Interactions between gastric volume and duodenal nutrients in the control of liquid gastric emptying

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Abstract

Moran, Timothy H., James B. Wirth, Gary J. Schwartz, and Paul R. McHugh. Interactions between gastric volume and duodenal nutrients in the control of liquid gastric emptying. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R997–R1002, 1999.—We examined the relationships between gastric volume and duodenal glucose load in the regulation of gastric emptying in adult male rhesus monkeys. Intragastric glucose loads (0.125 g/ml) of volumes ranging from 150 to 375 ml empty from the stomach at the same rate from 20 to 120 min. However, to achieve these equivalent emptying rates, progressively larger volumes were emptied in the initial 20 min with increasing gastric volume. Duodenal glucose infusions dose dependently inhibited the 10-min emptying of various volumes of intragastric saline. Although increasing gastric volume resulted in increased emptying, duodenal glucose right-shifted the relationship between initial gastric volume and volume emptied. These data demonstrate that liquid nutrient gastric emptying represents an interaction between gastric volume and nutrient-induced duodenal feedback. For controlled duodenal caloric delivery rates to be established, sufficient nutrient emptying must occur to increase the magnitude of duodenal feedback to withhold a given gastric volume.

The regulation of the passage of ingested nutrients from the stomach to the small intestine is complex. Rates of gastric emptying depend on nutrient state (solid or liquid), macronutrient character, volume, and concentration (5, 7, 13, 15, 17). The gastric emptying of liquid nutrients has been examined in multiple species using a variety of techniques. Although the specific factors regulating emptying and the mechanisms through which these act are not all understood, a number of major contributing factors have been identified. Liquid nutrient emptying has two phases: a rapid initial volume-sensitive phase during and immediately after gastric fill and a subsequent slower phase of emptying that depends on the nutrient character and concentration (2, 8, 14, 15, 17).

In rhesus monkeys, a duodenal feedback inhibition on gastric emptying has been demonstrated. Intraduodenal glucose has been shown to inhibit the rapid emptying of physiological saline (0.9% NaCl) from the stomach and does so as a function of the total intraduodenal caloric load (16). For a given intragastric saline volume, the duration of inhibition of gastric emptying is linearly related to the magnitude of the load of intraduodenal glucose such that for 100-ml intragastric saline volumes, gastric emptying is inhibited for ~2.5 min per intraduodenal glucose kilocalorie (16). This is the reciprocal of the rate of nutrient delivery of glucose in these monkeys of 0.4 kcal/min during the linear phase of emptying (15).

These data demonstrate a role for intestinal nutrient content in the controlled rate of nutrient gastric emptying, but they do not address 1) how the rapid initial phase of emptying relates to the emptying during the slower phase or 2) the nature of the overall relationship between duodenal calories and gastric volume. In the present experiments, we examined the role of gastric volume in the regulation of nutrient gastric emptying. This was done in two ways. In the first experiment, we determined the contribution of the initial gastric volume of a glucose test meal to the rate of emptying during both the initial rapid and the subsequent slower phases. In the second experiment, we assessed the ability of various intestinal glucose loads to affect the rate of gastric emptying of various volumes of intraduodenal isotonic saline. The data demonstrate that the effect of a given intraduodenal load on gastric emptying depends on the initial gastric volume. These data suggest that the switch between the rapid and slow phases of liquid nutrient emptying is the point at which initial rapid gastric emptying has delivered a sufficient nutrient load to the duodenum to produce an inhibitory signal sufficient to withhold a particular gastric volume. With larger volumes, a greater duodenal inhibitory signal is required to produce this switch.

METHODS

The subjects were male rhesus monkeys (Macaca mulatta) weighing 5–9 kg. Monkeys were housed in individual cages and maintained on a 12:12-h light-dark cycle. Chronic indwelling gastric cannulas (Dow Corning) were surgically implanted in the most dependent portion of the stomach along the greater curvature as previously described (16). The cannula permitted the infusion into and withdrawal of liquids from the stomach. The cannula was exteriorized through a puncture wound in the back at the level of the stomach. Monkeys were maintained in light canvas jackets, and the cannula was protected by a multiflexible stainless steel cable attached to the vest that ran through the back of the cage.

