Oral glucose is the prime elicitor of preabsorptive insulin secretion

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Grill, Harvey J., Kent C. Berridge, and Deborah J. Ganster. Oral glucose is the prime elicitor of preabsorptive insulin secretion. Am. J. Physiol. 246 (Regulatory Integrative Comp. Physiol. 15): R88–R95, 1984.—Seven sugars, two sugar alcohols, and a nonnutritive sweetener were orally administered to naive rats with and without gastric drainage fistulas. Although all taste solutions were ingested, only glucose evoked a statistically significant elevation of insulin levels. This rise was independent of a rise in glycemia. The preeminence of oral glucose as an elicitor of preabsorptive insulin secretion is especially striking, considering that glucose is neither the most intense (as measured electrophysiologically) nor the most palatable (as measured by behavioral preference tests) taste stimulus tested. These results suggest the existence of a gustatory and/or gastrointestinal chemoreceptor that is most responsive to glucose.

1 Defining the nature of the eliciting stimulus for the PIR is an important issue, even though there is some debate about its effector mechanism. Two types of effector mechanisms might mediate a taste-elicited preabsorptive insulin secretion. The literature on diabetes has stressed the mediating role of enterohormones (18, 19, 43). Enterohormones, such as secretin, have a dual action on insulin secretion: preabsorptively, as secretagogues themselves, and postabsorptively, as potentiators of the action of nutrient secretagogues (19). The literature on diabetes has neglected a thorough consideration of a direct role for the nervous system in mediating the PIR. There are, however, excellent reasons for believing that preabsorptive insulin secretion is, at least in part, neurally mediated by the parasympathetic action of the vagus nerve on the pancreas. PIR is blocked by surgical or pharmacologic disruption of vagal function and by denervation and transplantation of islet tissue (6, 33, 41, 42). None of these procedures interfered with postabsorptive insulin secretion.

Methods

Surgery

Under ketamine anesthesia, naive male Sprague-Dawley rats (Charles River, 325–400 g) received an intraoral and a venous cannula. Either of two sites for venous cannulation was used: jugular vein (59 rats) or inferior vena cava (28 rats). Twenty-two additional rats received both a venous cannula and a gastric drainage fistula to circumvent intestinal absorption. The gastric procedure was done either 1 wk before intraoral venous cannulation.

In a variety of species, oral contact with food elicits an immediate elevation of plasma insulin levels even in the absence of a rise in glycemia (2, 16, 22, 33, 41). This immediate preabsorptive insulin response (PIR) persists for approximately 8–10 min after the beginning of a sham-fed meal (5). In a variety of testing conditions the amplitude of the preabsorptive insulin secretion can more than double insulin base-line levels (4, 11, 16, 22, 40, 41).

The present paper focuses on defining the afferent mechanisms that lead to this potent preabsorptive change in insulin secretion. A variety of cephalic stimuli may be able to trigger preabsorptive insulin secretion. Taste, however, has been the type of cephalic stimulation that has most often been manipulated. The purpose of the present experiments is to define the adequate taste stimuli for the PIR.

What is the evidence that oral chemoreceptors initiate a PIR? Complex nutritive and nutrient-free foods, as well as simple taste solutions, have each elicited a PIR (6, 11, 22, 33, 41). A variety of data make a strong case for oral chemoreceptors providing an afferent limb for the preabsorptive release of insulin.1 Gastric or esophageal application of nutrients, which would both stimulate digestive tract chemoreceptors and elevate enterohormone levels, did not elicit a PIR (16, 41). Furthermore isolated oral contact with food in the sham-fed esophageal-fistulated dog was sufficient to elicit preabsorptive insulin secretion (16).

