Peripheral Glucose Appearance Rate Following Fructose Ingestion in Normal Subjects

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Ingested fructose is rapidly utilized by the liver and is either stored as glycogen, converted to glucose, or oxidized to CO_2 for energy. The glycemic response to fructose is known to be modest. However, the relative importance of these pathways in humans is unclear. In the present study, a tritiated glucose tracer dilution technique was used to determine the effect of fructose ingestion on the glucose appearance rate (R_a) in the peripheral circulation over an 8-hour period beginning at 8:00 AM. Six normal healthy males ingested 50 g fructose with 500 mL water. On a separate occasion, the same subjects received 500 mL water without fructose as a control. Serum insulin, triglycerides, plasma glucagon, glucose, lactate, alanine, urea nitrogen, and total amino acids also were determined. The plasma glucose concentration was not significantly different following ingestion of fructose or water, other than a transient increase beginning at 8:30 AM of 0.8 mmol/L in response to ingested fructose. Glucose appearing in the peripheral circulation as a result of ingestion of 50 g fructose was calculated to be 9.8 ± 2.4 g. Following the ingestion of fructose, there was a small increase in glucagon but a 2-fold increase in insulin concentration. There was a large transient increase in lactate and alanine concentrations. The total amino acid concentration remained unchanged, as did the urea production rate. In summary, in men fasted overnight, ingestion of 50 g fructose resulted in a modest increase in the circulating glucose concentration. However, it is likely that a larger proportion of the ingested fructose was converted to glucose in the liver and stored as glycogen and that fructose substituted, at least in part, for lactate and alanine as a gluconeogenic substrate. The increase in glucose production occurred even in the presence of an increase in the insulin concentration and an unchanged glucagon concentration. The metabolic fate of the remaining fructose is yet to be determined.

FRUCTOSE is the second most common monosaccharide requiring metabolic disposition after a meal. It is found in fruits and vegetables, generally as the disaccharide sucrose or as the hydrolytic products of sucrose, ie, glucose and fructose. Highly refined sucrose (table sugar), high-fructose syrups, and honey are other common sources of fructose in the diet.

Sucrose is rapidly hydrolyzed in the upper intestine, and the resulting fructose and glucose are absorbed by independent carrier-mediated mechanisms.[1] The absorption rate is relatively slow for fructose compared with glucose. Indeed, it has been shown to be absorbed into the portal vein at a rate that allows the liver to metabolize it efficiently, without causing nucleotide depletion.[2,3] Intravenous administration of large amounts of fructose results in an abrupt decrease in the hepatic adenosine triphosphate concentration and increase in nucleotide deamination.[4] This also may occur following ingestion of large amounts of fructose, but only in people with fructose intolerance due to a deficiency of fructose 1-phosphate aldolase.[5,6]

Very little fructose passes through the liver into the general circulation. In the rat, the majority is stored as glycogen, although some is converted to glucose that is released into the circulation.[3] It also may be converted to lipids (reviewed in Nuttall and Gannon[7]).

In humans, less is known about the quantitative aspects of fructose metabolism. Ingested fructose is known to be converted to glucose 6-phosphate and to result in glycogen storage in the liver.[8,9] It also may result in an increase in circulating triglycerides and in cholesterol (reviewed in Nuttall and Gannon[7]).

In 1921,[10] it was reported that ingested fructose results in only a modest increase in the circulating glucose concentration in normal humans. This was subsequently confirmed by several investigators.[11-13] Fructose also results in a modest increase in the insulin concentration.[11-13]

To quantify the effect of ingested fructose on glucose production, we have determined the glucose appearance rate (R_a) by an isotope dilution method. The response to the ingestion of a large amount of fructose (50 g) was compared with the glucose R_a when the same normal male subjects ingested only water over the same period.

SUBJECTS AND METHODS

Six normal male volunteers were studied in the Special Diagnostic and Treatment Unit (SDTU). All subjects were in excellent health and had a mean age of 26 years, with a range of 19 to 39. All were within 10% of ideal body weight (mean, 78.5 kg; range, 56 to 95) using the 1959 Metropolitan Life Insurance tables.[14] The subjects provided written informed consent, and the study was approved by the VA Medical Center Committee on Human Subjects. All had ingested a diet containing at least 200 g carbohydrate per day, as well as their usual food energy intake, for the 3 days prior to the study.

