Fructose Prefeeding Reduces the Glycemic Response to a High-Glycemic Index, Starchy Food in Humans[1]

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ABSTRACT The study objective was to determine whether a small dose of fructose administered before or simultaneously with a high glycemic index, starchy food decreases postprandial glycemic response. Nondiabetic healthy adults ($n = 31$; mean $\pm$ SEM: age, 26 ± 1 y; weight, 66.1 ± 2.6 kg; body mass index, 23.3 ± 0.6 kg/m^2) were studied in a randomized crossover design. Treatments consisted of 50 g available carbohydrate from instant mashed potatoes fed alone (control) or with 10 g fructose fed 60, 30 or 0 min before the potato meal. Capillary finger-stick blood samples were analyzed for glucose concentration at -60, -30, 0, 15, 30, 45, 60, 90 and 120 min relative to the ingestion of the potato meal. Compared with the control, the positive incremental area under the glucose curve was reduced 25 and 27% ($P < 0.01$) when fructose was fed either 60 or 30 min before the meal, respectively. In contrast to previous studies demonstrating that immediate administration of a small amount of fructose lowers the glycemic response to a glucose solution, we found that fructose must be consumed before a starchy food to reduce postprandial glycemia. J. Nutr. 132: 2601–2604, 2002.

KEY WORDS: • fructose • glycemia • breath hydrogen • glycemic index • starch • humans

As the rates of obesity and diabetes continue to climb in the United States (1), the development of dietary methods for controlling postprandial glycemia is becoming increasingly important. The use of fructose as an alternative sweetener is one potential approach. Animal and human studies have demonstrated that fructose may play an active, catalytic role in the augmentation of hepatic glucose uptake and the subsequent lowering of the glycemic response to additional dietary carbohydrate (2–7). Although the findings from these previous studies indicate that the simultaneous administration of fructose lowered the postprandial glycemic response to a glucose load, we questioned whether the fructose-induced lowering of the glycemic response to the glucose solution could translate equally to a high glycemic index, starchy food, which is more similar to a meal.

The primary objective of this study was to determine the effect of the timing of fructose ingestion on the postprandial glycemic response of healthy nondiabetic adults to instant mashed potatoes, which contain a rapidly digested starch that normally elicits a high glycemic response. Secondary objectives of this study were to determine whether the malabsorption of carbohydrate from either fructose or mashed potatoes occurred (as assessed by the breath hydrogen method) and to compare the relative rankings of the glycemic responses to several dietary treatments in a repeated-measures design using a portable self-blood glucose monitoring device Accu-Chek Advantage Blood Glucose Monitoring System (AC;[3] Roche Diagnostics, Indianapolis, IN) and a standard laboratory glucose analyzer (YSI; YSI 2300 Stat Plus, Yellow Springs Instruments, Yellow Springs, OH).

SUBJECTS AND METHODS

Subjects. Nondiabetic, healthy subjects (13 men, 19 women) aged 20–41 y (mean $\pm$ SEM; 26 ± 1 y) were recruited for participation in the study by virtue of their responses to advertisements posted around the campus of The Ohio State University. One woman withdrew from the study due to inability to adhere to the study protocol; thus a total of 31 subjects completed the study. The body weight (mean $\pm$ SEM) of the remaining 31 subjects was 66.1 ± 2.6 kg (range = 45.2–96.2 kg). The body mass index was 23.3 ± 0.6 kg/m^2 (range = 18.3–29.7 kg/m^2). Before the study, blood glucose was measured for each fasting subject by capillary finger-stick using the AC monitor. The fasting plasma glucose of the subjects was 5.31 ± 0.06 mmol/L (range, 4.61–6.10 mmol/L). The self-reported ethnicity of the subjects was as follows: 20 Caucasian, 10 Asian or Pacific Islander, 1 Latino. Potential subjects were excluded from the study during an initial screening process if they had medical conditions or were taking medications (e.g., antibiotics) that would interfere with glucose metabolism or would alter the colonic bacteria. The Institutional Review Board Human Subjects Committee at The Ohio State University approved the experimental protocol. Informed consent was obtained from all subjects before the start of the study.

