Calories and gastric emptying: a regulatory capacity with implications for feeding

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McHugh, Paul R., and Timothy H. Moran. Calories and gastric emptying: a regulatory capacity with implications for feeding. Am. J. Physiol. 236(5): R254–R260, 1979 or Am. J. Physiol.: Regulatory Integrative Comp. Physiol. 5(3): R254–R260, 1979.—Gastric emptying in four unanesthetized male Macaca mulatta was studied with the serial test meal method of Hunt and Spurrell. Liquid meals were infused into the stomach through a chronic indwelling Silastic cannula. Saline meals emptied rapidly and exponentially. Doubling the volume of saline from 150 to 300 ml increased the emptying rate so that the half-life remained unchanged (15 min). The 150-ml glucose meals (0.05, 0.125, and 0.25 g/ml) emptied more slowly than saline, progressively more slowly with increasing concentrations (0.05–1.8, 0.125–0.78, and 0.25–0.37 ml/min) and linearly through most of their course. Doubling the volume of 0.125 g/ml-glucose meal did not change the rate of emptying. Converting grams of glucose to their caloric content, the emptying rate in kcal/min becomes constant (approx 0.4 kcal/min) in this range of concentrations. Isocaloric casein hydrolysate and medium-chain triglyceride oil meals at 0.5 kcal/ml empty at the same rate as glucose. The precision of this regulation is sufficient to give it a role in preabsorptive satiety and the control of caloric intake.

Behavior; regulation; Macaca mulatta; hunger; stomach; "preabsorptive" satiety

The concept that behavior serves to support the physiological integrity of the organism first emerged from the studies of Curt Richter. His “cafeteria” experiments demonstrated that feeding animals will seek and choose those nutrient constituents they need to maintain health, growth, and reproduction. Richter (20) said, “In the normal intact animal the maintenance of a constant internal environment depends not only on the physiological or chemical regulators but also on behavior...[and]...the effort to maintain a constant internal environment or homeostasis constitutes one of the most universal and powerful of all behavior urges or drives.” The discovery of physiological mechanisms linking the organism’s requirements and the homeostatic behaviors was the natural outcome of the Richterian concept. From it we appreciate such linkages as a role for angiotensin in thirst (13) and adrenocortical hormones in sodium appetite (18, 19).

Behavior regulates quantity as well as quality in nutrition. The exact mechanisms linking the alternations of hunger and satiety to the energy requirements of the organism are not identified despite the recognition of hypothalamic and visceral sites of influence. However, the regulation is not difficult to demonstrate. We (15, 16) have shown that in rhesus monkeys the quantity of food eaten each day is controlled, increasing or decreasing in response to deprivation or surfeit so that the mean daily caloric intake remains stable.

Precision in this regulation is demonstrable by infusing liquid nutrients into the stomach prior to feeding periods. In response the monkey will reduce the food it eats by an amount comparable to the caloric content of the infused “preload” maintaining total caloric intake constant. It does so with accuracy across a range of calories in the infusion (0–300 kcal) and equally well for infusions of carbohydrate, fat, and protein.

An intriguing aspect of this precise regulatory response can be discerned when an infusion given just prior to a feeding period is followed by x ray (15, 16). Infusions of 150 kcal are not completely emptied from the monkey’s stomach at the end of a 4-h feeding period. Despite this the reduction in feeding is 150 kcal. A gastrointestinal role in the caloric regulation of feeding and in the onset of satiation would appear necessary to provide the animal a means of estimating and responding with precision to the energy in the unabsorbed intestinal contents.

Some visceral mechanisms in satiety have been suggested. Cannon and Washburn (2), demonstrating that gastric distension can interrupt feeding, proposed that the stretching of the stomach induced by food within it is an important signal to satiety. Gibbs et al. (5, 6), demonstrating that cholecystokinin, a gut hormone released by nutrients entering the small bowel interrupted feeding in rats and monkeys, proposed that this hormone acts as a satiety signal.

