Contribution of different triggers to the gastric accommodation reflex in humans

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Vanden Berghe P, Janssen P, Kindt S, Vos R, Tack J. Contribution of different triggers to the gastric accommodation reflex in humans. Am J Physiol Gastrointest Liver Physiol 297: G902–G906, 2009. First published September 10, 2009; doi:10.1152/ajpgi.00046.2009.—Accommodation of the stomach consists of a vagally mediated relaxation of the proximal stomach, providing the meal with a reservoir. Our aim was to study whether, similar to other vagally mediated processes, the accommodation reflex is also determined by cephalic, oropharyngeal, gastric, and intestinal phases. Eleven healthy subjects underwent in randomized order five gastric barostat studies and two satiety drinking tests. In all studies, isobaric tone measurements (at minimal distending pressure + 2 mmHg) were performed 20 min before and 20 min after a nutrient stimulus. The stimuli included only visual and olfactory exposure to a meal (cephalic stimulation), taking liquid nutrient in the mouth without swallowing (sham feeding), ingestion of a 200-ml 300-kcal nutrient meal with blocked outflow to the pylorus (gastric retention), and meal infusion through a nasointestinal tube (duodenal instillation), or normal ingestion (control). During satiety testing, subjects ingested liquid nutrient at a fixed rate of 15 ml/min until maximum satiety, with an inflated or deflated intrapyloric balloon assembly. Progressively bigger gastric relaxatory responses were seen with cephalic stimulation (18 ± 19 ml), sham feeding (54 ± 21 ml), gastric retention (95 ± 47), duodenal instillation (144 ± 33), and control (232 ± 33 ml). The amount of nutrient ingested at maximum satiety was significantly lower with an inflated intrapyloric balloon (1,223 ± 103 vs. 1,392 ± 124 ml, P < 0.05). The accommodation reflex in humans lacks a cephalic phase, but it can be activated from the oropharynx, the stomach, and the duodenum. Blocking passage to the duodenum significantly decreases the amplitude of the accommodation reflex and induces early satiety.

During fasting, muscle fibers of the proximal stomach remain in a vagally mediated tonically contracted state, which generates gastric fundus tone. During and after meal ingestion, a long-lasting relaxation of the proximal stomach occurs, which creates a reservoir for the meal and enables the gastric volume to increase without a rise in pressure (1). This process, which is called “gastric accommodation,” also allows the stomach to retain food and to regulate passage to the duodenum at a rate that matches the duodenal absorptive capacity (3, 18). Recent studies have reported the occurrence of impaired gastric accommodation in patients with functional dyspepsia and a number of related disorders, and it has been suggested that this abnormality contributes to the pathogenesis of symptoms (5, 18, 30). On the basis of these studies, impaired gastric accommodation has been proposed as a target for therapeutic intervention in several functional and motor disorders of the upper gastrointestinal tract (5, 18).

Currently, the mechanisms that control gastric accommodation in humans are incompletely understood. On the basis of studies in animals, the accommodation reflex seems to consist of a vagovagal reflex pathway resulting in activation of nonadrenergic, noncholinergic nerves, including an important nitrergic component (2, 8, 12). These findings were confirmed in humans: a study that compared gastric accommodation in healthy volunteers and postvagotomy patients confirmed that gastric accommodation is a vagally controlled reflex (32). Furthermore, with the use of nitric oxide synthase inhibitors, the important role of nitrergic nerves in the gastric accommodation reflex in humans was confirmed (19, 29). Although these observations have lead to an understanding of the reflex arc and the effector side of the accommodation reflex, uncertainty remains regarding the triggering sites and factors.

It is well known that thought, smell, taste, and swallowing of food induce digestive responses as increased gastric acid secretion (16, 31). The cephalic phase of food ingestion also induces a relaxation of the stomach, as shown by measuring intragastric pressures (17). Relaxation of the proximal stomach in response to esophageal distension in conscious dogs was shown to be mediated via a noncholinergic vagal mechanism (10), and also in conscious cats the sham feeding-induced gastric relaxation was shown to be a vagal reflex (21). Apart from this cephalic phase, gastric accommodation can also be induced by gastric contents and/or distension (22). It has been shown in humans that after vagotomy this reflex is impaired, suggesting that stomach distension-induced gastric accommodation is mediated via the vagus nerve (26). Several studies have shown that instillation of nutrients in the duodenum or duodenal distention may induce a relaxation of the proximal stomach in humans (4, 14, 23).

The aim of the present study therefore was to investigate the relative importance of different triggering sites of the gastric accommodation reflex (cephalic, oropharyngeal, gastric, and intestinal) in humans, by using gastric barostat and nutrient challenge tests (28–30).

