Effects of intraduodenal glucose and fructose on antropyloric motility and appetite in healthy humans

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Rayner, C. K., H. S. Park, J. M. Wishart, M.-F. Kong, S. M. Doran, and M. Horowitz. Effects of intraduodenal glucose and fructose on antropicloric motility and appetite in healthy humans. Am. J. Physiol. Regulatory Integrative Comp. Physiol. 278: R360–R366, 2000.—Oral fructose empties from the stomach more rapidly and may suppress food intake more than oral glucose. The purpose of the study was to evaluate the effects of intraduodenal infusions of fructose and glucose on antropicloric motility and appetite. Ten healthy volunteers were given intraduodenal infusions of 25% fructose, 25% glucose, or 0.9% saline (2 ml/min for 90 min). Antropicloric pressures, blood glucose, and plasma insulin, gastric inhibitory peptide (GIP), and glucagon-like peptide-1 (GLP-1) were measured concurrently; a buffet meal was offered at the end of the infusion. Intraduodenal fructose and glucose suppressed antral waves (P < 0.0005 for both), stimulated pyloric pressure waves (P < 0.05 for both), and increased basal pyloric pressure (P = 0.10 and P < 0.05, respectively) compared with saline, without any significant difference between them. Intraduodenal glucose increased blood glucose (P < 0.0005), as well as plasma insulin (P < 0.0005) and GIP (P < 0.005) more than intraduodenal fructose, whereas there was no difference in the GLP-1 response. Intraduodenal fructose suppressed food intake compared with saline (P < 0.05) and glucose (P = 0.07). We conclude that, when infused intraduodenally at 2 kcal/min for 90 min 1) fructose and glucose have comparable effects on antropicloric pressures, 2) fructose tends to suppress food intake more than glucose, despite similar GLP-1 and less GIP release, and 3) GIP, rather than GLP-1, probably accounts for the greater insulin response to glucose than fructose.

monosaccharides; manometry; incretins; glucagon-like peptide-1; gastric inhibitory peptide

THE INTERACTION OF NUTRIENTS with the small intestine plays a major role in the regulation of gastric emptying (21, 31–33, 39). As a result of this negative feedback, which is dependent on both the length and region of small intestine exposed to nutrient (31), the overall rate of entry of nutrients into the duodenum usually approximates 2 kcal/min (3). The motor correlates of the slowing of gastric emptying triggered by the presence of nutrients in the small intestine include relaxation of the proximal stomach (2), suppression of antral motility (17), and perhaps most importantly, the stimulation of phasic and tonic contractions localized to the pylorus (18, 53). The presence of nutrients in the small intestine is also important in appetite regulation; for example, infusion of nutrients directly into the small intestine decreases the perception of hunger and suppresses food intake (26, 27, 29, 56). Gut peptides probably play a major role in mediating both the slowing of gastric emptying and the suppression of appetite stimulated by the presence of nutrients in the small intestine (26, 30).

The rate of gastric emptying differs between monosaccharides (9, 14, 19, 39, 48). Studies in both animals (39) and humans (9, 14, 19, 48) have established that fructose empties from the stomach more rapidly than isocaloric solutions of glucose. Although the gastric motor response to intraduodenal glucose infusion is well characterized (10, 11, 18), the motor correlates of the more rapid emptying of fructose than glucose from the stomach have not been evaluated.

Fructose may also differ from glucose in its effect on appetite, although this is controversial (13, 14, 25, 44, 49). In some studies, there was suppression of food intake by 50 g fructose, given as a drink before a meal, compared with 50 g glucose (44, 49), whereas another study reported no difference in the effects of 75 g of glucose or fructose on subsequent food intake (25). The relatively more rapid gastric emptying of fructose may potentially account for any difference in the effects of glucose and fructose on appetite; with fructose, it is possible that a greater length of small intestine would be exposed to nutrient (length of intestinal exposure is known to influence satiety; Ref. 38), whereas gastric distension may be less (22).

There are substantial differences in the effects of oral glucose and fructose on gut hormone release that may be relevant to their impact on gastric motility and appetite (19, 25). The plasma insulin response to oral glucose is ~50% greater than to the same amount of glucose given intravenously because of the release of the so-called incretin peptides from the small intestine (27, 52). It was recently established in healthy humans that secretion of the two known incretins, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), is much less in response to oral fructose than glucose (19, 25); in healthy subjects, plasma insulin...
METHODS

Ten healthy volunteers were studied (2 female, 8 male; median age 25 yr, range 19–37; median body mass index 24.6 kg/m², range 20.7–28.1). No subject had a history of systemic or gastrointestinal disease nor was taking medication at the time of the study. All subjects were unrestrained eaters (score ≤10 on the eating restraint factor of the Eating Inventory Questionnaire; Ref. 50). The study was approved by the Research Ethics Committee of the Royal Adelaide Hospital.

