Gastric and duodenal features of meals mediate controls of liquid gastric emptying during fill in rhesus monkeys

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Moran, Timothy H., Susan Knipp, and Gary J. Schwartz. Gastric and duodenal features of meals mediate controls of liquid gastric emptying during fill in rhesus monkeys. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R1282–R1290, 1999.—To study the dynamics of liquid gastric emptying in rhesus monkeys under conditions that simulated gastric fill during a meal, we measured the gastric emptying of liquid glucose at various concentrations and volumes when administered intragastrically at rates ranging from 12.5 to 37.5 ml/min. Glucose gastric emptying was faster during than following the period of gastric fill. At a single glucose concentration, volume infused rather than the rate of filling determined the volume emptied. Lower glucose concentrations emptied more slowly than physiological saline. As glucose concentration increased, emptying during fill slowed. Duodenal glucose infusions greatly slowed the rate of saline emptying during fill, demonstrating duodenal feedback control. Although casein hydrolysate emptied more rapidly than glucose, the dynamics of volume and concentration dependency and the role of duodenal feedback were similar. These data reveal that both gastric volume and duodenal negative feedback controls important in gastric emptying following stomach filling also contribute to its control during fill.

Nutrient (13–16).

Glucose; casein hydrolysate; duodenal feedback

The mechanisms underlying the control of liquid gastric emptying have been extensively studied in a variety of species (1, 6, 14–16, 19). Liquid nutrient emptying of a bolus volume is characterized by an initial rapid exponential phase followed by a slower linear phase of emptying that, over a range of caloric concentrations up to a maximum, delivers calories to the duodenum at a constant rate (5, 7, 16). Emptying during the rapid initial phase is primarily volume dependent, although postpyloric feedback related to the nutrient concentration also plays a significant role (13, 15, 18, 20, 21). Emptying during the slow linear phase is dependent on intestinal feedback and is relatively independent of gastric volume and the type of nutrient (13–16).

Kaplan et al. (10) have pointed out that the controls of gastric emptying evident for a liquid meal delivered to the stomach by bolus do not adequately reveal the factors at play during the ingestion of a meal. They demonstrated that, in the rat, the controls on gastric emptying during the period that the stomach is filling are quite different from those following fill. When the stomach is filled at rates mimicking normal rates of ingestion, emptying is more rapid than following fill, occurs at a constant rate for the duration of the fill period, and, for glucose, is completely a function of the gastric volume independent of glucose concentration. These relationships hold whether the glucose is delivered intragastrically or is orally consumed (10). The controls of emptying during gastric fill as identified by Kaplan and colleagues (8–10) appear to differ from those governing the initial rapid phase of emptying following bolus delivery in that, during fill, only gastric volume is critical, whereas nutrient concentration and duodenal feedback are not important factors.

We and others have suggested that the nutrient controls of emptying provoke gastric and intestinal states that provide feedback signals important to the controls of food intake (3, 16, 17). Kaplan and colleagues (8–10) have pointed out that the nature of the controls of gastric emptying during the period that the stomach is filling will determine the degree of intestinal or gastric stimulation at any point during a meal and will, in turn, determine the potential range of feedback signals that could provide important information for meal termination.

To generalize the findings of Kaplan and colleagues to another species and to more fully characterize the factors controlling liquid gastric emptying during fill, we examined aspects of the controls of gastric emptying during fill in rhesus monkeys when the stomach was filled at rates that span their normal rates of liquid glucose ingestion (22). We compared rates of glucose gastric emptying during and following fill and independently evaluated the roles of infusion rate, infusion volume, and glucose concentration on the controls of gastric emptying during fill. We also examined the role of duodenal negative feedback on emptying during fill, and we have begun to assess the generalizability of the control factors by comparing the during-fill emptying of glucose and casein hydrolysate.

