Duodenal nutrient exposure elicits nutrient-specific gut motility and vagal afferent signals in rat

GARY J. SCHWARTZ AND TIMOTHY H. MORAN
Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205-2196

Schwartz, Gary J., and Timothy H. Moran. Duodenal nutrient exposure elicits nutrient-specific gut motility and vagal afferent signals in rat. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R1236–R1242, 1998.—Volume and chemical characteristics of meals in the gut have been postulated to generate vagal afferent signals that mediate the negative feedback control of ingestion and gastric emptying. Furthermore, duodenal nutrients elicit changes in gastrointestinal motility that may stimulate mechanosensitive vagal afferents. The degree to which the activity of an individual vagal afferent fiber can be modified by both mechanical and nutrient properties in the gut remains unclear. The present studies evaluated the relationships between distal antral and proximal duodenal load-sensitive vagal afferent activity and gastroduodenal motility in response to duodenal nutrient exposure in ketamine-xylazine-anesthetized rats. Duodenal carbohydrate (glucose) and amino acid (peptone) infusions (0.2 ml/min, 0.2–0.5 kcal/ml) stimulated concentration-dependent increases in 1) antroduodenal contractions and 2) antral and duodenal vagal afferent activity beyond those attributable to osmolality alone. In addition, duodenal peptone was more effective than equicaloric glucose in eliciting this vagal activity. These data demonstrate that the proximal duodenum can discriminate its nutrient chemical contents and that gastroduodenal load-sensitive vagal afferents indirectly transduce nutrient chemical information.

METHODS

In vivo vagal and gastric activity. Male Charles River Sprague-Dawley rats (300–400 g) that were food deprived overnight served as subjects in all experiments. Rats were anesthetized with a mixture of ketamine HCl (Aveco) (90 mg/kg) and xylazine (15 mg/kg) (Mobay) administered intramuscularly, and supplemental injections were administered as necessary to maintain a surgical level of anesthesia. Body temperature was monitored and maintained at 36–37°C with a warm-water heating pad (K Module; Baxter).

Surgical procedures. A tracheostomy was performed to facilitate respiration, and then a laparotomy was performed and the stomach and duodenum were exposed. A double-lumen 5-Fr tube consisting of an inner lumen for the drainage of gastric juices and an outer lumen for the inflation of a latex balloon was inserted through a 2-mm-diameter puncture wound in the most proximal and lateral portion of the fundus. This gastric tube was advanced ∼ 3 cm into the stomach and oriented such that when inflated with 1 ml of saline, the balloon would distend the distal antrum adjacent to the pylorus. This tube and the balloon position in the distal antrum were held in place by a purse-string suture in the fundus, and the tube was exteriorized through the left lateral
abdominal muscle wall and surrounding skin by a puncture wound. A 3-Fr tube attached to a latex balloon was inserted through a small puncture wound made by a 20-gauge needle in the ventral duodenal wall 4 cm distal to the pylorus and was oriented such that when inflated with 0.2 ml saline, the balloon would distend a 1-cm segment of the proximal duodenum adjacent to the pylorus. A 2-mm puncture wound was then made in the ventral duodenal wall 5 cm distal to the pylorus with a 22-gauge needle, and a Silastic tube (0.3 mm ID × 0.63 mm OD) for duodenal infusions was advanced 1 cm into the wound so that the tip rested at a point 4 cm distal to the pylorus. This placement of the cannula tip was chosen because it is consistent with previous studies evaluating the ability of duodenal nutrient infusions to inhibit food intake (11, 26). The exteriorized portion of this cannula was attached to tubing from a peristaltic pump for the infusion of duodenal nutrients. The heat-flared end of a 5-cm segment of PE-190 tubing for duodenal drainage was also inserted 0.2 mm into the wound, and both duodenal infusion and drainage tubes were fastened in place with silk suture. The drainage tubing was attached to a 40-cm length of 0.5 cm ID × 0.65 cm OD Silastic tubing that fed into a 4-liter collection flask placed 1 m under the surgical table. The initial PE-190 length of the drainage catheter lay on the same horizontal plane as the rat and when attached to the larger drainage catheter did not alter normal periarterial activity in the cannulated duodenal segment or 2) induce a vacuum of duodenal tissue against the drainage cannula. This arrangement of duodenal infusion and drainage catheters permitted nutrients to be exposed to the first 5 cm of duodenal lumen distal to the pylorus. The portion of intestine distal to the exit of the duodenal drainage catheter was ligated with 4–0 silk.