MATERIALS AND METHODS

Subjects. Only healthy volunteers were recruited for this study. None of the subjects had symptoms or a history of gastrointestinal disease or drug allergies, nor were they taking any medication. Written, informed consent was obtained from each participant. The protocol was approved by the Ethics Committee of the University Hospital. All subjects underwent, in randomized order, five gastric barostat studies and two satiety drinking tests on 7 separate days, with at least a 4-day interval.

Gastric barostat study. After an overnight fast of at least 12 h, subjects presented to the motility laboratory in the morning where a double-lumen polyvinyl tube (Salem sump tube 14 Ch. Sherwood Medical, Petit Rechain, Belgium) with an adherent polyethylene bag (maximal volume 1,200 ml; 17 cm maximal diameter) was introduced

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through the mouth and secured to the subject’s chin with adhesive tape. The correct position of the bag in the gastric fundus was checked fluoroscopically. The polyvinyl tube was then connected to a programmable barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). To unfold the bag, it was inflated with a fixed volume of 300 ml for 2 min with the subject in a recumbent position and again deflated completely. The subjects were then positioned in a comfortable sitting position with the knees bent (80°) and the trunk upright in a specifically designed bed.

For duodenal nutrient infusion studies a nasointestinal feeding tube (outer diameter 2 mm) was introduced through the nose, positioned into the second part of the duodenum under fluoroscopic control. For pyloric obstruction studies (see below), an intestinal suction tube (Salem sump tube 14 Ch, Sherwood Medical, Petit Rechain Belgium), with four suction openings at the tip and a wedged balloon (maximum capacity 900 ml, 10 cm long, wedged shape) 5 cm from the tip, was positioned under fluoroscopic control with the balloon straddling the pyloric sphincter. After a 30-min adaptation period, both for the barostat balloon in the proximal stomach and, if applicable, for the wedged balloon in the pylorus the minimal distending pressure (MDP) was determined by increasing the intrabag pressure with 1 mmHg every 3 min, until a volume was reached on which respiratory variations could be noticed (30 ml or more). Subsequently, after a 10-min recovery period, the pressure level in both balloons was set at MDP + 2 mmHg 20 min before and 20 min after a nutrient stimulus. In the first protocol (cephalic stimulation), the volunteers could only see and smell a standard lunch meal [200 g mashed potatoes, 200 g applesauce, and 100 g minced veal (13% proteins, 51% fat, and 36% carbohydrates; 884 kcal)]. In the second protocol (sham feeding), subjects were allowed to take liquid meal (50 ml in total composition; see below) into the mouth but were instructed to spit it out without swallowing. In the third protocol (gastric retention), the mixed liquid meal (200 ml, 300 kcal; 13% proteins, 48% carbohydrates, 39% lipids; vanilla flavor Nutridrink, Nutricia, Bornem, Belgium) was completely ingested, but passage to the duodenum was blocked by an intrapyloric balloon assembly. To control for leakage past the balloon into the duodenal bulb, continuous postpyloric aspiration was performed by means of a vacuum pump, to detect appearance of nutrient in the duodenum. In the fourth protocol (normal ingestion), the mixed liquid meal was completely ingested with unobstructed passage to the duodenum. In the fifth protocol (duodenal instillation), the liquid meal was instilled via a nasoduodenal catheter at a rate of 1 ml (1.5 kcal) per minute (Fig. 1).

**Satiety drinking test.** A nutrient drinking test to quantify nutrient tolerance and the occurrence of meal-induced satiety was performed in the morning after an overnight fast. An intestinal suction tube with four suction openings at the tip and a wedged balloon 5 cm from the tip (see above) was positioned under fluoroscopic control with the balloon straddling the pyloric sphincter. The nutrient drinking test was performed with the balloon deflated or inflated to block pyloric outflow, in a randomized order. During the study with the balloon inflated, continuous postpyloric aspiration was performed by means of a vacuum pump, to detect appearance of nutrient in the duodenum. A peristaltic pump (Minipuls2; Gilson, Villiers-Le-Bel, France) filled one of two beakers at a rate of 15 ml/min with a liquid meal (Nutridrink, Nutricia). Subjects were requested to maintain intake at the filling rate, thereby alternating the beakers as they are filled and emptied. At 5-min intervals, they were asked to score their satiety using a separate graphic rating scale that combined verbal descriptors on a scale graded 0–5 (1 = threshold, 5 = maximum satiety). Meal intake was stopped when a score of 5 was reached.

