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Effect of Occluding the Pylorus on Intraoral Intake: A Test of the Gastric Hypothesis of Meal Termination

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SEELEY, R. J., J. M. KAPLAN AND H. J. GRILL. *Effect of occluding the pylorus on intraoral intake: A test of the gastric hypothesis of meal termination.* PHYSIOL BEHAV **58**(2) 245–249, 1995.—Meal size does not change in response to food being restricted to the stomach by occlusion of the pylorus. This result has been used as evidence for a gastric model of meal termination where feedback arising solely from the stomach is taken to underlie satiation. Such data provide support for the gastric model, however, only if the rate of gastric emptying during ingestion in the unoccluded condition is slow, such that comparable amounts of food would be found in the stomach at the end of the meal in both the pylorus-occluded and unoccluded conditions. To evaluate this issue directly, rats were implanted with pyloric cuffs and gastric cannulas and given an intraoral intake test of a 10.5% glucose solution with either the pylorus occluded or unoccluded. At the end of each intraoral intake test, the content of the stomach was removed via the gastric cannula and it's volume and concentration measured. Occlusion of the pylorus did not change meal size, but both the volume and grams of glucose solute found in the stomach were substantially greater in the pylorus-occluded condition. These results are not consistent with the hypothesis that the stomach is the sole source of inhibitory signals that terminate a meal. Cumulative intake would appear to be accurately tracked regardless of its distribution within the digestive tract.

Intraoral intake Pyloric cuff Meal size Gastric emptying Stomach Satiety Satiation Glucose Ingestive behavior

THE CONTRIBUTION of various portions of the gastrointestinal (GI) tract to the termination of a meal has been widely studied and debated. Deutsch and his colleagues have proposed that inhibitory signals from the stomach are alone responsible for meal termination with a familiar food (4–6). This gastric model of satiation has been influential in the design and interpretation of subsequent studies. For example several investigators have attempted to correlate changes of meal size with changes in gastric emtpying (9,17,18,20,22,23). Recent work in our lab, however, has suggested that the gastric model may be incorrect (10,11,25).

Support for the gastric model has been derived in part from experiments using a pyloric cuff that when inflated prevents food from emptying from the stomach. Several laboratories have found that pyloric occlusion does not effect meal size (4,5,14,21). This finding makes a strong case for the sufficiency of inhibitory signals from the stomach determining when a meal is terminated. What remains open to interpretation, however, is what these studies indicate about the role the stomach plays in the more normal situation where ingested food is simultaneously present in the intestine and the stomach.

The standard interpretation of such results from pyloric cuff experiments is that they provide strong support that the stomach alone provides feedback for meal termination under normal conditions with familiar foods. This interpretation, however, depends critically on an assumption about the rate of gastric emptying during the meal. If gastric emptying during feeding proceeds slowly, very little of what has been ingested would pass from the stomach. The amount of food remaining in the stomach at the end of the meal in the condition where gastric emptying proceeds normally, therefore, would be very close to the amount in the condition where the pylorus is not occluded. Until recently, little was known about the rate of gastric emptying during ingestion. Gastric emptying after either an ingested meal or a bolus delivered directly into the stomach is relatively slow (16,19). Recently, however, data from our laboratory indicate that gastric emptying is much more rapid during ingestion than it is after ingestion for glucose solutions (10,11). In fact, when rats consume a glucose solution delivered via an intraoral cannula, 25–40% of the meal empties by the time ingestion ends.

If rats with an uninflated pyloric cuff also demonstrate this rapid gastric emptying during the test meal, the interpretation of studies involving the pyloric cuff should be altered. In the pylorus-occluded condition, the 25–40% that would normally empty during ingestion would remain in the stomach. Because animals ingest the same amount in the two conditions, there would be considerably more food in the stomach at the end of a

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meal in the pylorus-occluded condition than in the unoccluded condition. If so, it would appear that a greater amount of food is required in the stomach to terminate the meal when postgastric stimulation is prevented. When viewed in this light, pyloric cuff studies would provide evidence against, rather than in support of the hypothesis that meals are terminated solely on the basis of negative feedback from the stomach.

