Whole body and splanchnic oxygen consumption and blood flow after oral ingestion of fructose or glucose

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Brundin, Tomas, and John Wahren. Whole body and splanchnic oxygen consumption and blood flow after oral ingestion of fructose or glucose. *Am. J. Physiol.* 264 (*Endocrinol. Metab.* 27): E504-E513, 1993.—The contribution of the splanchnic tissues to the initial 2-h rise in whole body energy expenditure after ingestion of glucose or fructose was examined in healthy subjects. Indirect calorimetry and catheter techniques were employed to determine pulmonary gas exchange, cardiac output, splanchnic blood flow, splanchnic oxygen uptake, and blood temperatures before and for 2 h after ingestion of 75 g of either fructose or glucose in water solution or of water only. Fructose ingestion was found to increase total oxygen uptake by an average of 9.5% above basal levels; the corresponding increase for glucose was 8.8% and for water only 2.5%. The respiratory exchange ratio increased from 0.84 in the basal state to 0.97 at 45 min after fructose ingestion and rose gradually after glucose to 0.86 after 120 min. The average 2-h thermic effect, expressed as percent of ingested energy, was 5.0% for fructose and 3.7% for glucose (not significant). Splanchnic oxygen consumption did not increase measurably after ingestion of either fructose or glucose. The arterial concentration of lactate rose, arterial pH fell, and P_{CO_2} remained essentially unchanged after fructose ingestion. Glucose, but not fructose, elicited increases in cardiac output (28%) and splanchnic blood flow (56%). Fructose, but not glucose, increased arterial blood temperature significantly. It is concluded that both fructose and glucose-induced thermogenesis occurs exclusively in extrasplanchnic tissues. Compared with glucose, fructose ingestion is accompanied by a more marked rise in CO_2 production, possibly reflecting an increased extrasplanchnic oxidation of lactate and an accumulation of heat in the body.

energy expenditure; indirect calorimetry; thermogenesis; blood temperature

THE TERM nutrient-induced thermogenesis refers to the rise in resting energy expenditure after the ingestion of a meal (26, 30, 41). Protein elicits a greater response than carbohydrate or fat (16, 26, 30, 34, 37). The precise mechanism(s) whereby nutrients stimulate energy expenditure in humans is controversial. Likewise, the site(s) in the body at which the postprandial rise in energy expenditure occurs is incompletely known. Recently, it was demonstrated that almost one-half of the rise in energy expenditure after a mixed meal occurs in the splanchnic tissues (10, 11). Among the extrasplanchnic tissues, it is primarily in skeletal muscle that a marked stimulation of energy expenditure is believed to take place, particularly after carbohydrate-rich meals (2–4). This stimulation is considered to be mediated in part by central activation of the sympathoadrenal system (2, 3, 6, 28).

Earlier studies have examined the total thermogenic responses to glucose and fructose. Fructose is reported to elicit a somewhat greater increase in energy expenditure and a more marked rise in lactate levels than glucose (44, 45). However, neither the regional distribution of the response in energy expenditure nor the circulatory changes that accompany the ingestion of glucose or fructose are known.

Several studies have described the metabolism of fructose administered intravenously or by oral ingestion (1, 4, 12, 22, 25, 35, 43–45, 48). Ingested fructose is primarily taken up and phosphorylated by the liver and subsequently converted to triose phosphates. The latter may be used as substrates for hepatic gluconeogenesis or, alternatively, for either lactate formation or oxidation. However, some of the ingested fructose escapes hepatic uptake and is drained by the hepatic venous blood into the systemic circulation and may be taken up and oxidized by fat or skeletal muscle. In contrast, ingested glucose is readily taken up and metabolized by several tissues, partly due to the action of insulin. Unlike fructose, glucose may be stored as glycogen in both splanchnic (liver) and extrasplanchnic (muscle) tissues. The quantitative ratio of splanchnic to extrasplanchnic handling of ingested fructose remains to be assessed.