Electrophysiological recordings. The vagus nerve was exposed in the neck, and small bundles of nerve fibers from the left cervical vagal trunk were peeled off and the distal cut ends were placed on tungsten metal wire electrodes (A-M Instruments). Vagal afferent discharges were amplified using standard techniques and were monitored by oscilloscope and audio monitor. The activity of individual fibers was discerned by finer dissection of the nerve trunk and use of a dual time-amplitude window discrimination of spike activity. The dual time-amplitude window discrimination and window discrimination of individual units with unique time-amplitude signatures. Vagal impulses were recorded on videotape for online and subsequent analysis of spike frequency and number using computerized hardware and software (SuperScope; GW Instruments).

Experimental protocol. To identify a unit for investigation, each fiber isolated as described above was screened for its spontaneous discharge activity. Only fibers that demonstrated some spontaneous activity were screened for their response to a 2 ml/5 s antral gastric balloon load stimulus or a 0.1 ml/5 s proximal duodenal balloon load stimulus. A response to gastric or duodenal balloon load was defined as an increase in the number of discharges in the first 30-s post-stimulus interval of at least 1.5 standard deviations above the average number of discharges occurring in 30-s bins of spontaneous prestimulus activity. The receptive fields of each unit were then determined by probing the ventral gastric or duodenal surface with a blunt-tipped glass rod (tip diameter <1 mm). Gastric mechanoreceptive fields of units tested in this study were all localized to the distal ventral antrum (0.5–1.0 cm proximal to the pyloric torus), whereas duodenal mechanosensitive units were localized to the proximal 0.5–1 cm of the ventral duodenal wall. After identification of each duodenal or gastric vagal afferent load-sensitive unit with the corresponding balloon, the balloon was deflated and was not reinflated for the remainder of the study. Thus no gastric load was in place during any of the duodenal infusions. After identification of a unit that responded to gastric or duodenal loads, for the measurement of muscle tension in the ventral distal antral and the ventral proximal duodenal walls, two miniature strain gauges (3 × 3 mm; Bass Instruments, Madison, WI) were calibrated using von Frey hairs (Stoelting). One was sewn onto the ventral distal antrum, and the other was sewn onto the ventral proximal duodenum. For duodenal mechanosensitive units, the duodenal strain gauge was mounted overlapping as closely as possible the mechanical duodenal receptive field of the unit, and in all cases it was centered no more than 5 mm distal to the pylorus. Similarly, for gastric mechanosensitive units, the gastric strain gauge was mounted overlapping as closely as possible to the mechanical gastric receptive field of the unit, and in all cases it was centered no more than 7 mm proximal to the pylorus. Both strain gauges were implanted in the orientation of the longitudinal muscle using 5–0 silk suture. Thus, during the course of one experiment, the vagal afferent activity of one single vagal afferent unit with either a gastric or duodenal mechanosensitive field was recorded, and longitudinal muscle contractile activity was recorded simultaneously from both distal antral and proximal duodenal sites for all identified units.

Gastric antral and duodenal wall muscle tension signals were fed to amplifiers (World Precision Instruments), and output was recorded on to computer hard disk and videotape for subsequent analysis using computerized hardware and software (SuperScope; GW Instruments).