Each of these visceral mechanisms could produce a satiation effect in feeding before all ingested nutrients were absorbed from the gut. However with none of these proposals with the potential for “preabsorptive” satiety has any connection to the energy in food been demonstrated. If animals can regulate their caloric intake with accuracy before absorbing all the calories they have ingested then some quantitative linkages between intraintestinal calories and the mechanisms inducing satiety must exist.

Important preliminary evidence of such a relationship was reported by Hunt and Stubbs (10). These investigators by means of a retrospective study of previously...
published experiments in man recognized a slowing of gastric emptying with increasing caloric density of meals. The linkage between gastric emptying and calories did not seem to provide a regulatory capacity since the slowing of gastric emptying as caloric concentration increased was not sufficient to make the flow of calories from the stomach constant. But their report suggested that gastric emptying is in some fashion tied to the energy content of nutrients. This relationship must be further explored because any demonstration of quantitative accuracy in the function of this organ to the caloric content of ingested foods might form a mechanism for precision of preabsorptive satiety and the regulation of caloric ingestion.

Consequently we have directly examined gastric emptying in the rhesus monkey by employing gastric infusions of liquid meals of varying concentration of calories and varying nutrient constituents. In this series of experiments we sought information on four points: 1) is there caloric regulation of gastric emptying in rhesus monkeys; 2) over what range of energy densities, if any, is there a stabilization of energy delivery to the duodenum; 3) can isocaloric concentrations of carbohydrate, protein, and fat produce equal gastric slowing in the monkey; and 4) is the precision of any demonstrated control sufficient to give it a possible role in feeding where behavior regulates energy intake? Preliminary reports of these findings have been presented (14, 17).

METHODS

The experimental animals were four male *Macaca mulatta* weighing between 6 and 8 kg. They were housed in individual cages and had access to food in the form of monkey chow in a fashion different from saline. Even for the concentration osmotically comparable to physiologic saline the emptying of glucose is slower (saline 4.25 and glucose 1.81 ml/min) and more linear. This latter feature is displayed in Fig. 3 where the emptying curves of 150 kcal/g casein and 9 kcal/g for MCT. Osmolarity of appropriate meals was measured with the vapor pressure osmometer.

Results were analyzed using the least-squares linear regression method.

RESULTS

All results are summarized in Table 1 where the rates of emptying of the test meals can be compared.

**Physiologic saline (287 mosmol/L).** As shown in Fig. 1, test meals of physiologic saline (NaCl 0.9%) empty rapidly and exponentially from the monkey's stomach. Increasing the volume of the test meal from 150 to 300 ml increases the rate of emptying. The logarithmic display (Fig. 2) reveals parallel log regression lines with essentially identical half-lives. These saline emptying curves conform to an exponential (first-order kinetic) equation with a significance level of P < 0.001.

**Glucose.** Test meals of glucose empty from the stomach in a fashion different from saline. Even for the concentration osmotically comparable to physiologic saline the emptying of glucose is slower (saline 4.25 and glucose 1.81 ml/min) and more linear. This latter feature is displayed in Fig. 3 where the emptying curves of 150 kcal/g casein and 9 kcal/g for MCT. Osmolarity of appropriate meals was measured with the vapor pressure osmometer.

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**TABLE 1. Rates of gastric emptying of experimental meals**