**Data analysis.** To evaluate gastric tone before and after nutrient challenge, mean intraballloon volume was calculated over consecutive 5-min intervals of the measurement. Gastric accommodation was quantified as the volume increase over the mean volume prior to nutrient administration and expressed as means ± SE. We also determined the time needed to reach maximum relaxation and the slope of the relaxation (slope of the linear regression obtained from volume changes during the first 10 min). Comparison of gastric accommodation under the different conditions was done by paired t-test and repeated-measures ANOVA with Tukey-Kramer multiple-comparisons testing.

**RESULTS**

**Conduct of the studies.** Eleven healthy subjects (3 men, age 21–29) were recruited for the studies. Each of the protocols was well tolerated, and all subjects underwent the studies as planned. In two subjects, nutrient was aspirated from the duodenum during the satiety drinking test protocol with pyloric obstruction. These studies were interrupted and repeated on another day.

**Meal-induced accommodation in the control condition.** The MDP was 7.4 ± 0.2 mmHg. Prior to nutrient ingestion, the intraballloon volume was 134 ± 15 ml. Meal ingestion was followed by a rapid increase in intraballloon volume of on average 232 ± 33 ml, resulting in a mean postingestion volume of 366 ± 39 ml (P < 0.001) (Fig. 2). The time to reach the maximum intraballloon volume was 13.2 ± 1.4 min, with a relaxation rate of 19.8 ± 6.2 ml/min during the first 10 min. Repeated-measures ANOVA confirmed highly significant vari-
Intraduodenal instillation of nutrient induced a significant increase in intraballoon volume from 161 ± 26 to 305 ± 42 ml ($P = 0.001$). The time to reach the maximum intraballoon volume was 11.8 ± 1.5 min, with a relaxation rate of 7.6 ± 1.7 ml/min during the first 10 min (both NS compared with control condition). The nutrient-induced volume increase (144 ± 33 ml) did not differ significantly from the control condition (Fig. 3).

**Nutrient drinking test with and without pyloric outlet obstruction.** With inflated balloon, the amount of liquid nutrient meal ingested until the occurrence of maximum satiety was 1,392 ± 124 ml. With inflated pyloric balloon, this was significantly reduced to 1,223 ± 103 ml ($P = 0.03$). No statistically significant differences between both treatment modalities were obtained for the satiety scores at 5-min intervals.

**DISCUSSION**

The gastric accommodation reflex is considered a major factor in the control of food intake, and abnormalities in its control have been implicated in the pathogenesis of a variety of disorders (3, 18, 30). Detailed knowledge of the control mechanisms of the accommodation reflex is a prerequisite for better understanding of the pathophysiological abnormalities underlying impaired accommodation and for the development of therapies aimed at correcting this disorder. Studies in experimental animals have provided a model for the control of the gastric accommodation reflex, including vagal afferents that transmit information on the presence of nutrients to the brain stem, and integration of the reflex in the brain stem followed by vagal efferent signaling to intrinsic inhibitory motor neurons in the proximal stomach, which relaxes gastric circular muscle through release of nitric oxide, vasoactive intestinal polypeptide, and other nonadrenergic, noncholinergic inhibitory neurotransmitters (18). Studies in rodents have suggested involvement of serotonin (5-HT) in the effenter limb of the reflex (6, 24).

Also in humans it has been shown that vagovagal reflexes are the major contributor of the gastric accommodation reflex (32). In fact, in postvagotomy patients, the gastric accommodation reflex was shown to be impaired as in functional dyspeptic patients (26). 5-HT (27) and nitric oxide (19, 29) are...
regarded as important mediators of this reflex. Little, however, is known about the afferent limb of the accommodation reflex. Some evidence suggests that gastric accommodation may have a cephalic, oropharyngeal, gastric, and intestinal component (4, 10, 14, 16, 17, 21–23, 26), yet their relative importance to a standard meal is unknown. Duodenal distention and duodenal nutrient infusion are able to induce a gastric relaxation, which is reminiscent of the accommodation reflex during nutrient ingestion (4, 14, 23). However, it is unclear whether this is part of the accommodation reflex or merely part of the duodenogastric feedback mechanisms to slow down gastric emptying upon duodenal exposure to calories.

In the present study we compared the ability of different triggering sites to induce gastric accommodation and demonstrated significant differences in the size of meal-induced accommodation under these conditions. To block duodenal passage and for duodenal perfusion studies, we used a nasointestinal feeding tube, an intestinal suction tube, and an intrapyloric balloon assembly. To decrease discomfort for the volunteers, these devices were only introduced in the relevant studies. Since we observed no significant differences between the MDP and the intraballoon volumes before the respective challenges, we assume that the presence of these assemblies had no influence on gastric tone, and it is therefore likely that they also had no influence on gastric accommodation.