Gastric and duodenal motility and vagal afferent responses to duodenal luminal infusions of nonnutrient saline and nutrients were assessed in a total of 19 vagal afferent fibers (1 per rat, 19 rats) with either distal antral receptive fields (n = 10) or proximal duodenal receptive fields (n = 9), as described above. For each unit, six stimuli were tested in random order: physiological saline (300 mosM, 0.9%), 750 mosM saline (2.25%), 300 mosM (0.2 kcal/ml, 50 g/l) and 750 mosM (0.5 kcal/ml, 125 g/l) glucose (United States Biochemical), and 300 mosM (0.2 kcal/ml, 50 g/l) and 750 mosM (0.5 kcal/ml, 125 g/l) peptone (Sigma P8388 Primatone from meat, ~98% amino acids). Peptone was chosen as a mixed amino acid source based on previous studies demonstrating that the vagus contributed to the control of gastric emptying of peptone in rats maintained on a standard Purina Lab Chow 5001 diet (31). Distilled water served as the solvent for all solutions, with low heating (20–30°C) and stirring as necessary to dissolve the solute. All test solution infusions were delivered at 36–37°C at pH 7.0, at a rate of 0.2 ml/min for 2 min, and these infusions were allowed to drain freely from the duodenum through the duodenal drainage catheter. This rate is intermediate with respect to studies demonstrating that duodenal infusions using rates ranging from 0.05–0.44 ml/min suppress food intake and gastric emptying (11, 28, 38). This rate was chosen from pilot experiments demonstrating that this was the maximum rate of infusion that 1) would completely expose the duodenal segment to the infusate, 2) would not appear in the stomach, and 3) would not produce a decrease in gastric pressure as measured against a gastric balloon inflated to 2 ml. In addition, at this rate of infusion, the fluid dripped evenly from the cannulated duodenal segment without developing a vacuum of tissue against the drainage tube. The 2-min duration of the infusion was based on pilot experiments demonstrating that it was sufficiently long to produce significant changes in motility and vagal afferent activity, yet short enough to permit testing of multiple infusions while maintaining the viability of a single
Vagal afferent fiber. The 7.0 pH was chosen to minimize the possibility that the acidity of the infusate would influence the response to duodenal infusion, because small intestinal vagal chemoreceptors have been reported to be stimulated by low-pH solutions (24). Gastric or duodenal vagal afferent activity (spikes/s), ventral distal antral, and ventral proximal duodenal longitudinal muscle tension (g) were monitored during all duodenal infusions as described above. A contractile response to a duodenal infusion was defined as a minimum of three consecutive contractions whose peak tension was at least 1.5 SD above the mean spontaneous peak tension; contractile response onset was defined as the time of the first contraction peak. Once a contractile response had begun, the end of the response was defined by reaching either one of the following two criteria: 1) an absence of contractions for at least 1 min or 2) a return to baseline levels of contractile activity, characterized by three consecutive contractions each <1 SD above the mean spontaneous peak tension; contractile response offset was the time of the peak of the first of these contractions. Peak tension during contractions, the duration of the pattern of contractions elicited, and mean vagal afferent spike rate during contractions were determined for each infusion trial. Recordings were made for 10 min after the end of the infusion period. At the end of this 10-min period, a 1-ml duodenal infusion of physiological saline rinse was delivered over 5 min, followed by a 5-min rest period. Peak contraction tension and vagal afferent activity during contractions returned to prestimulus baseline levels before administration of each duodenal infusion.

Data analysis. For each group of vagal afferent units examined (gastric antral and duodenal receptive fields), two-way repeated-measures ANOVA comparisons were made to evaluate the effect of the duodenal infusion type (saline vs. glucose vs. peptone) and concentration (300 vs. 750 mosM) on 1) mean peak tension during distal antral and proximal duodenal contractions, 2) duration of the contractile effect of duodenal infusions, and 3) vagal afferent firing rate during contractions. For each of these three measures, significant differences between individual load type-concentration pairs were determined using planned t-test comparisons (P < 0.05).

RESULTS

Low-grade (<1 g) spontaneous contractions were recorded in both distal antral and proximal duodenal regions occurring at an average rate of 3.5 ± 0.3 per minute. These spontaneous contractions were frequently accompanied by brief bursts of activity in gastric and duodenal vagal load-sensitive afferents. Duodenal infusions of saline, glucose, and peptone all stimulated concentration-dependent 1) increases in mean peak contraction strengths in the proximal duodenum and distal antrum and 2) activation of gastric and duodenal vagal afferent load-sensitive fibers in all 19 fibers tested. The latency to elicit a contractile response ranged from 15 to 30 s after the end of the duodenal infusion. An example of the contractile and vagal afferent responses to a duodenal infusion of 750 mosM glucose (125 g/l) for a single gastric and a single duodenal vagal load-sensitive unit is shown in Fig. 1, A and B, respectively. During infusions, no inhibition of the prestimulation baseline levels of contractile activity was observed (e.g., Fig. 1A). Increasing osmolarity of duodenal saline infusions resulted in increases in the strength of duodenal [F(1,18) = 34.1, P < 0.01] and antral [F(1,18) = 9.95, P < 0.01] contractions (Fig. 2A). Increasing caloric concentrations of glucose produced dose-dependent increases in the strength of duodenal [F(1,18) = 28.3, P < 0.01] and antral [F(1,18) = 100.2, P < 0.01] contractions, and these were significantly greater than those produced by equiosmotic saline infusions (P < 0.01). Duodenal peptone infusions also produced concentration-dependent increases in duodenal [F(1,18) = 57.3, P < 0.01] and antral [F(1,18) = 18.7, P < 0.01] contraction strength, and these were significantly greater than those produced by equivalent glucose and equiosmotic saline infusions (P < 0.05).

