Effects of intravenous fructose on gastric emptying and antropyloroduodenal motility in healthy subjects

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Am J Physiol Gastrointest Liver Physiol 297: G1274–G1280, 2009. First published October 1, 2009; doi:10.1152/ajpgi.00214.2009.—Gastric emptying (GE) of glucose is regulated closely, not only as a result of inhibitory feedback arising from the small intestine, but also because of the resulting hyperglycemia. Fructose is used widely in the diabetic type 2 diabetic diet and has largely replaced sucrose in a type 1 patients (51). As with the effects of small intestinal nutrients, the slowing of gastric emptying induced by acute hyperglycemia is associated with suppression of antral pressure waves (3, 50) and their propagation (50), stimulation of basal and phasic pyloric pressure waves (13), an increase in proximal gastric compliance (20, 21), and suppression of duodenal motor activity (49). Acute hyperglycemia also affects the perception of sensations arising from the gut, including fullness and nausea (20, 21, 31, 38). In view of the well-documented effects of hyperglycemia, it is surprising that there is no information about the potential effects of intravenous fructose on gastric emptying or gastric motility.

Fructose consumption has increased markedly in the last 20–30 yr (17, 54). Fructose is sweeter than isoenergetic glucose and, as such, offers the same level of sweetness for a lower energy burden (15, 18). Fructose is used widely in the type 2 diabetic diet and has largely replaced sucrose in a number of processed foods, particularly beverages (15, 57). The glycemic response to fructose is also substantially less than to glucose (4, 9, 24, 33, 57). There are also substantial differences in the effects of oral glucose and fructose on the release of gastrointestinal hormones, including insulin (57) and the “incretin” hormones glucagon-like peptide (GLP)-1 (33, 55, 57) and glucose-dependent insulinotropic-polypeptide (GIP) (57). Fructose-induced insulin release is glucose dependent in that insulin secretion following intravenous (10) and oral (48) fructose is greater during hyper- than during euglycemia.

The primary aims of this study were to determine whether intravenous fructose affects gastric emptying and antropylo-
rododental motility and, if so, how these effects compare to those induced by intravenous glucose.

MATERIALS AND METHODS

Subjects

Six healthy men (mean age: 26.7 ± 3.8 yr, body mass index: 26.4 ± 1.4 kg/m²) were studied. Subjects were randomly selected from volunteers who responded to advertisements posted on university notice boards. Subjects were asked to maintain a normal diet for three days before each study, and smokers were required to abstain from tobacco for at least 12 h before each study day. No subject had a history of diabetes mellitus, gastrointestinal disease or surgery, significant respiratory, cardiac, or hepatic disease, chronic alcohol abuse, gout, or epilepsy. No subject was taking medication known to influence gastrointestinal function.

Each subject provided written, informed consent prior to involvement. The protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital, and all studies were performed in accordance with the Declaration of Helsinki.

Experimental Protocol

Each subject underwent three randomized, single-blind studies, separated by at least three days. During each study, subjects received an intravenous infusion of either fructose or glucose (0.5 g/kg body wt dissolved in sterile water as 0.2 g/ml, for both monosaccharides) or placebo (saline 0.9% wt/vol), administered over 20 min, i.e., the total volume infused varied between subjects depending on body weight. The dose of the monosaccharides was selected on the basis of previous studies (1, 10, 12).

On each study day, subjects attended the Department of Nuclear Medicine, PET and Bone Densitometry at the Royal Adelaide Hospital, and all studies were performed in the absence of a pressure wave of onset within 5 s of the pyloric wave, occurring in the antral or duodenal side holes, of amplitude >10 mmHg), and 3) number and amplitude of duodenal pressure waves (waves in any of the first 3 duodenal side holes of amplitude >10 mmHg); using custom software (written by Prof. A. Smout, Utrecht, The Netherlands). The number and amplitude of pressure waves was determined manually by visual inspection of manometric recordings, and measurements of amplitude were corrected by subtraction of baseline pressure recordings. Because of the intermittent position of the sleeve sensor, basal pyloric pressure was not recorded. The number of antral pressure waves observed in the first 30 min following intravenous glucose and fructose was too small to allow meaningful analysis of patterns of antral wave propagation.