The men were admitted to the SDTU on the evening before the study and received a standardized meal at 5:00 PM. Subsequently, only water ad libitum was allowed. The following morning at 3:00 AM, two indwelling venous catheters were inserted, one in the antecubital vein and the other in the dorsum of the contralateral hand. The hand was kept warm with a heating pad, and the catheters were kept patent with a slow infusion of 0.9% saline. An infusion of tritium-labeled glucose ^{3}H-carbon 3 (New England Nuclear, Boston, MA) was started at 3:00

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Table 1. Plasma Values for Control (water) Versus Fructose Ingestion

	Fructose (mmol/L)		C-Peptide (nmol/L)		Glucagon (ng/L)		NEFA (μmol/L)		Triglyceride (mmol/L)	
Time	Control	Fructose	Control	Fructose	Control	Fructose	Control	Fructose	Control	Fructose
8:00 AM	0.05 ± 0.01	0.06 ± 0.02	0.16 ± 0.02	0.16 ± 0.02	393 ± 85	388 ± 75	543 ± 61	501 ± 49	1.13 ± 0.37	1.12 ± 0.26
8:15	0.06 ± 0.02	0.13 ± 0.03	0.17 ± 0.03	0.16 ± 0.02	405 ± 109	400 ± 70	553 ± 73	558 ± 48	1.11 ± 0.36	1.18 ± 0.29
8:30	0.06 ± 0.02	0.36 ± 0.06*	0.16 ± 0.03	0.24 ± 0.03*	328 ± 73	402 ± 66	573 ± 62	492 ± 53	1.12 ± 0.36	1.20 ± 0.29
8:45	0.03 ± 0.01	0.31 ± 0.03*	0.16 ± 0.03	0.25 ± 0.02*	339 ± 47	399 ± 70	548 ± 39	363 ± 41*	1.14 ± 0.37	1.17 ± 0.30
9:00	0.03 ± 0.02	0.33 ± 0.04*	0.17 ± 0.04	0.25 ± 0.04*	338 ± 52	390 ± 87	586 ± 47	271 ± 39*	1.12 ± 0.36	1.12 ± 0.28
9:15	0.03 ± 0.01	0.23 ± 0.02*	0.17 ± 0.03	0.25 ± 0.03*	348 ± 56	349 ± 49	593 ± 40	211 ± 25*	1.12 ± 0.36	1.09 ± 0.29
9:30	0.04 ± 0.02	0.18 ± 0.03*	0.16 ± 0.03	0.22 ± 0.03*	331 ± 50	364 ± 46	568 ± 33	218 ± 34*	1.11 ± 0.36	1.02 ± 0.29
10:00	0.03 ± 0.02	0.16 ± 0.01*	0.16 ± 0.03	0.20 ± 0.02*	322 ± 66	429 ± 62*	601 ± 44	232 ± 46*	1.10 ± 0.36	1.02 ± 0.28
10:30	0.03 ± 0.02	0.12 ± 0.03*	0.14 ± 0.03	0.17 ± 0.02	330 ± 60	462 ± 58*	616 ± 56	264 ± 47*	1.06 ± 0.32	1.05 ± 0.28
11:00	0.02 ± 0.02	0.10 ± 0.03	0.15 ± 0.03	0.15 ± 0.02	339 ± 60	430 ± 56*	691 ± 85	378 ± 96*	1.09 ± 0.35	1.07 ± 0.26
11:30	0.02 ± 0.01	0.12 ± 0.02*	0.15 ± 0.03	0.14 ± 0.02	371 ± 67	431 ± 61	691 ± 80	466 ± 95	1.06 ± 0.34	1.11 ± 0.28
12:00 PM	0.02 ± 0.01	0.14 ± 0.06*	0.15 ± 0.03	0.13 ± 0.02	382 ± 93	427 ± 74	702 ± 91	613 ± 88	1.10 ± 0.34	1.13 ± 0.25
1:00	0.02 ± 0.01	0.09 ± 0.02	0.13 ± 0.02	0.13 ± 0.02	340 ± 62	408 ± 76	755 ± 87	764 ± 105	1.10 ± 0.35	1.18 ± 0.23
2:00	0.02 ± 0.01	0.05 ± 0.02	0.14 ± 0.03	0.13 ± 0.02	364 ± 67	412 ± 85	894 ± 115	791 ± 91	1.18 ± 0.39	1.23 ± 0.22
3:00	0.02 ± 0.01	0.04 ± 0.01	0.14 ± 0.03	0.12 ± 0.02	374 ± 54	393 ± 86	1,166 ± 154	819 ± 75	1.21 ± 0.37	1.29 ± 0.23
4:00	0.03 ± 0.02	0.03 ± 0.02	0.14 ± 0.03	0.12 ± 0.02	386 ± 59	418 ± 95	1,182 ± 97	886 ± 100	1.22 ± 0.37	1.29 ± 0.25

NOTE. Values are the mean ± SEM.