Information on the sites of energy expenditure and the circulatory responses to the ingestion of fructose and glucose may help to further our understanding of the mechanisms whereby the carbohydrates are metabolized in humans at rest. Consequently, we have studied whole body and splanchnic energy expenditure and blood flow in healthy subjects before and after oral ingestion of either glucose or fructose. In addition, thermistor-equipped catheters were used to measure simultaneously the arterial and hepatic venous blood temperatures to determine the whole body heat accumulation and to quantify the splanchnic drainage of heat after ingestion of fructose or glucose. Because the carbohydrates were dissolved in water, a control group receiving an equal volume of water only was also studied.

METHODS

Twenty-eight male volunteers (Table 1) were studied by indirect calorimetry before and after oral ingestion of either fructose (12 subjects), glucose (6 subjects), or water (10 controls). In six subjects in the fructose group, in all six subjects in the glucose group, and in seven subjects in the control group, splanchnic and whole body metabolic and circulatory responses were studied by means of hepatic venous and pulmonary arterial catheterization. The remaining six subjects in the fructose group were examined with regard to the possible occurrence of hyperventilation after fructose ingestion. In these six subjects, only one catheter was inserted for arterial blood gas samples. To avoid possible effects on energy expenditure caused by muscular activity associated with the suction or swallowing procedures, 3 of the 10 control subjects received water infused via a gastric tube, inserted before the study. These three subjects were studied by indirect calorimetry only. The subjects were informed of the nature, purpose, and possible risks of the study before giving their voluntary consent to participate. The study protocol was reviewed and approved by the institutional ethics committee.

The subjects came to the laboratory in the morning after an

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Table 1. *Anthropometric data*

Group	No.	Age, yr	Height, m	Weight, kg	Body Mass Index	Calculated Basal Energy Expenditure, W
Fructose	12	30±2	1.83±0.01	79±2	23±1	90±1
Glucose	6	27±2	1.82±0.02	74±3	22±1	88±1
Water controls	7	28±2	1.81±0.02	77±3	24±1	89±1

overnight (12- to 14-h) fast. They were studied in the supine position, comfortably dressed in a cotton shirt and shorts, and covered by a thin blanket. The room temperature was 20–22°C. Respiratory gas exchange was measured by computerized open-circuit indirect calorimetry using the ventilated hood system (39). The whole body and regional splanchnic oxygen consumption and blood flow, the regional splanchnic heat drainage, and substrate balance data were measured in 19 subjects as specified above. Under local anesthesia and fluoroscopic control, two thermistor-equipped catheters (EDSLAB 93A-131-7F; Edwards, Santa Ana, CA) were inserted, one from the femoral vein into a right-sided hepatic vein and the other from an antecubital vein into the pulmonary artery. An arterial catheter including a thin thermistor probe (EDSLAB T.D. probe 94-030-2.5F) was inserted percutaneously from a femoral artery into the abdominal aorta. After the catheterization, infusion of indocyanine dye (Cardio-Green; Hynson, Westcott & Dunning Products, Becton Dickinson, Cockeysville, MD), blood thermometry, and respiratory gas analysis were started and continued for 1 h to reach basal steady-state levels before one of the carbohydrate solutions (or water only) was given. The dye was infused into the right atrium via the side hole of the pulmonary artery catheter. At ~1 h after the catheterization, baseline measurements were performed, and 75 g of either fructose or glucose dissolved in 375 ml water were given. The control group received 375 ml water only. The total energy content of the carbohydrate solutions constituted 15–17% of the individual basal 24-h requirement calculated from body size and age (19). The carbohydrate solutions and the water were heated to 36.5°C and administered via a straw (in 3 subjects water was infused via a gastric tube) during 2–4 min. Blood samples for oxygen content, hemoglobin, and indocyanine dye were drawn from the arterial and hepatic venous catheters immediately before and at 15, 30, 45, 60, 90, and 120 min after ingestion of the test solution. The blood temperatures were recorded continuously from the thermistor-equipped catheters at a sampling frequency of 1 Hz, as described earlier (8, 9). The splanchnic blood flow was estimated by the continuous indocyanine infusion technique (7, 40). Blood content of oxygen and hemoglobin was analyzed spectrophotometrically (OSM 3 Hemoximeter, Radiometer, Copenhagen, Denmark). In the six subjects receiving fructose, studied to assess whether hyperventilation occurred, only one catheter was inserted into a brachial artery from which blood was drawn every 10 min for analyses of P_{O_2}, P_{CO_2}, and pH by means of an automated blood gas analyzer (ABL 3; Radiometer).