The goal of the present study was to provide a critical reevaluation of experiments involving the use of the pyloric cuff. Experiment 1 was intended to replicate the finding that the pyloric cuff does not affect meal size using (i) a stimulus (glucose) that is prototypical for studies of gastric emptying and (ii) a method (the intraoral intake test) in which the rate of gastric emptying during the meal is well documented. In Experiment 2, we used rats fitted with both a pyloric cuff and a gastric cannula so that the contents of the stomach could be measured at the end of meals in the pylorus-occluded and unoccluded conditions. Support for the gastric model would be provided only if rats consume the same amount and comparable amounts of ingesta are found in the stomach in both the pylorus-occluded and unoccluded conditions.

The intraoral intake test method is crucial for making the necessary comparisons because it provides an unambiguous criterion for the end of the meal so that the amount of food in the stomach can be measured as soon as ingestion stops. Standard meal size measures entail a test period of arbitrary duration [e.g., (21)] or an open-ended test using an arbitrary meal termination criterion [e.g., 5 min with no ingestion observed (1)]. The use of such procedures would have biased our results against the gastric hypothesis because emptying that occurred after ingestion had stopped would have been added to the emptying that occurred during ingestion resulting in an overestimate of the amount that left the stomach during the meal.

EXPERIMENT 1

METHODS

Subjects

Subjects were 9 male Sprague–Dawley (Charles River Co.) rats weighing between 375 and 435 g and housed individually with ad lib access to standard rat pellets and water on a 12:12 light:dark schedule. Rats were tested approximately 4 hours into the light phase.

Surgical Procedures

Two intraoral cannulas and the pyloric cuff were implanted under anesthesia (ketamine: 86 mg/kg and xylazine:12.9 mg/kg). The intraoral cannulas (PE-100 tubing) were implanted so as to pass from just anterolateral to the first maxillary molar, through the temporalis muscle, to the top of the skull where a 1 cm piece of 19 gauge tubing was press fit into the PE-100 tubing. Both cannulae were then anchored to the skull with screws and dental acrylic [a more detailed description can be found in (7)].

The pyloric cuff was made of silastic sheeting, silastic tubing (Dow Corning), and silicone adhesive according to the method of Young and Deutsch, (28). The cuff was approximately 4 cm in length and 1 cm in width. The pylorus was exteriorized and the cuff was gently passed under the pylorus and the two ends stitched together to make a loose ring. The cuff was then inflated by injecting a volume of water sufficient to produce a noticeable paling of the tissue around the pylorus. This volume was then used in the subsequent experiments to inflate the cuff and occlude the pylorus. The silastic tubing was then passed subcutaneously to emerge at the headcap where it was anchored along with the intraoral cannulae.

Intraoral Intake Test

Meal size was assessed using the intraoral intake test. A 10.5% glucose solution was infused directly into the oral cavity at a rate of 1.5 ml/min via the indwelling intraoral cannula. Because this rate is well within the rate observed of rats consuming solutions from a spout (26), the rate of infusion equals the rate of ingestion. Satiation Criterion: When the rat ceased ingesting the solution as evidenced by the infused glucose dripping from the oral cavity, the infusion was stopped for 30 s. If the rat stopped ingesting again within 60 s of infusion reinitation the test was terminated. In the rare instances when the rat did not stop ingesting during the 60 s time period, the next occasion where the rat stopped ingesting results in another 30 s no infusion period. The procedure is continued until the rat stopped ingestion during the 60 s period after a 30 s no infusion period.

Design

Ten days of habituation started 7 to 10 days after surgery. On an habituation day, rats were placed in the testing chamber and given an intraoral intake test as described above. Once rats had completed the habituation phase, they were given 4 consecutive experimental sessions. Of these sessions, 2 were run in the pylorus-occluded condition and 2 were run in the unoccluded condition in an ABBA design with condition order counterbalanced across subjects. The first pyloric-occluded condition was the first inflation of the cuff since its surgical implantation.