*Statistically significantly different *v* controls at the same time point ($P \leq .05$).

AM at a constant rate of about 3.5 nCi/min/kg. This was continued until 4:00 PM.

At 8:00 AM, either 50 g fructose in 500 mL water or water alone was administered in random order. During the subsequent 8-hour period, the subjects were allowed to consume water ad libitum. Arterialized blood samples were drawn from the hand hourly from 3:00 to 7:00 AM and then every 15 minutes until 8:00 AM. Subsequently, blood samples were drawn at 15-minute intervals for 90 minutes, then at 30-minute intervals for 150 minutes, and then every hour for the final 4 hours of the study. Subjects were studied over an 8-hour period to ensure complete absorption of the 50 g fructose. This amount of fructose was well tolerated. None of the subjects complained of any untoward effects.

Plasma glucose was determined by a glucose oxidase method using a Beckman glucose analyzer with an O_2 electrode (Beckman Instruments, Fullerton, CA). Plasma fructose was determined by the method of Bernt and Bergmeyer.[15] The serum immunoreactive insulin level was measured by a standard double-antibody radioimmunoassay (RIA) method using kits produced by Endotech (Louisville, KY). Glucagon was determined by RIA using 30K antiserum purchased from Health Sciences Center (Dallas, TX). The C-peptide level was measured using a double-antibody RIA method with kits produced by Incstar (Stillwater, MN); the antibody to C-peptide has only a 4% cross-reactivity with proinsulin. Serum nonesterified fatty acids (NEFAs) were determined by the colorimetric assay of Duncombe.[16] Triglycerides and urea nitrogen were determined using an EktaChem analyzer (Eastman Kodak, Rochester, NY). Plasma lactate was determined by the method of Hohorst[17] using lactate dehydrogenase. Plasma alanine was determined by the method of Williamson[18] using alanine dehydrogenase. The total α-aminonitrogen was determined by the method of Goodwin.[19] This is an index of the total amino acid concentration in serum.

^{3}H-3-glucose in plasma was determined by drying a protein-free plasma filtrate under forced air and resuspending it in water. An aliquot of the resulting sample was added to Ultima Gold (Packard, Meriden, CT) scintillation cocktail and counted in a beta counter. Plasma samples obtained before isotope infusion and an aliquot of the radioactive infusate were treated in a similar manner to serve as negative and positive controls, respectively.

The peripheral glucose R_a was calculated using the non–steady-state equations of Steele et al[20] as modified by deBodo et al.[21] To correct for the noninstantaneous mixing of glucose, a correction factor of partial volume (Vp) = 0.65 was used.[22] The volume of distribution for glucose was considered to be 26% of body weight. In humans, the volume has been variously reported as 24% to 37%.[23] The fasting baseline data in the results represent the mean values of data for the four blood samples obtained from 7:00 to 8:00 AM for each individual. Quantitation of the subsequent 8-hour integrated glucose R_a was determined as the area above or below the mean fasting R_a using the steady-state equation over the period from 7:00 to 8:00 AM. This area was calculated by the trapezoid rule[24] using a program developed in our laboratory.* The data are presented as the mean ± SEM. Statistical analysis was performed using Student's paired *t* test or Wilcoxon's signed rank test. A *P* value of .05 or less is the criterion for significance.

RESULTS

Plasma fructose was barely detectable following the ingestion of water alone (Table 1). Following fructose ingestion, it increased modestly, reached a peak of 0.36 mmol/L at 8:30 AM, and slowly decreased. It returned to the basal concentration at 2:00 PM.

Following the ingestion of water alone, plasma glucose decreased modestly from 5.0 ± 0.3 mmol/L (90 ± 5.4 mg/dL) to 4.3 ± 0.05 mmol/L (77 ± 1 mg/dL) by 2:00 PM. Other than a transient increase of 0.8 mmol/L (15 mg/dL) beginning at 8:30 AM, the plasma glucose concentration did not change significantly following ingestion of fructose (Fig 1). These differences were not statistically significant.

The mean R_a for glucose in the fasted subjects (water controls) decreased from 11.8 ± 0.8 μmol/min/kg at 8:00 AM to 10.7 ± 0.8 μmol/min/kg at 4:00 PM. Following ingestion of fructose, the R_a increased from an initial value of 10.4 ± 0.9 μmol/min/kg to a maximum of 16.9 ± 2.2 at 8:30 AM. It then rapidly decreased and remained stable at approximately 10 μmol/min/kg (Fig 2).

