described above. The first theme is that digestion itself is a regulatory process. Three of the papers included in this special issue deal with this concept in different ways. In the first paper, Nigel Bunnett highlights the physiological and pathophysiological signalling roles of bile acids and the TGR5 receptor (also known as G-protein bile acid receptor 1 or GPBAR-1) in the GI tract (Bunnett, 2014). Bile acids are released into

Keith Sharkey is Killam Professor of Physiology and Pharmacology, and the Crohn's and Colitis Foundation of Canada Chair in IBD Research, at the University of Calgary. His research is focused on understanding the physiology and pathophysiology of the enteric nervous system in intestinal inflammation and on aspects of brain–gut interactions in health and disease. Dr Sharkey is a Reviewing Editor of *The Journal of Physiology*. **Gary Mawe** is Professor of Neurological Sciences and Adjunct Professor of Pharmacology and Medicine at the University of Vermont. Dr Mawe directs a translational research programme that focuses on how the nervous system regulates motor activity in the intestines and biliary tract in normal and pathological conditions, and he is also interested in how key elements of mucosal serotonin signalling are altered in animal models and human disorders. Dr Mawe is a Reviewing Editor of *The Journal of Physiology*.

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the gut lumen in a regulated manner both postprandially and interprandially, and are well known for their involvement in the digestion and absorption of lipids. TGR5 is a G protein-coupled receptor that mediates the non-genomic actions of bile acids in the gut. For example, TGR5 activation on enteroendocrine cells mediates the release of glucagon-like peptide 1 that contributes to the postprandial incretin effect, lowering blood glucose levels following a meal. TGR5 expressed on enteric nerves contributes to the regulation of intestinal motility; mice that lack this receptor are constipated, whereas TGR5 over-expression leads to accelerated colonic transit. Rod Dimaline and Andrea Varro discuss novel roles of gastrin, the first gut hormone to be discovered (Dimaline & Varro, 2014). Gastrin is well known for its ability to stimulate gastric acid secretion secondary to stimulating histamine release from enterochromaffin cells and via direct actions on parietal cells. However, like bile acids, it also contributes to an incretin effect, probably working together with glucagon-like peptide-1. The third paper in this theme is from Michel Neunlist and Michael Schemann who describe the process of nutrient sensing by the enteric nervous system (Neunlist & Schemann, 2014). Nutrient sensing is well known to involve enteroendocrine cells of the mucosa; however, Neunlist and Schemann highlight recent discoveries that illustrate long term effects of diet on the plasticity of the enteric nervous system. Moreover, they show that in obesity, there is an adipocyte–enteric neuron interaction at the level of the submucosal plexus, through fat infiltration in the gut wall. Adipocyte factors, including leptin, can then have a direct action on enteric neurons, altering their physiology and the physiology of the gut in obesity (Neunlist & Schemann, 2014).

The second theme of these papers in this special issue of *The Journal of Physiology* is that neurohumoral mechanisms contribute to the pathophysiology of GI disease. Rod Dimaline and Andrea Varro discuss the proliferative capacity of gastrin in relation to cancers of the GI tract (Dimaline & Varro, 2014). Gastrin is formed from a precursor, progastrin, and normally circulates as a family of amidated peptides. In some cases, the post-translational processing is incomplete, giving rise to longer, glycine-extended forms of the molecule. These have growth stimulating properties in the colonic and oesophageal mucosa and may contribute to the development of cancers in these regions (Dimaline & Varro, 2014). Michael Camilleri builds on the physiology of digestion to illustrate how neurohumoral mechanisms underlie the pathophysiology of irritable bowel syndrome, the most common GI disorder experienced by patients (Camilleri, 2014). No clear causal factor has been identified to explain the signs and symptoms of irritable bowel syndrome, and it is highly likely that a constellation of conditions including stress, genetic predisposition and gut health history contribute to the manifestation of this disorder. The article by Camilleri sheds light on potential contributing factors such as changes in the availability of mucosal signalling molecules such as serotonin and glucagon-like peptide-1, low level inflammation, and increased stimulation of bile acid receptors, as well as stress hormones.

The final theme of this special issue of *The Journal* is the microbiota–gut–brain axis. Two papers that are included, one by Aziz and colleagues (Farmer *et al.* 2014) and the other by Verdu and colleagues (De Palma *et al.* 2014), nicely illustrate how enteric bacteria shape behavioural responses, particularly in conditions of stress. Farmer *et al.* advance the phrase 'state of gut' (rather than the 'state of mind'), as they contend that the gut microbiota shape the brain during development, and behavioural responses in a variety of situations. Whilst much remains to be understood about the relationship of the host with the billions of bacteria that colonize the bowel, emerging data reveal important mechanistic links between the luminal environment of the gut and the brain. It has become clear that alterations in the gut microbiome can affect not only behaviours, pain thresholds and emotional states, but also metabolic activities and inflammatory responses throughout the body. Along a related vein, De Palma *et al.* focus on stress and the role of the microbiota–gut–brain axis. They point out the complex, bidirectional nature of stress on the GI tract (De Palma *et al.* 2014). On one hand, stress alters the composition of the microbial populations in the gut, and on the other, changes in the microbiome alter the organism's responsivity to stress. A complete understanding of 'what comes first' – the stress or the altered microbes – is a challenge that will require considerable effort to solve. Nevertheless, by using gnotobiotic facilities and molecular techniques for the identification of bacterial species, together with the application of 'omic' technologies, it should be possible to make the key advances that will ultimately allow us resolve the complex mutualism that evolution has conferred upon us. This will clearly be a burgeoning research area in the future.

In summary, our understanding of the complexity and diversity of neurohumoral signalling mechanisms in the GI tract has increased dramatically in the 21st century. Whilst many signalling mechanisms have been elucidated in reduced preparations or using cell systems, a full appreciation of the subtleties and sophistication of these mechanisms has arisen through the application of molecular biological approaches in models of integrative GI physiology. Emerging from these studies are major advances in our understanding of digestive system physiology, many of which are expertly covered in this issue of *The Journal of Physiology*. We are now on the verge of breakthroughs in the translation of this knowledge to the benefit of patients suffering from the many common and debilitating GI and metabolic disorders that plague society today.

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Additional information

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