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 antropyloric 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 antropyloric 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). Antropyloric 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 antropyloric 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

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concentrations are concomitantly less after fructose than glucose (7, 19, 25). GLP-1 may slow gastric emptying (46, 57, 58) and suppress antral motility (46), and this could potentially explain why the emptying of glucose is slower than that of fructose. The release of gut peptides is known to be important in mediating the satiating effects of intraduodenal nutrients (26, 29). When the release of gut peptides, including incretins, is inhibited by the somatostatin analog octreotide, the satiating effect of intraduodenal glucose is abolished (26). Administration of exogenous GLP-1 suppresses food intake (15). However, the less potent stimulation satiating effect of intraduodenal glucose is abolished (26). The release of glucose is slower than that of fructose. The release of intestin feedback on antropyloric motility and glucose can be accounted for by differences in small intestinal feedback on antropyloric motility and 2) the comparative effects of intraduodenal fructose and glucose on appetite and stimulation of GIP and GLP-1 secretion.

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, randomized 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 transmural potential difference between stomach and duodenum with a sterile saline-filled 20-gauge catheter inserted subcutaneously into the forearm as the reference electrode (18). An intravenous cannula was also inserted into a forearm vein to enable blood sampling.

After an episode of phase III of the migrating motor complex (t = −15 min), fasting motility was recorded for 15 min. An intraduodenal infusion of either 25% glucose, 25% fructose, or 0.9% saline was then commenced (at t = 0 min), using an infusion port in the catheter, at a rate of 2 ml/min (equivalent to 2 kcal/min for glucose and fructose) and continued for 90 min (i.e., 45 g of glucose or fructose in total). At t = 90 min, the catheter was removed and subjects were offered a buffet meal with quantities of food in excess of what they would be expected to eat (total energy content ~2,400 kcal; Refs. 25–27).

Visual analog scales (100 mm in length) evaluating desire to eat, fullness, and nausea were completed at t = −15, −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 mm Hg in any of the 6 antral side holes); 2) number, frequency, and amplitude of isolated pyloric pressure waves (waves of amplitude >10 mm Hg 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 (Refloxx II M, Boehringer Mannheim, New South Wales, Australia). The rest of each blood sample was placed on ice in EDTA tubes containing a protease 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 (Phade- eship 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 = −15, −5, and 0 min; Ref. 1). The energy and macronutrient content of the food consumed at the buffet meal were calculated using the DIET/4 program (Xyris Software, Highgate Hill, Queensland, Australia; Refs. 25–27).

Statistical analysis. Statistical comparisons were made using repeated-measures analysis of variance (SuperANOVA, SAS Institute, Cary, NC). All data are presented as means and standard errors. A P value <0.05 was considered significant.

RESULTS

All subjects tolerated the study well.

Antropyloric pressures. Intraduodenal glucose and fructose both suppressed antral pressure waves (P < 0.0005 for each) and stimulated isolated pyloric pressure waves (IPPWs) compared with saline (P < 0.05 for each; Fig. 1, A and B), without any difference between them. The amplitudes of antral pressure waves and IPPWs were not influenced by the type of infusion (data not shown). Basal pyloric pressure was greater during infusion of glucose than saline on direct comparison of the two (P < 0.05) and tended to be greater during fructose than saline infusion (P = 0.10; Fig. 1C); there was no difference between intraduodenal glucose and fructose.

Blood glucose and plasma insulin, GIP, and GLP-1. Blood glucose (P < 0.0005), plasma insulin (P < 0.0005), GIP (P < 0.005), and GLP-1 (P < 0.005) were higher during intraduodenal glucose than saline infusion
Intraduodenal glucose (*P < 0.005) and fructose (†P < 0.0005) both suppressed antral waves compared with saline, without any difference between them. B: frequency of isolated pyloric pressure waves (no. per 10 min) before (t = −10–0 min) and during (t = 0–90 min) intraduodenal infusion. Intraduodenal glucose (‡P < 0.05) and fructose (†P < 0.05) both stimulated isolated pyloric pressure waves compared with saline, without any difference between them. C: change in basal pyloric pressure during intraduodenal infusion (t = 0–90 min). Basal pyloric pressure was greater during infusion of glucose than saline (‡P < 0.05) and tended to be greater during fructose than saline infusion (†P = 0.10); there was no difference between intraduodenal glucose and fructose.

(Fig. 2). 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. With both intraduodenal glucose and fructose, the magnitude of the rise in GLP-1 was small. 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.

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. 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.
on both appetite and gastric motor function may, there-
ination (45). The differential effects of glucose and fructose
example, by gastric distension has received little atten-
is a "gastric" phase of GLP-1 secretion induced, for
for GLP-1 release. An additional possibility that there
more rapid, period of gastric emptying while the stom-
rate of emptying of nutrients from the stomach (3), but
the same amount of glucose is infused intraduodenally
further GLP-1 release. It was also reported that the
monosaccharide and does not occur after intravenous glucose or
GLP-1, higher fructose loads would be likely to exceed
oral glucose was much greater than to fructose,
and GIP (27, 40) are unlikely to have major effects in the regulation of
gastric motor function (46, 57, 58) by intraduodenal mono-
differences in the secretion of gut peptides may account for the effects of glucose and fructose on
appears to be a major role in mediating both the
 suppression of appetite (26) and the intestinal feedback on
gastric motility (46, 57, 58) by intraduodenal mono-
saccharides. Differences in the secretion of gut peptides
acid, 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 mono-
saccharides. 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
gastric motor function 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) demon-
strated 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 adminis-
tration (oral, small intestinal, intravenous) appear to
be important determinants of GLP-1 secretion. Stimu-
lization of GLP-1 release requires absorption of monosac-
charide 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 stom-
ach 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 atten-
tion (45). The differential effects of glucose and fructose
on both appetite and gastric motor function may, there-
fore, 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. Interest-
ingly, 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 intraduo-
denal glucose was much greater than to fructose,
and GLP-1, and that this was associated with a greater GIP re-
sponse 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 ac-
counted 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 intraduo-
denal loads of glucose and fructose on appetite, antropy-
loric pressures, and the release of insulin, GLP-1, and
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
(undiscovered) incretin hormone, has potential implica-
tions for the therapy of diabetes mellitus.

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