Statistical Analysis

Data (blood glucose, gastric emptying, and IPPWs) were evaluated using repeated-measures ANOVA and are shown as means ± SE. The number and amplitude of both antral and duodenal pressure waves were analyzed using Wald statistics with generalized estimating equations (GEE) (35, 58) on the basis of chi-square distribution to determine the effect size of the Friedman criteria, and their amplitude was fine tuned TMPD criteria, and the number and amplitude of isolated pyloric pressure waves (IPPPWs) (IPPPWs recorded by the sleeve sensor in the absence of a pressure wave of onset within 5 s of the pyloric wave, occurring in the antral or duodenal side holes, of amplitude >10 mmHg), and 3) number and amplitude of duodenal pressure waves (waves in any of the first 3 duodenal side holes of amplitude >10 mmHg), using custom software (written by Prof. A. Smout, Utrecht, The Netherlands). The number and amplitude of pressure waves was determined manually by visual inspection of manometric recordings, and measurements of amplitude were corrected by subtraction of baseline pressure recordings. Because of the intermittent position of the sleeve sensor, basal pyloric pressure was not recorded. The number of antral pressure waves observed in the first 30 min following intravenous glucose and fructose was too small to allow meaningful analysis of patterns of antral wave propagation.
and amplitude of antral pressure waves. Likewise, measurements from the first three sideholes in the duodenum were grouped for the analysis of number and amplitude of duodenal pressure waves. For analysis of the number and amplitude of antral and duodenal pressure waves, data are expressed as means with upper and lower 95% confidence interval (95% CI) limits. Student’s t-tests were used to assess paired comparisons. A P value < 0.05 was considered significant in all analyses.

RESULTS

All subjects tolerated the saline and glucose studies well. During fructose infusion, four subjects volunteered epigastric discomfort (mild and transient), and, of these, two reported nausea.

Blood Glucose

Baseline blood glucose did not differ between study days (saline 5.4 ± 0.3 mmol/l; glucose 5.5 ± 0.3 mmol/l; fructose 5.2 ± 0.2 mmol/l) (Fig. 1). Mean blood glucose (calculated using 30-min blood glucose levels from t = 0–120 min) was greater following glucose (7.5 ± 0.3 mmol/l) compared with both saline (5.5 ± 0.2 mmol/l; P = 0.0008) and fructose (5.3 ± 0.2 mmol/l; P = 0.0002) infusions, with no difference between saline and fructose (P = 0.47). During glucose infusion, the peak blood glucose concentration was 16.4 ± 0.6 mmol/l, and the time to peak was 20 ± 3 min. At t = 120 min, blood glucose was less after glucose compared with both saline (P = 0.0005) and fructose (P = 0.009) infusions, with no difference between saline and fructose (P = 0.35).

Gastric Emptying and Intragastric Distribution

The overall gastric emptying pattern approximated a linear function after an initial lag phase (Fig. 2A). The lag phases, as measured by the arrival of food in the duodenum, were 18.7 ± 2.9 min, 34.7 ± 7.3 min, and 35.3 ± 9.8 min for saline, glucose, and fructose studies, respectively (P = NS for all comparisons), although there were trends for the lag phase on the saline day to be shorter than the glucose (P = 0.07) and fructose (P = 0.09) days. Similarly there was no significant difference in the time for 10% of the meal to empty between either saline (35.5 ± 5.0 min) or fructose (47.8 ± 11.9 min) with glucose (52.7 ± 7.3 min) although the time was shorter (P = 0.04) after saline compared with glucose. There was a treatment-by-time interaction (P = 0.0001) for total gastric emptying; gastric emptying from the total stomach was slower with both glucose and fructose compared with saline between t = 45–120 min (P < 0.005 for all), with no significant difference between glucose and fructose. From t = 45 min, gastric emptying was slowest with glucose compared with both fructose (P < 0.05) and saline (P < 0.0001) although fructose was slower than saline (P < 0.0001). In five of the six subjects, gastric emptying was substantially slower after intravenous fructose than after intravenous saline, and, in the remaining one, gastric emptying was comparable. Between t = 45 and 120 min, there was no difference in total gastric emptying between the three treatments: saline 55.7 ± 2.7%, glucose 58.2 ± 6.3%, and fructose 53.2 ± 6.3% (P = NS for all).

Fig. 1. Effects of intravenous fructose (F), glucose (G), and saline (S) (infused between t = 0–20 min) on the blood glucose concentration following ingestion of 100 g ground beef. Data are means ± SE.

Fig. 2. Effects of intravenous fructose, glucose, and saline (infused between t = 0–20 min) on total (A), proximal (B), and distal (C) gastric emptying of 100 g ground beef. Data are means ± SE.
There was a treatment-by-time interaction \((P = 0.0001)\) for proximal gastric emptying (Fig. 2B); retention in the proximal stomach was greater with glucose compared with saline (from \(t = 15–90\) min; \(P < 0.05\) for all) and greater with fructose compared with saline (from \(t = 15–105\) min; \(P < 0.01\)), with no difference between glucose and fructose.

There was a treatment-by-time interaction \((P = 0.0001)\) for distal gastric emptying (Fig. 2C); retention in the distal stomach was initially greater after saline than both glucose (from \(t = 15–30\) min; \(P < 0.002\)) and fructose (from \(t = 15–45\) min; \(P < 0.01\)), with no difference between glucose and fructose (from \(t = 15–45\) min). Retention in the distal stomach was subsequently less with saline compared with both glucose (from \(t = 75–120\) min; \(P < 0.001)\) and fructose (from \(t = 90–120\) min; \(P < 0.05\)), with no difference between glucose and fructose (between \(t = 105\) and 120 min).

