Acute Effects of Fructose and Glucose Ingestion With and Without Caffeine in Young and Old Humans

Naomi K. Fukagawa, Helen Veirs, and Gail Langeloh

Aging is associated with a decline in energy expenditure (EE), glucose intolerance, and a reduction in body nitrogen content. In addition, a reduction in the thermic response to glucose but not to fructose or protein has been reported in the elderly. The present study was conducted to further examine nutrient-induced thermogenesis and the effects of specific sugars on amino acid metabolism in relation to age. After 3 days on a weight-maintaining, 250-g carbohydrate diet, 16 healthy non-obese men and women in two age groups (18 to 29 and 66 to 80 years) consumed on 4 different days 500 mL of either a 75-g fructose or 75-g glucose solution, with or without 300 mg caffeine or vitamin C as a placebo. Blood substrate and hormone levels and EE, using indirect calorimetry, were measured at timed intervals for 3 hours after consumption of the drinks. There was no difference in the carbohydrate-induced increase in EE in either young or old even after adjustments for body weight and fat-free mass (FFM). An approximately 20-fold increase in serum caffeine levels increased EE in both groups ($P < .003$), but had minimal effects on substrate and hormone responses. In contrast to glucose, fructose induced a marked elevation in plasma alanine from combined basal levels of 301 ± 24 to approximately 500 ± 18 μmol/L (mean ± SEM) in both groups ($P < .001$). However, both fructose and glucose ingestion resulted in a similar decline in branched-chain and aromatic amino acids. The older group had higher insulin ($P < .06$) and glucose ($P < .03$) levels overall than the young, although both responded with a similar magnitude of change after both meals. Insulin and glucose levels were higher after glucose than after fructose, whereas uric acid levels, reflecting adenine nucleotide catabolism, increased 20% within 90 minutes of ingestion of fructose but not glucose. These findings bring into question the existence of diminished carbohydrate-induced thermogenesis in the old, emphasizing the need for further investigation before dietary or therapeutic recommendations are made.

A DECLINE IN ENERGY expenditure (EE) is commonly associated with advancing age.[1-5] We previously reported that there was no effect of age on the postprandial increase in EE after a protein meal.[6] In contrast, a reduced thermic response to glucose has been reported in the elderly,[2,3,7] and was attributed in one study[7] to insulin resistance and shown to be alleviated by an isocaloric amount of fructose. With the underlying premise that there is indeed an age-related difference in specific nutrient effects on EE, we designed the present study to examine the possible mechanisms underlying differences in the metabolic response to nutrients in young and old volunteers.

Both fructose and caffeine are common food additives reported to influence EE. Fructose, a naturally occurring carbohydrate in food and honey, has been widely used in processed foods since the introduction of high-fructose corn syrup in the late 1960s. Since neither the transport of fructose into the cell nor its subsequent metabolism is dependent on an increase in plasma insulin concentration,[8-10] it has been recommended as a sweetener for diabetic, insulin-resistant, or obese individuals. Caffeine, used in food and pharmaceutical preparations, is a known stimulant of metabolic rate in humans.[11-13] Both fructose and caffeine influence adenine nucleotide pathways. Fructose alters adenine nucleotide catabolism, thereby accounting for the hyperuricemic effects of the sugar.[9] Caffeine is a competitive inhibitor of adenosine receptors, and it and other xanthines have been shown to potentiate the thermic effects of ephedrine by influencing negative-feedback mechanisms operating both extracellularly (eg, via adenosine) and intracellularly (eg, via cyclic adenosine monophosphate phosphodiesterases).[14,15] Therefore, the present study was conducted to determine whether either caffeine or fructose, alone or in combination, would ameliorate the age-related differences in glucose-induced thermogenesis (GIT).

The results of this study indicate that the age-related difference in the thermic response to glucose and fructose is smaller than expected, and suggest that the thermic response to a nutrient is more a function of the nutrient itself rather than of an individual's body size or mass.

SUBJECTS AND METHODS

Subjects

Sixteen healthy non-obese volunteers in two age groups participated in the study. The young group (age range, 18 to 29 years) consisted of six men and two women, and the elderly group (66 to 80 years), four men and four women. Characteristics of the subjects are listed in Table 1. None of the volunteers were taking medications, and none had any known abnormalities of carbohydrate metabolism. Before participation in the study, each subject gave informed voluntary written consent. The research protocol was reviewed and approved by the Committee on Clinical Investigation at Beth Israel Hospital and the Committee on the Use of Humans as Experimental Subjects at Massachusetts Institute of Technology.

Study Design

Subjects were admitted to the Clinical Research Center at Beth Israel Hospital or Massachusetts Institute of Technology on four separate occasions in the evening before each study. All subjects

From the Clinical Research Center, Massachusetts Institute of Technology, Cambridge; and Beth Israel Hospital, Harvard Medical School, Boston, MA.

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Address reprint requests to Naomi K. Fukagawa, MD, PhD, The Rockefeller University, 1230 York Ave, New York, NY 10021-6399.

