

# Nonruminant Nutrition Symposium: Nutrient and Neuroendocrine Regulation of Gastrointestinal Function

**529 Involvement of gut neural and endocrine systems in pathological disorders.** J. B. Furness\*, *Department of Anatomy and Cell Biology, University of Melbourne, Melbourne, Australia.*

The gastrointestinal tract depends on a complex, integrated neural and endocrine control which has major influences on its functions, particularly on the secretion of water and electrolytes, motility, blood flow and mobilisation of digestive juices. Pathologies involving the enteric nervous system can be life threatening, including diarrheas in which toxins, such as cholera toxin, massively excite secretomotor neurons and Chagas' disease, in which trypanosomes cause degeneration of enteric neurons. Gut endocrine cells are involved in serious pathologies, including in the acute effects of gluten challenge in celiac disease, Zollinger-Ellison syndrome and watery diarrhea syndrome. There are also important interactions between the immune system and enteric neural and endocrine control systems, that are manifested in inflammatory bowel diseases and in ischemia/reperfusion injury to the intestine, for example. The enteric nervous system is also a conduit for the transmission of infective prions. This is important for major commercial herd animals, such as sheep and cattle, in which the enteric nervous system may have a role in sporadic prion disease becoming endemic. There is now a comprehensive knowledge of the organization and functioning of the neural and endocrine control systems of the healthy digestive tract, with some exceptions, such influences on nutrient absorption being under researched. In contrast, in many cases there is very poor understanding of the changes in enteric neurons and endocrine cells in disease states, to the extent that it may not be clear whether changes that are observed are causes or consequences of the disorder. There has been a corresponding failure to identify suitable therapeutically-relevant molecular targets within the enteric nervous system and entero-endocrine cells. A new approach to digestive disorders that is being investigated is the use of neural stem cells. It has recently been shown that neural stem cells that are transplanted into the region of enteric ganglia can proliferate, differentiate into several appropriate phenotypes, and can integrate into existing nerve circuits.

**Key words:** enteric neurons, entero endocrine cells, digestive diseases

**530 Neurogastroenterology and food allergies.** J. D. Wood\*, *Department of Physiology & Cell Biology and Internal Medicine The Ohio State University, Columbus.*

Neurogastroenterology is a subspecialty encompassing relations of the nervous system to the gastrointestinal tract. The central concept is emergence of whole organ behavior from coordinated activity of the musculature, mucosal epithelium and blood vasculature. Behavior of each effector is determined by the enteric nervous system (ENS). The ENS is a minibrain positioned close to the effectors it controls. ENS neurophysiology is in the framework of neurogastroenterology. The digestive tract is recognized as the largest lymphoid organ in the body together with a unique compliment of mast cells. In its position at the "dirtiest" of interfaces between the body and outside world, the mucosal immune system encounters food antigens, bacteria, parasites, viruses and toxins. Epithelial barriers are insufficient to exclude fully the antigenic load thereby allowing chronic challenges to the immune system. Our observations in antigen-sensitized animals document direct communication between the mucosal immune system and ENS. Communication is functional and results in adaptive responses

to circumstances with the lumen that are threatening to the functional integrity of the whole animal. Communication is paracrine and incorporates specialized sensing functions of mast cells for specific antigens together with the capacity of the ENS for intelligent interpretation of the signals. Immuno-neural integration progresses sequentially beginning with immune detection followed by signal transfer to the ENS followed by neural interpretation and then selection of a neural program with coordinated mucosal secretion and a propulsive motor event that quickly clears the threat from the intestinal lumen. Operation of the defense program evokes symptoms of cramping abdominal pain, fecal urgency and watery diarrhea. Our approaches to immuno-ENS interactions merge the disciplines of mucosal immunology ENS neurophysiology into the realm of neurogastroenterology.

**Key words:** enteric neurons, entero endocrine cells, food allergies

**531 Nutrient and neuroendocrine regulation of intestinal glucose absorption.** S. P. Shirazi-Beechey\*<sup>1</sup>, A. W. Moran<sup>1</sup>, D. M. Bravo<sup>2</sup>, and M. Al-Rammahi<sup>1</sup>, <sup>1</sup>*University of Liverpool, Liverpool, United Kingdom.* <sup>2</sup>*Pancosma, Geneva, Switzerland.*

The intestinal Na<sup>+</sup>/glucose cotransporter, SGLT1, is the major route for the transport of dietary sugars from the lumen of the intestine into enterocytes. Regulation of this protein is essential for the provision of glucose to the body and avoidance of malabsorption. Data produced in various laboratories have suggested that the intestinal luminal sugar concentration, the gut hormone, GLP-2, and the enteric nervous system participate in pathways regulating SGLT1 expression. To this end, it has been shown that i) expression of SGLT1 is upregulated in response to increased dietary sugars, ii) the serosal application of GLP-2 enhances SGLT1 expression, iii) raised luminal glucose concentrations in the ileum results in SGLT1 upregulation in more proximal regions and iv) the upregulation of SGLT1 in response to high luminal glucose is only achieved in intact mucosa and not in isolated enterocytes. However detailed network of pathways by which the luminal sugar, gut hormones and the enteric nervous system interact to regulate SGLT1 expression has not been known. Experimental evidence in our laboratory has shown that the intestinal glucose sensor, the taste receptor1 subunit heterodimers, T1R2+T1R3, expressed on the luminal membrane of endocrine cells, senses luminal glucose concentration. Luminal glucose when above a threshold activates in endocrine cells, a signalling pathway involving T1R2+T1R3, the transducer G-protein, gustducin, and other signalling elements, resulting in secretion of GLP-1, GLP-2 and GIP. Binding of GLP-2 to its receptor on enteric neurons elicits a neuronal response which is transmitted to sub-epithelial regions evoking the release of a neuropeptide. Binding of the neuropeptide to its receptor on the basolateral membrane of absorptive enterocytes enhances intracellular cAMP, thereby increasing the stability of SGLT1 mRNA and levels of functional SGLT1 protein. The identification of molecular and cellular processes controlling SGLT1 expression will assist recognition of targets for modulating the capacity of the gut to absorb dietary sugars. This has important nutritional and clinical implications.

**Key words:** enteric neurons, entero endocrine cells, glucose absorption

**532 The role of GLP-2 in controlling intestinal function in human infants: Regulator or bystander?** D. Sigale<sup>\*</sup>, *Alberta Children's Hospital / University of Calgary, Calgary, AB, Canada.*

The regulation of nutrient absorptive capacity is a critical factor in the normal growth and development of an infant. This is especially important following surgical resection; the process of adaptation, or upregulation of nutrient transport capacity is the physiologic process which allows patients to transition to enteral feeding. The specific mechanisms which control this are still relatively poorly understood. Many actions of the entero-endocrine hormone, Glucagon-like Peptide 2,

suggest that it may be a key regulator both in regulating physiological nutrient absorptive capacity and the process of adaptative upregulation of nutrient absorption following resection. This talk will review the biology of GLP-2 including the production in the L cell, regulation of GLP-2 release, sites of action, which include the enteric neurons, and pericryptal myofibroblast, and the effects on the intestinal mucosa. We will examine ontogeny of this system in the developing human infant and the evidence that GLP-2 is pivotal in the regulation of adaptation, with the implications for clinical practice.

**Key words:** enteric neurons, entero endocrine cells, ontogeny