Analytical Methods

Enzymatic techniques were employed for the determination of blood concentrations of fructose (5), glucose (24), lactate (36), pyruvate (27), and glycerol (47). Plasma insulin concentration was determined by radioimmunoassay (21).

Calculations

The total energy expenditure was calculated from oxygen uptake and respiratory exchange ratio (29, 49). Cardiac output, regional splanchnic oxygen uptake, and splanchnic heat drained via the liver veins were calculated according to the Fick (15) principle. Venoarterial heat differences and specific heat for the blood were calculated from the regional venous hemoglobin concentrations according to Mendlowitz (31) and Van Slyke et al. (46) as described earlier (8).

Statistics

Data for the whole postprandial period were first analyzed by repeated-measures analysis of variance. Differences between the groups were calculated by post hoc testing (42). Data in the text, Tables 1–5, and Figs. 1–8 are given as means ± SE.

RESULTS

Pulmonary Gas Exchange

Oxygen consumption. The pulmonary oxygen uptake in the basal state was similar in the three study groups. The ingestion of water, with or without carbohydrate content, caused a prompt increase in oxygen consumption during 15 min, similar in time course and magnitude after water and glucose but more marked after fructose ($P < 0.05$). After the initial rise the oxygen uptake fell to a level slightly above basal in the control group receiving water only. The average water-induced increase during the 2-h observation period was 7 ± 1 ml/min, corresponding to 2.5% above the basal level. In the fructose and glucose groups the rise in oxygen uptake continued beyond 15 min and reached relatively steady levels from 35 min after the ingestion until the end of the observation period. The average increments over 2 h were 26 ± 1 and 23 ± 1 ml/min, corresponding to 9.5 and 8.8% above basal for the fructose and glucose groups, respectively. Apart from the steeper initial rise caused by fructose, there was no statistically significant difference between the two carbohydrate groups (Fig. 1, Table 2). In the three subjects receiving water via gastric tubes, the pulmonary oxygen uptake increased by 13 ± 1 ml/min or 5 ± 1% of basal levels during the entire 2-h observation period.

CO_2 production. In the basal state, CO_2 production and the respiratory exchange ratio were similar in the three groups. After fructose intake, CO_2 production rose steeply within the first 6–8 min, attaining its maximum level within 30 min. In the glucose group the increase was significantly smaller and more gradual during the first postprandial hour, closely following the curve of the water control group during the first 30 min. It did not reach a maximum until 80 min after the glucose ingestion. The

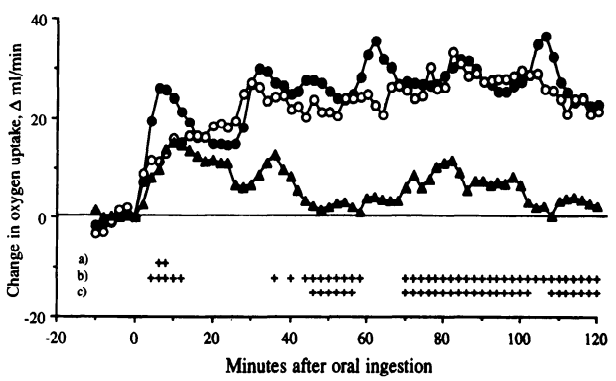

Fig. 1. Change in pulmonary oxygen uptake after oral ingestion of 375-ml water solution of 75 g fructose (n = 12 subjects; ●—●), 75 g glucose (n = 6; ○—○), or 375 ml water only (n = 7; ▲—▲). + Statistical significance between fructose and glucose groups (a), fructose and water groups (b), and glucose and water groups (c).