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Table 1. Subject Characteristics

Subject No.	Sex/Group	Age (yr)	Height (cm)	Weight (kg)	FFM* (kg)	Fasting Glucose (mg/dL)	Fasting Insulin (μU/mL)	RMR (kcal/min)
1	M/Y	29	185.0	86.1	62.6	93	5.5	1.57
2	M/Y	19	181.2	66.5	52.3	91	6.4	1.39
3	M/Y	19	172.7	62.2	47.9	79	4.7	1.15
4	M/Y	19	190.7	74.5	59.9	78	5.1	1.48
5	M/Y	18	179.2	69.6	54.1	85	4.4	1.28
6	M/Y	24	171.5	69.9	53.2	81	4.8	1.00
7	F/Y	20	163.6	60.9	35.3	86	7.1	0.98
8	F/Y	19	166.5	60.7	45.6	80	3.4	1.06
9	M/O	75	164.0	71.5	49.3	101	5.3	1.05
10	M/O	75	171.9	85.4	50.7	99	8.4	1.18
11	M/O	74	174.2	79.9	61.2	89	5.4	1.08
12	M/O	80	173.6	73.9	52.5	77	4.7	1.04
13	F/O	69	165.2	51.2	32.2	96	6.2	0.85
14	F/O	72	157.0	48.0	35.0	80	5.4	0.88
15	F/O	66	158.8	60.6	32.9	92	6.8	0.83
16	F/O	76	153.5	48.3	27.9	109	7.7	0.82
Mean ± SEM								
Y		21 ± 1	176.3 ± 3.3	68.8 ± 3.0	51.4 ± 3.0	84 ± 2.0	5.2 ± 0.4	1.24 ± 0.08
O		73 ± 2	164.8 ± 2.8†	64.8 ± 5.2§	42.7 ± 4.3§	93 ± 3.8§	6.2 ± 0.5§	0.97 ± 0.05‡

NOTE. Values are the mean ± SEM.

Abbreviations: Y, young; O, old.

*Estimated from bioelectrical impedance measures.

†$P < .02$, ‡$P < .01$, §P = NS: young *v* old.

consumed a diet containing at least 250 g carbohydrate and less than 200 mg caffeine per day during the 3 days preceding each of the four separate admissions. Young women were studied during the follicular phase of the menstrual cycle; elderly women were postmenopausal and not on hormone replacement therapy. An index of body composition was obtained, as previously described,[4] using a Bioelectrical Impedance Analyzer (RJL Systems, Detroit, MI). After a 10- to 12-hour overnight fast, an intravenous catheter was inserted into an arm vein, kept patent with heparinized saline solution (1 mU heparin/mL), and used for obtaining blood samples at timed intervals. After a 30- to 45-minute rest in bed or in a reclining chair, continuous respiratory exchange measurements were begun as previously described using a ventilated-hood system.[4,6] After a 30-minute measurement of resting metabolic rate (RMR), each subject consumed, on separate days, one of four drinks: 75 g fructose with 300 mg vitamin C (placebo), 75 g fructose with 300 mg caffeine, 75 g glucose with 300 mg vitamin C (placebo), or 75 g glucose with 300 mg caffeine. It should be noted that there is a limitation to how much simple sugar can be consumed orally by an individual at one time. The choice of a 75-g dose of glucose was made based on it being a recognized standard dose for oral glucose tolerance tests, and the dose of fructose was limited by symptoms experienced by the volunteers. It would not have been possible to select a higher dose to try to elicit differences because the results would have been confounded by heightened symptoms. The fructose or glucose was dissolved in 500 mL water flavored with lemon. Vitamin C was chosen as a placebo because the tablet was identical in appearance to caffeine—pilot studies demonstrated that the volunteers' behavior was altered when they were informed that they were ingesting caffeine tablets. There was no evidence in the literature that a single dose of 300 mg vitamin C would alter EE. The studies were performed in a randomized order at 1- to 3-week intervals. All subjects completed all four tests. Indirect calorimetry measurements were continued for 180 minutes after initial ingestion of the drink. Blood samples for determination of glucose, amino acid, insulin, and glucagon concentrations were obtained at 30-minute intervals, and for cholesterol, uric acid, and phosphate levels, at 90-minute intervals, during the basal state and throughout the study. Arterial blood pressure and pulse were measured every 15 minutes using an automated sphygmomanometer (Dinamap, Critikon, Applied Medical Research, Tampa, FL).

Analytical Procedures

Plasma glucose was determined by the glucose oxidase method using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Serum insulin and plasma glucagon levels were measured by standard radioimmunoassay (Coat-a-Count Diagnostic Products, Los Angeles, CA). Plasma amino acid and caffeine concentrations were measured using high-performance liquid chromatography (Beckman Instruments). Uric acid and cholesterol levels were measured in the clinical laboratory at Beth Israel Hospital by a computerized analyzer (SMAC II, Technicon Instruments, Tarrytown, NY).