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. Water was available ad libitum except during gastric emptying experiments. Food was available during the afternoon for 4 h/day. Monkeys adapted quickly to this feeding schedule and maintained normal weights. Chronic indwelling gastric cannulas (Dow Corning, Midland, MI) were surgically implanted in the most dependent portion of the stomach along the greater curvature as previously described (18). The cannula permitted the infusion into and withdrawal of liquids from the stomach. For some experiments, a smaller Silastic cannula was threaded through the gastric cannula until the
tip of the small cannula was 20 cm beyond the tip of the gastric cannula as previously described (20). The natural motoric activity of the stomach carried the end of the small cannula through the pylorus and into the duodenum over the course of several days. The position of the duodenal cannula and the state of the stomach were checked daily before each gastric emptying experiment as previously described (20). Gastric emptying experiments were carried out between 9:00 and 11:00 AM after at least a 16-h period of food deprivation. All experiments were conducted with a repeated-measures design. All monkeys within an experiment received every testing condition. No particular testing sequence was followed. Monkeys were tested 5 days/wk, and only one experiment was done per day with any individual monkey. In the initial experiment, we attempted to replicate the basic phenomena demonstrated by Kaplan et al. (10) in the rat, that emptying during fill occurs at a more rapid rate than emptying following fill. Thus the differences between emptying during and following a glucose infusion were assessed in four monkeys. Loads of 75, 150, or 225 ml of 12.5% glucose (dextrose anhydrous [a-D-(+)-glucose], USB, Amersham containing phenol red were instilled through the gastric cannula into the stomachs of the monkeys at a rate of 25 ml/min beginning at time 0. At intervals of 0, 10, 20, and 40 min following the end of the infusion period, 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 and volume passed at each time point were ascertained for each initial gastric volume using the dye-dilution technique of Hunt and Spurrell (6). Emptying rates during fill and from the end of the infusion period to 40 min were obtained for each monkey using linear regression analyses. Emptying rates during and following fill were compared by repeated-measures ANOVA.

In the second experiment, the effect of gastric infusion rate on gastric emptying during fill was assessed (n = 4). Glucose (12.5 or 25%) in volumes of 75, 150, 225, 300, and 375 ml was infused at rates of 12.5, 25, or 37.5 ml/min. At the end of the infusion periods, remaining gastric volumes were then immediately withdrawn and the volumes remaining and volumes passed were calculated as above. Because of the different infusion rates, the duration of the infusion periods varied. The infusion periods for the various rates and volumes are shown in Table 1. Data from this experiment were analyzed in two ways. Initially, emptying rates during fill were calculated across the infusion volumes by linear regression for each infusion rate and concentration. Emptying rates were compared by repeated-measures ANOVA. Data were then expressed as volume emptied during fill as a function of volume infused at each infusion rate and glucose concentration. The effects of infusion rate, infused glucose concentration, and infused volume were then assessed by repeated-measures ANOVA for the volumes passed at each final infusion volume. As an additional assessment of the effect of infusion rate, we also compared the emptying of 12.5% glucose during a 25 ml/min infusion and during bolus infusion ~100 ml/min (n = 5). Again, volumes of 75, 150, 225, 300, and 375 ml were infused. Gastric contents were withdrawn immediately at the end of the infusions. Volume emptied during fill for each infusion volume was analyzed by repeated-measures ANOVA for the factors of infusion rate and volume. Because the results of the second experiment revealed that for any gastric infusion volume, infusion rate did not affect the volume emptied, we examined the effect of glucose concentration on emptying when the infusion rate was held constant. In the third experiment, the effect of glucose concentration on emptying during fill was more thoroughly assessed (n = 4). Glucose in concentrations of 0 (physiological saline), 3.125, 6.25, 12.5, and 25% was infused at a single rate of 25 ml/min. The volumes infused were 75, 150, 225, 300, and 375 ml. At the end of the infusion period, the volume remaining in the stomach was withdrawn, the stomach was washed, and the volumes remaining and passed were calculated as above. Volumes emptied for each infusion volume were analyzed by repeated-measures ANOVA for the factors of infusion concentration and infusion volumes. Planned t-comparisons were used to assess significant differences among concentrations. Data were also analyzed by ANOVA in terms of grams of glucose emptied as a function of infusion volume and glucose concentration. Again, planned t-comparisons were used to assess differences among glucose concentrations.

