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Novel developments in vagal afferent nutrient sensing and its role in energy homeostasis

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Abstract

Vagal afferent neurons (VANs) play an important role in the control of food intake by signaling nutrient type and quantity to the brain. Recent findings are broadening our view of how VANs impact not only food intake but also energy homeostasis. This review focuses exclusively on studies of the vagus nerve from the past 2 years that highlight major new advancements in the field. We firstly discuss evidence that VANs can directly sense nutrients, and we consider new insights into mechanisms affecting sensing of gastric distension and signaling by gastrointestinal hormones ghrelin and GLP1. We discuss evidence that disrupting vagal afferent signaling increases long-term control of food intake and body weight management, and the importance of this gut–brain pathway in mediating beneficial effects of bariatric surgery. We conclude by highlighting novel roles for vagal afferent neurons in circadian rhythm, thermogenesis, and reward that may provide insight into mechanisms by which VAN nutrient sensing controls long-term control of energy homeostasis.

The vagus nerve is involved in numerous physiological processes important for survival [1]. Notably, vagal afferent fibers innervating the stomach and small intestine are implicated in sensing volume and type of ingested nutrients, and convey this information to the nucleus tractus solitarius (NTS) in the hindbrain to control meal size and duration [1]. Diets high in fats and sugars lead to disrupted vagal afferent signaling, and reduced sensitivity to peripheral signals, which correlates with overconsumption and weight gain in rodents [1]. This is particularly relevant given that our environment is saturated with cheap, palatable, calorie-dense diets. In this article we review novel developments in vagal afferent nutrient sensing and highlight major conceptual advances of the past two years as they relate to vagal afferent neuron (VAN)'s role in energy homeostasis.

New developments in vagal afferent nutrient sensing

VANs are a key component of the nutrient sensing mechanism that provides negative feedback to terminate a meal. The classical view involves mechanical sensation of ingested

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volume and chemical sensation of gastrointestinal hormones released in response to macronutrients. Although it has been clear for some time that mechanosensitivity of VANs can be modulated by gastrointestinal hormones [2], the range of factors involved in modulating plasticity of mechanosensitive VANs has expanded recently to include novel gastrointestinal hormones [3], transmitters [4], time of day [5^{*}], and diet [6]. Glucagon-like peptide 1 (GLP1) may also regulate gastric distension; recent evidence suggests that GLP1 receptor (GLP1R)-expressing VANs are activated by gastric distension rather than nutrients in the small intestine [7^{**}]. Curiously, these neurons failed to respond to exogenous GLP1 agonists [7^{**}], although this could be explained by the fact that GLP1 signaling in VANs is dependent on nutrient availability, with GLP1R localization to the cell membrane present in fed, but not fasted, conditions [8]. The role of VANs in modulating the metabolic effects of GLP1 are not in question since selective knockdown of GLP1R from VANs increases meal size, accelerates gastric emptying and contributes to the postprandial neuroincretin effect [9^{**}]. A recent finding demonstrates that lipid infusion in the small intestine activates vagal afferent fibers in a paracrine manner [10], suggesting this might be the site of action of GLP1 released by lipids. However, this may only account for a fraction of vagally mediated GLP1 signaling, since the majority of GLP1R-encoded VANs innervate the stomach [7^{**}].

The orexigenic gastrointestinal hormone ghrelin has also been extensively studied. The well-established hyperpolarization of VANs following ghrelin activation of its receptor was found to depend upon opening of KATP channels triggered by a PI3K-Erk1/2 signaling cascade [11]. Unexpectedly, ghrelin-induced Erk1/2 signaling in nodose ganglia was drastically reduced in mice after 11 weeks of high-fat feeding [12]. Interestingly, ghrelin resistance in VANs coincided with increased inflammatory markers in nodose ganglia [12]. Given that peripheral ghrelin protected against one-day high-fat diet-induced inflammation in nodose ganglia [13], it is possible that the loss of ghrelin signaling in VANs promotes inflammation in nodose ganglia in obesity. However, whether reduced inflammation in nodose ganglia is a direct effect of ghrelin on VANs, the mechanisms by which this occurs, and consequences of nodose ganglia inflammation on energy homeostasis remain unclear.