Cuff Verification

After completing the experiment, the effectiveness of the cuff was evaluated by measuring plasma glucose levels after a glucose solution was delivered by gavage. Rats were food deprived for 24 h and 7 tail blood samples were taken over the course of 3 h. Each sample was centrifuged and plasma glucose was measured using a Beckman glucose analyzer. The first two samples were taken 15 min apart. Just prior to the second sample, the pyloric cuff was inflated as it had been for the experimental sessions. After the second sample, 8 ml of a 10.5% glucose solution was delivered by gavage. While the cuff was inflated, 3 more blood samples were taken 20, 60 and 120 min after the gavage. The cuff was then released and two more blood samples were taken 15 and 30 min later. If blood glucose values were higher during the period when the cuff was inflated as compared to the period after the cuff was released, it was assumed that the pyloric cuff failed to keep glucose from emptying from the stomach.

RESULTS

Cuff Verification

In 4 rats plasma glucose values while the cuff was inflated were greater than after the cuff was released. In those cases, the cuff was deemed ineffective and those data were removed from the analysis. For the 5 remaining rats, a one-way repeated measures ANOVA yielded a significant main effect for plasma glucose over time [$F(6, 24) = 9.53$, $p < 0.001$]. Planned comparisons reveal that this effect was due to a significant rise in blood glucose only after the cuff was released (Fig. 1). For these rats, the cuff was judged effective at preventing substantial gastric emptying.

Behavioral

For each rat, an average intake for each of the two conditions was computed. These averages were used in a paired samples t-test (Fig. 2). Occluding the pylorus did not significantly affect the amount consumed in the intraoral intake test [$t(4) = 1.67$, p

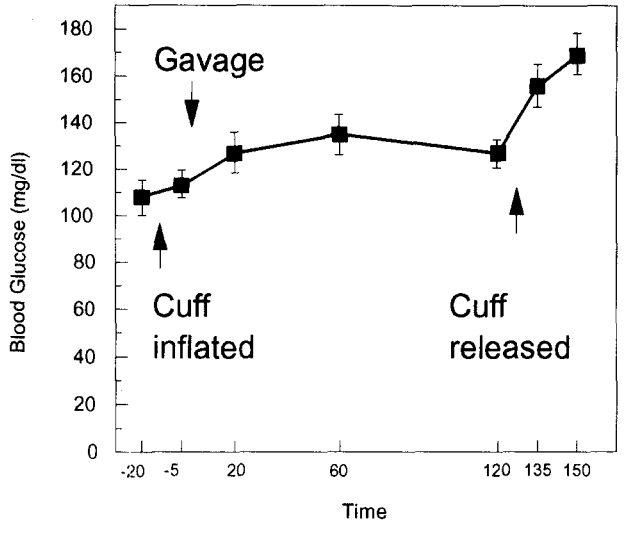

FIG. 1. Mean (±SEM) plasma glucose as a function of time after a gavaged load of 8 ml of a 10.5% glucose solution. Time 0 is the time of the load with the pyloric cuff inflated. At time 120, the cuff was released.

= 0.17 NS]. This was also the case for the first pylorus-occluded condition as compared to the first unoccluded condition [$t(4) = 1.63$, $p = 0.18$, NS]. The nonsignificant difference that can be seen in Fig. 2 is almost completely attributible to one rat which consumed less than 3 ml in one of the pylorus-occluded sessions.

EXPERIMENT 2

METHODS

Subjects

Six naive male Sprague–Dawley rats (Charles River Co.) weighing from 385 to 440 g were used for Experiment 2.

Procedure

Gastric cannula. As described for Experiment 1, rats were implanted with intraoral cannulae and a pyloric cuff. During the same surgery, a stainless steel gastric cannula was implanted into the ventral forestomach. The cannula allowed the contents of the stomach to be removed and analyzed at the end of an intraoral intake test (for a more detailed description of the method see 10,27).