In the fourth experiment, the role of duodenal feedback on emptying during fill was assessed (n = 4). Duodenal cannulas were threaded through the gastric cannulas and allowed time for the tip to migrate to the duodenum. In these experiments, we evaluated the effect of duodenal glucose or saline infusions on the emptying of physiological saline during fill. The duodenal glucose or saline was infused at rates mimicking those normally emptied during fill when glucose was infused intragastrically. Thus we compared the emptying of 25 ml/min physiological saline at volumes of 75, 150, 225, 300, and 375 ml with and without a concurrent duodenal infusion of 5 ml/min 6.25% glucose or saline and with and without a duodenal infusion of 2.65 ml/min 25% glucose. These data were also compared with those obtained when the matching glucose concentration was infused intragastrically across the volumes of 75-375 ml in the absence of any duodenal infusion. Data were compared by separate ANOVA for the two duodenal glucose infusions across the four conditions: intragastric saline, intragastric saline plus intraduodenal saline, intragastric glucose, and intragastric saline plus intraduodenal glucose. Individual differences were assessed by planned t-comparisons. In the final experiment, the dynamics of the emptying of casein hydrolysate (enzymatic digestion, USB, Amersham, Arlington Heights, IL) during fill were examined in four monkeys. Casein hydrolysate and glucose were infused in concentrations of 12.5 and 25% at a rate of 25 ml/min. Again, the volumes infused were 75, 150, 225, 300, and 375 ml. At the end of the infusion period, the volume remaining in the stomach was withdrawn, the stomach was washed, and the volumes remaining and passed were calculated as above. The emptying of casein hydrolysate and glucose were compared by repeated-measures ANOVA for the factors of infusion type, concentration, and volume. As in experiment 4, we also examined the effect of a duodenal casein hydrolysate infusion on saline emptying during fill. Twenty-five percent casein hydrolysate was infused into the duodenum at a rate equal to that used for 25% glucose (2.65 ml/min), whereas saline was infused into the stomach at a rate of 25 ml/min. Infusions continued for 3, 6, 9, 12, or 15 min for total saline volumes of 75, 150, 225, 300, and 375 ml. Data were analyzed

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Table 1. Infusion durations for varying infusion rates and volumes

<table>
<thead>
<tr>
<th>Infusion rate</th>
<th>Volumes, ml</th>
<th>75</th>
<th>150</th>
<th>225</th>
<th>300</th>
<th>375</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 ml/min</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>25 ml/min</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>37.5 ml/min</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
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</table>

Data are in minutes.
by ANOVA comparing emptying during fill of intragastric saline alone, 25% intragastric casein hydrolysate, and intragastric saline plus intraduodenal casein hydrolysate. Individual differences were assessed by planned t-comparisons.

RESULTS

The first experiment contrasted gastric emptying during and following a period of filling. The results indicated that when the stomach was filled with 12.5% glucose at a rate of 25 ml/min, the emptying during the period of fill was significantly faster than that obtained following fill \[ F(1,3) = 39.084, P < 0.01 \]. As demonstrated in Fig. 1, when the stomach was emptied at the end of the infusion of volumes of 75, 150, and 225 ml, the rate of emptying obtained was linear and emptying occurred at a rate of 4.4 ml/min. After fill, the rates of emptying were slower, ranging from 0.90 to 1.07 ml/min, but they were again linear, and the initial volume did not significantly affect the rate of emptying following fill \[ F(2,6) = 1.15, P > 0.37 \], e.g., the emptying curves during the postfill period were parallel.

The remaining experiments focused on the controls of emptying during the period of gastric fill. Experiment 2 examined the effect of infusion rate on the rate of emptying during fill. As demonstrated in Fig. 2, varying the infusion rate from 12.5 to 37.5 ml/min significantly affected the rate of emptying during fill for both the 12.5 and 25% glucose \[ F(2,6) = 8.945, P < 0.016 \]. The more rapid the infusion rate, the more rapid the rate of emptying. However, when the data are expressed as volume emptied per volume infused, the total volume infused and the glucose concentration affected the volume emptied, whereas varying the infusion rate from 12.5 to 37.5 ml/min did not (Fig. 3). Results of the three-way repeated-measures ANOVA indicated a significant effect of infusion volume \[ F(4,12) = 36.512, P < 0.0001 \] on volume emptied. There was no significant effect of the rate of infusion across a range of 12.5 to 37.5 ml/min on emptying during fill \[ F(2,6) = 1.036, P > 0.41 \] at glucose concentrations of 12.5 or 25%. However, glucose concentration had a significant effect on emptying rate during fill \[ F(1,3) = 173.296, P < 0.001 \], i.e., more concentrated glucose emptied more slowly. Finally, there was no interaction of infusion rate with infusion concentration \[ F(2,6) = 0.083, P > 0.92 \]. Thus

![Fig. 1. Glucose gastric emptying during and following gastric fill at a rate of 25 ml/min for 3 final gastric volumes: 75, 150, and 225 ml. Emptying was measured immediately following and 10, 20, and 40 min after the gastric infusion.](image1)