Based on the differences in the integrated area over 8 hours, the calculated total glucose appearing in the circulation as a result of fructose ingestion was 9.8 ± 2.4 g (range, 4.4 to 20.1;

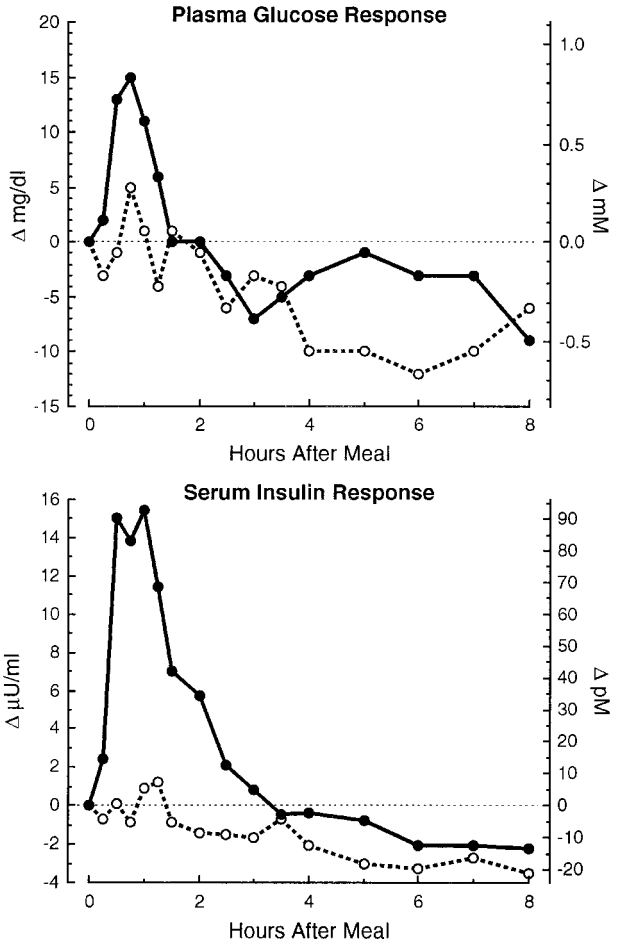

Fig 1. Change (Δ) in arterialized plasma glucose and serum insulin following ingestion of 50 g fructose (●) or water alone (control, ○) in 6 normal male subjects. The differences in glucose concentration were not statistically significant. The mean baseline glucose concentration was 5.0 ± 0.3 and 4.7 ± 0.2 mmol/L (90 ± 54 and 86 ± 3 mg/dL) for water and fructose, respectively. The mean baseline insulin concentration was 2.9 ± 0.5 and 2.7 ± 0.3 pmol/L (17.1 ± 3.2 and 16.6 ± 2.0 μU/mL) for water and fructose, respectively. The insulin concentration differences were statistically significant at 0.5, 0.75, and 1 hour after the meal.

54 ± 13 mmol). This was statistically significant ($P < .05$). Interestingly, using the steady-state equation, it was 8.2 ± 3.3 g (46 ± 18 mmol). Using different estimated glucose volumes of distribution also had little effect on this value (data not shown).

Following ingestion of water alone, there was a slow decline in the insulin concentration of 0.6 pmol/L, from 2.9 ± 0.5 pmol/L at time zero to 2.3 ± 0.4 pmol/L at 4:00 PM (~21% decrease; Fig 1). The mean serum insulin increased by 2.6 pmol/L, from 2.7 ± 0.4 to a maximum of 5.3 ± 1 pmol/L at 9:00 AM in response to fructose ingestion, and then gradually decreased to the value for the water control by 11:30 AM, where it remained until the end of the study. The insulin concentration differences were statistically significant at 8:30, 8:45, and 9:00 AM. The C-peptide concentration also increased following fructose ingestion and the time course was similar to that for insulin. The mean plasma glucagon after 9:30 AM showed a small increase from a basal level of 388 ± 75 ng/L following ingestion of fructose. The increase was statistically significant at 10:00, 10:30, and 11:00 AM. Following ingestion of water alone, it decreased slightly (Table 1).