**Antropyloroduodenal Manometry**

Antral pressure waves. There was no significant difference in the number of antral waves at baseline between the three studies [saline: 4.9 (95%CI: 1.7, 14.6); glucose: 2.8 (95%CI: 2.4, 3.3); fructose: 1.9 (95%CI: 1.0, 3.9)] (Fig. 3A). There was a significant treatment-by-time interaction between the three infusions \((P < 0.0001)\). There was a significant increase in the number of antral waves following the meal during saline, glucose, and fructose \((P < 0.0001)\) for all infusions. The rise in the number of antral waves from baseline occurred promptly following meal ingestion (i.e., \(t = 0–30\) min) during infusion with saline \((P = 0.02)\) but not during glucose \((P = 0.21)\) or fructose \((P = 0.65)\), i.e., the stimulation of antral waves was attenuated by infusion of glucose and fructose. In contrast, the rise in the number of antral waves was not evident until \(t = 30–60\) min after fructose \((P < 0.0001)\) and \(t = 90–120\) min after glucose \((P < 0.0001)\). Over the 120-min period, the number of antral waves was greater after saline compared with both fructose \((P = 0.002)\) and glucose \((P < 0.0001)\) infusion and greater for fructose compared with glucose \((P = 0.0004)\).

The amplitude of antral pressure waves at baseline was higher for saline \([33.9\) mmHg (95%CI: 24.8, 46.4)] than glucose \([17.5\) mmHg (95%CI: 11.7, 26.2)] \((P = 0.01)\) and tended to be greater compared with fructose \([20.6\) mmHg (95%CI: 16.4, 25.8)] \((P = 0.09)\), with no significant difference between fructose and glucose \((P = 0.49)\). Following meal ingestion, there was no significant difference in the amplitude of antral pressure waves between the three infusions (data not shown).

**IPPWs.** There was no difference in the number of IPPWs at baseline between the three studies (saline: 2.0 \(\pm\) 0.6; glucose: 3.7 \(\pm\) 1.8; fructose: 1.3 \(\pm\) 1.0) (Fig. 3B). There was a significant \((P = 0.0001)\) time effect for the duration of the study. There was an increase in the number of IPPWs from baseline to 30 min immediately following meal ingestion (i.e., \(t = 0–30\) min) during infusion with glucose \((P = 0.003)\) but not with saline \((P = 0.21)\) or fructose \((P = 0.06)\), i.e., the number of IPPWs was increased during infusion of glucose but not fructose or saline. The rise in the number of IPPWs was not evident until \(t = 30–60\) min for both saline \((P = 0.018)\) and fructose \((P = 0.0002)\). For the period \(t = 0–120\) min, there was no treatment effect on the number of IPPWs.

There was no significant difference in the amplitude of IPPWs at baseline between the three treatments (data not shown). There was a significant \((P = 0.0001)\) time effect for the amplitude of IPPWs with the three treatments for the duration of the study. There was a significant increase in the amplitude of IPPWs from baseline immediately following meal ingestion (i.e., \(t = 0–30\) min) during infusion with saline \((P = 0.02)\), glucose \((P = 0.0005)\), and fructose \((P = 0.04)\). The magnitude of the increase in amplitude at \(t = 0–30\) min was greater with glucose compared with fructose \((P = 0.05)\) but not saline \((P = 0.37)\), and there was no difference in the amplitude of IPPWs at \(t = 0–30\) min between saline and fructose \((P = 0.28)\) (data not shown).

**Duodenal pressure waves.** There was no significant difference in the number of duodenal waves at baseline between the
three infusions [saline: 11.1 (95%CI: 5.4, 22.7); glucose: 7.8 (95%CI: 4.4, 13.7); and fructose: 6.83 (95%CI: 3.35, 13.95)] (Fig. 3C). There was a significant increase in the number of duodenal waves from baseline following meal ingestion (i.e., \( t = 0\)–30 min) during infusion with saline (\( P < 0.0001 \)) and glucose (\( P < 0.0001 \)) but not fructose (\( P = 0.27 \)). However, for the 120-min period, the number of duodenal waves was not significantly different between the three infusions.

There was no significant difference in the amplitude of duodenal pressure waves at baseline or after the meal between the three infusions (data not shown).

**DISCUSSION**

This study establishes that, when given intravenously, fructose has the capacity to slow gastric emptying and modulate antropyloroduodenal motility in healthy subjects and that the magnitude of these effects is comparable to those induced by an identical intravenous glucose load. In particular, intravenous administration of fructose resulted in a transient slowing of gastric emptying and intragastric distribution of a solid meal, associated with suppression of antral and duodenal pressure waves and (nonsignificant) stimulation of IPPWs.