The duration of duodenal contractile responses did not significantly increase with increasing concentration for any of the infused solutions (Fig. 2B) (P > 0.3). However, increasing the duodenal infusate concentration significantly increased the duration of the antral contractile responses to saline [F(1,18) = 12.4, P < 0.01], glucose [F(1,18) = 21.1, P < 0.01], and peptone [F(1,18) = 8.6, P < 0.01]. Furthermore, the duration of duodenal and antral contractile responses to peptone solutions significantly outlasted those for equiosmotic saline and glucose (P < 0.01).

Duodenal infusions stimulated vagal activity arising from proximal duodenal and distal antral mechanosensitive afferents, respectively (Fig. 2C). For saline infusions, increased osmolarity elicited dose-dependent increases in mean vagal afferent spike rate during contractions [duodenal units F(1,8) = 34.4, P < 0.01; antral units F(1,9) = 11.2, P < 0.01]. Increasing glucose concentration dose-dependently increased antral and duodenal vagal afferent spike rates [duodenal units F(1,8) = 50.8, P < 0.01; antral units F(1,9) = 14.2, P < 0.01], and these were significantly greater than rates produced by equiosmotic saline (P < 0.01). Peptone also elicited concentration-dependent increases in both duodenal and antral vagal afferent activity [duodenal units F(1,8) = 14.5, P < 0.01; antral units F(1,9) = 12.4, P < 0.01]. At each concentration, peptone produced greater spike rates than either equiosmotic saline or equivalent caloric glucose (P < 0.01).

Finally, comparison of the ratio of vagal afferent response to contractile response revealed that at the 300 mosM concentration, peptone was significantly more effective in generating antral and duodenal vagal afferent responses than what would be predicted based on the contractile response alone [duodenum F(1,8) = 12.3, P < 0.01; antrum F(1,9) = 10.2, P < 0.01] (Fig. 2D).

DISCUSSION

These results demonstrate that proximal duodenal amino acid and carbohydrate infusions elicit distinct patterns of distal antral and proximal duodenal contractile activity. The rat proximal duodenum is differentially sensitive not only to osmolarity, but also to the type and amount of nutrient infused. In addition, duodenal nutrient infusions elicit nutrient and concentration-dependent increases in vagal afferent activity in distal antral and proximal duodenal vagal load-
sensitive fibers. This discussion will focus first on the assessment of the duodenal nutrient-elicited gastrointestinal motility changes, followed by consideration of the contribution of the motility changes to vagal afferent responses.

The increase in duodenal motility after duodenal infusions is consistent with the ability of such infusions to alter myoelectric and contractile activity in the small intestine. In intestinal electromyographic studies in rats, hyperosmotic saline produced more spiking activity than normal saline, hyperosmotic glucose produced more spiking activity than equiosmotic saline, and amino acids were more effective than glucose in eliciting continuous spiking electrical activity (30). A variety of studies using perfused catheter manometry to evaluate the extent of changes in upper gastrointestinal motility after duodenal nutrient infusion have demonstrated duodenal and pyloric responses. In humans, the number of coordinated pyloroduodenal and duodenal contractile events increased significantly in the first hour after a milk meal (16). Furthermore, duodenal infusions of dextrose in overnight-fasted humans have been shown to elicit dose-dependent increases in the rate of isolated pyloric pressure waves (IPPW) over a range of 5–25%. Fone et al. (9) have demonstrated that in overnight-fasted humans, 25% intraduodenal dextrose infusions increased duodenal pressure waves within the first 5 min of the infusion. Increases in
duodenal pressure waves after of 0.9 (300 mosM) and 2.7% (900 mosM) saline infusions as well as 25% dextrose solutions have also been reported (15). Increases in IPPWs are associated with the obstruction of transpyloric flow (34) and are negatively correlated with the rate of gastric emptying, suggesting a functional role for these contractions. In the awake pig, duodenal normal saline infusions stimulated antral-pyloric waves and rapid gastric emptying, whereas duodenal infusion of dextrose solutions dose-dependently increased IPPW rate (35).