In analyzing the nature of the taste stimuli adequate for eliciting a PIR, the present experiments focus on the category of “sweet” taste stimuli (sugars and nonsugars). Some investigators have remarked that the sweet quality is by itself an adequate stimulus for the PIR (4, 28). Sweet taste stimuli are believed to act on the same type of oral chemoreceptor mechanism (33). If the stimulation of this oral sweet receptor is a condition sufficient to elicit a PIR in the naive animal, then the efficacy of a taste to stimulate this receptor, as evidenced by the activity of peripheral gustatory nerve, should correlate with the PIR amplitude elicited. In other words, a correlation between the amplitudes of the electrophysiological response and the PIR might exist. The present experiments should also enable a test of whether a correlation exists between the magnitudes of the behavioral ingestive response and the PIR.

1 Defining the nature of the eliciting stimulus for the PIR is an important issue, even though there is some debate about its effector mechanism. Two types of effector mechanisms might mediate a taste-elicited preabsorptive insulin secretion. The literature on diabetes has stressed the mediating role of enterohormones (18, 19, 43). Enterohormones, such as secretin, have a dual action on insulin secretion: preabsorptively, as secretagogues themselves, and postabsorptively, as potentiators of the action of nutrient secretagogues (19). The literature on diabetes has neglected a thorough consideration of a direct role for the nervous system in mediating the PIR. There are, however, excellent reasons for believing that preabsorptive insulin secretion is, at least in part, neurally mediated by the parasympathetic action of the vagus nerve on the pancreas. PIR is blocked by surgical or pharmacologic disruption of vagal function and by denervation and transplantation of islet tissue (6, 33, 41, 42). None of these procedures interfered with postabsorptive insulin secretion.
or at the same time. For a minimum of 3 days before surgery, rats were familiarized with routine handling and with the milk diet they would subsequently receive. Twenty-four hours of food deprivation preceded surgical procedures.

**Intraoral cannulas.** Rats were implanted with two intraoral cannulas. Each cannula was placed just antero-lateral to the first maxillary molar, brought out subcutaneously, and anchored to the skull with dental acrylic. Obturators of PE-10 tubing (polyethylene tubing, Clay-Adams) heat sealed to PE-100 tubing were inserted to keep the cannulas patent during the course of the experiment. During the same surgery session a venous cannula was installed.

**Venous cannulas.** The method of Kaufman (17) was used to implant a nonocclusive vena cava cannula. A midline abdominal incision was made, and the intestines were wrapped in sterile moistened gauze and gently laid to the side. The peritoneal membrane was cleared away from a section of vena cava extending approximately 1–3 cm below the renal veins. The vein was punctured, and a cannula made from Silastic tubing (0.019 in. ID, 0.025 in. OD) was inserted approximately 6 cm (e.g., level with the xiphisternum). The cannula was secured with 4-0 silk sutures and filled with heparinized saline; the intestines were returned to their original position, and muscle and skin were closed separately. The distal end of the cannula was secured to the dental acrylic on the skull. The cannula was then capped with a metal obturator; its patency was checked daily.

With the procedure of Steffens (38), rats were fitted with an intrajugular cannula (overall length, 10 cm; length inserted into the vein, 35 mm). The cannula was sutured to the muscle overlying the jugular vein, subcutaneously positioned, and anchored to the skull. The cannula was then filled with a viscous mixture of polyvinylpyrrolidone and heparinized saline and sealed with a plastic cap. This mixture was replaced daily to maintain patency.

**Gastric drainage fistula.** An incision was made on the midline of the abdomen to expose the stomach when this surgery preceded the vena cava implant or when this surgery accompanied the jugular cannula. When gastric surgery accompanied the vena cava implant, the same midline incision was used for both procedures. The method of Weingarten and Powley (45) was used to make a small stab wound in the forestomach. With an atraumatic needle and 6-0 silk, two concentric purse-string sutures were sewn into the external muscle layers of the stomach around the stab wound. The notched external edge of the stainless steel fistula was rotated into the stomach through the stab wound. The fistula was then secured to the stomach by tightening the purse-string sutures. A 15 mm disk of polypropylene mesh was then placed onto the center of the cannula to aid in securing the cannula to the abdominal muscle. Lateral to the midline, a hole was punched through the abdominal muscle and skin. The external end of the cannula was pushed through the guide hole, and a stainless steel cap was threaded into the protruding portion of the cannula. The midline laparotomy was closed in two layers: first the abdominal muscle, then the overlying skin. Rats recovered from all surgery for 3–7 days before adaptation began.

