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Roles for gut vagal sensory signals in determining energy availability and energy expenditure

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Abstract

The gut sensory vagus transmits a wide range of meal-related mechanical, chemical and gut peptide signals from gastrointestinal and hepatic tissues to the central nervous system at the level of the caudal brainstem. Results from studies using neurophysiological, behavioral physiological and metabolic approaches that challenge the integrity of this gut-brain axis support an important role for these gut signals in the negative feedback control of energy availability by limiting food intake during a meal. These experimental approaches have now been applied to identify important and unanticipated contributions of the vagal sensory gut-brain axis to the control of two additional effectors of overall energy balance: the feedback control of endogenous energy availability through hepatic glucose production and metabolism, and the control of energy expenditure through brown adipose tissue thermogenesis. Taken together, these studies reveal the pleiotropic influences of gut vagal meal-related signals on energy balance, and encourage experimental efforts aimed at understanding how the brainstem represents, organizes and coordinates gut vagal sensory signals with these three determinants of energy homeostasis.

Graphical abstract

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Keywords

vagus; energy expenditure; brown adipose tissue thermogenesis; gut-brain axis; gut peptides; hepatic glucose production

Introduction

Body weight and body adiposity are the results of behavioral, physiological and biochemical processes that mediate the availability of nutrients as well as the expenditure of energy. Increases in systemic energy availability primarily result from the ingestion and subsequent absorption of nutrients following a meal, the fundamental behavioral unit of energy intake in humans and mammals. Systemic energy availability is also determined by the de novo generation of fuel, primarily by hepatic metabolism and by the liberation of stored fuel, e.g., free fatty acids, by lipolysis in white adipose tissue. The last decade of research has increasingly demonstrated a significant role for the central nervous system in coordinating energy availability and energy expenditure to determine body weight in adulthood. This central neural coordination requires both sensors of nutrient availability and effectors that respond to feedback signals arising from those sensory systems. Accordingly, the gastrointestinal tract and hepatic portal vein of the liver are richly endowed with sensory innervation arising from visceral afferent fibers that comprise both subdiaphragmatic vagal afferents as well as non-vagal splanchnic afferents (Fox et al., 2000) (Berthoud et al., 1997) (Berthoud et al., 1992) (Berthoud et al., 1995).

The presence of food in the gut during a meal elicits multiple mechanical, nutrient chemical and gut peptide signals in gastrointestinal and hepatic vagal afferents that are important not only in the digestion and absorption of nutrients, but also in the negative feedback control of food intake that limits subsequent nutrient availability. These meal-related gut vagal afferent negative feedback signals are conveyed to the central nervous system at the level of the caudal brainstem, in the region of the nucleus of the solitary tract (NTS) and the circumventricular area postrema (AP), whose fenestrated capillaries permit enhanced brain parenchymal access to circulating endocrine factors and nutrient feedback signals. Importantly, the NTS is also neurally linked to forebrain hypothalamic, striatal and limbic structures that mediate feeding, as well as to circuits that determine sympathetic and parasympathetic autonomic outflow. Thus NTS/AP is an important candidate site of convergence and integration of nutrient availability signals and is a central node in the neural circuitry that mediates the control of both energy intake and energy expenditure. Taken together, the neurohumoral connections between the gut afferent vagus and the brainstem NTS/ AP form the primary gut-brain axis that ties meal related gut feedback signals to central and peripheral neural pathways to control energy availability and energy expenditure.

Challenges to the gut–brain axis

Results from neurophysiological recordings, surgical and chemical transections, and genetic model studies each reveal the critical roles for meal-related gut vagal afferent feedback signals in the control of energy availability by limiting food intake. In vivo extracellular neurophysiological recording studies of single vagal afferent fibers identify punctate, well-