![Fig. 2. Rates of gastric emptying during gastric fill up to final volumes of 375 ml when the stomach is filled with 12.5 or 25% glucose at infusion rates of 12.5, 25, and 37.5 ml. Volumes remaining were measured following infusions of 75, 150, 225, 300, and 375 ml, and emptying rates were calculated by linear regression. Increasing infusion rate increased the rate of emptying. †Significant difference from 12.5 ml/min infusion rate; §significant difference from 25 ml/min infusion rate; *significant difference from emptying rate with 12.5% glucose.](image2)

![Fig. 3. Volumes emptied at different infusion volumes of 12.5 and 25% glucose given at rates of 12.5, 25, and 37.5 ml/min. For either glucose concentration, volume infused rather than infusion rate determined volume emptied.](image3)
in this experiment, the amount emptied during fill at any initial volume infused was a function of the total volume infused and its concentration but did not depend on the infusion rate up to rates of 37.5 ml/min. However, as demonstrated in Fig. 4, infusion rate can affect the emptying when the infusion rate becomes very large as with a bolus infusion. ANOVA of the volumes emptied at different infusion volumes demonstrated a significant effect of the infusion rate [F(1, 4) = 16.861, P < 0.015], infusion volume [F(4, 16) = 589.423, P < 0.0001], and a significant rate by volume interaction [F(4, 16) = 5.747, P < 0.005]. A significantly greater proportion of the infused volume emptied during the bolus infusion than during the 25 ml/min infusion. This occurred despite the longer time over which the 25 ml/min infusion was given.

The effect of glucose concentration on emptying during fill was more completely assessed in experiment 3. Because the results of experiment 2 demonstrated no effect of rate of infusion over a range of 12.5 to 37.5 ml/min, we chose a single infusion rate of 25 ml/min to assess the effect of glucose concentration. As shown in Fig. 5, there was an overall effect of glucose concentration on the volume emptied during fill [F(4, 12) = 46.11, P < 0.0001]. There was a significant effect of volume [F(4, 12) = 101,259, P < 0.0001] and a significant concentration by volume interaction [F(16, 48) = 16.405, P < 0.0001]. Saline emptied more rapidly than any glucose concentration (P < 0.01), and as glucose concentration increased from 3.125 to 25%, the rate of emptying decreased. However, the decrease in the rate of emptying for increasing glucose concentration was not sufficient to compensate for the change in glucose concentration, e.g., emptying slowed but not enough to result in a constant rate of glucose delivery. As shown in Fig. 6, when the data are plotted as grams of glucose emptied as a function of the volume and glucose concentration infused, increases in glucose concentration resulted in more glucose emptying [F(3, 9) = 24.487, P < 0.0001]. Whereas the amounts of glucose passed for the 3.125 and 6.25% concentrations did not differ (P > 0.05), the rate of glucose emptying increased in a dose-dependent manner for higher concentrations (P < 0.05). Thus both volume and glucose concentration contribute to the rate of emptying during fill. Figure 7 shows a comparison of the actual emptying rates during fill across glucose concentration to hypothetical rates that would occur if emptying rate were either completely volume or concentration dependent. The actual emptying rates are different from both, but
concentration appears to play a greater role than volume in determining the rate of emptying during fill. Experiment 4 was aimed at identifying a role for duodenal feedback in gastric emptying during fill. Intraduodenal glucose infusions at rates mimicking those that would normally empty during fill exerted a profound inhibitory effect on saline emptying during fill (Fig. 8). ANOVA comparing the effect of intraduodenal saline and 6.25% intraduodenal glucose on saline emptying demonstrated an overall significant effect of experimental condition \[ F(3,9) = 708.741, P < 0.0001 \], and a significant condition by volume interaction \[ F(12,36) = 23.337, P < 0.0001 \]. Duodenal saline infusion significantly affected saline emptying during fill \( P < 0.05 \), although the effect was small and only evident at the 150- and 375-ml volumes. Duodenal infusion of 6.25% glucose at a rate of 5 ml/min significantly inhibited the emptying at all infusions of 150 ml and greater \( P < 0.01 \), but the volumes emptied were significantly greater than those obtained when 6.25% glucose was infused intragastrically \( P < 0.01 \). The results for duodenal infusion of 25% glucose were somewhat different. Again, there was a significant effect of experimental condition \[ F(3,9) = 968.163, P < 0.0001 \] and a significant condition by volume interaction \[ F(12,36) = 40.158, P < 0.0001 \]. Duodenal infusion of 25% glucose at a rate of 2.7 ml/min significantly slowed saline emptying during fill \( P < 0.01 \) and did so to the rate at which gastrically infused 25% glucose would normally empty. There were no differences in the emptying of saline when 25% glucose was infused into the duodenum and the emptying of 25% glucose when it was infused intragastrically.