**Postsurgical Maintenance**

Rats were housed individually and maintained under a normal light-dark cycle (LD 12:12). Venous cannulas were flushed daily to maintain patency and also to familiarize the animals with this procedure. Gastric fistulas were checked daily. Each rat had access to 50 ml of milk diet. The body weights, milk intake, health, and overall appearance of each rat were observed and recorded daily. Any rat that did not gain or maintain weight under these conditions was given a number of intragastric meals sufficient to maintain weight. Rats received prompt medical attention whenever any evidence of illness or infection was found.

**Adaptation**

Handling of rats to be tested occurred for several days before and after surgery. An adaptation period of a minimum of 2 days followed recovery from surgery and preceded testing. Adaptation consisted of familiarizing rats with the presence of venous withdrawal tubing, taste delivery tubes, the oral delivery of fluid in the test chamber, and in some cases the gastric drainage tubing.

**Rats without gastric fistulas.** On each adaptation day food was removed from the cages and rats were given a 6-ml tube-fed meal of an isotonic diet (Precision, Doyle Pharmaceuticals) 3 h before the adaptation session to standardize the level of glycemia at the time of testing. Stimulus delivery tubes were attached to the oral cannula, and venous withdrawal tubing was attached to the cap of the venous catheter.

Rats were allowed to habituate to the cylindrical plastic chamber for a minimum of 10 min, after which they received a 1.1-ml oral infusion of distilled water over a 1-min period. Rats were then allowed to habituate 10 min more before they were removed from the test chamber. This 20-min period in the test chamber plus the 1-min stimulus infusion paralleled the 10-min habituation, 1-min infusion, and 8-min blood sampling that occurred on test days. Rats were returned to their home cages and allowed free access to liquid diet until the next adaptation or test day.

**Rats with gastric fistulas.** The adaptation procedure was the same as that described above, with some additions due to the presence of the gastric fistulas. These additions were as follows. Those rats bearing gastric fistulas received approximately 10 ml of tap water by gavage 20 min before the test session. This facilitated the subsequent rinsing of the stomach. Ten minutes later, the gastric fistula was opened, and the stomach was rinsed several times with warm isotonic saline. Drainage tubing was attached, and the rat was placed in the test chamber. A slit in the testing chamber floor permitted the drainage tube to hang vertically, optimizing stimulus recovery, while allowing the rat to move about freely. The ingested liquid was removed via the gastric drainage tubing, and the amount of fluid re-
covered was recorded. Before returning to their cages, those rats with gastric fistulas were removed from the chamber, their stomachs were rinsed with warm saline, and the gastric cannulas were closed.

Taste Stimuli

By assuming that the PIR-eliciting quality of tastes represents an innate reflex, the PIR literature has diminished a role for conditioning in the modification of this insulin response. (3, 4, 28). Berridge, Grill, and Norgren (3), however, demonstrated the lability of the taste-elicited PIR following taste-LiCl association. A single pairing of oral glucose with an intraperitoneal injection of LiCl eliminated the PIR-eliciting qualities of subsequent oral glucose administrations. These results suggested that novel tastes should be utilized in defining the adequate taste stimuli for the PIR to avoid the potential confounding effects of conditioning.

Taste stimuli used during testing sessions were equimolar sugars and sugar alcohols (0.8 M) with the exception of 0.5 M lactose (due to the limits of its solubility at room temperature) and a nonnutritive sweetener, 0.15% sodium saccharin [this concentration had been used by Berthoud et al. (6)]. The 10 sweet compounds tested were glucose, sucrose, fructose, maltose, galactose, mannose, lactose, glycerol, sorbitol, and sodium saccharin. All solutes were reagent grade (Pfanstiehl or Sigma Laboratories), and the solvent was distilled water.