In addition to indirect sensing of volume and type of food ingested, vagal afferent fibers can directly respond to absorbed macronutrients. VANs express the necessary machinery to sense circulating fatty acids (FA) [14,15]. Long-chain and medium chain FA directly activate cultured VANs by a mechanism involving fatty acid oxidation [14], possibly *via* the fatty acid receptor GPR40 [16]. Expression of genes involved in cholesterol and fatty acid homeostasis are up-regulated in nodose ganglia in response to agonists of the lipid-sensing nuclear receptor LxR, and high-fat fed mice lacking LxR have increased cholesterol levels in VAN [17]. Furthermore, the active steroid-like component of ginseng, ginsenoside (Rb1), requires an intact vagus nerve to decrease food intake [18], although it remains unclear whether Rb1 activates VANs directly or indirectly. The carbohydrate, glucose, acts directly on VANs regulating the density and function of 5-HT₃ receptors [19], and affecting 5-HT-induced depolarization of VANs. Glucose-mediated 5HT activation of VANs occurs independent of body weight changes, indicating that this may be an early event in diet-induced obesity [20]. While there is no direct evidence that VANs sense proteins, acute intragastric administration of the amino acid L-ornithine in lean rats requires an intact vagus nerve to increase sympathetic tone [21].

Downstream mechanisms required for satiation involve postprandial glutamate release from central VAN terminals activates NMDA receptors on NTS neurons [22]. Recent studies identified a role for melanocortin 3/4 receptor on VANs in synaptic recruitment and satiation by controlling glutamate activation of NMDA receptors on NTS neurons [23,24]. Asynchronous release of glutamate is mediated by transient receptor potential vanilloid (TRPV1) in VANs, prolonging postsynaptic NTS neuron excitability and spiking [25]. A role for TRPV1 in satiation was supported by evidence that TRPV1 agonism increased mechanosensitivity of tension receptors of *ex vivo* mouse gastro-oesophageal vagal afferents [26]. Neuropeptides expressed by VANs have also been proposed to play a role in control of food intake [27]. Although direct evidence that neuropeptides are required for feeding control is lacking, hyperphagia induced by genetic [28**], pharmacological [29*] and diet-induced [30] mechanisms coincided with disrupted expression of the neuropeptides cocaine and amphetamine regulated transcript and melanin concentrating hormone.

VANs in long-term control of food intake

An important development in the last couple of years is the demonstration that vagal afferent signaling controls long-term caloric intake, in addition to its established role in meal termination. This was convincingly demonstrated in a study using conditional knockout mice lacking leptin receptor selectively from VANs to disrupt postprandial gut–brain signaling. These mice had sustained larger meals throughout the dark phase driving increased daily food intake, body weight and adiposity compared to control mice [28**]. In a separate study, implantation of osmotic minipumps to provide sustained release of microbial breakdown product lipopolysaccharide, to mimic chronic low-grade metabolic endotoxemia found in obese subjects and diet-induced obese rodents [31], led to leptin resistance in VANs and was associated with decreased satiation and increased daily caloric intake [29*]. Together with previous data showing that leptin resistance is an early event in diet-induced obesity [30,32], these findings indicate that disruption of vagal afferent signaling, possibly following dysbiosis, is sufficient to initiate obesity. In support of this, switching high-fat fed obese mice to chow substantially restores leptin sensitivity in mechanosensitive gastric vagal afferents, coinciding with a lasting absence in weight gain compared to mice maintained on high-fat diet that continue to exhibit hallmarks of vagal leptin-resistance [6]. Interestingly, peripheral injection of oxytocin depolarizes leptin-resistant VANs and reduces overconsumption in leptin receptor knockout mice (db/db) [33*], suggesting that restoring vagal gut–brain signaling may prove an effective treatment for obesity and that oxytocin agonists are an attractive putative target.