Experiment 5 compared the emptying of glucose and casein hydrolysate during gastric fill. Similar characteristics of emptying during fill as those demonstrated above for glucose were found for casein hydrolysate. As shown in Fig. 9, increasing the duration (volume) of the infusion resulted in a linear increase in the amount emptied for both 12.5 and 25% casein hydrolysate \[ F(4,8) = 17.093, P < 0.001 \]. Doubling the casein hydrolysate concentration from 12.5 to 25% resulted in a significant slowing of emptying during fill \( P < 0.01 \). Figure 9 compares the emptying of glucose and casein hydrolysate.
casein hydrolysate and glucose at 12.5 and 25% concentrations at the same infusion rate. Casein hydrolysate empties more rapidly than glucose, as indicated by a significant macronutrient by volume interaction [F(4, 12) = 4.410, P < 0.02]. Unlike glucose, increasing the casein hydrolysate concentration from 12.5 to 25% resulted in sufficient slowing to compensate for the increased casein hydrolysate concentration so that the rate of casein hydrolysate delivery for the two concentrations was the same (Fig. 10).

Figure 11 demonstrates the effect of an intraduodenal casein hydrolysate infusion on the emptying of saline during fill. In this experiment, there was an overall effect of infusion condition on emptying [F(2, 6) = 3065.9, P < 0.0001]. Duodenal infusion of 25% casein hydrolysate at a rate of 2.65 ml/min significantly slowed the rate of saline emptying during fill (P < 0.01). However, unlike the results for intraduodenal 25% glucose above, casein hydrolysate infused at this rate did not slow saline emptying to the rate that this concentration of casein hydrolysate empties during fill. The emptying of intragastric casein hydrolysate was significantly slower than the emptying of intragastric saline in the presence of intraduodenal casein hydrolysate (P < 0.01).

**DISCUSSION**

The results of these experiments characterize the gastric emptying of glucose solutions that are infused into the stomach at rates that mimic the rates at which such solutions would normally be consumed. As shown in experiment 1, emptying during the period of gastric filling occurs at a much more rapid rate than following infusion termination. During fill, 12.5% glucose empties at a rate of >4 ml/min, whereas following infusion termination, the rate of emptying slows to ~1 ml/min. During the period that the stomach was being filled, a constant proportion of the infused volumes emptied and this proportion remained the same for the duration of the infusion. As demonstrated in subsequent experiments, a constant proportion of infused glucose emptied during the infusion period, even when the range of glucose infusion volumes was extended to 375 ml. Thus emptying rate during the period of gastric fill remains constant for the duration of the infusion.

The rate of infusion over a threefold range from 12.5 to 37.5 ml/min did affect the emptying rate (Fig. 2) but did so such that for any final infusion volume the same amount emptied at the three infusion rates (Fig. 3). Faster infusions empty more rapidly so that for any final infusion volume, the volume emptied remains constant. This occurred despite a threefold difference in infusion duration for the different infusion rates. Bolus delivery did result in significantly more emptied per volume infused than emptied when the stomach was filled at rates approximating those that occur when the monkey is consuming glucose (Fig. 4). Increased emptying during bolus delivery occurred despite the shorter infusion duration.

The findings of more rapid emptying during than following fill, constant emptying rate for the duration of the infusion, and a lack of an effect of infusion rate replicate the findings of Kaplan and colleagues in the rat (9, 10). However, unlike the results of Kaplan et al. (10) in rats, glucose concentration greatly affected emptying during fill in the monkey. This was evident in a number of ways. First, saline emptied much more rapidly than any of the glucose concentrations tested, including 3.125%, which is hypoosmotic compared with physiological saline. Saline and glucose emptying were not compared in the Kaplan experiments (8–10). Second, whereas infusion rate did not affect emptying in experiment 2, increasing glucose concentration from
12.5 to 25% did. The higher concentration solution emptied more slowly than the lower concentration. Finally, as shown in experiment 3, increasing glucose concentration across a range of 3.125 to 25% produced a progressive slowing of gastric emptying during fill (Fig. 5). As shown in Fig. 7, rates of emptying during fill more closely approximated those that would be expected if glucose delivery were held constant than if volume delivery were the controlled variable. However, unlike the effect of glucose concentration following fill (16), the progressive slowing with increasing concentration was not sufficient to keep glucose emptying constant. More glucose emptied at each final gastric volume for higher than for lower glucose concentrations (Fig. 6).

