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The Vagus Nerve Mediates Gut-Brain Response to Duodenal Nutrient Administration

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Abstract

Background: Obesity contributes significant disease burden worldwide, including diabetes, cardiovascular disease, and cancer. While bariatric surgery is the most effective and durable obesity treatment, the mechanisms underlying its effects remain unknown. Although neuro-hormonal mechanisms have been suspected to mediate at least some of the gut-brain axis changes following bariatric surgery, studies examining the intestine and its regionally specific post-gastric alterations to these signals remain unclear.

Materials and methods: Vagus nerve recording was performed following the implantation of duodenal feeding tubes in mice. Testing conditions and measurements were made under anesthesia during baseline, nutrient or vehicle solution delivery, and post-delivery. Solutions tested included water, glucose, glucose with an inhibitor of glucose absorption (phlorizin), and a hydrolyzed protein solution.

Results: Vagus nerve signaling was detectable from the duodenum and exhibited stable baseline activity without responding to osmotic pressure gradients. Duodenal-delivered glucose and protein robustly increased vagus nerve signaling, but increased signaling was abolished during the co-administration of glucose and phlorizin.

Discussion: Gut-brain communication via the vagus nerve emanating from the duodenum is nutrient sensitive and easily measurable in mice. Examination of these signaling pathways may help elucidate how the nutrient signals from the intestine are altered when applied to obesity and bariatric surgery mouse models. Future studies will address quantifying the changes in neuroendocrine nutrient signals in health and obesity, with specific emphasis on identifying the changes associated with bariatric surgery and other gastrointestinal surgery.

Keywords

bariatric surgery, metabolic surgery, vagus, obesity, gut brain communication

Introduction

Obesity contributes to significant disease burden worldwide, including diabetes, cardiovascular disease, and cancer.[1] Bariatric surgery is the most effective and durable obesity treatment, and neuro-hormonal mechanisms within the gut-brain axis have been suspected to mediate at least some of the behavior and food preference changes following bariatric surgery.[2-4] However, we still have a relatively poor understanding of these neurophysiological mechanisms, and studies examining the intestine and the regionally specific post-gastric alterations to these signals remain unclear.

Gut-brain communication of intestinal carbohydrate is believed to occur through the vagus nerve via neuropod cells, a type of epithelial sensory cell within the duodenum that synapses with vagal neurons.[3] The caudal nucleus of

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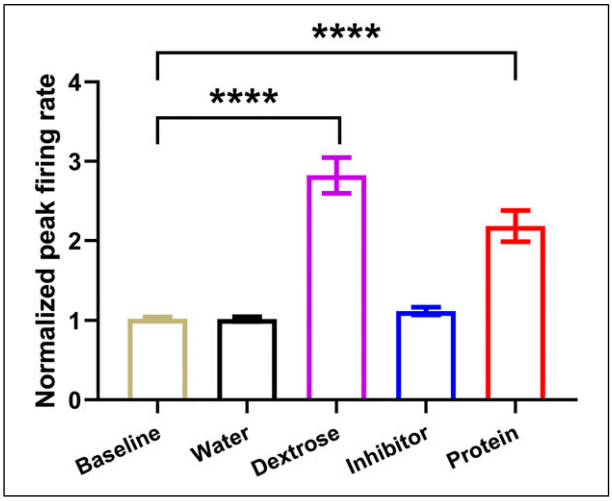

Figure 1. Vagal response to nutrient administration.

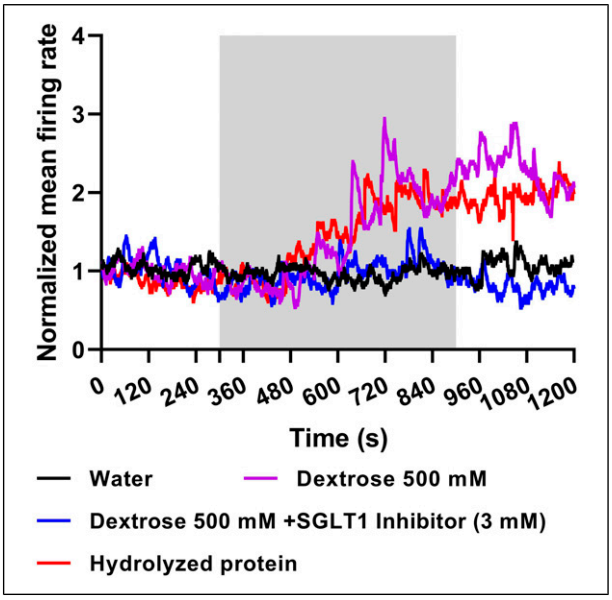

Figure 2. Vagal response to nutrient administration over time.