Table 2. *Pulmonary oxygen uptake, respiratory quotient, total energy expenditure, cardiac output and arteriopulmonary arterial oxygen difference, splanchnic oxygen uptake, splanchnic blood flow, and arteriohepatic venous oxygen difference*

	Basal	Minutes After Carbohydrate Meal					
		15	30	45	60	90	120
Pulmonary oxygen uptake, ml/min							
Fructose	270±9	282±9	283±10	291±12	292±11	296±13	290±12
Glucose	263±8	283±10	290±13	284±12	289±13	292±12	284±11
Water controls	270±7	278±7	277±9	274±8	270±7	275±8	284±6
Respiratory quotient							
Fructose	0.84±0.02	0.87±0.03	0.96±0.02	0.97±0.02	0.94±0.02	0.93±0.02	0.93±0.02
Glucose	0.79±0.01	0.77±0.01	0.79±0.01	0.81±0.02	0.84±0.02	0.85±0.01	0.86±0.02
Water controls	0.81±0.01	0.80±0.01	0.80±0.01	0.81±0.02	0.80±0.02	0.81±0.01	0.81±0.03
Energy expenditure, W							
Fructose	90±3	96±3	98±3	101±4	101±4	102±4	100±4
Glucose	88±3	94±3	96±4	95±4	98±5	99±4	96±4
Water controls	90±2	93±2	93±2	92±2	90±2	92±3	95±2
Cardiac output, l/min							
Fructose	5.68±0.39	5.81±0.45	5.67±0.42	5.73±0.25	5.92±0.34	6.03±0.33	6.05±0.31
Glucose	5.30±0.26	6.41±0.38	6.78±0.51	6.25±0.27	6.45±0.24	6.15±0.29	6.56±0.35
Water controls	6.76±0.52	6.58±0.50	7.29±0.51	6.81±0.48	6.52±0.39	6.86±0.49	7.64±0.41
Arteriopulmonary arterial oxygen difference, ml/l							
Fructose	48±3	50±3	51±3	51±2	49±2	49±3	48±3
Glucose	50±2	45±2	43±2	46±2	45±2	48±2	43±2
Water controls	41±2	43±2	39±2	39±2	42±2	41±2	39±2
Splanchnic oxygen uptake, ml/min							
Fructose	66±4	67±6	72±2	68±5	65±7	60±5	65±6
Glucose	66±4	72±4	73±6	66±6	68±6	61±3	60±8
Water controls	61±5	64±4	57±5	58±3	60±5	62±11	62±3
Splanchnic blood flow, l/min							
Fructose	1.31±0.07	1.43±0.10	1.44±0.06	1.30±0.07	1.33±0.10	1.43±0.08	1.48±0.06
Glucose	1.17±0.08	1.82±0.14	1.83±0.23	1.52±0.16	1.49±0.12	1.41±0.09	1.40±0.15
Water controls	1.20±0.08	1.26±0.11	1.19±0.07	1.24±0.03	1.14±0.07	1.24±0.15	1.24±0.03
Arteriohepatic venous oxygen difference, ml/l							
Fructose	50±3	47±3	50±2	53±4	48±3	42±3	43±3
Glucose	60±2	41±3	42±3	44±1	46±2	43±2	43±3
Water controls	51±4	50±4	47±4	49±2	52±3	49±3	49±3

Values are means ± SE from 24 male volunteers before and at timed intervals after oral ingestion of 375-ml water solution of 75 g fructose ($n = 6 + 6$) or glucose ($n = 6$) or 375 ml water only ($n = 7$). For all fructose groups except pulmonary oxygen uptake, respiratory quotient, and energy expenditure, $n = 6$ subjects.