Design. After 7 days of recovery, rats were given 10–15 days of habituation with intraoral intake tests. Each animal was run twice in the two conditions (pylorus-occluded vs. unoccluded). The conditions were presented in an ABBA order and counterbalanced across subjects. One hour before the intake test, each rat's gastric cannula was opened and the contents of the stomach were rinsed out with a warm saline solution. Rats were then given an intraoral intake test and immediately at its conclusion, the contents of the stomach were withdrawn through the gastric cannula.

Cuff verification. Since the rats in Experiment 2 had a gastric cannula as well as the pyloric cuff, the effectiveness of their cuffs could be assessed by more direct means than the blood glucose test in Experiment 1. The effectiveness of the pyloric cuff was assessed by measurement of the amount of solution removed from the stomach following occlusion and its glucose concentration (to correct for gastric secretions) with a Beckman glucose analyzer. Additionally, we measured the glucose concentration of the actual solution that was used in the intraoral intake test. The concentration of the solutions used averaged 10.5% but there was some variance in the solutions that were made each day. In this way we could compare the total amount of glucose consumed to the total amount of glucose recovered. For the course of the experiment, we set 95% recovery of ingested glucose solute as the criterion for successful pyloric occlusion. It is important to note that this criterion is relatively stringent compared to that used by other laboratories using the pyloric cuff procedure. Some labs have used a criterion in which 100% of the volume ingested must be recovered [e.g., (3)]. Such a criterion ignores the substantial release of gastric fluids that occurs during ingestion. Hence, recovering only 100% of the volume ingested leaves open the possibility that a substantial amount of the glucose might have left the stomach. By measuring the glucose content of the stomach, this limitation was avoided. To reach the 95% criterion, three rats required an increase in the volume used to inflate the cuff over the amount determined sufficient during the surgical implantation. Additionally, in four of the 24 sessions during the experiment, we failed to recover 95% of the glucose. Those sessions were rerun the following day.

RESULTS

As in Experiment 1, occluding the pylorus did not affect the amount consumed in the intraoral intake test [$t(5) = 0.97$, $p = 0.38$] (Fig. 3). The pylorus-occluded condition, however, resulted in a larger stomach volume [$t(5) = 6.83$, $p = 0.001$] and more glucose solute [$t(5) = 4.21$, $p = 0.008$] retrieved from the stomach at the end of the intraoral intake test than occurred in the unoccluded condition. A mean of 31% of the glucose solution ingested in the unoccluded condition emptied during the course of the meal.

GENERAL DISCUSSION

Experiments 1 and 2 replicated the behavioral findings of Deutsch et al. (4,5), Kraly and Smith (14), Rauhoffer et al. (21) and Sclafani and Nissenbaum (24) that occluding the pylorus does not change meal size. These experiments also extended those results in several ways. First, the nutritive stimulus for the present experiment was a simple glucose solution. Second, the method for assessing meal size was different from that used in previous studies. In the present experiment, rats did not lick the stimulus from a spout but rather had the stimulus infused directly

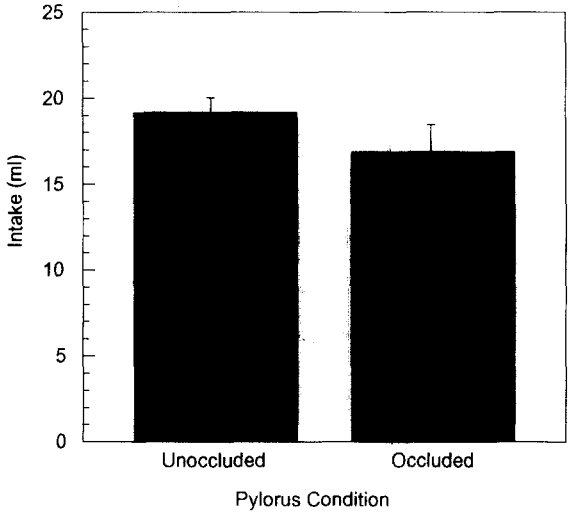

FIG. 2. Mean (±SEM) amount consumed in ml of a 10.5% glucose solution in an intraoral intake test in the pylorus occluded and unoccluded conditions.