Feeding protocol. The study was a double-masked, crossover design in which subjects participated in four separate 2-h meal glucose tolerance tests. The tolerance tests were spaced 2–7 d apart for each subject. Subjects were randomly assigned to 1 of the 24 possible treatment sequences provided to subjects in sealed envelopes on d 1

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[3] Abbreviations used: AC, Accu-Chek Advantage blood glucose monitor; AUC, area under the curve; BMI, body mass index; F(−60), fructose fed 60 min before the mashed potato meal; F(−30), fructose fed 30 min before the mashed potato meal; IF, fructose fed immediately with the mashed potato meal; NF, control meal containing no additional fructose; RGR, relative glycemic response; YSI, YSI 2300 Stat Plus glucose analyzer.

of treatment. After an overnight fast of 10–12 h, subjects consumed a portion of instant mashed potatoes (61.1 g Hungry Jack instant mashed potatoes, Pillsbury, Minneapolis, MN; prepared with 360 mL boiling water) containing 50 g available carbohydrate. The effects of the timing of fructose ingestion were evaluated by having the subjects consume a solution of 10 g fructose (Now Foods, Bloomingdale, IL) dissolved in 60 mL tap water at 60, 30 or immediately (0 min) before the instant mashed potato meal [treatments F(−60), F(−30) and IF, respectively]. Subjects received 60 mL of plain tap water at each time point when the fructose was not consumed. The control meal (treatment NF) consisted of the mashed potatoes with no supplemental fructose. Finally, all subjects were allowed to consume an additional 240 mL of tap water to facilitate their consumption of the mashed potato meal. They consumed the mashed potato meal within 10 min.

To ensure that subjects had similar glycogen stores on the 4 test days, they were instructed to consume a high carbohydrate diet (minimum 150 g carbohydrate/d) for 3 d before each meal glucose tolerance test and were also instructed to avoid exercise 24 h before the experiment. Adequate carbohydrate intake was verified by 3-d diet records. On the evening before each meal glucose tolerance test, all subjects consumed a low residue dinner that was provided to them. After the low residue evening meal, they were instructed to fast overnight, during which time only the consumption of water was allowed. Smoking was prohibited.

Blood glucose analysis. Finger-prick capillary blood glucose samples were obtained at −60, −30 and 0 min before the mashed potato meal as well as at 15, 30, 45, 60, 90 and 120 min after the start of the mashed potato meal. Blood samples were analyzed utilizing two methods of glucose determination. The AC monitor measures the glucose concentration in whole blood using a test strip containing glucose dehydrogenase (8–10). The blood glucose concentration is measured in whole blood and then the system mathematically adjusts the result to approximate plasma glucose. Thus, results from the AC analyzer will be referred to as "plasma glucose," even though whole blood was analyzed. From the same finger stick, another 250 µL of blood was collected into a capillary tube containing EDTA for analysis of glucose in whole blood (within 30 min of collection) using the YSI glucose analyzer (glucose oxidase method). At a few time points, the technicians were unable to collect enough blood for the additional YSI analysis and these points are reported as missing values. However, complete data were collected for the AC monitor.

Calculation of blood glucose area under the curve (AUC) and relative glycemic response (RGR). The positive incremental AUC, ignoring any areas below the baseline, for the blood glucose concentrations from 0 to 120 min after the mashed potato meal were calculated according to the method of Wolever et al. (11). The RGR of treatments F(−60), F(−30) and IF were calculated for individual subjects according to the following formula: [(glucose AUC for treatment)/(glucose AUC for NF control)] × 100.

Breath hydrogen analysis. A subset of 10 subjects was randomly selected and underwent further testing for malabsorption of the carbohydrates fed in this study. Breath hydrogen and methane concentrations were monitored hourly (beginning at −60 min) during the 2-h meal glucose tolerance test, and the subjects continued to collect hourly breath samples for an additional 6 h after the meal glucose tolerance test. The concentrations of carbon dioxide, hydrogen and methane in breath samples were analyzed by gas chromatography (Microlyzer Gas Analyzer, model SC; Quintron Instruments, Milwaukee, WI). Subjects were classified as having carbohydrate malabsorption if their breath hydrogen concentrations increased by > 10 ppm (0.9×10^{-6} g hydrogen/L of air or 0.45 µmol/L) above baseline (12).