The cable acted as a leash and only minimally restrained the animals. Access to the cannulas was at the back of the cage, and infusions and withdrawals could be done with only minimal disturbance to the animals. Monkeys were allowed to recover from surgery for 2 wk before testing. For the second experiment, a smaller Silastic cannula (Dow Corning 602–135, 0.02 in. ID, 0.037 in. OD) was threaded through the gastric cannula until the tip of the small cannula was 20 cm beyond the tip of the gastric cannula. The activity of the stomach carried the end of the small cannula through the
pylorus and into the duodenum over the course of several days.

Water was available ad libitum except during gastric emptying experiments. Food was available during the afternoon for 4 h per day. Monkeys adapted quickly to this feeding schedule and maintained normal rates of weight gain.

Gastric emptying experiments were carried out between 9:00 and 11:00 AM after at least a 16-h period of food deprivation. Thirty minutes before each gastric emptying experiment, the position of the duodenal cannula and the state of the stomach were checked. Two milliliters of concentrated phenol red solution were infused through the duodenal cannula, and 50 ml of isotonic saline (0.15 M NaCl) were infused through the gastric cannula. The gastric contents were immediately withdrawn and checked for the presence of phenol red and food. If the gastric contents were clear of phenol red, we concluded that the tip of the duodenal cannula was not in the stomach. Only if the withdrawn gastric contents contained no phenol red or food was an experiment carried out on that day. Only one experiment was done per day with any individual monkey.

In the initial experiment, 150-, 225-, 300-, or 375-ml loads of 0.125 g/ml glucose containing phenol red were rapidly instilled through the gastric cannula into the monkeys’ stomachs (~100 ml/min) beginning at time zero. At intervals of 20, 40, 60, 90, or 120 min, the volume remaining in the stomach was withdrawn, the stomachs were washed, and the volume of the initial test meal remaining was calculated. In each of four monkeys, volume remaining at each time point was ascertained for each initial gastric volume using the dye-dilution technique of Hunt and Spurrell (7). Data were analyzed by repeated-measures ANOVA. Emptying rates from 20 to 120 min and extrapolated y-intercepts were obtained using linear regression analyses.

In the second experiment, various volumes of 0.25 g/ml glucose were instilled into the duodenum, yielding 0, 3.75, 7.5, 15, or 30 kcal (duodenal infusion volumes were 0, 3.75, 7.5, 15, and 30 ml delivered at a rate of 3.75 ml/min). Immediately after the duodenal infusion, various volumes of isotonic saline containing phenol red as a marker were infused intragastrically at a rate of ~100 ml/min and left in place for 10 min. Gastric volumes were then withdrawn, and the volumes of saline remaining in the stomach were determined using the dye-dilution technique of Hunt and Spurrell (7). Because pilot experiments demonstrated that larger duodenal loads completely inhibited the emptying of smaller gastric volumes, the gastric volumes studied varied somewhat across the levels of intraduodenal calories such that only larger volumes were studied with the higher levels of intraduodenal calories (0–7.5 kcal: 150, 300, 400, and 500 ml; 15 kcal: 225, 300, 400 and 500 ml; 30 kcal: 300, 400, and 500 ml). The emptying of each gastric volume at each duodenal glucose load was examined twice for each monkey. Each data point for an initial gastric volume at each duodenal glucose load was further assessed by a comparison of the amount of glucose passed to the duodenum and the gastric volume remaining at the point at which controlled emptying is reached. Once this phase was reached, volume over the range tested (150–375 ml) no longer played a role in the emptying rate, as indicated by the parallel slopes in Fig. 1. The nature of the effect of volume on initial gastric emptying rate and the point at which controlled emptying is reached was further assessed by a comparison of the amount of glucose passed to the duodenum and the gastric volume remaining at the y-intercept. This comparison yielded a logarithmic relationship such that the magnitude of the volume remaining at the y-intercept was a linear function of the log of the amount of duodenal glucose (Fig. 3).