Protocol. Each subject was studied on 3 days; on each study day, a different intraduodenal infusion was administered (either fructose, glucose, or saline) in single-blind, random-ized order. After an overnight fast, a multilumen manometric assembly was passed through an anesthetized nostril into the stomach and positioned with a sleeve sensor spanning the pylorus and the tip in the duodenum. The position of the catheter was monitored continuously by measurement of the transmucosal potential difference between stomach and duo-denum with two additional pyloric side holes on the side opposite the sleeve, and a duodenal side hole at the distal end of the sleeve. An additional lumen, terminating 10 cm distal to the sleeve, was used for intraduodenal infusions. Intraluminal pressures were recorded at 10 Hz using custom software (DAD, written by G. S. Hebbard using Labview, National Instruments). Automated analysis was performed (MAD, written by C. H. Malbert using Labview) with subsequent exclusion of artifacts by visual inspection of each recording. Variables assessed were (1) 1) number, frequency, and amplitude of antral pressure waves (waves of amplitude >10 mmHg in any of the 6 antral side holes); 2) number, frequency, and amplitude of isolated pyloric pressure waves (waves of amplitude >10 mmHg recorded by the sleeve sensor in the absence of a pressure wave of onset within 5 s of the pyloric wave in the adjacent antral or duodenal side holes); and 3) basal pyloric pressure (measured as the mean pressure recorded by the sleeve sensor, excluding any phasic waves, in each minute, compared with the baseline pressure measured in the adjacent antral side hole). Results are expressed as change in basal pressure during the intraduodenal infusion, using mean basal pyloric pressure in the 15 min preceding the infusion as a baseline.

Glucose, insulin, GIP, and GLP-1 concentrations. Blood glucose concentrations were measured immediately using a glucometer (Reflex II M, Boehringer Mannheim, New South Wales, Australia). The rest of each blood sample was placed on ice in EDTA tubes containing a proteinase inhibitor (Trasylol, Bayer, Leverkusen, Germany) centrifuged at 4°C, and the plasma was stored at −70°C until assayed. Plasma insulin was measured by radioimmunoassay (Phadeseph Insulin RIA; Pharmacia Diagnostics, Uppsala, Sweden), GIP (19, 59) and GLP-1 (25, 27) were measured with established immunoassays.

Appetite. Visual analog scores for desire to eat, fullness, and nausea are presented as change from baseline (mean of scores at t = 5, 0, 5, 15, 30, 45, 60, 75, and 90 min (47)). Blood was sampled at the same time intervals; blood glucose was measured, and the plasma was stored for subsequent measurement of insulin, GIP, and GLP-1 (19, 25, 27, 34).

Antropyloric pressures. The silicone rubber manometric catheter (Dentsleeve, Adelaide, Australia) incorporated six antral side holes at 1.5-cm intervals, a 4.5-cm sleeve sensor with two additional pyloric side holes on the side opposite the sleeve, and a duodenal side hole at the distal end of the sleeve. An additional lumen, terminating 10 cm distal to the sleeve, was used for intraduodenal infusions. Intraluminal pressures were recorded at 10 Hz using custom software (DAD, written by G. S. Hebbard using Labview, National Instruments). Automated analysis was performed (MAD, written by C. H. Malbert using Labview) with subsequent exclusion of artifacts by visual inspection of each recording. Variables assessed were (1) 1) number, frequency, and amplitude of antral pressure waves (waves of amplitude >10 mmHg in any of the 6 antral side holes); 2) number, frequency, and amplitude of isolated pyloric pressure waves (waves of amplitude >10 mmHg recorded by the sleeve sensor in the absence of a pressure wave of onset within 5 s of the pyloric wave in the adjacent antral or duodenal side holes); and 3) basal pyloric pressure (measured as the mean pressure recorded by the sleeve sensor, excluding any phasic waves, in each minute, compared with the baseline pressure measured in the adjacent antral side hole). Results are expressed as change in basal pressure during the intraduodenal infusion, using mean basal pyloric pressure in the 15 min preceding the infusion as a baseline.