localized gastric and duodenal receptive fields that are rapidly and reversibly activated by multiple meal-related gut stimuli shown to limit food intake during a meal, including: 1) mechanical distension of the gut (Mathis et al., 1998), 2) intestinal infusions of macronutrients, including fat emulsions and fatty acids, carbohydrate solutions, and amino acids or protein solutions (Schwartz and Moran, 1998), 3) and gut satiety peptides such as cholecystokinin (CCK), which is released from gut enteroendocrine cells by the presence of nutrients in the duodenum (Schwartz and Moran, 1994). Interruption of these gut vagal neurophysiological responses, either by surgical transection of gastrointestinal vagal afferents, by local luminal anesthesia using tetracaine, or by gut vagus nerve application of the selective sensory neurotoxin capsaicin, blocks the ability of the above meal-related signals to limit food intake during a meal, and can result in larger and longer meals (Schwartz et al., 1999) (Greenberg et al., 1990) (Moran et al., 1997). Gut vagal afferents express type A CCK receptors (CCKAR) (Corp et al., 1993), and pharmacological blockade of CCKAR using the selective antagonist devazepide increases food intake and prevents the reductions in food intake produced by intestinal infusions of nutrient secretagogues of CCK (Reidelberger et al., 2003). Gut vagal afferent terminations of the gut-brain axis in the brainstem NTS/AP, as well as NTS neurons themselves, each express glutamatergic NMDA receptors, and brainstem pharmacological blockade of these receptors increases food intake and blocks the feeding inhibitory effects of gastrointestinal meal-related negative feedback stimuli (Guard et al., 2009a; Guard et al., 2009b). Finally, genetic absence of CCKA receptors in Long Evans Tokushima Fatty rats leads to obesity secondary to hyperphagia and increased meal size, with no change in meal frequency (Moran et al., 1998). Overall, results from these challenges to the structural and functional integrity of the gut sensory vagus nerve support a potent negative feedback role for food stimulated vagal afferent signals in the control of meal size, nutrient availability, and ultimately energy balance.

Non-canonical roles for gut vagal afferent signaling

The above approaches, developed to identify an important role for gut vagal afferent signaling in the negative feedback control of food intake, have also been fruitfully employed to identify new and unanticipated vagal sensory controls of two other major determinants of energy balance - hepatic metabolism and energy expenditure. Gastrointestinal infusions of lipid emulsions similar to those that are sufficient to reduce meal size also rapidly limit endogenous nutrient availability by suppressing hepatic glucose production (HGP) during a hyperinsulinemic-euglycemic clamp (Wang et al., 2008). This suppression is blocked by local gut application of the anesthetic tetracaine, and by selective surgical transection of gastrointestinal vagal afferents. These data demonstrate that intestinal vagal sensory innervation mediates the gastrointestinal control of HGP. At the brainstem level of the gut-brain axis, both fourth ventricular and local parenchymal NTS administration of the non-competitive NMDA receptor antagonist MK801 prevents gut lipid-induced reductions in HGP, as does selective surgical transection of the hepatic branch of the vagus, completing a regulatory loop, whereby the sensing of increased gut nutrient availability acts via a negative feedback gut-brainstem-liver circuit to limit endogenous nutrient availability by suppressing HGP. Subsequent studies have identified a similar pathway mediating the negative feedback control of hepatic metabolism via the nutrient stimulated gut satiety peptide CCK. Results

from these studies show that duodenal CCK acts via gut CCKA receptors to reduce HGP. These data support a role for gut CCK as a molecular mediator of the circuit that links increases in gastrointestinal nutrients to decreases in hepatic nutrient availability (Cheung et al., 2009). Importantly, the ability of this gut-brain-liver circuit to reduce HGP is markedly attenuated in diet induced obesity (DIO), demonstrating that metabolic context determines the potency of gut-brain-liver circuitry in the control of nutrient availability. Like DIO, exogenous administration of corticosteroids can induce hepatic insulin resistance, hyperglycemia and hyperinsulinemia. Selective chemical or surgical interruption of hepatic vagal afferent fibers each block these deleterious hepatic and systemic metabolic consequences (Bernal-Mizrachi et al., 2007). Similarly, genetically-induced hepatic steatosis can be blocked by selective surgical or chemical interruption of hepatic vagal afferent nerves (Uno et al., 2006). Taken together, these findings identify a potent contribution of the gut-brain axis to nutrient availability via hepatic metabolism.