**RESULTS**

Experiment 1. As shown in Fig. 1, different initial volumes of 12.5% glucose ranging from 150 to 375 ml emptied from the stomach in linear parallel fashion during the slow phase from 20 to 120 min. Repeated-measures ANOVA across volumes and times revealed significant effects of both volume \(F(3,9) = 24.363, P < 0.0001\) and time \(F(4,12) = 43.553, P < 0.00001\) but no interaction between volume and time. That is, the rate of emptying from 20 to 120 min was the same for all initial volumes. At all volumes, the data fit to linear equations with slopes of ~1 ml/min emptied (150 ml: \(0.981 \pm 0.100, 225 ml: 1.065 \pm 0.112, 300 ml: 1.030 \pm 0.129, 375 ml: 1.120 \pm 0.197\)). Transforming the data to log of the amount of duodenal glucose revealed that there was a significant increase in the value of the y-intercept with increasing initial gastric volume \(F(3,9) = 7.104, P < 0.01\). The magnitude of this increase was constant for each increase in initial gastric volume, yielding a linear function (Fig. 2). For larger initial gastric volumes, a greater amount of glucose gastricemptying occurred before the controlled emptying phase was reached. Once this phase was reached, volume over the range tested (150–375 ml) no longer played a role in the emptying rate, as indicated by the parallel slopes in Fig. 1. The nature of the effect of volume on initial gastric emptying rate and the point at which controlled emptying is reached was further assessed by a comparison of the amount of glucose passed to the duodenum and the gastric volume remaining at the y-intercept. This comparison yielded a logarithmic relationship such that the magnitude of the volume remaining at the y-intercept was a linear function of the log of the amount of duodenal glucose (Fig. 3).

Experiment 2. Figure 4 plots the volumes emptied in 10 min for different initial gastric saline volumes with and without duodenal glucose infusions. In the absence of a duodenal glucose infusion, the volume of 300 mosmol saline emptied at 10 min increased with increasing initial gastric volume \(F(3,12) = 34.349, P < 0.0001\). Volume emptied was a linear function of the
initial gastric volume. A constant proportion of the infused volume emptied within 10 min for volumes ranging from 150 to 500 ml, resulting in a linear relationship of volume passed to initial gastric volume of the form volume emptied = 0.462(initial volume) + 42.2. The infusion of glucose into the duodenum before the infusion of the gastric saline load did not change the overall effect of initial volume on emptying; volume emptied continues to increase with initial gastric volume for all intestinal glucose loads, and the magnitude of increase with each increase in gastric volume also remained constant.

Slopes relating initial volume to volume emptied were not different from one another: 0 kcal = 0.462 ± 0.051; 3.75 kcal = 0.48 ± 0.034; 7.5 kcal = 0.475 ± 0.038; 15 kcal = 0.496 ± 0.059; 30 kcal = 0.559 ± 0.082. Increasing duodenal glucose loads did, however, result in a dose-dependent, parallel downward shift in the function relating volume emptied to initial gastric volume or change in y-intercept. Overall ANOVA of the data from initial gastric volumes of 300–500 ml (the gastric volumes that were run for all levels of duodenal glucose) resulted in significant effects for gastric load \[ F(2,8) = 49.788, P < 0.0001 \] and duodenal glucose load \[ F(4,12) = 23.167, P < 0.0001 \], but no significant interaction \[ F(8,24) = 0.813, P > 0.5 \].

From the linear regression equations, we calculated the extrapolated initial gastric volume at which no emptying would occur for each level of duodenal glucose. These values are the x-intercepts. These extrapolated values are plotted in Fig. 5 as a function of duodenal glucose caloric load. This comparison yielded a logarithmic relationship such that the x-intercept values, the initial volumes at which no emptying would occur, were linearly related to the log of the duodenal glucose calories.