Intolerance symptoms. Subjective gastrointestinal tolerance ratings of the frequency and intensity of nausea, abdominal cramping, abdominal distention and flatulence were obtained for the 24-h period after the test by using visual analog rating scales (0 = usual, 100 = more than usual; 0 = absent symptoms, 100 = severe symptoms). Similar analog scales for measuring gastrointestinal symptoms have been used in previous studies (13).

Statistical analysis. Using data from a previous study, a power analysis conducted before this study indicated that 30 subjects would

be required to detect a 20% difference in peak glucose concentrations with 80% power.

The data for adjusted peak glucose and also for glucose AUC were examined for normality using the Shapiro-Wilk test (14). Because these data were normally distributed, parametric methods were used. A First-Order Carry-Over Model with Period Effects was fit to the data (SAS, version 8.0 for Windows, SAS Institute, Cary, NC). No evidence of a carry-over effect was observed; thus, these data were analyzed by ANOVA for a randomized block design, with subjects serving as the blocks. Any significant ANOVA result (significance was defined as $P < 0.05$) was followed by the Tukey-Kramer post-hoc test for paired comparisons (15). Data for plasma and blood glucose at individual time points were also examined for normality using the Shapiro-Wilk test. Normally distributed data were analyzed via parametric methods, whereas nonnormally distributed data were analyzed by the Friedman rank test (15). The Tukey-Kramer method was again used for paired comparisons when there was a significant ANOVA result.

For each of the treatments, the differences in relative glycemic responses between the two glucose analyzers were evaluated using separate Wilcoxon Rank Sum tests (with a Bonferroni correction), because the data were nonnormally distributed (NCSS 2000, NCSS Computing, Kaysville, UT). In addition, the plasma and blood glucose responses at all time points for the AC instrument and the YSI instrument were correlated using the Pearson method (15). The Cochran Q test was used to test whether the proportion of individuals having a positive breath hydrogen test differed among the 4 treatments (16).

RESULTS

Plasma glucose concentrations did not differ due to the treatments at the −60 min time point (**Fig. 1**). The administration of fructose at −60 min and at −30 min caused small, but significant increases in plasma glucose at the −30 ($P = 0.002$) and 0 min ($P < 0.001$) time points, respectively. For all 3 fructose treatments, the peak plasma glucose concentrations were observed at the 30-min time point, but plasma glucose did not peak until the 45-min time point for the control treatment. The F(−60) and F(−30) treatments decreased peak plasma glucose by 17 and 20% ($P < 0.010$), respectively, whereas the IF treatment caused a nonsignificant 6% increase ($P = 0.60$) compared with the NF control. Plasma glucose levels for all treatments returned to baseline levels by the 120-min time point. For statistical comparisons of treatments at each time point, see **Table 1**. The blood glucose
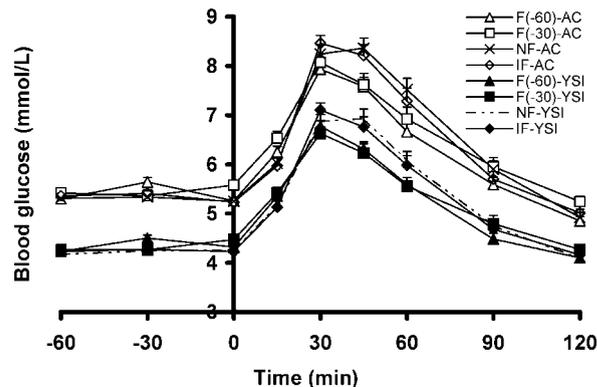

FIGURE 1 Plasma and blood glucose responses in humans administered a no fructose control treatment (NF) or fructose at −60 [F(−60)], −30 [F(−30)] or 0 min (IF) before a mashed potato meal. AC, Accu-Chek monitor, YSI, YSI instrument. Data points are the mean ± SEM ($n = 31$ for AC, $n = 27$–30 for YSI). Glucose (mmol/L) · 18.01 = glucose (mg/dL); thus, a blood glucose of 5 mmol/L ≈ 90 mg/dL.

responses as measured by the YSI instrument essentially paralleled those of the AC monitor, although the values for the YSI instrument for all the treatments at each time point were uniformly lower (by an average of 22%). This presumably was due to the mathematical correction that is made by the AC monitor to make the values resemble plasma glucose concentrations, a correction that is not made by the YSI instrument. Plasma glucose concentration is ~10–15% higher than that of whole blood, but is variable depending on the subject's hematocrit (17).