Calculations

Data for EE are also expressed as previously described,[2,3] where the thermic response to either glucose or fructose is expressed as a percentage increase over the premeal resting EE, or GIT, ie, GIT = [(postmeal EE − premeal EE)/premeal EE] × 100, and the change in EE is expressed as a percent of the energy content of the meal, ie, %E = [(postmeal EE − premeal EE)/3.74 × 75] × 180 × 100.

Statistical Analysis

All data are presented as the mean ± SEM. BMDPC Statistical Software (Los Angeles, CA) and Statistical Analysis System (Cary, NC) were used for all statistical analyses. Comparisons between groups in response to the test meals and caffeine were evaluated using ANOVA with repeated measures using one grouping variable (age) and up to three within-group variables as appropriate (meal, drug, and time) and analysis of covariance with fat-free mass

(FFM) or body weight as the covariate. Post hoc comparisons for differences in amino acid levels relative to baseline values were made using the Student-Neuman-Keuls test on those amino acids demonstrating a significant meal × time interaction on initial ANOVA. Other comparisons were made using Student's *t* test. *P* values greater than .05 are reported as not significant.

RESULTS

All subjects maintained their body weight within 5% of their starting weight throughout the study. RMR within each subject varied less than 15% between study days (coefficient of variation, 1.6% to 6.6%). Four young and four elderly volunteers experienced increased flatulence and bowel movements after the fructose meal, but the symptoms were not severe enough to require alteration in the study procedures. Because there was no detectable gender effect, results for men and women were combined in both age groups. FFM was estimated using bioelectrical impedance analysis, applying regression equations generated as a function of measured body water using ^{18}O-labeled water.[4] Average FFM was 51.4 ± 3.0 kg in the young and 42.7 ± 4.3 in the old.

Baseline plasma caffeine concentrations averaged 0.3 ± 0.07 μg/mL in both groups. In response to 300 mg caffeine, both young and old showed an increase in plasma levels to a new plateau by 90 minutes (averaging 5.6 ± 0.3 and 7.0 ± 0.1 μg/mL, respectively, $P < .01$, but the response was not statistically significantly different between groups), which was maintained until the end of the study.

Metabolic Rate

Overall, estimates of EE were significantly lower in the elderly as compared with the young (group, $P < .01$). Adjustment for body weight, body impedance measurements, or an estimate of FFM did not affect the overall group difference nor the responses to the meals with or without caffeine.

EE increased in both age groups after both glucose and fructose (time, $P < .0001$; Fig 1). In contrast to previous reports, both meals resulted in a similar magnitude of increase in EE in either group, which was not influenced by an adjustment for FFM or body weight (meal × group interaction, $P = .88$; meal × group × time interaction, $P = .97$; Fig 1). Caffeine had an independent effect of increasing EE slightly (drug, $P < .003$) in both the young and the old (Fig 1). Fructose plus caffeine induced a greater increase in EE than glucose plus caffeine (drug × meal interaction, $P = .05$).

Table 2 lists the data calculated as described in previous reports and includes results from previously published studies.[2,3] The age-related difference in ΔEE (difference between premeal and postmeal EE) after glucose in the earlier study[2] appears to be related to a greater response in the young, whereas there were no age differences found in the second study.[3] The discrepancy may be related to the dose of glucose administered (100 *v* 75 g, respectively). However, as described earlier, using a 100-g dose of carbohydrate in the present study was not feasible because of the symptomatology. When EE data for both sugars with and without caffeine were collapsed into a single value, the differences remained insignificant (combined ΔEE without caffeine, 0.14 ± 0.01 in the young and 0.11 ± 0.01 in the old; with caffeine, 0.19 ± 0.01 and 0.18 ± 0.01 in the young and old, respectively).

There was no significant relationship between ΔEE and FFM after either glucose ($r = .19$, $P = .48$) or fructose ($r = .27$, $P = .32$). Similarly, ΔEE versus body weight was insignificant (glucose $r = .08$, $P = .76$; fructose $r = .07$, $P = .80$). This suggests that the thermic response to carbo-