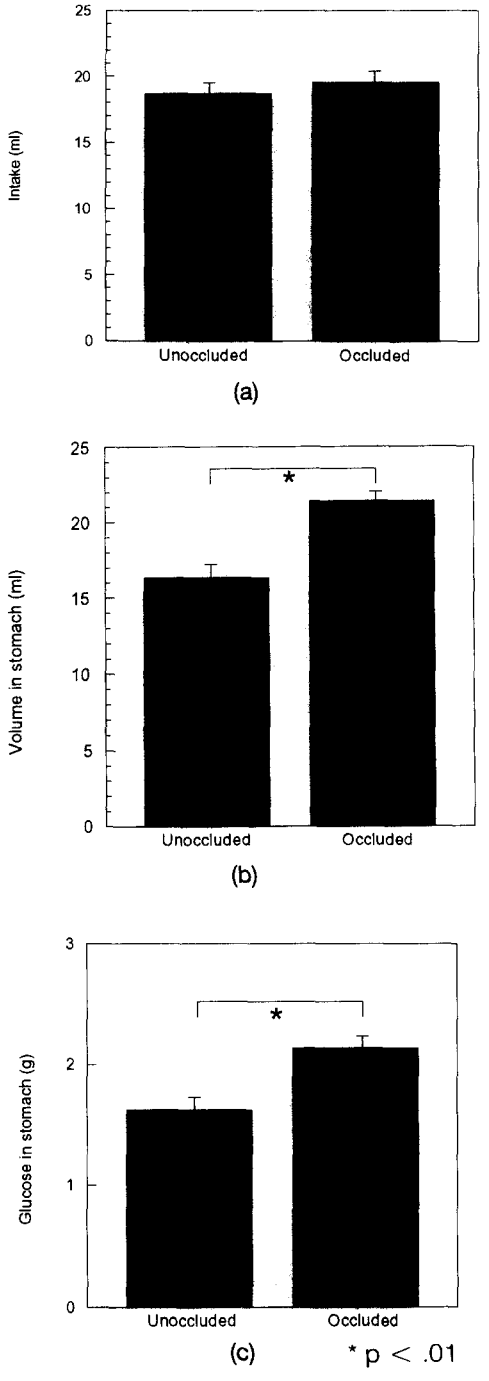

FIG. 3. (a) Mean (±SEM) amount consumed of a 10.5% glucose solution in an intraoral intake test in the pylorus occluded and unoccluded conditions. (b) Mean (±SEM) stomach volume in ml retrieved through a gastric fistula at the end of the intraoral intake test for both conditions. (c) Mean (±SEM) amount of glucose solute in g retrieved through a gastric fistula at the end of the intraoral intake for both conditions.

into the oral cavity at a constant rate. The comparability of the results from these different paradigms strengthens confidence in the generality of the result and provides another parallel between results obtained using the intraoral intake paradigm and results from more traditional intake tests [see (8) and discussions in (12,25)].

Finally, in Experiment 2, the rate of gastric emptying observed with the cuff open is well within the range of what we have observed in previous experiments with rats which did not have a pyloric cuff (10); approximately one third empties during the ingestion interval. It would appear that having the uninflated cuff installed around the pylorus, in and of itself, has little if any impact on gastric emptying. The high rate of gastric emptying observed when the pylorus was unoccluded obliges a reevaluation of these experiments as well as of Deutsch's gastric hypothesis of satiety (4–6).

Experiment 2 directly tested the hypothesis that inhibitory signals from the stomach are alone responsible for meal termination. Given that there were no differences in meal size, the gastric hypothesis would predict that the amount of food recovered from the stomach at the end of the pylorus-occluded condition should be the same as that recovered in the unoccluded condition. The volume of solution actually found in the stomach, however, was 31% greater at the end of the pylorus-occluded condition. This replicates the observations of Kraly and Smith (14) who also found a greater stomach volume in the pylorus-occluded condition. If stomach distention were the critical feedback signal for meal termination, rats would have consumed less food in the pylorus-occluded condition.