We found no evidence for significant involvement of a cephalic phase in the control of proximal stomach tone. This is in contrast with earlier findings in which a similar intragastric pressure decrease was observed during intragastric nutrient drink infusion as during sham feeding (17). In that study, however, the observed intragastric decrease in intraballoon volume during sham feeding was of short duration, and it is uncertain whether the intragastric pressure measured is relevant for the gastric accommodation that can be measured with a barostat balloon. The cephalic phase of food ingestion includes a number of responses, including increased gastric acid secretion and release of peptide hormones (16, 31). A limitation of the present study is that we did not measure these responses as a positive control to confirm the effectiveness of the cephalic stimulus that was used. In contrast to cephalic activation alone, we found a significant gastric accommodation response to oropharyngeal (“sham feeding” protocol) and gastric exposure to an ingested meal (“gastric retention” protocol). Different mechanisms have been described that could induce stomach relaxation by using the gastric retention protocol, e.g., esophageal distension (10), proximal stomach distension (22), and antral distension (7), the setup of our experiments could not distinguish between these different mechanisms. Previously, dual intragastric balloon studies had identified antral distention-induced relaxation of the proximal stomach as a likely contributor to the gastric phase of the accommodation reflex (7), and the present study is in agreement with such a mechanism. The largest nutrient-induced proximal stomach relaxation occurred with normal oral ingestion of the meal, followed by intraduodenal nutrient infusion. The relaxation that occurred during a pyloric obstruction protocol was smaller than the control and duodenal infusion conditions. These data suggest that duodenal presence of nutrients is the strongest contributing trigger for the accommodation reflex.

However, the contribution of duodenal nutrient exposure should be interpreted with caution. Previous studies using duodenal stimulation to induce relaxation of the proximal stomach have been interpreted to reflect a duodenal phase of the accommodation reflex (4, 14, 15, 23, 34). Lipid digestion and subsequent release of cholecystokinin (CCK) and activation of CCK A receptors are considered key factors in these events (14, 15, 34). However, studies using an orally ingested meal could not confirm the importance of lipid digestion and CCK release (11, 29). These data suggest that the main factors contributing to the triggering of the gastric accommodation reflex do not necessarily involve CCK-mediated duodenal feedback and that much of the relaxation observed during intraduodenal nutrient infusion reflects negative feedback on gastric emptying of lipids.

In the presence of a balloon blocking gastric outflow, slow ingestion of a liquid meal was still able to induce a progressively increasing sensation of satiety. This observation indicates that nutrient accumulation in the stomach alone is able to induce a feeling of satiety and that duodenal nutrient exposure is not a prerequisite for the occurrence of meal-induced satiety. These findings are in agreement with previous observations that inflation of a balloon in the stomach is sufficient to induce sensations of fullness and satiation (13, 33) and with the use of an intragastric balloon as a modality to reduce hunger and food intake in obesity (25).

Previously, we demonstrated that impaired gastric accommodation in functional dyspepsia is associated with early satiety and weight loss (30). In a number of acute pharmacological studies, using a satiety drinking test, we were able to demonstrate that inhibition of gastric accommodation in healthy subjects is associated with earlier satiation and decreased tolerance of a nutrient load (9, 28, 29). The decreased nutrient tolerance during the pyloric outflow obstruction in the present study, compared with the control condition, is in line with these observations and adds further support to the hypothesis that impaired accommodation decreases tolerance of a nutrient load.

The present study design also has a number of limitations. First of all, we investigated factors involved in triggering gastric accommodation, with a focus on maximal relaxatory responses. We did not address duration and speed of recovery of nutrient-induced accommodation, which are important parameters that may contribute to tolerance and processing of an ingested meal. Furthermore, we did not identify factors and mechanisms through which the presence of nutrients in a given segment contributes to the accommodation reflex. These factors could be mechanical (like distension, pressure, or friction) or chemical (pH, osmolality, caloric content), and the mechanisms could be neural or hormonal. Studying these aspects is beyond the scope of the present paper and will require additional specific experiments.

In conclusion, we demonstrated in our experimental setup that the accommodation reflex in humans lacks a significant cephalic phase, but it can be activated from the oropharynx, the stomach, and the duodenum. Duodenal presence of nutrients seems to be the relatively strongest trigger for the gastric accommodation reflex in humans, induced by a standard nutrient meal. Blocking passage of nutrients to the duodenum decreases the amplitude of the accommodation reflex and is associated with earlier satiation, indicating that nutrient accumulation in the stomach alone is able to induce a feeling of satiety. The observation that multiple sites are involved in the
initiation of the accommodation reflex increases the number of pathophysiological abnormalities that may underlie or contribute to impaired accommodation in patients with dyspeptic symptoms. Unraveling these mechanisms should be a topic of future studies in patients with impaired accommodation.

REFERENCES