Although the stimulation of duodenal motility by duodenal nutrients is consistent with manometric findings, the present results also demonstrate that duodenal nutrients elicit contractions in the longitudinal muscle of the distal antrum. This appears to contrast with results from manometric measurements, indicating that duodenal glucose and peptone exposure causes reductions in intragastric pressure and motility. The apparently contrasting results may depend on several important methodological differences between studies. Unlike our study, in which tension generated in the longitudinal muscle wall was directly measured, Raybould (26) reported changes in proximal gastric pressure against a fixed pressure load in the stomach. This method would not be sufficiently sensitive to reveal changes in distal antral motor activity. Furthermore, manometric measurements rely on the compression of fluid by movements of the gastrointestinal wall and may not capture events that are occurring at the outermost (longitudinal) muscle layer of the gastric wall. In the current study, no gastric load was in place. The presence of a gastric pressure load in the stomach may invoke antrocorpal relaxation reflexes that may modulate the contractility of the antrum (12). Finally, the close physical proximity of the distal antral strain gauge to the pylorus in the present study may reveal changes in longitudinal muscle tension secondary to duodenal nutrient-induced pyloric contractile events, such as IPPWs. These IPPWs may be electrically (see below) or mechanically transferred to adjacent antral musculature. As discussed above, IPPWs are readily and dose dependently induced by a variety of duodenal nutrient infusions.

The neural circuitry mediating the production of proximal duodenal and distal antral contractions after duodenal nutrient infusions is unclear. Two classes of neuronal mechanisms underlying these contractile responses may be suggested. The first class consists of events that are mediated by intrinsic neural circuits, whereas the second consists of events that rely on extrinsic vagal and/or splanchnic neural pathways. Intrinsically ascending enteric pathways may contribute to the propagation of duodenal contractile activity to pyloric and gastric sites. In the extrinsically denervated cat, electrical activity is transmitted through the gastroduodenal junction between distal antral, pyloric, and proximal duodenal sites (4), demonstrating a role for intrinsic neural circuitry in this transmission. Enteric motility reflexes oral to the site of small intestinal stimulation can be initiated through entirely intrinsic

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Fig. 2. Mean ± SE of peak tension (g) (A) and duration (min) (B) during proximal duodenal (left) and distal antral contractions (right) stimulated by duodenal infusions of saline, glucose, and peptone at 2 concentrations (300 and 750 mosM). The wt/vol concentrations of glucose and peptone at the 2 osmotic levels are 50 and 125 g/l, respectively. C: mean ± SE vagal afferent spike rate (spikes/s) in proximal duodenal (left) and distal antral (right) load-sensitive vagal afferents during proximal duodenal and distal antral contractions stimulated by duodenal infusions of saline, glucose, and peptone at the above concentrations. D: mean ± SE ratio of vagal afferent spike rate to peak tension during contractions stimulated by duodenal infusions of saline, glucose, and peptone at 2 concentrations (300 and 750 mosM). *Significant difference (P < 0.05) compared with equiosmotic saline and glucose infusions.
mechanisms in the guinea pig small intestine (10). There are no data available concerning the ability of nutrients to elicit changes in duodenal or distal antral motility in the extrinsically denervated gut. However, an intact enteric innervation can be shown to contribute to the transmission of duodenal events to more orad antropyloric sites. In pigs, surgical transection and reanastomosis of the duodenum, including the myenteric plexus, significantly attenuated the ability of duodenal infusion of dextrose, amino acids, and hyperosmolar saline to stimulate IPPWs (36).