<table>
<thead>
<tr>
<th>n</th>
<th>Meal</th>
<th>Caloric Content, kcal/ml</th>
<th>Vol, ml</th>
<th>Osmolality, mosmol/kg</th>
<th>Empting Rate, ml/min</th>
<th>Emptying Rate, kcal/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Saline</td>
<td>150</td>
<td>286</td>
<td>4.25</td>
<td>±0.577</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Saline</td>
<td>300</td>
<td>286</td>
<td>6.82</td>
<td>±0.926</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Glucose</td>
<td>0.2</td>
<td>150</td>
<td>272</td>
<td>1.814</td>
<td>0.363</td>
</tr>
<tr>
<td>32</td>
<td>Glucose</td>
<td>0.5</td>
<td>150</td>
<td>682</td>
<td>0.783</td>
<td>0.391</td>
</tr>
<tr>
<td>26</td>
<td>Glucose</td>
<td>1.0</td>
<td>150</td>
<td>1,364</td>
<td>±0.121</td>
<td>±0.024</td>
</tr>
<tr>
<td>18</td>
<td>Glucose</td>
<td>1.33</td>
<td>150</td>
<td>1,819</td>
<td>0.348</td>
<td>0.452</td>
</tr>
<tr>
<td>23</td>
<td>Glucose</td>
<td>2.0</td>
<td>150</td>
<td>2,728</td>
<td>±0.023</td>
<td>±0.29</td>
</tr>
<tr>
<td>36</td>
<td>Glucose</td>
<td>0.5</td>
<td>300</td>
<td>682</td>
<td>0.847</td>
<td>0.423</td>
</tr>
<tr>
<td>16</td>
<td>Casein hydrolysate</td>
<td>0.5</td>
<td>150</td>
<td>839</td>
<td>0.771</td>
<td>0.385</td>
</tr>
<tr>
<td>16</td>
<td>MCT</td>
<td>0.5</td>
<td>150</td>
<td>839</td>
<td>0.758</td>
<td>0.377</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n</th>
<th>Number of test meals. P values refer to comparisons of emptying rate with change in meal volume for <em>glucose 0.5 kcal/ml</em> and <em>physiologic saline.</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td><em>P &gt; 0.2.</em></td>
</tr>
<tr>
<td>20</td>
<td><em>P &lt; 0.02.</em></td>
</tr>
</tbody>
</table>
FIG. 1. Gastric emptying of 150- and 300-ml physiological saline over time. Points are means ± SE.

FIG. 2. Semilogarithmic display of gastric emptying of 150- and 300-ml physiological saline. T<sub>1/2</sub>, half-life.

ml of glucose in concentrations of 0.05 g/ml (272 mosmol/l), 0.125 g/ml (682 mosmol/l), 0.25 g/ml (1,364 mosmol/l) are shown. From 20 min after their infusion these glucose meals empty in a manner conforming to a straight line (zero order kinetic) equation with a significance level of P < 0.001. Increasing the glucose concentration of test meals results in a progressively slower rate of gastric emptying.

A regulatory implication of this progressive slowing of emptying with increasing concentrations of glucose in the meals is revealed when attention is directed to meal calories emptied over time rather than meal volume emptied over time. The y-axis of Fig. 3 can be changed from meal volume remaining in the stomach to meal calories remaining. Figure 4 is the result. With each increase in concentration of glucose there is an increase in the total calories in the stomach and thus a progressive elevation in the initial value. However, the rate of emptying of these calories shown by the slope of these emptying curves is the same. The three curves are parallel.

Thus Figs. 3 and 4 reveal that within a range of concentrations of glucose from 0.2 to 1.0 kcal/ml the rate of emptying of 150 ml of glucose changes sufficiently with changing concentration to stabilize the delivery of calories to the small intestine. That is, the rate of emptying of glucose is such that the product of energy density (kcal/ml) and emptying rate (ml/min) gives a constant rate of emptying of energy (kcal/min) from the stomach (Table 1).

A similar regulatory implication appears in another difference between the gastric emptying of saline and glucose. Doubling the volume of saline from 150 to 300 ml increases its emptying rate and keeps "half-life" constant: an exponential characteristic (Figs. 1 and 2). In contrast doubling the volume of a glucose meal (0.5 kcal/ml) from 150 to 300 ml does not significantly (P > 0.2) change its emptying rate (Table 1). Figure 5 draws out the regulatory implication to be derived from the loss of this exponential characteristic to the doubling of volume by depicting it together with the slowing of gastric emptying produced by doubling the concentration of glucose in a meal. The slopes of the emptying curves of 0.5-kcal/ml meals are comparable at 150 and 300 ml so that these curves appear as parallel lines. The emptying curve of the 150-ml 1.0-kcal/ml meal is superimposed in Fig. 5. This meal empties more slowly than the 0.5-kcal/ml meals but just slow enough so that it is completely emptied from the stomach in the same time as the 300-ml 0.5-kcal/ml meal. Thus it appears that 150 kcal of glucose empty completely from the stomach in the same period of time whether these calories are given in meals of higher concentration and lower volume (150 ml at 1.0 kcal/ml) or lower concentration and greater volume (300 ml at 0.5 kcal/ml).