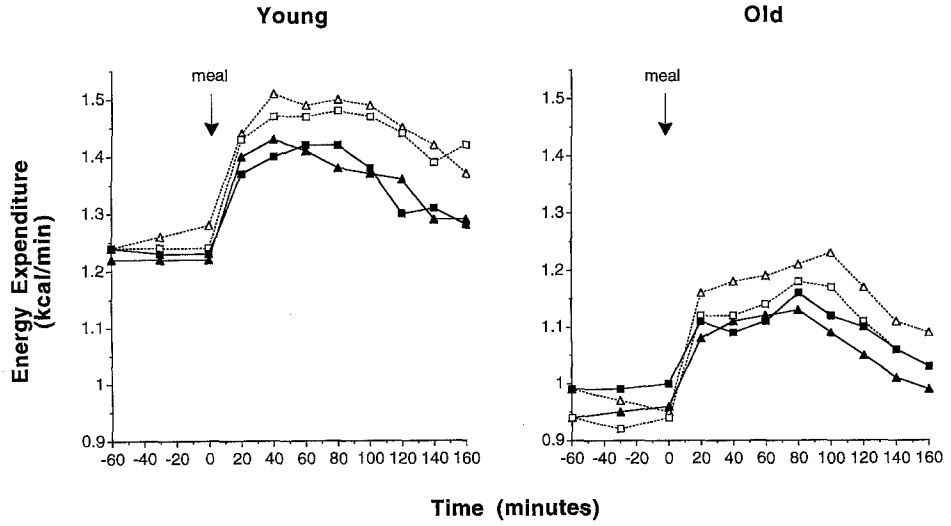

Fig 1. EE over time in young and old subjects and after 4 test meals: (■) glucose, (▲) fructose, (□) glucose and caffeine, (△) fructose and caffeine. $P < .01$ young *v* old; $P < .0001$ for increase after both meals in both groups; $P < .003$ caffeine *v* placebo. Values are the mean without error bars and *P* values for clarity; SEM ranged from ±0.04 to ±0.11.

Table 2. Changes in EE in Response to Oral Glucose and Fructose

Meal	Premeal EE (kcal/min)	Postmeal EE (kcal/min)	ΔEE (kcal/min)	GIT (%)	%E (%)
75 g glucose					
Without caffeine					
Young	1.23 ± 0.08	1.36 ± 0.08	0.13 ± 0.01	10.4 ± 0.08	8.10 ± 0.6
Old	0.99 ± 0.05	1.09 ± 0.06	0.10 ± 0.02	10.3 ± 2.0	6.5 ± 1.2
P	<.03	<.02	.26	.96	.27
With caffeine					
Young	1.24 ± 0.08	1.44 ± 0.09	0.19 ± 0.01	15.61 ± 1.03	12.33 ± 0.90
Old	0.93 ± 0.05	1.11 ± 0.05	0.18 ± 0.02	19.75 ± 2.42	11.49 ± 1.14
P	<.006	<.008	.58	.15	.57
75 g fructose					
Without caffeine					
Young	1.22 ± 0.08	1.36 ± 0.08	0.15 ± 0.02	12.0 ± 1.7	9.4 ± 1.5
Old	0.95 ± 0.06	1.07 ± 0.05	0.12 ± 0.0.02	12.8 ± 2.0	7.7 ± 1.2
P	<.01	<.01	.40	.76	.40
With caffeine					
Young	1.26 ± 0.09	1.45 ± 0.10	0.19 ± 0.02	15.28 ± 1.74	12.08 ± 1.50
Old	0.97 ± 0.06	1.16 ± 0.06	0.19 ± 0.02	19.77 ± 1.86	12.07 ± 1.04
P	<.02	<.03	.99	.10	.99
Glucose					
100 g					
Young*	1.21 ± 0.05	1.38 ± 0.06	0.17 ± 0.02	15.1 ± 0.1.0	8.6 ± 0.7
Old*	0.98 ± 0.05	1.10 ± 0.05	0.12 ± 0.01	10.9 ± 1.3	5.8 ± 0.3
P	<.001	<.001	<.001	<.002	<.002
75 g					
Young†	0.98 ± 0.04	1.11 ± 0.05	0.14 ± 0.01	ND	8.8 ± 0.7
Old†	0.83 ± 0.04	0.96 ± 0.03	0.12 ± 0.01		8.0 ± 0.5
P	<.02	<.02	NS	NS	NS

NOTE. *P* values are for comparisons between young and old.

Abbreviation: ND, not determined.

*From Golay et al.[2]

†From Bloesch et al.[3] *P* values not reported.

hydrate is linked to the nutrient itself rather than to body mass.

Substrate and Hormones

As expected, fasting plasma glucose and serum insulin concentrations were slightly higher in the old as compared with the young (Table 1), but the differences did not achieve statistical significance ($P < .06$ and $P < .10$, respectively). In both age groups, the glucose meal elicited a significantly greater increase in plasma glucose (meal, $P < .001$) and serum insulin (meal, $P < .0001$) as compared with the fructose meal (Figs 2A and B, respectively). Despite the overall higher glucose levels in the old (group, $P < .03$), there were no significant age-related differences in the relative glycemic response to either meal (meal × group interaction, $P = .12$; meal × group × time interaction, $P = .16$). Only two of the eight elderly met the National Diabetes Group criteria for impaired glucose tolerance. These two individuals did not differ from the others in the metabolic responses examined. The elderly group achieved slightly higher insulin levels than the young group after either glucose or fructose (group, $P < .06$), but as with glucose levels, the proportional changes in insulin concentrations were similar in the two age groups (meal × group, $P < .06$). Overall, the elderly group had significantly lower plasma glucagon concentrations than the young (group, $P < .01$). Both groups suppressed plasma glucagon levels to a greater extent and for a longer period of time after the glucose meal as compared with fructose (meal, $P < .0002$; meal × time, $P < .002$). The lack of age-associated differences in glucose and insulin responses is not uncommon.