The mean NEFA concentration gradually increased to a maximum of 1,182 ± 97 μmol/L throughout the 8 hours following water alone. Ingestion of fructose initially resulted in a decrease in NEFAs to a nadir of 211 ± 24 μmol/L at 9:15 AM, with a subsequent return to the initial value at 11:30 AM. This was statistically significant from 8:45 to 11:00 AM. Subsequently, the NEFA concentration increased but was lower versus water alone. This transient decrease in NEFAs correlated well with the observed increase in insulin. Following fructose ingestion, the triglyceride response was biphasic. First, it decreased slightly and transiently. Then, it increased slightly. Because of the large variability in the data, none of the differences were significant (Table 1).

The mean plasma lactate concentration did not change significantly following ingestion of water alone. Following fructose ingestion, plasma lactate rapidly increased from a basal concentration of 0.86 ± 0.09 mmol/L to a maximum of 3.36 ± 0.19 mmol/L at 9:00 AM. The increase was statistically significant from 8:30 to 10:00 AM. It then gradually decreased to the level of the water control by 11:30 AM (Table 2).

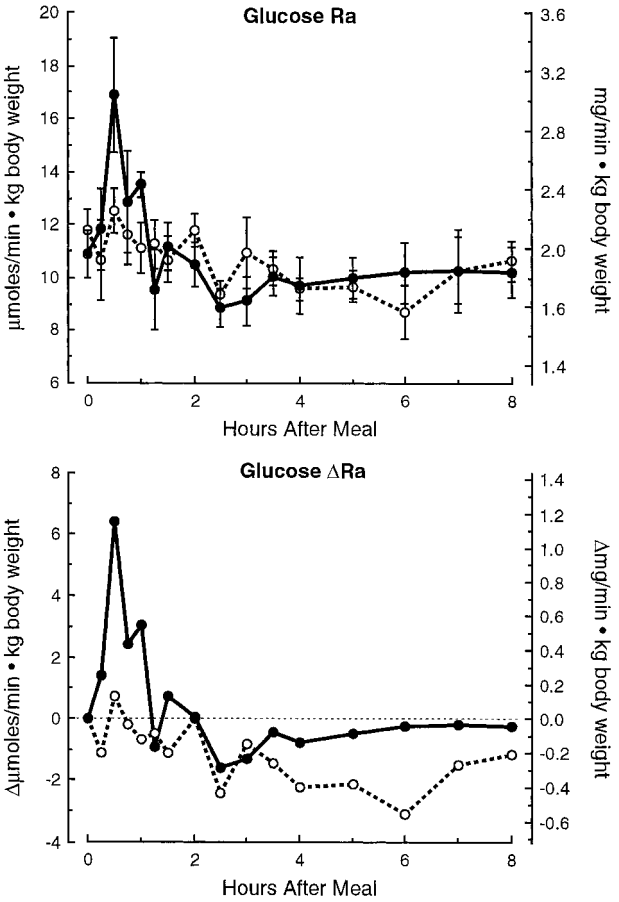

Fig 2. Calculated R_a of glucose following ingestion of 50 g fructose (●) or water alone (control, ○) in 6 normal male subjects. The differences were significant at 0.5 hours after the meal. Values are the mean ± SEM (top). Also shown is the change (Δ) in R_a (bottom).