The rats tested in these experiments had never been exposed to any of these taste stimuli; these stimuli can therefore be referred to as novel tastes. Each rat was exposed to a randomized order of these 10 novel taste stimuli during testing. Rats could be tested on less than 10 taste stimuli if their cannula clogged or if they exhibited signs of sickness.

Test Procedure

Testing began after a minimum of 2 days of adaptation. Rats were considered ready for testing based on their health, cannula patency, and successful adaptation. Rats that did not successfully adapt after 2 days were allowed 2 additional adaptation days. These rats were then either tested or eliminated from the subject population.

The procedure used in the test sessions was the same as that used during adaptation sessions, except that before stimulus delivery each venous cannula was flushed with heparinized saline and then attached to blood withdrawal tubing and a collecting syringe. On test days the distilled water oral stimulus was replaced with a taste stimulus.

Rats without gastric fistulas. Rats had ad libitum access to water overnight and were tube fed 6 ml of isotonic diet 3 h before the test. During this 3-h period they had access to water but not food. Before beginning the test, the venous cannula was flushed with a small amount of heparinized saline (0.3-0.6 ml), and blood withdrawal and stimulus delivery tubing were attached. The rat was placed in the test chamber and allowed to habituate for 10 min. At the end of habituation a 0.25-ml blood sample was collected over a time interval of 1 min and then placed on ice. The length of the venous cannula was calculated to contain the volume of one blood sample. Thus blood samples reflected the plasma insulin and glucose levels of the previous minute. After a 2-min wait, another sample was taken. A 1.1 ml taste stimulus was then orally delivered for 1 min (Harvard syringe pump), whereas another 0.25-ml blood sample was taken simultaneously (this sample is referred to as the base-line or unstimulated sample). Five more 0.25-ml blood samples were then collected in the 6 min that followed stimulation. Each sample was immediately placed on ice and then centrifuged in heparinized capillary tubes to obtain plasma.

Behavior of the rats was recorded, minute by minute, for the entire test period. Behaviors noted were taste reactivity (13), locomotion, grooming, and sleep. After testing each venous cannula was rinsed with 1.0 ml of heparinized saline, and the rat was returned to its home cage.

Rats with gastric fistulas. The procedure utilizing both venous cannulas and gastric fistulas was the same as that used in the adaptation sessions. Testing proceeded as above (habituation, blood sampling, and stimulus delivery). The orally infused fluid was recovered via the gastric drainage tubing, and the latency and the amount of fluid recovered was noted. Most of the 1.1-ml taste stimulus was consumed (Table 1). The amount rejected was noted in cases of incomplete ingestion.

Both groups. Every 2 days of testing was followed by 1 non-test day. Rats were tested for a maximum of 10 days (1 test day for each of the 10 randomly presented novel taste stimuli). This testing procedure (the use of oral, venous, and gastric cannulas and the volume of oral infusion and blood withdrawal) was selected, because it was very similar to procedures used by Berthoud and Jeanrenaud (5) and Hara and Saito (15).

Data Analysis and Selection

At the conclusion of testing, plasma samples were analyzed for glucose and insulin content. Plasma glucose was usually determined the same day with the glucose oxidase method. Plasma samples were stored at -20°C for subsequent insulin analysis. Insulin level was determined by a charcoal separation technique at the Diabetes Center of the University of Pennsylvania, using normal rat insulin as a standard. All statistical comparisons were made within the same experiment using paired two-tailed t tests.

<table>
<thead>
<tr>
<th>Taste stimulus intake</th>
<th>Values are means ± SE in ml</th>
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<tbody>
<tr>
<td>Maltose</td>
<td>1.00 ± 0.01</td>
</tr>
<tr>
<td>Sucrose</td>
<td>1.08 ± 0.01</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.07 ± 0.02</td>
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<tr>
<td>Fructose</td>
<td>1.07 ± 0.02</td>
</tr>
<tr>
<td>Mannose</td>
<td>1.07 ± 0.02</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>1.07 ± 0.02</td>
</tr>
<tr>
<td>Glycerol</td>
<td>0.95 ± 0.07</td>
</tr>
<tr>
<td>Lactose</td>
<td>0.91 ± 0.05</td>
</tr>
<tr>
<td>Sodium saccharin</td>
<td>0.85 ± 0.06</td>
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<tr>
<td>Galactose</td>
<td>0.79 ± 0.11</td>
</tr>
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</table>
RESULTS