Changes in plasma amino acid levels in response to glucose and fructose are listed in Table 3. *P* values in Table 3 represent significant changes from baseline values at the *P* less than .05 level after post hoc analysis of amino acids that demonstrated significant time × meal interactions. Caffeine did not significantly affect plasma amino acid concentrations, and therefore, the data are not presented. From a combined average basal concentration of 301 ± 24 μmol/L, plasma alanine concentrations increased significantly to 500 ± 18 μmol/L in both age groups (meal, $P < .001$) after fructose and minimally to 330 ± 20 after glucose (Fig 3). Both young and old experienced similar suppression of branched-chain (time, $P < .0001$) and aromatic (time, $P < .001$) amino acids after both meals (Table 3). Arginine and glycine transiently declined after both meals, but the differences achieved statistical significance only after glucose. The declines in histidine levels were statistically significant after glucose in the young, but

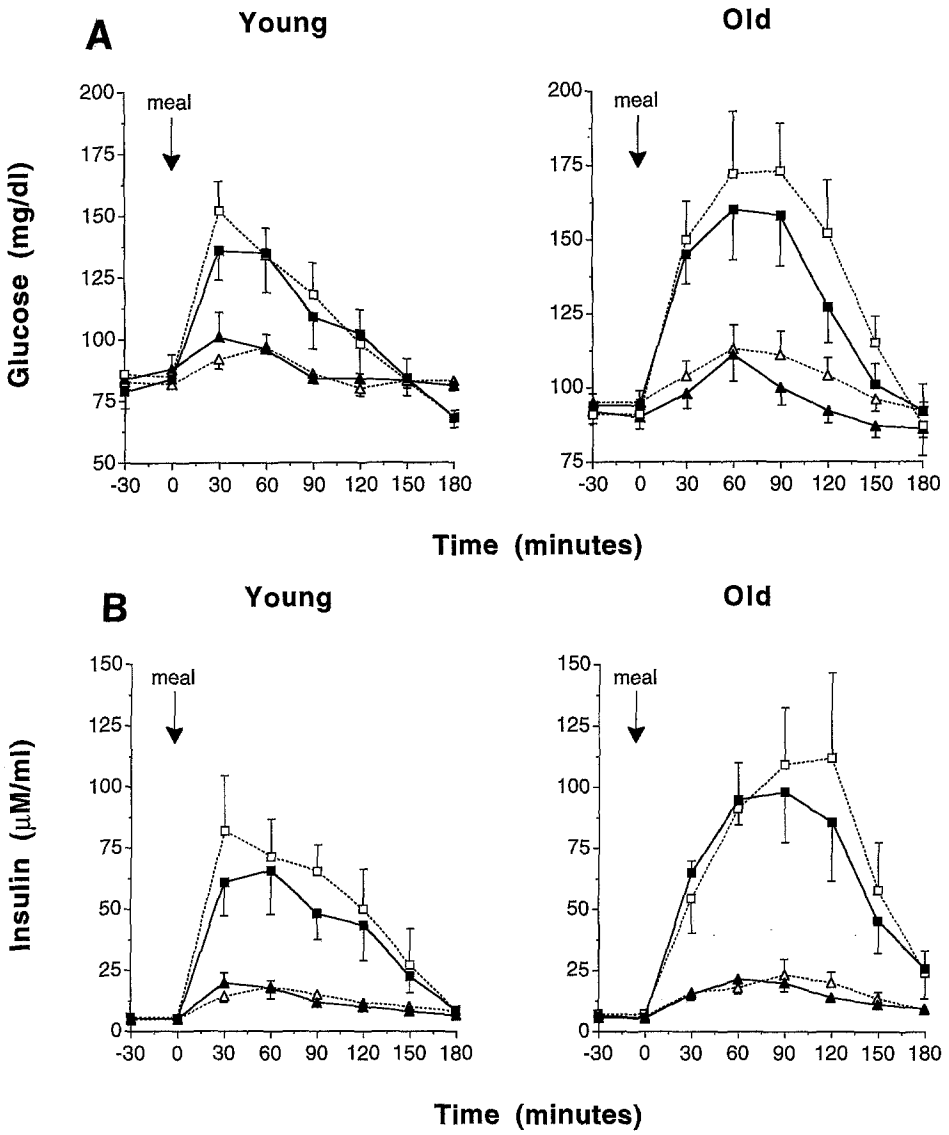

Fig 2. (A) Plasma glucose concentrations in young and old subjects after 4 test meals: (■) glucose, (▲) fructose, (□) glucose and caffeine, (△) fructose and caffeine. Values are the mean ± SEM. $P < .03$ young *v* old; $P < .0001$ glucose *v* fructose in both young and old. (B) Serum insulin concentrations in young and old subjects after 4 test meals: (■) glucose, (▲) fructose, (□) glucose and caffeine, (△) fructose and caffeine. Values are the mean ± SEM. $P < .06$ young *v* old; $P < .0001$ glucose *v* fructose in both young and old.

not after fructose nor in the old. Methionine and lysine were more affected by the glucose meal as compared with the fructose meal in both young and old.