average 2-h postprandial increase in CO_2 production was 50 ± 2 ml/min in the fructose group and 29 ± 2 ml/min in the glucose group ($P < 0.02$). Consequently, the postprandial rise in the respiratory exchange ratio was slower and significantly less marked ($P < 0.01$) in the glucose compared with the fructose group. Its maximum was observed at 120 min after the glucose intake. In the controls ingesting water only, the average 2-h increase in expired CO_2 was 7 ± 1 ml/min, with the respiratory exchange ratio remaining unchanged except for a slight initial rise (Fig. 2, Table 2), possibly reflecting hyperventilation in association with the feeding. In the subjects receiving water via gastric tube, CO_2 production, except for the initial rise, closely followed that of the water control group, with the respiratory exchange ratio remaining unchanged during the observation period.

Total Energy Expenditure

Total energy expenditure in the basal state was similar in the three groups (Table 2). The rise in calculated energy expenditure tended to reach consistently higher mean postprandial values in the fructose than the glucose group (Fig. 3). The average increase during the 2-h postprandial study period was 11 ± 0.3 W or 12% above basal in the fructose group and 9 ± 0.3 W or 10% above basal in the glucose group. Except for the initial steeper rise caused by fructose, the difference between the two carbohydrate groups did not reach statistical significance. In the control group the average increase in calculated energy expenditure after water administration was 2 ± 0.1 W, corresponding to 2% above the basal level during the 2-h observation period. In the three subjects receiving water via gastric tubes the energy expenditure rose by 5 ±

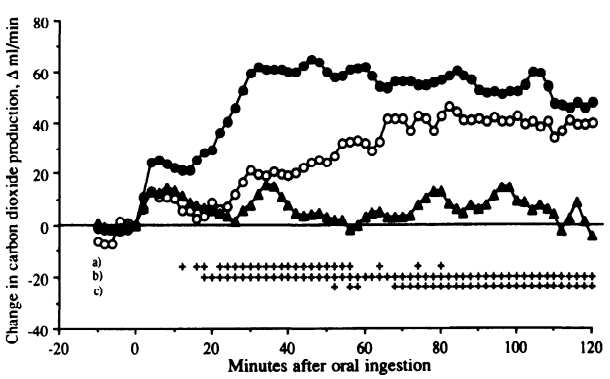

Fig. 2. Change in respiratory elimination of carbon dioxide after oral ingestion of 375-ml water solution of 75 g fructose ($n = 12$), 75 g glucose ($n = 6$), or 375 ml water only ($n = 7$). Symbols as in Fig. 1.

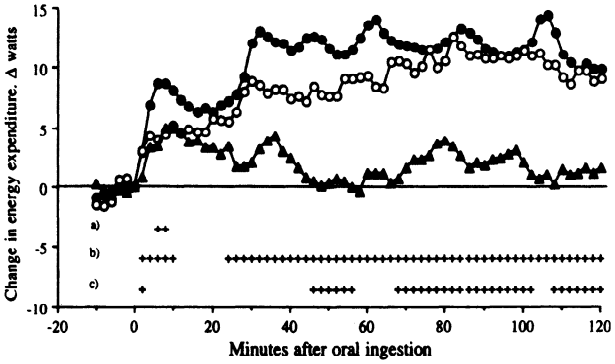

Fig. 3. Change in resting energy expenditure after oral ingestion of 375-ml water solution of 75 g fructose (n = 12), 75 g glucose (n = 6), or 375 ml water only (n = 7). Symbols as in Fig. 1.

1% of the basal level, with the respiratory quotient remaining unchanged.

The thermic effect of the carbohydrates was calculated as the net postprandial 2-h rise in energy expenditure (water effect subtracted) expressed in percent of the energy content of the nutrients ingested. It was 5.0% for fructose and 3.7% for glucose. The difference between the two carbohydrate groups did not attain statistical significance ($0.1 > P > 0.05$).