Rats Without Gastric Fistulas

Preliminary data analysis revealed that plasma glucose levels would usually begin to rise by the 3rd poststimulus min after the ingestion of glucose, maltose, or sucrose stimuli. This result is similar to that of Steffens (39). However, because the number of minutes before plasma glucose began to rise varied between one and five among animals, a preabsorptive criterion was established to ensure that only preabsorptive changes in insulin were included in this analysis. The standard error about the mean of the prestimulus minute was ±6 mg/100 ml. This value was used as a reference in establishing the preabsorptive criterion. To be included in the statistical analysis of a taste-elicited change in prestimulus insulin level, poststimulus plasma glucose values could not exceed the prestimulus base-line plasma glucose minute by more than 6 mg/100 ml. When any poststimulus plasma glucose value exceeded this criterion, it was eliminated from the data set; e.g., if the plasma glucose values for the prestimulus minute and poststimulus min 0-1, 1-2, 2-3, 3-4, 4-5, and 5-6 were 140, 140, 138, 147, 153, and 140 mg/100 ml, then the insulin values for min 0-1 and 1-2 would be included but those of min 2-6 would be excluded from the data set for that test. This procedure ensured that increases in postabsorptive plasma glucose could not be responsible for any rise in plasma insulin for rats who meet the criterion. This criterion was applied to tests of 70 rats. These 70 rats generated 189 test days distributed over the 10 taste stimuli. When applying the plasma glucose preabsorptive criterion to these 189 test sessions, 100% of the sessions met the criterion for min 0-1, 75% for min 1-2, 53% for min 2-3, 42% for min 3-4, 29% for min 4-5, and 21% for min 5-6.

Rats with Gastric Fistulas

Our use of the gastric fistula was designed to circumvent the need to impose a preabsorptive plasma glucose criterion. Kraly et al. (20) used a dye-dilution method to determine that no ingested fluid would reach the duodenum and therefore could not be absorbed if the fluid would begin to drain from the stomach within 15 s of its oral introduction and if at least 100% of the fluid volume was recovered. We therefore initially adopted these latency and recovery criteria for our fistulated rats. However, an analysis of plasma glucose levels of our rats revealed that plasma glucose levels frequently rose after maltose, glucose, or sucrose ingestion despite gastric recoveries of 100, 150, or even 200% of the orally presented volume. Therefore two types of preabsorptive criteria were used for these rats, a fluid recovery criterion and the plasma glucose criterion just described. Both criteria had to be met before any rat’s data were considered. Using both criteria, 17 rats were included in this population. The plasma glucose and insulin data for these 17 rats were examined in two ways: added to the data of the 70 rats without stomach fistula and separated from these 70 rats.

Both Groups

The change in plasma glucose level from the prestimulus base-line minute is shown for each taste stimulus in Figs. 1-3. In no case is there a significant increase in plasma glucose level in the poststimulation period. In only one case is there a decrease in plasma glucose level that persists for several minutes. Figure 2 shows that the ingestion of sodium saccharin significantly lowers plasma glucose levels for min 2-3 through 4-5 (P < 0.02). Plasma glucose was lowered for an isolated minute after glucose and lactose stimulation (Figs. 1 and 3).

Plasma Insulin

Both groups. Table 1 reveals that most of the infusion for all 10 sweet stimuli was ingested. Despite the relative equivalence in the volume of these sweet stimuli consumed, only one of these taste stimuli elicited a significant elevation of insulin levels. Figure 1 demonstrates an oral glucose-elicited PIR (P < 0.01) that began immediately in the 1st poststimulus min and persisted through the entire preabsorptive period, min 5. No other taste stimulus evoked either a sustained or intermittent PIR. Sodium saccharin, the only nonnutritive sweet stimulus used, evoked a significant decrease in plasma insulin levels that persisted for 2 min (P < 0.02).