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Intraduodenal fructose suppressed energy intake compared with intraduodenal saline ($P < 0.05$) and glucose ($P = 0.07$); in contrast, there was no significant difference between intraduodenal glucose and saline ($P = 0.75$). Consumption of protein ($P < 0.05$) and fat ($P = 0.09$) was affected by infusion type: intraduodenal fructose suppressed protein and fat intake compared with both saline ($P < 0.05$ and $P = 0.10$, respectively) and glucose ($P < 0.05$ for both protein and fat). Intraduodenal fructose tended to suppress carbohydrate intake when compared with saline ($P = 0.11$), but, overall, the type of infusion did not affect carbohydrate intake ($P = 0.27$). There were no differences in macronutrient content between intraduodenal glucose and saline.

**DISCUSSION**

The major observations in this study are that 1) the stimulation of pyloric and suppression of antral pressure waves by intraduodenal glucose and fructose when given at a rate of 2 kcal/min for 90 min are comparable, 2) intraduodenal fructose tends to suppress food intake more than intraduodenal glucose, despite a similar (minimal) stimulation of GLP-1 and reduced GIP stimulation, and 3) GIP, rather than GLP-1, probably accounts for the greater insulin response to intraduodenal glucose than intraduodenal fructose.

Although it is well established that oral fructose empties from the stomach more rapidly than oral glucose (9, 14, 19, 39, 48), the results of our study in which the monosaccharides were infused intraduodenally at the same rate suggest that this is not attributable to differences in small intestinal feedback on antropyloric motility. It should be recognized that we did not evaluate the response of the proximal stomach to the intraduodenal infusions; intraduodenal glucose is known to induce fundic relaxation (10), and this is associated with slowing of gastric emptying (16). To our knowledge, the response of the proximal stomach to intraduodenal or oral fructose has not been evaluated. It should also be recognized that there is a substantial variation in the magnitude of the differential rate of gastric emptying of oral glucose and fructose between studies (9, 14, 19, 39, 48), which may reflect variations in the monosaccharide load (21), volume of drink (6), and posture (8, 20), as well as species differences (39); in some cases, the difference in emptying rates between glucose and fructose was modest (19). Our observations, however, suggest that the mechanisms of intestinal feedback on gastric motor function may be similar with both monosaccharides; this may explain the previous finding that the rate of gastric emptying of both glucose and fructose increases in response to a diet high in glucose (19).

Intraduodenal fructose, but not glucose, suppressed food intake compared with saline. The magnitude of this suppression was small, and a direct comparison between fructose and glucose did not quite attain significance ($P = 0.07$), although this is likely to represent a type 2 error. The amount of monosaccharide delivered intraduodenally (45 g) was similar to the oral loads given in previous studies that reported...
suppression of appetite by fructose compared with glucose (44, 49), but less than in a recent study demonstrating that intraduodenal glucose given at a rate of 3.2 kcal/min suppresses food intake compared with saline (27). By infusing the monosaccharides directly into the duodenum, we established that any greater satiating effect of fructose is not dependent on more rapid gastric emptying of fructose compared with glucose. Glucose and fructose differ in their mechanisms of absorption: glucose is absorbed via the sodium-dependent SGLT-1 and GLUT-2 transporters, and fructose is absorbed via a less well-characterized so-

Fig. 2. Blood glucose (A), plasma insulin (B), plasma gastric inhibitory peptide (C; GIP), and plasma glucagon-like peptide-1 (D; GLP-1) concentrations. Blood glucose (*P < 0.0005) and plasma insulin (*P < 0.0005), GIP (*P < 0.005), and GLP-1 (*P < 0.005) were higher during intraduodenal glucose than saline infusion. Intraduodenal fructose also increased plasma insulin (*P < 0.0005), GIP (*P < 0.05), and GLP-1 (*P < 0.001), but not blood glucose, compared with saline. Blood glucose ($P < 0.0005) and plasma insulin ($P < 0.0005) and GIP ($P < 0.005), but not GLP-1, were higher during intraduodenal glucose than fructose infusion.

Fig. 3. Change in desire to eat (A), fullness (B), and nausea (C) from baseline during 90 min of intraduodenal infusion. Intraduodenal glucose (*P < 0.05) and fructose (*P = 0.08) suppressed desire to eat when each was compared with saline, with no significant difference between them. Fullness and nausea were not affected significantly by type of infusion.

Fig. 4. Energy (A; kcal) and macronutrient (B; g) content of buffet meal. Intraduodenal fructose suppressed energy intake compared with intraduodenal saline (†P < 0.05) and glucose (¶P = 0.07); there was no significant difference between intraduodenal glucose and saline. Intraduodenal fructose suppressed protein and fat intake compared with both saline (†P < 0.05 and #P = 0.10, respectively) and glucose ($P < 0.05 for both protein and fat). There were no differences in macronutrient content between intraduodenal glucose and saline.
dium-independent transport system (28, 42). Fructose absorption may be saturated by loads as small as 30 g (35). After absorption, fructose is transported in the portal circulation to the liver and metabolized to glucose, glycogen, lactate, and triglycerides (4, 55), which may also influence appetite. Although we used 0.9% saline as a control, it should be recognized that this controlled for volume of infusion, but not osmolarity. It is, accordingly, possible that the suppression of appetite induced by fructose compared with saline may reflect greater stimulation of osmoreceptors by unabsorbed monosaccharide. Furthermore, because of the differential absorption rates of glucose and fructose, the effects of the two monosaccharides on appetite may potentially be time dependent.