Fasting serum cholesterol levels were higher in the old (210 ± 3 mg/dL) than in the young (150 ± 5) (group, $P < .01$). Neither glucose nor fructose affected serum cholesterol concentrations, but the addition of caffeine to both meals in the old resulted in slightly higher cholesterol levels (meal × drug × group interaction, $P < .03$). As anticipated, serum uric acid levels increased from 5.6 ± 0.4 to 7.0 ± 0.4 mg/dL in the young and from 4.8 ± 0.6 to 6.1 ± 0.6 in the old, after fructose ingestion both with and without caffeine (meal, $P < .002$), reflecting adenine nucleotide catabolism.

Blood Pressure

The old had slightly higher systolic (125 ± 4 mm Hg), diastolic (70 ± 3), and mean arterial (87 ± 2) pressures than the young (110 ± 3, 64 ± 2, and 80 ± 2, respectively), but the differences were not statistically significant. Both groups experienced a transient 4% to 5% decline in blood pressure after the glucose and fructose meals, which was attenuated when combined with caffeine (no change to ~1% increase) and might be attributable to vitamin C,[16] although whether an acute dose would have an effect is uncertain. Heart rate was higher overall in the old (64 ± 7 *v* 54 ± 3 beats per minute, group, $P < .02$). Both groups had a 7% to 15% increase in the pulse rate at the end of the

Table 3. Plasma Amino Acid Levels Basally and 60, 120, and 180 Minutes After Glucose and Fructose Ingestion

Amino Acids (μmol/L)	Young								Old							
	Glucose				Fructose				Glucose				Fructose			
	Basal	60	120	180	Basal	60	120	180	Basal	60	120	180	Basal	60	120	180
Branched-chain																
Leucine	126 ± 11	94 ± 9*	78 ± 13*	79 ± 10*	121 ± 6	95 ± 7*	79 ± 7*	85 ± 6*	102 ± 6	85 ± 5*	57 ± 4*	60 ± 5*	96 ± 5	84 ± 6*	65 ± 4*	73 ± 6*
Isoleucine	65 ± 6	47 ± 5*	37 ± 5*	37 ± 5*	60 ± 4	45 ± 5*	36 ± 5*	40 ± 4*	50 ± 2	39 ± 2*	26 ± 2*	28 ± 2*	47 ± 3	38 ± 3*	29 ± 2*	34 ± 2*
Valine	223 ± 17	193 ± 14*	167 ± 15*	163 ± 13*	207 ± 10	185 ± 8*	157 ± 9*	161 ± 8*	209 ± 12	190 ± 10*	149 ± 9*	147 ± 9*	195 ± 12	181 ± 11*	154 ± 12*	162 ± 13*
Gluconeogenic																
Alanine	300 ± 35	318 ± 26	325 ± 21	294 ± 20	291 ± 37	495 ± 20*	459 ± 18*	432 ± 38*	303 ± 42	347 ± 29	294 ± 25	274 ± 31	303 ± 31	504 ± 31*	465 ± 38*	429 ± 43*
Arginine	101 ± 5	83 ± 6	99 ± 25	84 ± 16	95 ± 3	88 ± 10	84 ± 11	84 ± 10	111 ± 8	98 ± 13	84 ± 8*	80 ± 7*	105 ± 7	106 ± 10	90 ± 9	103 ± 14
Glycine	226 ± 17	204 ± 16	213 ± 19	212 ± 15	252 ± 39	211 ± 9	208 ± 8	221 ± 9	217 ± 9	210 ± 8	186 ± 6*	193 ± 7*	226 ± 12	223 ± 10	213 ± 5	224 ± 14
Histidine	87 ± 4	82 ± 4*	79 ± 6*	79 ± 4*	94 ± 8	92 ± 2	85 ± 2	89 ± 3	96 ± 8	90 ± 5	75 ± 3*	79 ± 4*	78 ± 4	93 ± 3	86 ± 5	89 ± 5
Methionine	20 ± 1	16 ± 1*	14 ± 2*	12 ± 2*	20 ± 2	20 ± 2	18 ± 2	20 ± 1	18 ± 1	18 ± 1	12 ± 1*	11 ± 1*	19 ± 1	19 ± 1	17 ± 1	17 ± 1
Phenylalanine	54 ± 1	45 ± 3*	42 ± 5*	41 ± 3*	53 ± 2	49 ± 1*	47 ± 2*	48 ± 1*	56 ± 3	54 ± 3	43 ± 3*	44 ± 3*	54 ± 3	51 ± 4	43 ± 4*	49 ± 5*
Tyrosine	58 ± 2	44 ± 3*	38 ± 4*	36 ± 3*	55 ± 4	49 ± 2*	43 ± 3*	44 ± 2*	54 ± 4	50 ± 3	37 ± 3*	36 ± 3*	53 ± 3	48 ± 4*	38 ± 3*	45 ± 4*
Other																
Lysine	193 ± 5	168 ± 4	180 ± 21	178 ± 14	193 ± 7	187 ± 8	173 ± 6	185 ± 4	224 ± 11	220 ± 10	195 ± 9*	192 ± 12*	238 ± 13	229 ± 14	198 ± 9*	208 ± 11*

NOTE. Values are the mean ± SEM.