The ingestion of food not only acutely increases nutrient availability, but has also been linked to increases in energy expenditure associated with the metabolic costs of processing and storing nutrients. Most recent results from studies of the gut-brain axis suggest an unexpected ability of gut nutrient sensing to increase energy expenditure via thermogenesis in metabolically active brown adipose tissue (BAT). Duodenal infusions of lipid emulsions at doses that reduce meal size also rapidly increase BAT temperature. As was the case for the gut-brain circuits mediating the negative feedback controls of nutrient availability (by suppressing food intake and limiting hepatic glucose production), the ability of gut nutrient infusions to increase BAT temperature was blocked by local intestinal application of the anesthetic tetracaine, as well as by peripheral administration of the CCKAR devazepide (Blouet and Schwartz, 2012). Furthermore, brainstem parenchymal administration of MK801 blocked gut lipid-induced increases in BAT temperature, supporting the suggestion of a novel gut-brainstem-BAT circuit in mediating energy expenditure via BAT thermogenesis. Interestingly, this circuit appears to extend to include forebrain hypothalamic neurons as well. Gastrointestinal infusions of nutrients, but not non-nutrients, rapidly reduce the neurophysiological activity of a subpopulation of hypothalamic neurons expressing orexigenic agouti related peptide (AGRP) (Beutler et al., 2017), and work of Blouet and colleagues has, in turn, implicated AGRP neuronal activity as an important determinant of BAT thermogenesis (Burke et al., 2017). Activating AGRP neurons reduces sympathetic outflow to BAT and reduces thermogenesis, while inhibiting these neurons leads to increased sympathetic outflow and increased BAT thermogenesis. Furthermore, the gut satiety peptide CCK reduces AGRP neuronal activity, while the gastric feeding stimulatory peptide ghrelin increases AGRP activity (Beutler et al., 2017). Overall, these findings support an emerging role for gut nutrient sensing acting via a gut vagal-NTS circuit involving AGRP neurons to increase energy expenditure.

Summary and perspective

The identification of dense extrinsic vagal sensory innervation of the gastrointestinal tract and liver has fostered experimental efforts to identify and characterize roles for gut vagal afferent signals related to nutrient availability, and roles for these signals in determining overall energy balance. Nutrient stimulation of the gut and gut hormones act via

gastrointestinal sensory fibers to limit future nutrient availability by reducing food intake and by reducing endogenous hepatic glucose production. These gut vagal meal-related signals require an intact link to the brainstem NTS/AP to drive changes in food intake and hepatic metabolism. Furthermore, gut vagal nutrients and gut peptide sensing also drive energy expenditure via BAT thermogenesis. These pleiotropic effects of gut vagal nutrient sensing on energy availability and energy expenditure occur rapidly upon gut nutrient exposure, are reversible with time, are blocked by impending gut vagal afferent signals, and depend on the energy balance status of the organism. It is tempting to speculate that these energy availability and energy expenditure effects are actively coordinated by the central nervous system to regulate overall energy balance, either acutely and/or in the long term. Progress in understanding the physiological relevance of these distinct behavioral and metabolic effectors of energy balance will require approaches that can: 1) identify and characterize the distinct neurochemical and neuroanatomical phenotypes of NTS/ AP populations important for the ability of gut nutrients to determine acute feeding, hepatic metabolism and BAT thermogenesis, 2) identify the temporal patterns of activity among NTS neuronal phenotypes during gut nutrient exposure that correlate with its consequences for feeding, hepatic metabolism and BAT thermogenesis, and 3) identify the neuroanatomical relationships among brainstem and hypothalamic neuronal populations implicated in these actions. Data from such studies will provide a foundation for developing more refined, mechanistic hypotheses aimed at establishing the causal neural links between gut nutrient sensing and each of these three determinants of energy balance, and how they are influenced by metabolic status.

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Abbreviations

NTS	nucleus of the solitary tract
AP	area postrema
CCK	cholecystokinin
DIO	diet induced obesity
HGP	hepatic glucose production
NMDA	n-methyl d-aspartate
BAT	brown adipose tissue
AGRP	Agouti related peptide

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HIGHLIGHTS

- The gastrointestinal tract and liver are richly innervated with extrinsic vagal sensory fibers
- These fibers communicate to the caudal brainstem via the gut-brain axis
- Meal-related nutrient and gut peptide stimuli activate gut vagal afferents
- Gut vagal nutrient sensing has pleiotropic effects on energy availability and energy expenditure
- Gut-brain axis activity affects feeding, hepatic metabolism, and brown adipose tissue thermogenesis