As shown in Fig. 6 and Table 1 when glucose concentration exceeds 1.0 kcal/ml, gastric emptying does not slow further. As a result with each increment in concentration above 1.0 kcal/ml, there is more rapid delivery of calories to the small bowel, i.e., a loss of regulation to caloric concentration.

Protein and lipid. To exclude the possibility that the feature controlling glucose emptying was coincidental to the nutrient content, we have examined the gastric emptying of nutrients of different chemical character but identical in caloric value. Isocaloric meals (150 ml at 0.5 kcal/ml) of casein hydrolysate and of a suspension of medium-chain triglyceride oil are compared in their gastric emptying with an isocaloric (150 ml at 0.5 kcal/ml) glucose meal in Fig. 7. The three regression lines of gastric emptying are superimposable. Isocaloric loads of three nutrient types (carbohydrate, protein, fat) empty from the stomach at the same rate (Table 1).

The results are summarized in Table 1. Saline empties exponentially and increasing its volume increases the rate of emptying. Glucose empties so as to maintain a constant rate of delivery of calories to the small intestine over a range of energy densities of 0.2–1.0 kcal/ml. Doubling the volume of a glucose meal does not significantly alter the rate of emptying. Isocaloric loads of carbohy-
From these data, it would appear that the rate of gastric emptying of liquid meals in rhesus monkeys is under the control of a regulatory system sensitive to some physical properties of nutrients associated with energy content. Nonnutrient physiologic saline empties in a different fashion, rapidly and exponentially, with the particular feature that the volume of infused saline affects the emptying rate while maintaining a constant half-life as first shown by Marbaix (12). With nutrient, the emptying is slower, the exponential character of saline emptying is replaced by a more linear one and the prominent effect of volume is lost. For meals within the range of 0.2–1 kcal/ml (the caloric density of most nutrients consumed by this primate in the wild) (13) the emptying is so controlled that the rates of delivery of

date, protein, and fat produce equal slowing of gastric emptying.

DISCUSSION

The method we have chosen to study gastric emptying is the traditional one—the serial test meal of Hunt and Spurrell (9). This method provides information about the emptying of the meal instilled and should be distinguished from the indicator-dilution method of George (4) that gives information about the total volume of gastric contents (meal plus secretion), without allowing any conclusions about the emptying rates of either meal or secretion specifically. It is the emptying of meals rather than total gastric contents that is our prime interest.
energy to the duodenum are equal (approx 0.4 kcal/min).

This finding differs from that of Hunt and Stubbs (10) who recognized slowing but not regulation in the emptying of calories. A distinction in method probably explains our differences. The linear emptying and caloric regulation is found only after filling the stomach. As the stomach is filled a sample of the infused meal regardless of concentration enters the duodenum and small intestine as a bolus of 20-30 ml (16, 22). The slowing of emptying follows this intestinal sampling of the gastric load. We can recognize this initial bolus both on x-ray (16) and from the fact that the linear regressions do not extrapolate back to intersect the y-axis at 150 ml, the infused volume, but fall below that point by 20-30 ml. If as with Hunt and Stubbs the time for a meal to be half emptied is employed as a measure of gastric emptying, the precision of regulation will be obscured by the unregulated calories in the initial bolus. Information on the dynamics of gastric emptying during the initial filling of the stomach is needed, but would not alter our point: within the

![FIG. 5. Emptying of 150 kcal of glucose in same time whether given in greater volume or in greater concentration. Meals of 0.5 kcal/ml (----); 1.0 kcal/ml meals (-----). ● lower line totals 150 ml and 75 kcals, upper line totals 300 ml and 150 kcal. ■ Line depicts meals totaling 150 ml and 150 kcal.]