Table 2. Plasma Values for Control (water) Versus Fructose Ingestion

	Lactate (mmol/L)		Alanine (mmol/L)		α-Amino Nitrogen (mmol/L)		Urea Nitrogen (mmol/L)	
Time	Control	Fructose	Control	Fructose	Control	Fructose	Control	Fructose
8:00 AM	0.97 ± 0.09	0.86 ± 0.09	0.30 ± 0.04	0.34 ± 0.06	2.77 ± 0.14	2.77 ± 0.07	4.32 ± 0.25	4.14 ± 0.43
8:15	0.96 ± 0.07	1.10 ± 0.11	0.28 ± 0.04	0.34 ± 0.08	2.63 ± 0.07	2.70 ± 0.07	4.18 ± 0.25	3.86 ± 0.46
8:30	0.91 ± 0.07	2.36 ± 0.26*	0.32 ± 0.05	0.43 ± 0.05	2.70 ± 0.07	2.77 ± 0.14	4.03 ± 0.32	3.78 ± 0.43
8:45	0.89 ± 0.09	2.94 ± 0.24*	0.27 ± 0.03	0.42 ± 0.02*	2.63 ± 0.07	2.70 ± 0.14	3.93 ± 0.21	3.71 ± 0.39
9:00	1.03 ± 0.12	3.36 ± 0.19*	0.27 ± 0.03	0.50 ± 0.06*	2.70 ± 0.14	2.70 ± 0.14	4.03 ± 0.32	3.50 ± 0.43
9:15	1.01 ± 0.11	2.99 ± 0.20*	0.30 ± 0.04	0.49 ± 0.05*	2.63 ± 0.14	2.63 ± 0.14	4.03 ± 0.32	3.57 ± 0.39
9:30	0.96 ± 0.10	2.47 ± 0.16*	0.30 ± 0.03	0.42 ± 0.02*	2.63 ± 0.07	2.56 ± 0.14	3.93 ± 0.21	3.36 ± 0.46
10:00	0.97 ± 0.11	1.88 ± 0.24*	0.29 ± 0.04	0.38 ± 0.02*	2.70 ± 0.07	2.63 ± 0.07	3.93 ± 0.21	3.43 ± 0.32
10:30	0.89 ± 0.04	1.24 ± 0.17	0.33 ± 0.05	0.33 ± 0.03	2.70 ± 0.07	2.63 ± 0.07	3.82 ± 0.32	3.28 ± 0.39
11:00	0.88 ± 0.07	0.94 ± 0.14	0.24 ± 0.04	0.31 ± 0.05	2.63 ± 0.07	2.63 ± 0.07	3.82 ± 0.32	3.28 ± 0.39
11:30	0.84 ± 0.10	0.86 ± 0.12	0.23 ± 0.04	0.32 ± 0.06	2.63 ± 0.07	2.56 ± 0.07	3.93 ± 0.21	3.28 ± 0.36
12:00 PM	0.90 ± 0.14	0.84 ± 0.13	0.24 ± 0.04	0.28 ± 0.07	2.63 ± 0.14	2.56 ± 0.07	3.93 ± 0.21	3.28 ± 0.39
1:00	0.78 ± 0.13	0.74 ± 0.11	0.23 ± 0.04	0.24 ± 0.05	2.56 ± 0.14	2.56 ± 0.07	3.68 ± 0.25	3.07 ± 0.32
2:00	0.77 ± 0.07	0.69 ± 0.11	0.19 ± 0.03	0.21 ± 0.02	2.56 ± 0.07	2.56 ± 0.14	3.32 ± 0.43	3.07 ± 0.32
3:00	0.82 ± 0.07	0.72 ± 0.07	0.20 ± 0.04	0.23 ± 0.07	2.56 ± 0.14	2.49 ± 0.14	3.39 ± 0.46	3.07 ± 0.32
4:00	0.81 ± 0.09	0.78 ± 0.16	0.19 ± 0.02	0.22 ± 0.06	2.56 ± 0.07	2.56 ± 0.07	3.32 ± 0.43	3.00 ± 0.29

NOTE. Values are the mean ± SEM.

*Statistically significantly different *v* controls at the same time point ($P \leq .05$).

The mean alanine concentration decreased modestly following ingestion of water alone. Following fructose ingestion, plasma alanine increased significantly from a basal concentration of 0.34 ± 0.06 mmol/L to a maximum of 0.50 ± 0.06 mmol/L at 9:00 AM. The increase was statistically significant from 8:45 to 10:00 AM. It then decreased to the control concentration by 10:30 AM (Table 2).

The mean α-amino nitrogen concentration (ie, total amino acids) decreased modestly and the decrease was similar when the subjects ingested fructose (2.77 ± 0.14 to 2.49 ± 0.14 mmol/L) or only water (2.77 ± 0.14 to 2.56 ± 0.14 mmol/L). Amino acids are the major gluconeogenic substrates for net glucose production in the liver. Ingested fructose also did not affect the amount of protein deaminated and the nitrogen subsequently converted into urea (Table 2). Based on the change in the endogenous urea nitrogen concentration and urea nitrogen excretion in the urine over the 8 hours of the study, the mean urea nitrogen production was 3.16 and 3.0 g after the ingestion of fructose and water, respectively.

DISCUSSION

As observed by others,[11,12,25] the ingestion of even large amounts of fructose results in only a modest increase in the glucose concentration in normal people. In the present study, the increase was only approximately 0.8 mmol/L (15 mg/dL). The glucose concentration also returned to the overnight-fasted value by 1.5 hours (Fig 1). Nevertheless, compared with the decreasing glucose values observed in the same individuals fasted over the same period, ingested fructose also resulted in a second modest increase in the glucose concentration after 3 hours.

Delarue et al[25] also reported a transient small increase in glucose with a maximum of 0.3 mmol/L (5.4 mg/dL) and 0.4 mmol/L (7.2 mg/dL) when normal subjects ingested 30 and 60 g, respectively. Thus, the increase in glucose was not proportional to the amount of fructose ingested. The increases also were smaller than in the present study.