Further evidence for a role of VANs in long-term control of food intake comes from bariatric surgery research. Bariatric surgery remains the only effective treatment for obesity, with the most widely used bariatric procedures being laparoscopic adjustable gastric band (LAGB), vertical sleeve gastrectomy (VSG), and Roux-en-Y gastric bypass (RYGB) [34]. The effectiveness of bariatric surgery results from voluntary reduction in food intake [35], implicating homeostatic control of satiation by VANs. In support of this concept, systemic capsaicin administration prevents beneficial effects of LAGB on weight loss, satiation, and loss of fat mass [36]. It is premature to conclude that VANs mediate these effects, given that capsaicin non-selectively targets all C-type sensory neurons, vagal motor neurons, and

ectopic central neurons [37]; nevertheless, these data provide compelling reasons to test the necessity of vagal afferent signaling for LAGB-induced weight-loss. In obese mice genetically expressing reporter tdTomato in all peripheral nerves, extrinsic innervation of the stomach was reduced and the morphology of the terminal endings was altered 35 days after RYGB with no such effect on neural innervation of intestines or glucostatic organs [38]. Along with previous data showing that esophageal truncal vagotomy blunts the effectiveness of RYGB [39], it suggests that intact vagal branches may be required for RYGB-induced weight loss and satiation, although this may not universally apply to all vagal branches. In humans, transection of the neurovascular bundle of the lesser omentum resulted in significant, but not clinically meaningful, reduction in weight loss in RYGB patients at the one-year follow-up, and was associated with increased complications, leading to calls for sparing of this bundle [40]. Selective branch vagotomy in rodents indicates that intact celiac branch [41], but not hepatic branch [42], is required for RYGB-induced weight loss and satiation; although, hepatic branch vagotomy blunted RYGB-induced increase in circulating GLP1 [43] and may improve hyperglycemia after RYGB.

Crucially, exaggerated activation of neural circuits, downstream of vagal afferent signaling, has been implicated in mediating the anorexigenic and glycemic improvements in a mouse model of RYGB [44*]. It is speculated that remodeling the gastrointestinal tract results in vagal afferents sensing abnormally high distension and undigested nutrients in the roux limb to activate an anorexigenic neural pathway involving the NTS, lateral parabrachial nucleus, and central nucleus of the amygdala that initially intensifies satiation and subsequently conditions for smaller, slower meals [44*]. The prospect that vagal afferent signaling influences this neural circuit is supported by the extensive remodeling of central vagal afferent fibers, and/or inflammatory response in the NTS of lean rats following RYGB [45**]. Conversely, VSG in lean rats results in sprouting of vagal afferent synapses in the NTS without evidence of inflammation, suggesting the possibility of hyperexcitation of hindbrain satiation circuits. These results highlight different putative vagal mechanisms for VSG and RYGB [45**].

Blocking vagal nerve signaling with an electrical device implanted at the gastroesophageal junction reduced body weight and improved hyperglycemia in obese and diabetic patients at a 2-year follow-up compared to sham treatment [46]. Importantly, vagal blockade resulted in voluntary reduction in food intake by increasing within meal satiation, and between-meal hunger in obese subjects [47*]. Electrical stimulation of the vagus nerve in animal models also blunts food intake and weight gain [1], and weight loss appears to occur even when stimulating the auricular branch of the vagus nerve (ABVN) [48]. These data provide further support for the importance of the vagus nerve in long-term control of body weight and food intake.

Novel roles of the vagus nerve in energy homeostasis

The classical role of the vagus nerve in the control of food intake is broadening. Studies over the past few years have implicated it in circadian rhythm, thermogenesis, and cognition that will all impact the long-term management of body weight.

Circadian rhythm

Gastric vagal mechanosensitivity is increased in the light, and reduced before the dark, when rodents eat the majority of their food [49]. These circadian changes in vagal mechanosensitivity persist in the absence of light cues [49], suggesting a possible role for vagal afferents as peripheral neural clocks. Importantly, following 12-week consumption of a 60% high-fat diet, the circadian sensitivity of gastric vagal afferents in mice is completely abolished and correlates with increased ingestion in the light phase [5*]. Although the mechanisms remain unclear, these data suggest that disruption in vagal afferent circadian rhythm may account for a proportion of the increased caloric intake in diet-induced obesity.