Slower gastric emptying with increasing glucose concentration depends on duodenal feedback in the control of gastric emptying following fill (11, 12). To assess the role of duodenal feedback in the control of emptying during fill, we examined the effect of duodenal saline and glucose infusions on the gastric emptying of different volumes of physiological saline. For these experiments, we infused either 6.25 or 25% glucose into the duodenum at rates at which these concentrations normally emptied during fill as found in experiment 3 (5 and 2.65 ml/min, respectively). Duodenal saline was infused at the infusion rate of the 6.25% glucose. Duodenal saline infusion had a small but significant effect on saline emptying during fill. It is important to point out that the combination of the duodenal infusion and the saline emptying during fill combined to increase the total duodenal volume. In the saline duodenal infusion condition, this increase appears to have been sufficient to exert a small inhibitory effect on emptying at two of the five gastric volumes (150 and 375 ml). In contrast to the minor effect of duodenal saline, infusing glucose into the duodenum had a profound inhibitory effect on saline gastric emptying during fill at all gastric volumes tested. At the lower 6.25% concentration, duodenal glucose infusion slowed the rate of saline emptying from >17 ml/min to <8 ml/min (Fig. 8). This represents a significant inhibition but does not quite match the even slower rate at which this concentration of glucose would normally empty from the stomach during fill (~5 ml/min). At the higher duodenal glucose concentration, saline emptying was slowed to a rate of ~2.65 ml/min, which matches the rate of gastric emptying for this glucose concentration that occurs during gastric fill. Therefore, at this concentration, duodenal glucose provided the sufficient stimulus to completely account for the emptying rate of gastric glucose during fill. This occurred despite the fact that the emptied saline doubled the duodenal volume and diluted the infused glucose by a factor of two. Thus the total duodenal glucose load, rather than the volume or concentration, appears to be critical. This is a similar result to that found in previous experiments examining other aspects of duodenal feedback control on gastric emptying (11, 18, 21).

The dynamics of casein hydrolysate emptying during fill were similar to those found for glucose. Casein hydrolysate emptied at a more rapid rate during fill than what we previously demonstrated following fill (16). The rate of casein hydrolysate emptying remained essentially constant for the duration of the infusion. However, casein hydrolysate emptied more rapidly than isocaloric glucose, and this more rapid emptying was evident at both the 12.5 and 25% concentrations. This result of more rapid casein hydrolysate emptying contrasts to what we previously demonstrated following fill (16). In those experiments, 12.5% glucose and casein hydrolysate emptied at the same rate. In contrast to the lack of full compensation for increasing concentration with glucose, doubling the casein hydrolysate concentration from 12.5 to 25% reduced the emptying rate by one half, such that, during fill, casein hydrolysate was delivered to the duodenum at the same rate for the two concentrations (Fig. 10). Why glucose and casein hydrolysate emptying during fill differ in these ways is unclear.

Duodenal casein hydrolysate infusion significantly affected the rate of saline emptying during fill (Fig. 11). Saline gastric emptying in the presence of the duodenal casein hydrolysate infusion was not as slow as the emptying of intragastric 25% casein hydrolysate. This may be a factor of the rate of duodenal casein hydrolysate delivery. The rate of the duodenal casein hydrolysate infusion was chosen based on what had been used in the glucose experiment. Because casein hydrolysate emptying during fill occurs at a more rapid rate than glucose emptying during fill, the duodenal infusion rate of 2.65 ml/min did not approximate the more rapid casein hydrolysate emptying rate of ~4 ml/min. Therefore, although a role for duodenal feedback in the emptying of casein hydrolysate during fill is demonstrated, we do not know whether duodenal feedback completely accounts for the casein hydrolysate emptying rate during fill.