Rats with Gastric Fistulas

The small size of this group did not permit the statistical analysis of many test minutes. Using the combined criteria mentioned above, as well as an additional criterion of a minimum group size of five, there was only 1 poststimulus min for glucose, 2 for sucrose and maltose, 3 for glycerol, and 4 for sodium saccharin. All other trials failed to meet the combined criteria and were discarded from the analysis. The data for this small sample, however, support the conclusions of the combined groups. Only oral glucose elicited a statistically significant rise in plasma insulin (min 0-1; P < 0.05). Sodium saccharin evoked a statistically significant reduction in plasma insulin during min 3-4 (P < 0.05).

DISCUSSION

Seven sugars, two sugar alcohols, and a nonnutritive sweetener were orally administered to naive rats with and without gastric drainage fistulas. Although all were equally ingested, only glucose evoked a statistically significant elevation of insulin levels. This rise was independent of a rise in glycemia. Oral glucose elicited a statistically significant PIR for all 6 preabsorptive min. No other sweet stimulus evoked a PIR for even an isolated minute. In this sense glucose was the most potent stimulus of those considered. These data are supported, in part, by the results of others. Hara and Saïto (15) demonstrated that the plasma insulin response...
FIG. 1. Relative mean (±SE) preabsorptive insulin and plasma glucose responses to oral 0.8 M glucose, sucrose, and maltose. Mean plasma insulin base lines (ng/ml): 1.64 (glucose), 2.27 (sucrose), and 1.89 (maltose). Mean plasma glucose base lines (mg/100 ml): 146.94 (glucose), 153.08 (sucrose), and 150.24 (maltose). *Changes from base line significant at $P < 0.05$; **significance at $P < 0.02$; ***significance at $P < 0.01$.

FIG. 2. Relative mean (±SE) preabsorptive insulin and plasma glucose responses to oral sodium saccharin (0.15%), fructose (0.8 M), and glycerol (0.8 M). Mean plasma insulin base lines (ng/ml): 1.78 (saccharin), 2.09 (fructose), and 1.95 (glycerol). Mean plasma glucose base lines (mg/100 ml): 142.55 (saccharin), 141.20 (fructose), and 148.75 (glycerol). Significance as in Fig. 1.

to oral glucose was greater than that of oral sucrose or fructose despite similar plasma glucose levels. Goldfine et al. (12) showed that glucose-flavored cola, but not saccharin-flavored cola or water, elicited a rapid elevation of plasma insulin levels in humans (see also 14, 44).

Recent data of Mei et al. (27) support an intestinal mediation for a carbohydrate-elicited PIR. Despite their use of the term intestinal "glucoreceptor" (27), these authors note (26) that the term glycosidoreceptor might be more accurate, since a variety of intestinally applied carbohydrates (e.g., sucrose, galactose, mannose, maltose, and fructose) evoked a similar electrophysiological response. Because our results demonstrate a superior sensitivity to glucose and the electrophysiological data of Mei et al. (27) do not, it appears that the intestinal mechanism they described cannot be mediating the PIR
we have described. At present our data do not allow us to discriminate between the afferent oral and gastric contribution to preabsorptive insulin secretion. Further experiments are planned to restrict the stimulus to the oral cavity and thereby directly test the exclusive oral mediation of this glucose-elicted PIR. Preintestinal (oral and/or gastric) and intestinal neural mechanisms eliciting preabsorptive insulin secretion may appear to be redundant, but additional work is required to specify the contribution of each to glucose homeostasis.