the solitary tract has been demonstrated to relay vagal communication to other portions of the brain and to mediate, at least in part, the behavioral preference to ingest sugar in mice.[4] Similar to sugar, post-ingestive intestinal fat sensing is believed to propagate via enteroendocrine cell receptor binding, signaling to vagal neurons, and vagal communication with the caudal nucleus of the solitary tract. This signal persists even in the absence of taste receptors, and preference for fat is abolished by interrupting this pathway.[5] Interestingly, investigation of individual vagal neurons in murine models has demonstrated heterogeneity in response to intestinal nutrients, with subgroups responding only to fat, sugar, or amino acids or to all 3 essential macronutrients.[5] Mechanisms of protein intestinal sensing, in contrast, are less clear. In rats, total subdiaphragmatic vagotomy prevents induced flavor preference to monosodium glutamate, suggesting the involvement of vagal afferents in the post-ingestive neurophysiologic response to some proteins.[6] Thus, as autonomic parasympathetics, primarily via the vagus nerve, contribute to food intake and body weight, these signaling mechanisms were examined in response to duodenal nutrient stimuli.

Materials and Methods

Experimental protocols were approved by the Institutional Animal Care and Use Committee at Pennington Biomedical Research Center and were performed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Seven male C57BL6/J mice (Jackson Laboratory, Bar Harbor, ME) aged 12 weeks were used in this pilot study. Vagal afferent fiber activity recording was performed using a technique modified from that recently demonstrated by Buchanan and Bohorquez.[7] Anesthesia was induced with ketamine and xylazine (100 mg/kg and 10 mg/kg, intraperitoneal). Mice were placed in the supine position and immobilized using a waterproof sterile barrier (Tegaderm, 3M), a ventral abdominal incision was made, and the greater curvature of the stomach exposed. A duodenal feeding tube (BTPE-20, Instech, 0.4 × 1.1 mm and Silastic Laboratory Tubing, DuPont, .51 × 0.94 mm) tip was inserted into the stomach via an incision in the greater curvature, advanced through the pylorus 1 cm into the duodenum, and sutured to the stomach. The cervical vagus was exposed and wrapped with 2 platinum iridium wires connected to a differential amplifier. Testing was performed under anesthesia during baseline, vehicle solution, nutrient delivery, and post-delivery. Solutions tested included water, 500 mm glucose, 500 mm glucose with an inhibitor of glucose absorption (phlorizin), and a hydrolyzed protein solution (Proteinex: sterile water 1:8, Proteinex, Miami, FL), each delivered via continuous automatic pump (KD Scientific, Holliston, MA) at 0.1 mL/min.

Investigators were not blinded to group allocation in this pilot study. All statistical analyses, including one-way ANOVA and two-tailed unpaired t test, were performed in GraphPad (Prism 9.3.1, GraphPad Software, Boston, MA).

Results

All animals were of equal age with a mean weight of 24.03 g (SE = .51). Baseline vagal firing rate was used within subject for comparison. Vagus nerve signaling in

response to duodenal administration of glucose or protein was detectable, demonstrated a robust increase in firing rate, and exhibited stable baseline activity without responding to osmotic pressure gradients (Figure 1 and Figure 2). The administration of water to the duodenum caused no significant change to baseline firing rate (1.020 vs 1.018, $P = .9574$). Dextrose infusion caused a significant increase in vagal firing over baseline (2.824 vs 1.020, $P < .05$, 95%CI 1.252-2.354). Co-administration of dextrose with phlorizin abolished this increase in firing (1.020 vs 1.119, $P = .12$). Finally, hydrolyzed protein administration resulted in significantly increased vagus nerve signaling compared to baseline (2.185 vs 1.020, $P < .05$, 95%CI 0.7340-1.596) in a similar effect size to dextrose (2.185 vs 2.824, $P = .09$, 95%CI -1.441-.1645).

Discussion

Protein is an essential energy source, and its intake is highly regulated. A portion of this regulation pathway involves autonomic parasympathetics, largely via the vagus nerve. In this study, we show that gut-brain communication via the vagus nerve emanating from the duodenum is protein sensitive and easily measurable in mice. Examination of these signaling pathways may help elucidate how the nutrient signals from the intestine are altered when applied to obesity and bariatric surgery mouse models. Future studies will address quantifying the changes in neuroendocrine nutrient signals in health and obesity, with specific emphasis on identifying the changes associated with bariatric surgery and other gastrointestinal surgery.

Declaration of Conflicting Interests

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