Extrinsic vagal and splanchnic reflex pathways may also contribute to the coordination of nutrient-elicited gastroduodenal myoelectrical activity and motility. The interdigestive patterns of upper gastrointestinal myoelectrical activity are disrupted by transection of the vagus and by removal of the celiac-superior mesenteric ganglia (20, 21). In humans, IPPWs generated by intraduodenal dextrose are significantly attenuated by atropine, suggesting that vagal cholinergic outflow may mediate these motility responses (14). Gastric and duodenal vagal afferent mechanoreceptors sensitive to active contraction and passive distension both inhibit and activate efferent vagal activity (7, 13), whereas duodenal infusions of hyperosmotic solutions increase vagal afferent neurophysiological activity (3). Vagal afferent signals mediate reflex contractile activity in the upper gut. For example, gastric distension produces antral contractions via vago-vagal reflex pathways (12). These contractions, in turn, likely provide further stimulation of gastroduodenal load-sensitive afferents.

The series of absorptive and local nutrient transport events intervening between the delivery of nutrients into the duodenal lumen and the initiation of gastroduodenal contractions and vagal afferent activity is unknown. Work of Raybould and Zittel (28) has shown that competitive blockade of small intestinal sodium-dependent glucose cotransporters inhibits the ability of duodenal glucose to alter gastric motor function. In contrast, application of glucose analogs that are absorbed but not metabolized also inhibits gastric motor function to the same degree as glucose. These data suggest that blockade of nutrient transporters, and not metabolism, may mediate the immediate effects of duodenal nutrients on gastroduodenal motility and associated vagal afferent activity. In the present study, the moment-to-moment availability and exposure of infused nutrients to critical nutrient transporters along the entire cannulated segment of duodenal lumen is unknown and may help determine the temporal relationship between the onset of the duodenal infusion and the observed contractile and vagal afferent responses.

Perspectives

We have previously shown that antral load-sensitive vagal afferents are not directly sensitive to the nutrient or osmotic composition of solutions confined to the stomach (22). However, the present results demonstrate that duodenal nutrient exposure elicits nutrient-specific activation of antral and duodenal load-sensitive vagal afferents consistent with nutrient-induced antral and duodenal contractions. Thus these vagal afferents are indirectly, rather than directly, chemosensitive. Vagal afferent responses to nutrients may also reflect an integrative process in which the vagal afferent response to contraction is modified by local nutrient-elicited paracrine or neural signals. We have shown that load-sensitive fibers supplying the stomach are capable of integrating at least two types of meal-related stimulation: distension provided by gastric loads and exogenous application of the gut-brain peptide CCK, normally released by endocrine cells in the presence of duodenal luminal nutrients. Specifically, CCK amplifies and potentiates the gastric vagal afferent responses to gastric-distending loads (32, 33).

CCK and other duodenal nutrient-elicited gut peptides and neurotransmitters may alter the local hormonal environment in which vagal afferent signals are generated and thereby modulate the resulting neurophysiological response. At the lower concentration of peptone tested (50 g/l), the elicited duodenal afferent activity ranged from 30 to 35 spikes/s and was greater than what might be expected based on the contractile activity alone. This range appears to be maximal for these afferents in our anesthetized rat preparations and may be due to the ability of peptone-elicited endogenous release of CCK to amplify the vagal afferent response to peptone-stimulated contractions. The apparent lack of amplification at the high dose of peptone may reflect the fact that 1) the maximal firing rate for individual vagal afferents was approached with the low dose, 2) the higher dose of peptone elicited significantly stronger contractions that the lower dose, and 3) any CCK release elicited by peptone would be unable to amplify single vagal afferent activity beyond the levels produced by the stronger contractions seen at the higher peptone dose.

Stimulation of the upper gastrointestinal tract with nutrients, nonnutrient chemicals, distension, and contraction has also been demonstrated to induce the neurophysiological activation and expression of c-fos protooncogene in the myenteric plexus (2, 8, 29). Neuroanatomical tracing studies have shown that upper gut vagal afferents terminate at or near myenteric and submucosal neurons, suggesting a potential signaling pathway from enteric neurons to gut vagal afferents (1, 19). Single vagal afferents with terminations in gut muscle layers also have arborsizations in the mucosal layer (19). Together, these data suggest that gut nutrients may also modulate the response of load-sensitive vagal afferent activity via 1) enteric neural activation or 2) nutrient activation of mucosal vagal afferent arborizations.

Finally, the current demonstration that duodenal nutrients elicit nutrient-specific, dose-dependent vagal afferent responses is consistent with the suggestion that these signals contribute to the ability of duodenal nutrient infusions to dose-dependently suppress feeding.

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REFERENCES