*$P < .05$ for comparisons between basal and 60-, 120-, and 180-minute values using post hoc analysis (Student-Neuman-Keuls).

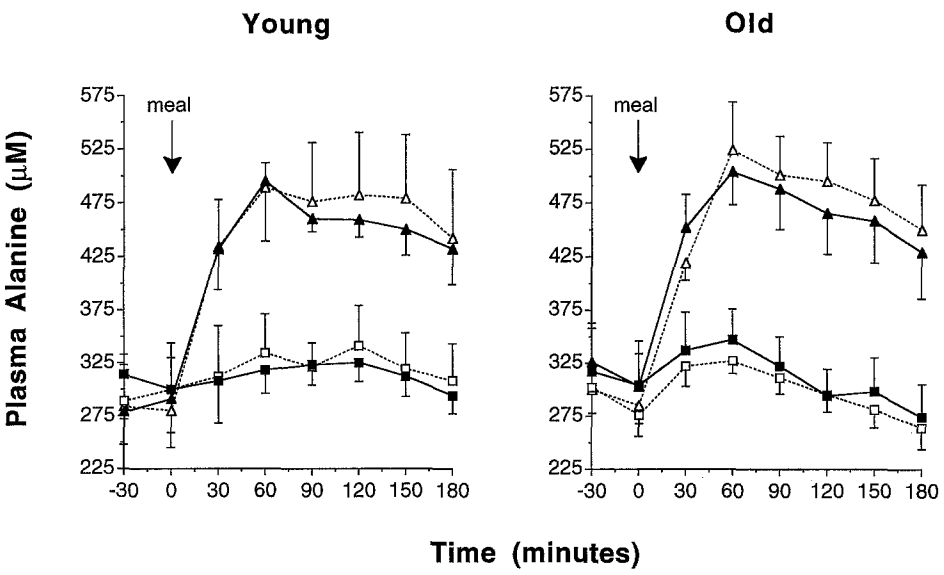

Fig 3. Plasma alanine concentrations in young and old subjects after 4 test meals: (■) glucose, (▲) fructose, (□) glucose and caffeine, (△) fructose and caffeine. Values are the mean ± SEM. $P < .001$ glucose *v* fructose.

studies, but there was no apparent difference in the responses to either meal with or without caffeine.

DISCUSSION

We previously reported that there was no effect of age on the postprandial increase in EE after a protein meal.[6] This study extends those findings to the acute effects of fructose and glucose, demonstrating a similar thermogenic response to equivalent amounts of the two carbohydrates in both young and old. These findings are in contrast to several reports demonstrating a greater thermic effect of fructose as compared with an isocaloric amount of glucose.[7,17-19] Furthermore, we were unable to show a diminished glucose-induced increase in EE in the elderly as suggested by other studies.[2,3] Differences in methodology and data analysis are likely to account for the discrepancy. The present data calculated as described by Golay et al[2] are almost identical to their values of premeal and postmeal EE in young and old subjects (Table 2). As expected, we both found lower absolute rates of EE in the old as compared with the young. However, Golay et al[2] found statistically significant differences between the two age groups in the calculated ΔEE and in the percentage change relative to RMR and the percentage of gross calories consumed. It is possible that the size of the glucose load (100 g) elicited the age differences, but a similar comparison may be made with Bloesch et al,[3] who administered a 75-g glucose load to 12 young and 12 old individuals. In this latter study, the investigators did not find age-related differences in the thermic response to glucose (Table 3). However, in a subset of six young and six old volunteers, the investigators compared the thermic effect of glucose with the EE response to 144 mg aspartame (Canderel; Searle, Chicago, IL). In this situation, they reported a significant age effect in the response expressed as a percentage of the caloric load. These latter results are difficult to interpret, since the older group experienced a significantly greater increase in EE after aspartame than the young. Therefore, it is not surprising that the difference between the change in response to glucose relative to the change in response to aspartame was lower in the old.

There is always a risk of committing a type II error when statistical analysis is applied to calculated variables, since one loses the true variance of the sample. Using the reported variances in both studies, a power analysis suggests that 28 to 29 subjects in each age group would be necessary in either study to achieve a significance of $\alpha = .05$ at 80% power.[20] This suggests that it is unlikely that age significantly attenuates the thermic response to single sugars, as we[6] and others[21] have shown for protein. Moreover, if a difference did exist, it is unlikely that it would be as important biologically as we had previously believed.

Thorne and Wahren[22] reported diminished meal-induced thermogenesis in the elderly, but they used a mixed meal and adjusted the dose according to measured RMR. As we previously pointed out,[6] selecting the caloric content of test meals based on an estimate of body size or EE would confound the results. Adjustment for an index of FFM did not affect the thermogenic responsiveness to glucose or fructose, as we have previously shown for protein.[6] Recently, Aksnes et al[23] reported similar glucose-induced increases in EE in normals and tetraplegic patients who had reduced FFM. Together, our findings support the notion that the thermic effect of a meal or a specific nutrient is independent of FFM. Since the thermic effect of a meal has been shown to be influenced by the caloric density,[24] studies using larger meals for heavier individuals may bias the data in favor of greater thermogenesis in those receiving more calories.