Overall, these data generalize aspects of the phenomena originally described on gastric emptying during fill in the rat by Kaplan and colleagues (8–10) to the monkey. Gastric emptying during fill has very different dynamics than emptying following fill. Emptying during the period in which the stomach is filling occurs at a faster rate, and that rate remains constant for the duration of the infusion. In previous work with bolus infusions, we demonstrated a relationship between duodenal nutrient content and gastric volume characterized by a dynamic interaction between gastric volume as a driving force and duodenal nutrients as an inhibitory brake (21). For any gastric saline volume, the magnitude of a duodenal nutrient load determines the volume that will be emptied from the stomach within a 10-min period. These data have been interpreted to imply that gastric propulsive forces related to gastric volume are balanced off by duodenal negative feedback (20). The current results both reinforce and expand on this perspective. As the stomach fills at rates comparable to those that would normally occur with liquid nutrient ingestion, gastric volume is constantly increasing and a portion of that volume passes to the duodenum. The nutrient content generates a duodenal...
feedback signal that determines the proportion of the infused volume that passes the pylorus. Different proportions of the infused volumes passed depending on the glucose concentration (lower proportions for higher concentrations).

We infer that the duodenal feedback signal at anytime is sufficient to "hold back" the gastric volume that led to that duodenal signal. As stomach filling continues, the magnitude of the gastric signal increases, allowing the high rate of emptying to continue. When stomach filling stops, the rate of emptying rapidly slows. At this point, for gastric concentrations up to 25% glucose, emptying occurs at a rate such that a constant delivery of calories to the duodenum occurs. If, instead, stomach filling continues, the gastric signal continues to outweigh the duodenal feedback signal and more rapid emptying continues.

As stated above, the dynamics of emptying during fill in the monkey exhibit an important difference from what has been demonstrated in the rat. In the monkey, as glucose or casein hydrolysate concentration increases, emptying during fill slows. In the rat, volume, rather than concentration, is the critical control feature; for any glucose concentration (from 6.25 to 25%), a constant proportion of the glucose infusion (1/3 or more) empties during the fill period. Kaplan et al. (8) stated that there is no evidence for a feedback regulatory control on emptying during fill in the rat. Our data demonstrating progressive slowing of emptying during fill with increasing glucose concentrations and the ability of duodenal glucose to greatly slow the emptying of gastric saline provide strong evidence for such feedback control in the monkey.

An important consideration in interpreting these data is that, although the infusions were given at rates similar to those at which the monkeys consume liquid nutrients, these were intragastric infusions. The solutions were not tasted or swallowed. In experiments with rats, Kaplan et al. (8) have compared the emptying of liquid nutrients that are either infused intraorally or intragastrically. Oral glucose infusions empty at the same rate as gastric glucose infusions. In contrast, intragastric corn oil emulsions empty much more rapidly than intraoral corn oil, suggesting that some controls may be bypassed by the gastric infusion. We do not yet know whether intragastrically infused and orally consumed glucose would empty with similar dynamics in the monkey. However, recent data from Cecil et al. (2) suggest that the difference between gastric emptying of oral versus gastric fat loads in rodents also applies to human primates. They demonstrated that a fat-containing soup meal empties more slowly than either covertly or overtly delivered intragastric loads of the same soup meal.

Perspectives

If the distribution of nutrients within the gastrointestinal tract is important for the generation of within-meal satiety signals, the rate of nutrient emptying within a meal becomes a critical variable (10). In prior conceptualizations of gastric and intestinal feedback signals, we assumed that the gastric emptying controls demonstrated when the stomach was filled by a bolus infusion also operated during the period when ingestion was occurring (16, 17). The demonstrations of Kaplan and colleagues (8–10) and the present data of different emptying dynamics during and following fill provide an important caution to this view. During ingestion of a liquid meal, emptying is much more rapid than following meal termination. During this period, calories are not delivered to the intestine at a constant rate regardless of gastric volume. In both the rat and the primate, as the rate of gastric filling increases, the rate of emptying increases. Therefore, to provide an accurate view of the nutrient content of a consumed liquid meal, we propose that three features should be ideally monitored: 1) the rate of intestinal nutrient delivery, 2) how that rate changes over the course of a meal, and 3) the rate of gastric volume increase during a meal.

Finally, it is important to point out that our conclusions apply to liquid meals and may not be relevant to mixed meals consisting of solids and liquids. Significant emptying of solids does not occur during ingestion and only occurs when food particles have been sufficiently broken down. Although within a mixed meal, liquids empty much more rapidly than solids, the presence of nutrient solids in the stomach slows the rate at which liquid nutrients empty (4). Thus emptying of mixed meals during ingestion may occur with very different dynamics.

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