The blood glucose AUC for the F(−60) and F(−30) treatments were lower ($P < 0.01$) than for either the IF treatment or the NF control, regardless of which blood glucose instrument was used (**Fig. 2**). In addition, there were no differences in blood glucose AUC between the F(−60) and F(−30) treatments or between the IF treatment and the NF control for either instrument.

The RGR (measured by AC) were 16, 20 and 1% lower than the NF control for the F(−60), F(−30) and IF treatments, ($P = 0.558$, $P = 0.899$, $P = 0.687$, respectively) (data not shown). Similar decreases of 15, 24 and 1% for the F(−60), F(−30) and IF treatments, respectively, were observed with the YSI instrument. There were no differences in the RGR between the two instruments for any of the treatments. In addition, there was a significant correlation ($r = 0.956$, $P < 0.001$) between the glucose concentrations as measured by the two instruments at the various time points.

The numbers of subjects (of 10 tested) who had a positive breath hydrogen test were not different among the 4 different treatments. Minimal effects on gastrointestinal symptoms including intensity ($\leq 5.03/100$) and frequency ($\leq 6.65/100$) of nausea, cramping, distention and flatulence were noted for each treatment. Thus, there was no further statistical evaluation of symptoms.

DISCUSSION

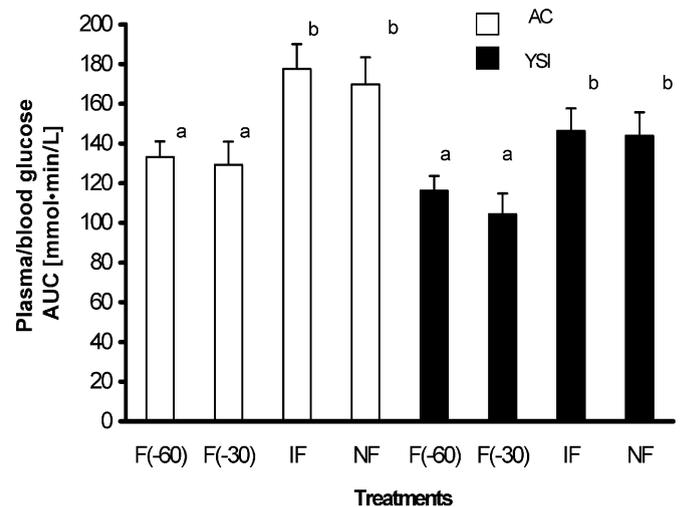This study demonstrates that administration of fructose either 60 or 30 min before a 50-g carbohydrate challenge from

TABLE 1

Results of Tukey-Kramer paired comparisons for plasma/blood glucose in humans administered a no fructose control treatment or fructose at −60, −30 or 0 min before a mashed potato meal[1]

Time interval (min)	Instrument	
	AC	YSI
−60	NS	NS
−30	F(−60) > F(−30), NF, IF	F(−60) > F(−30), NF, IF
0	F(−30) > F(−60), NF, IF	F(−30) > F(−60), NF, IF
15	F(−30) >, NF, IF	NS
30	IF > F(−60)	IF > F(−30)
45	IF, NF > F(−60), F(−30)	NF > F(−60), F(−30)
		IF > F(−30)
60	NF > F(−60), F(−30)	NF > F(−60)
	IF > F(−60)	
90	NS	NS
120	F(−30) > F(−60), NF	NS

[1] F(−60), fructose fed 60 min before mashed potatoes; F(−30), fructose fed 30 min before mashed potatoes; IF, fructose fed immediately with mashed potatoes; NF, no fructose (control). AC, Accu-Chek instrument; YSI, YSI instrument. NS, not significant, $P \geq 0.05$.