In people with untreated type 2 diabetes, we previously reported a highly curvilinear relationship between the oral fructose dose and the increase in the glucose area response. Only amounts of ingested fructose greater than 15 g increased the glucose area response at all. Thus, data obtained with a single large dose of fructose should not be extrapolated to an expected metabolic response when smaller and more physiologic amounts of fructose are ingested.[26]

In the study by Delarue et al,[25] the glucose concentration did not decrease below the initial value over the 6-hour period of study. Since a modest decrease in glucose with continued fasting is expected, as noted in the present study, it suggests that the ingested fructose in their study also resulted in the maintenance of a higher glucose concentration than would be expected with fasting over the same period. Fasting controls were not used for comparative purposes by the investigators.

In the present study, the increase in insulin and C-peptide concentrations could largely be explained by the increase in glucose. Whether fructose independently stimulates insulin secretion at physiologic concentrations remains uncertain. In normal subjects, bolus infusions of fructose clearly stimulated an increase in the insulin concentration per se, and the magnitude of the increase was dependent on the existing glucose concentration. However, the circulating fructose concentration at which an increase in insulin occurred was considerably greater than the level present in the peripheral circulation following fructose ingestion.[27,28] Because of the efficient extraction of fructose by the liver in association with the slow, metered absorption of fructose by the intestinal mucosa, peripheral fructose concentrations greater than 1 mmol/L (18 mg/dL) are not likely. Indeed, the present data, as well as data from other laboratories,[11-13,25] indicate that the concentrations are considerably less.

Interestingly, in people with untreated type 2 diabetes, a low dose of oral fructose clearly increased the insulin concentration without an increase in the glucose concentration.[26] Whether the higher ambient glucose facilitated a fructose-stimulated release of insulin, or whether it was due to gut incretin hormone release or to fructose sensors in the portal vein, remains to be

determined. In any regard, the insulin area response in individuals with type 2 diabetes was curvilinear, with the greatest relative increase in the insulin area occurring with the smallest dose of fructose. Thus, the curve was the opposite of that for the glucose concentration.[26]

As noted previously in people with type 2 diabetes,[26] ingested fructose stimulated a modest increase in the glucagon concentration (Table 1). However, the increase occurred only after glucose and insulin had returned to the overnight-fasted values. The bulk of the fructose had been absorbed at this time. Thus, the reason for the late increase in the glucagon concentration is not apparent. It may be due to a continued release of gut incretin hormones stimulated by fructose remaining in the lumen of the bowel. However, to date, an incretin hormone that stimulates glucagon release has not been identified. It is also possible that a fructose-stimulated increase in glucagon was opposed by the suppressive effects on glucagon secretion of the elevated glucose and insulin concentrations early in the time course. The modest but persistent increase in glucagon in the absence of a change in the insulin concentration could help to explain the small increase in the glucose concentration and glucose R_a that persisted after the 3-hour time point.

The ingested fructose resulted in a rapid, relatively large but transient increase in the glucose R_a compared with the overnight fasting value (Fig 2). However, whereas a slow decrease in the glucose R_a was present in the same subjects when fasting over the 8-hour period, the glucose R_a remained at the overnight-fasted level following fructose ingestion.

Other investigators using 30 and 60 g fructose also reported a similar sharp increase in the glucose R_a, but lasting only 1 hour. This was followed by a return to the initial overnight-fasted glucose R_a, which persisted for the 6-hour duration of the study.[25] As indicated previously, in that study, the subjects were not fasted over the same period as a control. Thus, a continued modest increase in the glucose R_a as compared with the fasting value also was likely to have been present. They documented a major contribution of ingested, labeled fructose to the glucose R_a. This continued for the entire duration of the study. The peripheral fructose concentration returned to the fasting value by 2 to 4 hours before the end of the study, suggesting that the majority of the fructose was absorbed.

Whether the continued major contribution of labeled fructose to the total glucose R_a was due to continued absorption of small amounts of fructose, followed by direct conversion of fructose to glucose in the liver, or was due to prior fructose conversion to glycogen, and then later release as glucose cannot be determined from the data. Since oral fructose administration strongly stimulates glycogen synthase and is an excellent substrate for glycogen synthesis in rats[3,29] and probably in humans,[9] it is likely that an early storage of glycogen was the indirect source of glucose contributing to the later continued glucose release. In the present study (Table 2) and that reported by Delarue et al,[25] the lactate concentration increased only transiently. Similarly, in our study, the increase in alanine was transient. Thus, these gluconeogenic precursors are not likely to have been a significant indirect source of glucose formation later in the study period.

