OVERVIEW

Targeting the gut to treat obesity and its metabolic consequences: view from the Chair

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The neurohumoral signaling systems of the gastrointestinal (GI) tract are considered the most significant of the peripheral inputs controlling both food intake in the short term and energy balance over a longer time course. The importance of the GI tract in the control of energy balance is underscored by the marked beneficial effects of bariatric surgeries for the treatment of obesity. Despite their effectiveness, the mechanisms of bariatric surgery remain to be fully elucidated. Considerable new evidence points to the importance of gut–brain communication, gut barrier function and microbial signaling as three of the most important mechanisms of bariatric surgery-induced weight loss. These mechanisms are reviewed in the present article and the accompanying four papers.

International Journal of Obesity Supplements (2016) 6, S3–S5; doi:10.1038/ijosup.2016.2

Obesity and its metabolic complications remain one of the most challenging health issues facing society today. The rapidity with which shifts in the average weight of populations have increased since the late 1970s is remarkable. For example, in Canadian adults, rates of obesity have more than doubled from around 10% in the early 1970s to ~25% today.^{1–3} Similar trends have been seen around the world. These rapid shifts in weight over such a short time suggest that changes in diet, lifestyle and/or other environmental factors have a critical role in the expression of obesity. Although genetic factors may confer vulnerability (or protection) towards obesity, these are not likely to be the dominant cause of obesity in the majority of people.

Obesity is ultimately caused by a state of positive energy balance. Whilst energy expenditure is an important determinant of overall energy balance, excessive energy intake is generally regarded as the major determinant of obesity.⁴ There are numerous peripheral and central nervous system signaling systems involved in the regulation of food intake and energy balance. Of these, the neurohumoral signaling systems of the gastrointestinal (GI) tract are considered the most significant of the peripheral inputs controlling both food intake in the short term and energy balance over a longer time course.^{5,6} Gut-derived signals impact other peripheral organs and tissues, such as the liver and adipose tissue, influencing their functions in ways that may increase or reduce the propensity for obesity.⁵

The importance of the GI tract in the control of energy balance is underscored by the marked effects of bariatric surgery.^{7,8} Altering the manner and quantity with which food is delivered to the small intestine either by greatly limiting the size of the stomach (as in vertical sleeve gastrectomy) or bypassing the majority of the stomach (as in Roux-en-Y gastric bypass) leads to marked and sustained reductions in body weight.^{8,9} Considerable research effort has been expended to determine the mechanisms underlying the remarkable effects of bariatric surgery and the articles that follow this overview review much of the current thinking on this important topic.

The aim of the 17th Annual International Symposium of the Université Laval Research Chair in Obesity was to explore the role of the GI tract in the treatment of obesity and its metabolic comorbidities. The morning session focused on basic mechanisms and the four speakers gave insightful presentations of critical topics in integrative GI physiology in which the major players in gut–brain signaling in the control of food intake and energy balance were considered. In order to set the scene for these four articles it is helpful to briefly review some of the pertinent aspects of the anatomy and physiology of the GI tract and gut–brain signaling.

A single layer of epithelial cells covers the entire GI tract and this is all that separates the luminal contents from the rest of the body. This intestinal epithelial barrier prevents the unwanted translocation of luminal contents and microbes, while allowing the passage of nutrients and water.^{10,11} Though the gut is richly innervated, sensory nerves do not penetrate the GI epithelium and so luminal sensing mechanisms have developed to transduce information about the presence and nature of nutrients in the gut.^{12–14} These ‘tasting’ mechanisms involve the expression of taste receptors, similar to those of the tongue, and other mechanisms that detect and transduce luminal signals. In addition, there are also receptors for bacteria and bacterial products, notably free fatty acids and other metabolites, which are also sensed as part of the luminal detection systems.^{15,16} Many of these receptors are localized on enteroendocrine cells in the gut.¹⁷ Enteroendocrine cells are specialized cells scattered throughout the GI epithelium that upon stimulation release a variety of peptides and amines that serve as paracrine mediators, acting locally, and/or hormones, acting via the circulation.¹⁴ Recent evidence supports the idea that these cells have a central role in the expression of diet-induced obesity and that gut peptides have a critical role in the control of hunger, satiety, glucose metabolism, metabolic and nutrient sensing.^{5,14,17–19} The subpopulation of enteroendocrine cells that contain and release serotonin (5-HT) are also involved in the stimulation of propulsive and segmental motility, epithelial secretion and vasodilation, as well as nausea

and vomiting, and recent evidence supports a proinflammatory action of enteroendocrine 5-HT.²⁰

Enteroendocrine cells release their contents basolaterally into the lamina propria where they can enter the mucosal microcirculation and lymphatic systems, and they can interact with the dense innervation that lies beneath the epithelium. In some cases, however, these cells have a basal extension that extends in close apposition to neighboring epithelial cells, nerves and the processes of subepithelial enteric glial cells.^{21,22} These basal processes have been termed 'neuropods' because they possess the proteins that are involved in vesicular release at synapses.^{21,22} This anatomical arrangement suggests a tighter release-effector cell relationship than was previously appreciated, which allows for far more precise temporal and spatial signaling for gut peptides and their target cells. In the case of enteric glia, this seems to be for the maintenance of epithelial barrier function.¹¹ In the case of nerves, which can be both intrinsic enteric nerves and extrinsic vagal or spinal primary afferent nerves, it is for the initiation of reflexes that control the numerous gut functions and gut-brain signaling functions described above. It seems highly likely that enteroendocrine cells are the principle cellular elements that initiate the adaptive changes that occur after bariatric surgery, which improve glucose metabolism and ultimately lead to reduced body weight. Exactly which cell populations, and how this is accomplished requires further research.