Neural and humoral mechanisms interact in mediating the effects of small intestinal nutrients on appetite and motility (36). For example, the stimulation of pyloric motility by intraduodenal glucose (11) and lipid (12) is dependent on muscarinic mechanisms. Our study has focused on the release of gut peptides, which are likely to have a major role in mediating both the suppression of appetite (26) and the intestinal feedback on gastric motility (46, 57, 58) by intraduodenal monosaccharides. Differences in the secretion of gut peptides may account for the effects of glucose and fructose on appetite and gastric emptying observed previously. Recent studies suggest that insulin (5, 24) and GIP (27, 40) are unlikely to have major effects in the regulation of appetite and gastric motility in humans. The observed stimulation of plasma GLP-1 by intraduodenal glucose in our study was small and did not differ from intraduodenal fructose, whereas Kong et al. (25) demonstrated that the increment in plasma GLP-1 is much greater after 75 g oral glucose than oral fructose. Both the quantity of monosaccharide and its site of administration (oral, small intestinal, intravenous) appear to be important determinants of GLP-1 secretion. Stimulation of GLP-1 release requires absorption of monosaccharide and does not occur after intravenous glucose or oral administration of nonabsorbable carbohydrates (43, 51, 54). Whereas higher loads of glucose are absorbed efficiently and result in greater stimulation of GLP-1, higher fructose loads would be likely to exceed the capacity for absorption (35) and fail to stimulate further GLP-1 release. It was also reported that the GLP-1 response to oral glucose is greater than when the same amount of glucose is infused intraduodenally (45). The rate of intraduodenal infusion in our study (2 kcal/min) was chosen to approximate the physiological rate of emptying of nutrients from the stomach (3), but it should be recognized that there may be an initial, more rapid, period of gastric emptying while the stomach is being filled (23, 45), providing a greater stimulus for GLP-1 release. An additional possibility that there is a “gastric” phase of GLP-1 secretion induced, for example, by gastric distension has received little attention (45). The differential effects of glucose and fructose on both appetite and gastric motor function may, therefore, be dependent on the degree to which glucose can stimulate GLP-1 release, the extent of small intestinal exposure to fructose as a result of its limited absorption (35), as well as the potential satiating effects of fructose and its metabolites in the portal circulation (4, 55). The relative contribution of each of these factors at different time points after the onset of infusion might vary, so that the apparent effects of the monosaccharides on satiety may be influenced by the timing of the buffet meal. Although there is evidence that only carbohydrates with affinity for the glucose transporter (i.e., glucose but not fructose) induce satiation in the rat (37), this clearly does not apply in humans. Interestingly, there are also significant interspecies variations in the effects of fructose on the secretion of GLP-1 (42).

It has been suggested that GLP-1 may be more important than GIP as an incretin peptide (40). We, however, observed that the insulin response to intraduodenal glucose was much greater than to fructose, despite minimal (and similar) stimulation of GLP-1, and that this was associated with a greater GIP response to glucose. Hence, GIP appears to be the major incretin in our model, unless we postulate the existence of a third (as yet unknown) incretin. It should also be noted that the insulin response to fructose is enhanced when the blood glucose concentration is increased to postprandial levels (41). This is apparently not accounted for by a greater GLP-1 response (25), but it is not known whether GIP secretion is increased in these circumstances.

Perspectives

This study compared the effects of isocaloric intraduodenal loads of glucose and fructose on appetite, antropylorlic pressures, and the release of insulin, GLP-1, and GIP. This experimental design was chosen because of the known difference in rates of gastric emptying of these two sugars after oral administration. The observations, when considered in context with those of previous studies, indicate that the monosaccharide load is a critical determinant of the release of gut peptides, especially GLP-1, and the effects on appetite. The impact of the timing of a meal after a monosaccharide “preload” and the potential contribution of gastric distension to the stimulation of GLP-1 release require clarification. The apparently minor incretin effect of GLP-1 in this model, relative to that of GIP or another (undiiscovered) incretin hormone, has potential implications for the therapy of diabetes mellitus.

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REFERENCES