The data collected clearly support a receptor mechanism that is most responsive to glucose. As glucose is neither the most nor least osmotic of the sugars tested, it seems likely that this receptor is not activated by osmotic properties of taste stimuli. If this receptor is an oral chemoreceptor, is there any other evidence to support an oral chemoreceptor with similar response properties? A variety of evidence has been marshaled to support the hypothesis that a single type of sweet receptor located on the taste cell membrane mediates responses to all sweet stimuli (sugars and nonsugars) (36). For example, when receptors for a given sweet taste stimulus are fatigued by prolonged stimulation, they become much less responsive not only to that particular stimulus (adaptation), but to all sweet stimuli regardless of their chemistry [cross adaptation (25)]. Furthermore there are several procedures by which sweet taste responses can be selectively blocked (36). The best known of these is gymnema sylvestre. Treatment of the oral cavity with gymnema sylvestre selectively blocks human sweetness judgments for all sweet stimuli applied, while leaving salt, bitter, and sour judgments unimpaired (21).

Other data, however, raise the possibility that more than one type of oral sugar receptor may exist. An analysis of squirrel monkey single chorda tympani fibers responding to sugars revealed two classes of responses (32). Fibers that responded better to sugars were more sensitive to sucrose than fructose. Other fibers that responded better to salts were more sensitive to fructose than sucrose. Other work has shown that adaptation to sucrose reduced the sweetness of sucrose and fructose 75–80%, whereas taste of glucose was reduced less than 50% (25). The oral administration of L-iodobenzoate in rats reduces the magnitude of the peripheral nerve response to glucose approximately 40%, whereas the response to fructose and other sugars was reduced by less than 10% (35). Competitive binding experiments using a variety of sugars and purified bovine taste papillae suggest a specific glucose-binding site (24). In addition, several reports of decreased taste sensitivity to glucose in diabetic patients have led some investigators to hypothesize that some diabetics have a general insensitivity to glucose (14, 37). Until alternate explanations for these data can be eliminated, however, these data remain suggestive.

Although there is some evidence to support different types of oral sweet receptors, there is currently no clear support for an oral chemoreceptor that is best stimulated by glucose. The pancreatic β-cell is a digestive tract chemoreceptor selective to glucose in its secretory response, but it appears to operate differently from the taste cell (1). Our data raise the possibility that an extrapancreatic glucose-sensitive receptor exists. It is possible that, like the β-cell, this extrapancreatic chemoreceptor may detect glucose intracellularly.

In his discussion of the cephalic phase hypothesis, Polley (34) predicts that taste palatability determines PIR amplitude. Data of Louis-Sylvestre and Le Magnen (23) support a direct relationship between taste palatability and PIR amplitude, as do the taste aversion data of Berridge et al. (3). This suggests that PIR and behavioral ingestion are parallel responses controlled by the same central regulatory mechanism and perhaps even by the activation of the same oral chemoreceptors. However, it has recently been shown that taste palatability and PIR amplitude can be dissociated. Isotonic sodium chlo-
ride-evoked consistent amplitude can be dissociated. Iso-
tonic sodium chloride evoked consistent behavioral ingestion but failed to elicit a PIR (3), suggesting that palatability is not the sole control of the PIR.

The present experiments enable the further analysis of the relationship between sweet stimulus palatability and the PIR amplitude. We have found that sweet stim-
ulus palatability is not the sole control of the PIR. Neither novel sucrose nor novel maltose was effective in eliciting a PIR, whereas novel glucose was. A variety of data demonstrate that maltose and sucrose are much more palatable than glucose in postigestive feedback free tests (7–9). The following palatability hierarchy can be generated for the sweet stimuli used in our experi-
ments on the rat: maltose > sucrose > fructose = glucose (9, 30; our unpublished observations).

Using integrated chorda tympani activity as an index of taste receptor activation, the PIR amplitude evoked by sweet stimuli was shown not to correlate with receptor activation. Examining 7 of the 10 stimuli of the present experiment, Noma et al. (30) obtained the following hierarchy of rat integrated chorda tympani activity for 0.6 M sugars and sugar alcohols: sucrose > fructose > sorbitol > mannose = glucose > maltose > galactose. In the present experiments sucrose, fructose, sorbitol, or mannose did not evoke a PIR, whereas glucose did.

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TASTE AND PREABSORPTIVE INSULIN RESPONSE