In the present study, the amount of fructose that could be accounted for by an increase in the glucose R_a over the same period as when the subjects were fasting was calculated to be 9.8 ± 2.4 g. Interestingly, this is similar to that calculated previously by integrating the area under the plasma glucose curve in response to 50 g fructose ingestion by subjects with type 2 diabetes.[26] Undoubtedly, the additional amount of glucose appearing in the circulation is an underestimation of the total contribution of ingested fructose to glucose appearance in the circulation and its subsequent oxidation. However, the present study was not designed to trace the overall fate of the ingested fructose. This would require the use of labeled fructose. As already indicated, ingested fructose has been reported to replace other sources of glucose formation and release.[25] Thus, it diminishes their contribution to the glucose R_a. Indeed, ingestion of 1.0 g/kg (60 g) resulted in greater than 50% of the glucose appearance in the circulation over a 6-hour period being due to the ingested fructose. For the most part, this glucose was metered into the circulation at a rate just sufficient to maintain the glucose level at the overnight-fasted concentration, as also observed in the present study. As indicated by the present data, this rate was greater than the fasting value. One can speculate that the transient but large increase in lactate after fructose ingestion noted in both studies and the increase in alanine in the present study were due to a reduced utilization of these substrates for glucose production in the presence of an increased utilization of fructose in the gluconeogenic pathway. This remains to be documented. In the rat, oral administration of a large amount of fructose did not diminish lactate utilization by the liver.[3]

α-Amino nitrogen and urea nitrogen concentrations following fructose ingestion were similar to the control levels (Table 2). Thus, in the present study, fructose ingestion did not affect overall protein metabolism.

There is an evolving concept that the liver maintains a constant glucose R_a even when excessive amounts of gluconeogenic substrates are provided. That is, in the overnight-fasted (or postabsorptive) state, it is the intrahepatic enzymic activity that determines the glucose R_a and not the provision of gluconeogenic substrate. Most likely, this constant glucose R_a is the result of a reciprocal relationship between the rates of glycogenolysis and gluconeogenesis. Also, it is likely that an excess of one gluconeogenic substrate results in the diminished utilization of others without significantly changing the glucose R_a. Most of the data have been obtained in studies in which the gluconeogenic substrate was provided intravenously.[30-32] With the exception of a small transient increase in the glucose R_a after fructose administration, the data obtained by Delarue et al[25] are compatible with this concept. However, in none of the studies cited herein were subjects fasted for the same period of time for comparative purposes. Our data indicate that there was a relatively large transient increase in the glucose R_a in response to fructose administration and a subsequent small but persistent increase that lasted for the 8 hours of the study. This indicates that the provision of an exogenous gluconeogenic substrate increases the glucose R_a when compared with the fasted state.

The early transient near-doubling in the glucose R_a occurred in the presence of a considerable increase in the insulin concentration (Fig 1) and little change in the glucagon concentration (Table 1). Insulin is generally considered to strongly suppress glucose production.[33] Thus, the increase in the glucose

R_a noted in the present study suggests either that intrahepatic mechanisms regulating glucose production are not responsive to this increase in insulin or that the insulin suppressive effect on the glucose R_a is blunted when fructose is ingested. Similar data were obtained in rats previously.[3] Fructose is reported to activate glucokinase through the production of fructose 1-phosphate.[34,35] It is not known to affect glucose 6-phosphatase activity, the rate-limiting step in glucose production.

Animal data indicate that dietary fructose is a better precursor of triglyceride formation in the liver than is glucose. Large amounts of fructose also may delay triglyceride clearance from the circulation after a meal (reviewed in Nuttall and Gannon[7]). A late increase in the triglyceride concentration was noted by others[25] and was attributed to the ingested fructose. In the present study, a similar slight elevation was noted, but this was not significantly greater than when the same subjects were fasted. Thus, fructose conversion to triglyceride and release into the circulation is not likely to be quantitatively important, at least under the conditions of the present study (Table 1).

In summary, ingestion of 50 g fructose by normal male subjects fasted overnight resulted in a modest but prolonged elevation in the plasma fructose concentration. There was a rapid but transient increase in glucose. The glucose concentration then returned to the initial overnight fasting value but remained higher versus the value obtained when the subjects were starved over the same period (ie, controls). The glucose R_a correlated with the changes in the plasma glucose concentration. On a weight basis, only about 20% of the ingested fructose could be accounted for as glucose appearing in the circulation. Presumably, the remaining fructose was stored as glycogen.

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