The gastric hypothesis, however, does not rely upon gastric distention as the critical variable but rather suggests that the number of calories in the stomach is responsible for meal termination (4,6). It is possible that the increased volume observed in Experiment 2 was due solely to increased gastric secretions and that the actual calories in the stomach could be comparable. To test this possibility, we analyzed the fluid retrieved to determine the amount of glucose (and hence the number of calories) in the stomach at the end of the meal in the pylorus-occluded and unoccluded conditions. The amount of glucose in the stomach was 31% greater in the occluded than in the unoccluded condition. The increased volume retrieved from the stomach was not due to additional gastric secretions but rather to the prevention of the substantial gastric emptying that normally occurs during a glucose meal. The current data, therefore, do not support Deutsch's interpretation of pyloric cuff experiments. Since both the gastric volume and the gastric nutrient content were different in the pylorus-occluded and unoccluded conditions, it seems unlikely that the stomach alone provides the critical feedback for meal termination in these experiments.

Support for the gastric hypothesis does not derive solely from pyloric cuff experiments. It has also been supported by experiments in which food was removed from the stomach at the end of a meal. When this occurs, rats promptly ingest an amount that corresponded to the amount withdrawn even when it is replaced by an equal volume of saline before the second bout of ingestion (6). These data support the gastric hypothesis only if the rate of gastric emptying during the second opportunity to ingest is slow. Using the intraoral intake test, our laboratory replicated previous behavioral observations that rats accurately replace glucose withdrawn from their stomachs. The amount of glucose recovered from the rat's stomach at the end of the second opportunity to ingest was substantially less than that recovered after the first opportunity to ingest (13). Therefore, while it is true that rats do compensate for the glucose that is withdrawn from the stomach, the termination of the meal cannot be based on gastric feedback alone.

In light of the outcomes with pyloric occlusion and gastric withdrawal experiments, the gastric hypothesis of meal termination would appear untenable. These experiments, however, do demonstrate an important role for the stomach. It would appear, however, not to be the sole source of signals that terminate a meal. We believe a better account is a "summative" model

where signals from both gastric and postgastric sites are combined to produce meal termination. When the cuff is inflated and the pylorus occluded, all feedback is derived necessarily from the stomach. Yet in the normal case when the pylorus is unoccluded, the meal is terminated at the same point despite less inhibition coming from the stomach. The reduced inhibition from the stomach must be balanced by increased inhibition originating from postgastric sites. It would appear that the animal is able to integrate inhibitory signals from gastric and postgastric sites to maintain a constant meal size in the face of manipulations which greatly change the distribution of the ingesta in the GI tract.

The results of these experiments must be interpreted within the relatively narrow confines of our experimental setting. The limitation of the current results to glucose solutions is important and it is problematic to extend these conclusions to mixed solutions and solid foods without further data. In addition, the current data only address the impact of gastric emptying during a ingestion on the size of that meal. Data from this laboratory show that gastric emptying after a glucose meal may be an important determinant in how much is consumed in a subsequent meal (12). Despite these limitations, the data do provide a compelling disconfirmation of a strict gastric model and support for a summative model of meal termination.

One straight-forward prediction of the summative model is that manipulations that affect gastric emptying during a meal will not necessarily change meal size. As mentioned in the introduction, there have been many attempts to explain anorexigenic treatments as a product of changes in gastric emptying. Indeed, many of these attempts have ultimately shown a clear dissociation between the anorexigenic and gastric emptying effects of these manipulations (e.g., 2,15,17,20). The current results extend this dissociation to its logical extreme. The pyloric cuff reduces gastric emptying during a meal to essentially zero, yet has no impact on meal size.

Much of the literature on meal size control has been aimed at assessing the contributions of particular portions of the GI tract to satiation. The current data suggest that multiple portions of the G.I. tract (and possibly sites beyond) contribute to control meal size. They also suggest that those contributions are linearly related to the amount of food currently in that portion of the G.I. tract and that signals are combined with equal weightings (i.e., summated). We hope that the focus of research on meal size control can begin to change from which site provides the critical signal for meal termination, to how signals of disparate origins and modalities are combined so that total food intake can be accurately tracked.

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