The regulation of epithelial barrier function is a critical determinant of intestinal homeostasis.^{10,23} Moreover, enhanced intestinal permeability appears to be an important factor in the development or maintenance of obesity.^{24,25} High-fat diets in particular have been implicated in reducing epithelial barrier function.^{18,26} The epithelial barrier consists of two major elements, a physical barrier that is made up of the tight junctions, adherens junctions and desmosomes linking adjacent epithelial cells and a secretory barrier of mucus, water, antimicrobial peptides and secretory IgA.^{10,23} Altogether, the host secretory products help shape the nature of the microbial community of the gut and prevent pathogens from entering the body. The control of the epithelial barrier is incompletely understood. Enteric nerves, enteric glia and certain enteroendocrine peptides are all involved, as are innate immune signals, and microbial signals, highlighting the commensal relationship between host and microbe in the GI tract. Bariatric surgery alters the microbial communities in the gut and this perturbation will impact gut barrier function.^{9,27} The extent this occurs and the manner to which individuals respond may be factors in the success of these surgeries.

The innervation of the gut is complex, consisting of nerves from all three divisions of the autonomic nervous system—parasympathetic, sympathetic and enteric.²⁸ The gut communicates with the brain and spinal cord through vagal and spinal primary afferent nerves.²⁸ Perhaps of the greatest significance in terms of gut-brain signaling for the control of food intake and energy balance is the vagus nerve.^{26,29} Vagal afferents have a vital role in detecting changes in the mechanical and chemical environment of the GI tract.^{26,30} Vagal mechanoreceptors in the circular muscle or myenteric plexus respond directly to changes in tension or contractility in the wall of the GI tract.³¹ Mucosal vagal chemoreceptors may respond directly to or indirectly through the release of enteroendocrine cell peptides or amines.³⁰ Vagal afferents terminate in the nucleus of the solitary tract and area postrema in the caudal brainstem. The area postrema is one of the sensory circumventricular organs and receives inputs from the GI tract through the circulation.³² Vagal afferents initiate reflex outputs back to the GI tract through mono- and polysynaptic pathways in the dorsal vagal complex.²⁹ This reflex pathway is important in regulating meal size by monitoring and altering accommodation of the stomach. Neurons of the nucleus of the solitary tract also integrate multiple energy status signals from vagal afferents, the area postrema and forebrain regions in order

to provide outputs the control behavioral, autonomic, and endocrine responses that govern energy balance.³³ After bariatric surgery, the integrated vagal inputs are altered, and these mechanisms also contribute to the adaptive responses.

Helen Raybould began the symposium focusing on the important role of the vagus nerve and presented strong evidence in support of a hypothesis that high-fat diets cause impairments in vagal afferent signaling leading to increased food intake and increases in body weight (Hamilton and Raybould, this issue). Of particular importance, this presentation highlighted the opportunities to manipulate gut microbiota using pre- and probiotics in order to restore gut barrier function and prevent excessive weight gain (Hamilton and Raybould, this issue). This topic was further explored by Patrice Cani. He focused on the role of the innate immune system in sensing microbial dysbiosis and how this contributes to alterations in metabolism that lead to the development of obesity (Cani, this issue). Specifically, he and his colleagues have discovered that blocking the function of the bacterial sensing receptor adapter protein MyD88 in intestinal epithelial cells partially protects against diet-induced obesity, diabetes and inflammation (Cani, this issue). The mechanism of this involves amongst other things increases in anti-inflammatory endocannabinoids. These bioactive lipids have also been shown by Cani and his colleagues to be an important link between the gut microbiota and the regulation of metabolism through alterations in intestinal permeability (Cani, this issue).

The other two presentations focused on gut hormones. Lawrence Miller outlined new developments in our understanding of the cholecystokinin (CCK) type 1 receptor and their significance for the prevention and management of obesity (Desai *et al.*, this issue). CCK is a key enteroendocrine peptide released from intestinal I cells that regulates gastric emptying and intestinal transit and induces satiety. Based on recent developments in the molecular biology of this receptor, his presentation focused on positive allosteric modulation of the CCK1 receptor as a novel strategy that could be used for inducing satiety, and correcting obesity (Desai *et al.*, this issue). Thomas Lutz focused on two additional gut hormones, glucagon like-peptide-1 (GLP-1) and amylin (Lutz, this issue). Amylin is released from pancreatic beta cells and GLP-1 from enteroendocrine L cells in response to a meal. Amylin acts via the area postrema and some other brain regions including the ventral tegmental area, while GLP-1 acts via vagal afferents. Both peptides reduce food intake, as well as having metabolic actions and effects on energy expenditure. What was stressed were the interactions between these peptides and other signaling peptides, such as leptin (released from adipose tissue), CCK and the sex hormone estradiol (Lutz, this issue).

Altogether, these four presentations, described fully in the four articles that follow, demonstrated the importance of gut neurohumoral signaling in the control of food intake and energy balance. These papers illustrate the complexity of gut signaling systems and together they highlight the prominent role of gut peptides, vagal afferent signaling and enteric microbiota as key mechanisms in the peripheral control of food intake and energy balance. On the basis of the available data, it seems that together these basic mechanisms may explain many of the beneficial effects of bariatric surgeries. They also provide a strong illustration of the benefits of understanding integrative physiology as a way of approaching the challenges of understanding pathophysiology and disease.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ACKNOWLEDGEMENTS

Publication of this article was sponsored by the Université Laval's Research Chair in Obesity in an effort to inform the public on the causes, consequences, treatments and prevention of obesity. KAS is the Crohn's Colitis Canada Chair in IBD Research at University of Calgary.

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