Cardiac Output

Cardiac output in the basal state was similar in all groups (Table 2). Glucose ingestion was accompanied by a prompt rise in cardiac output, amounting to 1.12 ± 0.21 l/min or 21 ± 4% above basal already within 15 min. At 30 min after glucose the rise was 1.49 ± 0.27 l/min or 28 ± 5% above the basal level. The average 2-h postprandial rise was 1.13 ± 0.09 l/min, corresponding to 21 ± 2% of the basal value. In contrast, fructose ingestion resulted in only minimal and insignificant changes in cardiac output. At 90 and 120 min, there were small increments of 0.36 ± 0.17 and 0.37 ± 0.18 l/min (Fig. 4). In the water control group, cardiac output did not change significantly from basal during the study period.

The arteriopulmonary arterial oxygen difference was in the basal state 48 ± 3, 50 ± 2, and 41 ± 2 ml/l in the fructose, glucose, and water control groups, respectively. After glucose, this variable fell by 7 ± 2 ml/l ($P < 0.01$) during the first 30 min, whereas no significant changes occurred in the fructose or control groups.

Splanchnic Blood Flow and Oxygen Uptake

In the basal state the splanchnic blood flow was 1.1–1.4 l/min, accounting for 22–23% of the simultaneous cardiac output in the different groups. After glucose ingestion the splanchnic blood flow rose within the first 30 min by 0.66 ± 0.04 l/min, corresponding to 56 ± 3% of its basal value. This level was maintained at 30 min after the meal and represented a blood flow rise that accounted for 60–70% of the simultaneous increase in cardiac output. Thereafter, splanchnic blood flow decreased to a level of 20–25% above basal in the glucose group. Fructose ingestion did not elicit significant changes in the splanchnic blood flow (Fig. 5).

The arteriohepatic venous oxygen difference in the basal state was 60 ± 2 ml/l in the glucose group and somewhat higher than in the fructose and control groups, where it was 50 ± 3 and 51 ± 8 ml/l, respectively. During the postprandial period the arteriohepatic venous oxygen difference fell significantly in the glucose group to 42–46 ml/l. No significant changes occurred for this variable in the fructose or control groups.

Splanchnic regional oxygen uptake, calculated as the product of splanchnic blood flow and arteriohepatic venous oxygen difference, was in the basal state 66 ± 4 ml/min in both the fructose and glucose groups, accounting for 25 ± 2% of their simultaneous pulmonary oxygen uptake (Table 2). After carbohydrate ingestion, splanchnic oxygen consumption tended to rise initially, but the increase was not significant in any of the groups. Due to the postprandial rise in pulmonary oxygen uptake and an almost constant level of the postprandial splanchnic oxygen uptake, the regional splanchnic proportion of the whole body oxygen consumption fell slightly, with its average 2-h postprandial proportion being 21–22% of the whole body oxygen uptake in the carbohydrate groups (Table 2).

Blood Temperatures and Venous Drainage of Splanchnic Heat

The arterial blood temperatures in the basal state were 36.4–36.5 in all groups. In the fructose group the arterial temperature increased significantly, especially during the second postprandial hour, and had at the end of the study period risen by 0.205 ± 0.039°C, indicating a significant heat accumulation in the body. In the glucose group the arterial blood temperature showed only a slight tendency to rise during the last 10 min of the postprandial study

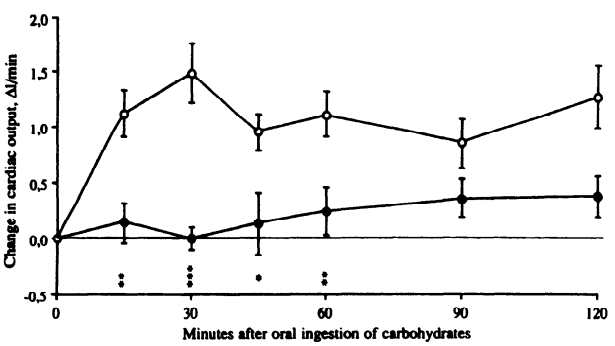

Fig. 4. Change in cardiac output after oral ingestion of 375-ml water solutions of 75 g fructose (n = 6; ●—●) or glucose (n = 6; ○—○). * Statistical significance between groups.