The demonstrated effects of intravenous glucose, resulting in peak plasma glucose concentrations of \( \sim 16 \) mmol/l, on gastric emptying (40, 50, 51) and antropyloroduodenal motility (13, 49, 50) are consistent with previous reports. As has been shown, these effects were transient, indicating that they were secondary to hyperglycemia. The effects of intravenous glucose and fructose to slow gastric emptying evident during the initial phase of emptying, which as is to be expected for the solid meal studied, were dominated by the lag phase (8). This was anticipated given that the infusions were administered over \( 20 \) min, immediately after meal consumption, and that effects on emptying and motility would only be expected when blood concentrations of glucose (13, 40) and fructose were elevated. Hence, the timing and duration of the infusions diminished the capacity to observe any effect on the postlag emptying slope. Because patterns of emptying from the proximal stomach closely paralleled emptying from the total stomach, it is possible that differences in intragastric distribution affected motility. This appears, however, unlikely given that acute hyperglycemia has been shown to stimulate pyloric (13) and suppress antral (19) motility in the fasted state and that differences in distal stomach content were modest. The mechanism(s) mediating the effects of hyperglycemia on gastric motility are poorly defined but appear to involve nitric oxide pathways (34). Glucose-dependent neurons are also known to be present in the myenteric plexus (39) and central nervous system (44). The effect of acute hyperglycemia, to slow gastric emptying, is apparently not mediated by changes in plasma osmolality (46). Although plasma fructose was not quantified, the dose used was identical to that in a previous study (10), and the effects of fructose on gastric emptying/motility are probably, like glucose, dependent on the plasma concentrations. As expected, intravenous fructose had no effect on plasma glucose (1, 10, 56), nor would it be expected to affect insulin secretion (10). Intravenous glucose has no effect on the secretion of GLP-1 or GIP, which are released by enteral glucose and account for the so-called “incretin effect” (43). Hence, it appears that both glucose and fructose have the capacity to slow gastric emptying both as a result of their interaction with the small intestine (11, 17, 24, 52) and also the elevation of plasma monosaccharide concentrations. Accordingly, although we did not observe differences in the magnitude of the delay in gastric emptying when equivalent doses of monosaccharides were given intravenously, this does not exclude a difference following oral administration, particularly because ingested fructose is absorbed from the intestine much more slowly (via glucose transporter 5) than glucose and, hence, results in lower plasma concentrations than oral glucose (via sodium-glucose cotransporter 1) (30, 53). It should be recognized that we studied only a relatively small number of subjects, and the possibility that there are modest differences in the effects of intravenous fructose and glucose, which may potentially contribute to the slightly more rapid gastric emptying of oral fructose compared with oral glucose, cannot be excluded (11, 17, 24, 45, 52) although this may well be explicable by the differential effects on gut hormone release, particularly GLP-1 (33, 47, 57). Four subjects experienced transient, mild epigastric discomfort during intravenous fructose infusion. This has been reported during rapid fructose infusion in much higher doses (0.5 g/kg in 5 min to 1.5 g/kg in 60 min) (12), and its cause remains uncertain. In the present study, the severity and duration of discomfort did not compromise the completion of the experiments, and the effects of fructose on gastric emptying appeared consistent in both symptomatic and asymptomatic subjects. While in view of our observations that it would be of interest to evaluate the effects of different, particularly lower doses of fructose and glucose, it should be recognized that the blood glucose concentrations observed after intravenous glucose (peak \( \sim 16 \) mmol/l) are comparable to those observed in uncomplicated type 2 diabetes patients after oral 50-g or 75-g glucose loads (32). Because of the substantial effect of the menstrual cycle on gastric emptying (6), we elected to study only males. Hence, our observations should be extrapolated to females circumspectly.

That fructose has the capacity to slow gastric emptying as a result of its plasma levels is not surprising given that intravenous administration of high-caloric nutrients (parenteral nutrition) has been reported to delay solid (41) and liquid (7) gastric emptying in humans. It has been suggested that this reflects the stimulation of gastric acid secretion by the amino acid content of the parenteral feed (29, 42), with a concomitant suppression of pancreatic and biliary secretion and a reduction in the buffering capacity of the duodenum (7). Energy intake may also be suppressed during parenteral nutrition, possibly as a result of slower gastric emptying (27). Intravenous administration of high-dose amino acids has also been shown to decrease antral motility (16). As with fructose, the mechanisms mediating these effects remain to be determined.

In conclusion, in healthy subjects, intravenous fructose has the capacity to slow gastric emptying and modulate gastric motility; the magnitude of the delay in gastric emptying appears comparable to that induced by intravenous glucose.

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