These findings raise the interesting, yet unanswered question about the regulation of the thermic effect of a meal. Unlike the known pharmacologic responses to an

orally administered drug whose effect is commonly dose-dependent and influenced by an index of body size, it appears that the thermogenic response to a single nutrient is tightly regulated and not affected by its relationship to body size; that is, a 46-kg individual has the same relative responsiveness to a meal as a 70-kg person receiving the identical meal. Under the conditions of this study, the only difference between the two groups was the absolute value of EE, not the relative change after consumption of either glucose or fructose.

The present study demonstrates identical changes in EE after both glucose and fructose ingestion in all volunteers. Methodologic and subject differences are likely to account for the discrepancy with previous reports.[7,17-19] Schwarz et al[18] used a liquid-formula meal of fixed energy intake with either 75 g glucose or 75 g fructose as the carbohydrate source, and concluded that fructose induced a larger increase in carbohydrate oxidation and thermogenesis than glucose. The interactions of different nutrients in a mixed meal may have influenced the magnitude and nature of the responses. In other reports also suggesting higher fructose-induced thermogenesis,[7,17] the 75 g fructose was administered as a 250- to 300-mL solution, which, in our hands, resulted in significant abdominal discomfort including flatulence, diarrhea, agitation, and pain in four individuals studied under pilot conditions. The severe physical discomfort may have resulted from changes in osmolality and rendered the results of the pilot studies uninterpretable. Consequently, all subsequent studies were conducted with both sugars provided as a 15% solution. Another consideration is the means of expressing the data. Many of the previous reports define the thermic effect as a percentage of the change in EE relative to the caloric content infused[19] or consumed.[17] As previously discussed, this approach may be a confounding factor.

Fructose intake is known to alter adenine nucleotide catabolism, thereby accounting for the hyperuricemic effects of the sugar.[9] Fructose is also known to alter the availability of adenosine triphosphate at the cellular level. Adenosine is an intermediary in purine nucleotide metabolism and has been implicated in energy metabolism.[25] Since caffeine is a known competitive inhibitor of adenosine receptors and since caffeine and other xanthines have been shown to potentiate the thermic effects of ephedrine by influencing the negative-feedback mechanisms operating both extracellularly (eg, via adenosine) and intracellularly (eg, via cyclic adenosine monophosphate phosphodiesterases),[15] one potential outcome of this study would have been modification of the thermic response to fructose in the presence of caffeine. We found that caffeine plus fructose induced a greater increase in EE than caffeine plus glucose in both young and old. These findings may indeed be related to interactions between fructose-induced alterations in purine nucleotide catabolism and caffeine's negative-feedback effects, and have potentially important implications for our understanding of the interaction between nutrients and drugs. Investigators have suggested that caffeine may be used to enhance thermogenesis in obese individuals and consequently promote weight loss.[26,27] It would appear that consideration must also be given to the nature of the diet composition when using caffeine as an adjunct to weight-loss regimens.

Glucose-induced changes in plasma amino acid levels after glucose ingestion are consistent with previous reports.[28-31] On the other hand, the effects of fructose on protein or amino acid metabolism are less well documented. Gelfand and Sherwin[32] showed that low-dose fructose administration attenuated the decrease in plasma alanine and increase in branched-chain amino acid concentrations after a 10-day fast. Nuttall et al[33] demonstrated a reduction in α-amino nitrogen and urea concentrations after various doses of oral fructose in type II diabetes mellitus subjects, but did not report fructose-induced changes of individual amino acids. The present data show selective changes in plasma amino acid levels, reflecting the complex interrelationship between carbohydrate intake and amino acid metabolism. Whereas the reduction in branched-chain and aromatic amino acid levels is probably related to the increase in plasma insulin, the marked elevation in alanine may be related to either increased availability of pyruvate for transamination into alanine or restriction of alanine utilization for gluconeogenesis. The response of other gluconeogenic amino acids (eg, glycine, arginine, histidine, and methionine) was more variable, suggesting that alterations in gluconeogenesis would be less likely.

Finally, concern about postprandial blood pressure reduction in the elderly has been raised.[34-36] Reports have suggested that blood pressure decreases after glucose ingestion, but not after fructose, fat, or protein. The present study did not find an age-associated difference in the response to either glucose or fructose. Similarly, we have previously reported that the blood pressure in young and old responded similarly to protein ingestion (Am J Physiol, in press). Studies in animals have linked fructose ingestion with hyperinsulinemia and hypertension.[37] The present study shows no effect of acute fructose intake, but the long-term effects on blood pressure regulation in humans should be explored.

In summary, these data shed new light on the issue of nutrient-induced thermogenesis in the elderly. It appears that reduced glucose-induced thermogenesis with advancing age is not as significant as previously reported. These data suggest that the thermogenic response to a nutrient is more a function of the nutrient itself rather than of body mass. Although we were unable to elicit age-related differences in a number of metabolic responses studied, further investigation is warranted before dietary or therapeutic recommendations are made.

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