Thermogenesis

Following original work demonstrating intra-duodenal lipid activation of a cholecystokinin-mediated neural pathway increases thermogenesis [50], three recent studies using genetic and electrical stimulation approaches provide further evidence that disrupting sensory neurons can have a prolonged effect on body weight through their role in thermogenesis. Knockout of either lipid-sensing nuclear receptors peroxisome proliferator-activated receptor- γ (PPAR- γ) in Phox2b neurons [15], or LxR α/β in Nav1.8-expressing peripheral sensory neurons [17] increases energy expenditure in response to a western diet by increasing uncoupling protein 1 (UCP1) expression in brown adipose tissue (BAT) and in beige reprogrammed subcutaneous adipose. However, due to the promiscuity of the promoters, it remains unclear whether the receptors on VAN are responsible for the thermogenesis and weight loss. In particular, there are question marks over the role of VAN PPAR- γ in diet-induced obesity, since chronic ingestion of high-fat diet blunts PPAR- γ expression in VANs, which according to PPAR- γ knockout data should confer resistance to diet-induced obesity [15]. Electrical stimulation of the ABVN for 6 weeks reduced body weight in rats fed a high-fat diet compared to positive controls [48]. Energy expenditure was not directly measured, but the lack of reduction in food intake, increased BAT weight, and elevated UCP1 and adrenergic receptor $\beta 3$ expression in BAT suggests that ABVN stimulation is involved in thermogenesis. Notably, there was no change in food intake after ABVN stimulation compared to obese controls, suggesting ABVN stimulation-induced weight loss is controlled by energy expenditure. However, obese rats did not overconsume compared to chow-fed negative controls [48], which makes absence of hypophagia in ABVN stimulated rats difficult to interpret. While conclusive evidence for a direct role of VANs in thermogenesis remains elusive, there are indications that this pathway may be a novel mechanistic target to confer resistance to diet-induced obesity.

Reward and learning

Post-oral nutrients in rodents have been reported to behave as conditioned cues, producing long-lasting flavor preferences when paired with non-caloric flavored liquids [51] by a mechanism involving dopamine release in the dorsal striatum [52]. Crucially, ablation of the vagus nerve with capsaicin treatment or vagotomy abolishes dopamine efflux in the dorsal striatum in response to post-oral lipids [53*]. Diet-induced obesity reduces dopamine-induced reward to intra-gastric fats which may be a mechanism driving overconsumption in obesity. A similar dopamine efflux in the dorsal striatum has been reported following intra-

gastric infusion of metabolically active sugar, but not non-nutritive sweetener [54], and these effects are abolished when the duodenum is bypassed [55]. This suggests a novel role of vagal signaling in lipid-induced, and possibly carbohydrate-induced, reward and learning. Although, VAN-mediated carbohydrate-induced learning remains controversial [51]. Intriguingly, vagal afferent signals from the periphery may also play a role in extinguishing conditioned learning to negative cues [56]. Further work will be required to determine the full extent of vagal afferent signaling on conditioned learning of positive and negative cues and the importance in the pathophysiology of eating disorders.

Conclusion

The advent of technological improvements in vagal afferent research, replacing outdated surgical and chemical lesioning approaches, is transforming our understanding of the role of this gut–brain pathway in energy homeostasis. In addition to the well-defined role of VANs in meal-to-meal control of food intake, there is now direct evidence that chronically increasing meal size, by targeted knockdown of selected genes in VANs, can lead to long-term changes in food intake. Furthermore, the vagus nerve is increasingly implicated in multiple facets of energy homeostasis, supporting a role for this pathway in the long-term safeguarding of body weight control. Prolonged exposure to calorie-dense nutrients disrupts vagal afferent signaling, and based on recent developments discussed above, may promote weight gain by a variety of mechanisms. These recent developments also provide a justification for developing therapies targeting VANs to simultaneously improve multiple aspects of eating disorders. Although conclusive causative evidence is often missing, this should be addressed in coming years with the use of viral and genetic tools.

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