**DISCUSSION**

The data collected in these experiments provide a number of insights into the interactions between gastric volume and duodenal nutrients in the control of gastric emptying. As demonstrated in experiment 1, gastric glucose meals over a physiological range of initial volumes empty from the stomach so as to deliver
a constant rate of calories to the duodenum over the majority of the emptying period. This result extends prior data in the rhesus monkey demonstrating similar rates of caloric emptying for glucose meals of 150 and 300 ml (15). Although volume does not affect emptying rate after the initial arbitrarily chosen 20 min time point, volume does play a role in the initial rapid rate of emptying. We do not have sufficient temporal resolution to identify the exact time period during which volume is the critical variable. However, extrapolation of the y-intercepts for the different emptying curves revealed that for increasing initial gastric volume a greater amount emptied before the period of controlled caloric emptying was achieved. This increase was linear and represented a constant proportion of the initial gastric volume (15%). These data demonstrating first-order kinetics over a range of volumes from 150 to 500 ml replicate previous findings in the dog over an eightfold range of 150–1,200 ml (13). Further extrapolation of the relationship between duodenal glucose and gastric volume at the hypothetical point at which controlled emptying was reached revealed that there was a linear relationship between the log of duodenal calories delivered and the gastric volume withheld.

Our data in the rhesus monkey are somewhat at odds with data examining the effect of volume on carbohydrate gastric emptying in humans. Hunt et al. (6), using a similar sampling technique, had demonstrated that although volume had its major effect during the initial 30-min emptying period, there remained a significant effect of volume from 30 to 120 min: greater meal volumes resulting in more rapid duodenal caloric delivery. The reason for this difference is unclear.

The second experiment was aimed at verifying the relationships revealed from the data from experiment 1. Rather than extrapolating from calories passed to the duodenum to gastric volume, we directly varied the duodenal glucose calories and assessed the effect on the gastric emptying of different volumes of physiological saline. In these results there was again a main effect for volume. As the initial gastric saline volume increased, a constant proportion was emptied within the 10-min experimental period. Beyond the initial 150-ml volume, for each increment in initial gastric volume ~50% emptied during the 10-min period. This was true in both the absence and presence of duodenal glucose. There was a main effect of duodenal glucose on saline emptying, but this was to change the position of the function rather than change the nature of the effect of additional volumes on emptying. Increasing duodenal glucose shifted the function relating initial volume to volume emptied to the right. For every doubling of duodenal calories there was an equivalent stepwise shift in this function such that the logarithm of duodenal calories was linearly related to the gastric volume withheld.

In this experiment, we derived the amount of duodenal glucose that would be predicted to result in the stomach completely maintaining its contents, i.e., zero emptying. This derivation allowed us to identify the nature of the relationship between duodenal glucose load and the gastric volume that would be withheld. Although Miller et al. (18) did not observe a complete inhibition of gastric emptying in response to distal duodenal nutrient infusions, we did find in preliminary studies that large duodenal glucose loads completely inhibited the gastric emptying of small gastric saline volumes during the 10-min test period. Thus we only used larger gastric loads in combination with the 15 and 30 kcal duodenal glucose infusions because none of an initial gastric volume of 150 ml emptied from the stomach with these duodenal loads. We have observed zero emptying under a variety of conditions in rhesus monkeys in these shorter time intervals (16, 19). For example, intravenous cholecystokinin infusion completely prevented a saline gastric load from emptying from the stomach for the duration of the cholecystokinin infusion (19).