![FIG. 6. Rates of gastric emptying of 150-ml glucose meals differing in caloric concentrations.](http://ajpregu.physiology.org/)

Downloaded from http://ajpregu.physiology.org/ by 10.220.33.3 on July 27, 2017
range 0.2–1.0 kcal/ml the change in the rate of gastric emptying produced by changing the caloric concentration of liquid meals makes the rate of entry of calories into the small bowel equal for all these meals over a substantial portion of their emptying periods.

The mechanisms that lead to the changes in gastric emptying with nutrients are not presently elucidated. They can be the results of changes in activity of stomach, pylorus, and duodenum, or combinations of the three. Some receptor function presumably in small intestine is likely. Hunt and others (1, 7, 8) have proposed that duodenal receptors monitor the osmolarity of gastric efflux and by a feedback-loop influence the rate of gastric emptying. Identification of either the receptors or the pathways, neural or humoral, by which they might exert their control is lacking. The data presented here for glucose might depend on osmoreception, as the relationship between osmolarity and energy density is constant. However, such a mechanism can not be easily called upon to explain the differences in gastric emptying between saline and a glucose solution of comparable osmolarity. Also the emptying of fat cannot depend on osmolarity.

Whatever the mechanisms, this phenomenon has several critical implications. As far as we know this is the first demonstration of precise functional regulation to calories found in the activity of a physiological system tied directly to feeding behavior—the stomach and small bowel. This fact in itself suggests that some aspect of the controlled emptying of the stomach may play a role in feeding and particularly in the precision of satiety. Other possibilities exist however.

This regulatory function may not be an element in the links between food consumption and satiety but may be either an independent or a parallel regulatory event. Thus the controlled slowing of gastric emptying by food might be an independent gastrointestinal function with the effect of avoiding either osmotic overloading of the intestine or the wastage of nutrients, as might occur if renal thresholds were exceeded by an excessively rapid intestinal absorption of nutrients such as glucose. It is also possible that satiety for food and the caloric regulation in gastric emptying are parallel functions provoked by similar signals but in no direct fashion depending on one another. The present data cannot refute these possibilities and only a complete comprehension of the mechanisms, receptors, transmitters, and sites of action that produce satiety and influence gastric emptying will resolve them.

However, there are some aspects of our observations to suggest that this regulation of caloric delivery by the stomach could have a direct role in the control of food intake. Thus although this mechanism does avoid osmotic overloading and renal wastage of glucose, it also regulates the emptying of lipid calories exactly as glucose even though this nutrient is without osmotic effects and lacks a renal threshold. Also it seems unlikely that the phenomena demonstrated here, i.e., the rapid elimination of nonnutrient saline but retention and gradual regulated release of nutrients from the stomach, would have no satiety influence. Distension of the stomach has long been demonstrated to interrupt feeding (2, 11, 21). The precise control of gastric emptying may in fact provide a quantitative basis for relating Cannon’s observations on the effects of gastric distension to a dynamic physiology with behavior.

Thus that the stomach empties at a rate determined, within limits, by the caloric concentration and not by weight, bulk, volume, or character of its nutrient contents makes its emptying a potential visceral sensory event that could lead to accuracy in estimating the calories that have been ingested. Such a sensory event may function in conditional or unconditional reflexes. Its effects may be modified by other influences such as the
presence of solids in the stomach, the state of circulating or stored nutrients (blood sugar, fat, glycogen) or by activity in the ventromedial or lateral hypothalamus. But with the demonstrated precision it is exactly the kind of phenomenon needed for preabsorptive satiety, a crucial feature in the behavior of feeding. For feeding is an activity that occurs intermittently, ceases before ingested nutrients are metabolized, but maintains a remarkable balance between intake and need. The stomach and small bowel, by showing similar regulation in the management of nutrients within them, are sites capable of generating from their responses to these contents a quantitative influence on the behavior.

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REFERENCES