FIGURE 2 Incremental areas under the glucose curves for humans administered a no fructose control treatment (NF) or fructose at −60 [F(−60)], −30 [F(−30)] or 0 min (IF) before a mashed potato meal. AC, Accu-Chek monitor, YSI, YSI instrument. Data points are the mean ± SEM ($n = 31$ for AC, $n = 27$–30 for YSI). Values for each instrument not sharing a letter differ, $P < 0.01$.

a high glycemic index, starchy food can substantially lower postprandial glycemic response. These results at least partially confirm the findings of Moore et al. (6,7), who reported that a small dose of fructose (7.5 g) reduced the glycemic response to a 75-g glucose solution in 11 healthy adults and also in 5 adults with type 2 diabetes. However, the fructose was given simultaneously with the glucose solution in those studies, whereas we found no effect of the immediate administration of fructose on the glycemic response to starch from mashed potatoes. Differences in the type and the amount of carbohydrate fed in the studies of Moore et al. (6,7) compared with this study may explain the discrepancy. They fed glucose, which requires no hydrolysis for absorption, as opposed to the starch fed in this study. It has been established that the absorption of fructose from the intestine is greatly facilitated by the presence of free glucose (18–20). The hydrolysis of starch by amylase results in mainly di-, tri- and oligosaccharides in the lumen, rather than free monosaccharides (which occur primarily at the brush border). Because there does not appear to be a disaccharidase-related fructose transport system in humans (21), the absorption of fructose in the presence of di-, tri- and oligosaccharides from starch hydrolysis might not have been as rapid as it would have been in the presence of free glucose. In addition, the larger carbohydrate challenge fed in the study of Moore et al. compared with this study (75 vs. 50 g) may have enhanced the sensitivity for detecting changes in the glycemic response when fructose was given simultaneously with the carbohydrate challenge.

Potential mechanisms for the decreased glycemic response caused by fructose in the present study include: *1*) enhanced insulin secretion or a variant of the Staub-Trauggot effect (22); *2*) fructose-induced malabsorption of carbohydrate; or *3*) fructose-induced stimulation of hepatic glucose uptake via the pathway described by Agius and Peak (2) and Van Shaftingen et al. (3). The first hypothesis is not likely because, although insulin was not measured in the present study, the previous studies by Moore et al. (6,7) showed either no change or a decrease in insulin secretion in normal subjects and subjects with type 2 diabetes, respectively. The second hypothesis is probably also not correct given that there were no differences

in breath hydrogen excretion after the 4 treatments in the subset of 10 subjects presently studied. The most likely explanation is that small doses of fructose can stimulate hepatic glucose uptake. Briefly, fructose, upon its arrival in the hepatocyte, is rapidly phosphorylated to fructose-1-phosphate, which then competes with fructose-6-phosphate for binding on a glucokinase regulatory protein that is anchored in the hepatocyte nucleus (2,3). This competitive inhibition causes glucokinase to be released from its regulatory protein, enabling the liberated and active glucokinase to diffuse to the cytosol. In support of this hypothesis, studies in dogs (4,5) have demonstrated that small amounts of fructose infused intraportally or included with an intraduodenal glucose load increased hepatic glucose uptake and reduced postprandial hyperglycemia, respectively.

In summary, we found that a small dose of fructose consumed 30 or 60 min before a high glycemic index, starchy food decreases the glycemic response compared with either immediate or no fructose treatments. This finding may have practical applications because the small amount of fructose used in this study could easily be obtained in the diet via fruits (e.g., an apple has 9–10 g fructose) (23). In addition to the previously described increase in the satiety response to subsequent food intake by preingestion of highly fibrous fruits (24), the fructose content of these fruits may confer further benefits by lowering glycemia. It is not known whether the dose of fructose used in this study represents the optimal dose of fructose or whether other doses of fructose might change the timing of when fructose should be given relative to the ingestion of the test carbohydrate; thus, future studies should focus on these questions. Finally, we demonstrated that a portable self-blood glucose-monitoring device yields glycemic response rankings similar to those of a standard laboratory analyzer.

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