In prior work, we had demonstrated a temporal negative feedback effect of duodenal glucose on the emptying of constant saline volumes from the stomach (16). That is, for every duodenal glucose calorie, saline emptying was inhibited for 2.5 min. The present work explores the relationship between the degree of duodenal feedback and the effect of increased intragastric volume at a single time point. These data reveal that the effect of duodenal glucose depends on the initial gastric volume: for any duodenal glucose load there is a corresponding gastric volume that will be withheld. We feel that the effect of duodenal glucose infusions is due to the caloric nature of the glucose. We have demonstrated previously that it was the total glucose load rather than the volume or the osmotic concentration of the load that determined the duration of the inhibitory feedback (16), and Lin et al. (11) have demonstrated that within the range of 0.25–1.0 M, the glucose concentration of intestinal infusions did not play a significant role in the regulation of gastric emptying in
dogs. It appears to be the length of intestine that is exposed to nutrient rather than the particular intestinal segment that determines the extent of feedback (11, 12). Additionally, there is a close relationship between the energy-dependent absorption of nutrients and the energy-dependent feedback inhibition on gastric emptying (24).

The data from the two experiments make a number of common points. In both cases, increasing the initial gastric volume results in a linear increase in the volume emptied at any time. Each increase in gastric volume is accompanied by an increase in emptying such that, over an extended range of volumes and for both saline and glucose, a constant proportion of the increased volume is emptied in the initial emptying period. This result is similar to the findings from the experiments of Kaplan et al. (10) examining gastric emptying during periods of gastric fill in rats. Their data demonstrate more rapid emptying during, as compared with after, fill and a constant rate of emptying throughout the entire period of gastric fill. This similarity suggests that the controls of emptying during the initial rush after the administration of a gastric volume by bolus and during gradual fill, simulating the rate of gastric fill during ingestion, are similar. During both of these periods, gastric volume is a major determinant of gastric emptying rate.

The present experiments also have the common finding of a linear relationship between the log of duodenal nutrient load and the corresponding gastric volume withheld. Liquid gastric emptying is thought to be the outcome of a coordination of relative contractile forces and pressure gradients (18) in the antrum, pylorus, and duodenum. Increasing gastric volume results in distention of the proximal stomach and an increase in corporeal and antral peristaltic contractions (4). Further increases in gastric volume do not affect antral activity but produce fundal distention and inhibition of fundal tone (1, 4). As emptying occurs, duodenal nutrients decrease both intragastric pressure and antral motor activity (3) and increase pyloric contractions (22). All of these actions result in decreased transpyloric flow, i.e., decreased gastric emptying. In contrast, nonnutrients will produce a distention of the duodenum that will result in greater fundic relaxation, allowing a greater gastric volume to accumulate and reducing the driving force for emptying. Duodenal nonnutrients will not affect antral peristaltic contractions, allowing rapid emptying to continue.

Perspectives

The present results elucidate the quantitative relationship between the feedback signals generated by duodenal nutrients and the propulsive signal produced by gastric volume. As the stomach fills, the duodenum is initially empty. The forces controlling emptying are all propulsive and related to gastric volume. As calories become available to the duodenum, a feedback inhibition on gastric emptying occurs, resulting in increased gastric capacity and decreased propulsive activity. Once a balance between volume-stimulated gastric propulsion and duodenal feedback is reached, regulated emptying occurs, resulting in a constant delivery of calories to the duodenum across nutrient type, ranges of gastric volumes, and caloric concentrations. There is evidence that some of the gastrointestinal substrates mediating gastric emptying during the gradual fill or immediately after bolus loading differ from those during subsequent controlled slower emptying. Vagotomy increases emptying during fill or in response to bolus loads but does not greatly affect subsequent emptying (9, 20). In contrast, keeping the pylorus open with a cannula in place has little effect on initial emptying characteristics (21). Although data such as these suggest differing relative importance of sensory and effector systems during the two phases of gastric emptying, it remains the case that the initial characteristics of emptying result in the establishment of a balance between gastric propulsion and duodenal feedback that allow the stomach to deliver its contents to the intestine in a regulated fashion, maintaining intraduodenal loads within the limits of nutrient absorptive capacity (23) and potentially providing signals for the ongoing control of food intake.

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