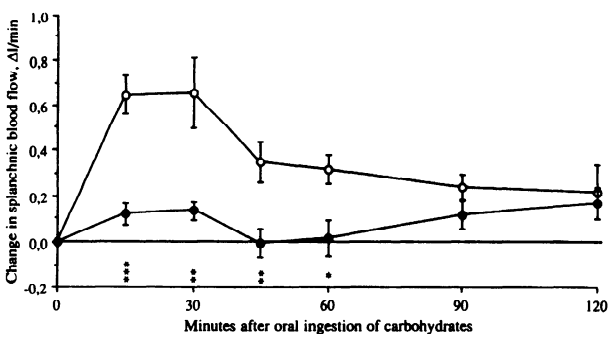

Fig. 5. Change in splanchnic blood flow after oral ingestion of 375-ml water solution of 75 g fructose (n = 6) or glucose (n = 6). Symbols as in Fig. 4.

period (Fig. 6). In the control group the arterial blood temperature remained at the basal level throughout the observation period.

The hepatic venous blood temperature in the basal state was 36.5–36.6°C in all groups. After ingestion of fructose, it rose in parallel with the arterial temperature, whereas, after glucose, it only tended to rise at the end of the postprandial period. The hepatic venous-arterial temperature differences were similar in the three groups, as was the calculated splanchnic venous heat drainage, both in the basal state and after the carbohydrate meals or water (Table 3). In relation to splanchnic oxygen consumption, the splanchnic heat recovered in the hepatic venous blood was 11–12 J/ml O_2 in the basal state, similar in all groups, and unchanged during the postprandial period.

Arterial pH and P_{CO_2}

In six subjects who received fructose, the arterial pH and P_{CO_2} were followed every 10 min. In the basal state the pH was 7.41 ± 0.01. After fructose the pH started to fall within 10 min and reached a minimum of 7.37 ± 0.01 at 90 min after the ingestion (Fig. 7). The P_{CO_2} was 5.50 ± 0.17 kPa in the basal state and showed only a slight and insignificant tendency to decline after fructose. Its minimum, 5.35 ± 0.21, was recorded at 60 min after the fructose ingestion (Fig. 7).

Substrate and Insulin Balance

After fructose. The arterial blood concentration of fructose increased to a maximum of 0.68 ± 0.06 mmol/l at 45 min after the meal (Table 4). The average postprandial release of fructose from the splanchnic region was 0.24 ± 0.04 mmol/min. There was a small initial rise in splanchnic release of glucose, with the arterial blood glucose concentration increasing from basal 4.5 ± 0.3 to 5.3 ± 0.3 mmol/l within 45 min after the meal. Lactate was released from the splanchnic tissues, reaching a peak value of 1.1 ± 0.3 mmol/min as early as 30 min after the meal (Fig. 8). The arterial blood concentration of lactate rose to >2 mmol/l within 30 min after the meal and was still elevated at the end of the 2-h postprandial observation period. The splanchnic release of pyruvate increased to 0.24 ± 0.05 mmol/min after 30–45 min with arterial concentrations of 0.3 mmol/l. The blood concentrations of glycerol fell slightly after the meal. The arterial insulin level rose fourfold above basal after fructose ingestion. Insulin release from the splanchnic region showed a small increase from a basal value of 5 ± 2 to a maximum of 10 ± 2 mU/min at 30 min after the fructose meal.

After glucose. The concentration of glucose in arterial blood and the splanchnic glucose output increased during the first postprandial hour (Table 5). The arterial glucose concentration was still elevated, 6.7 ± 0.4 mmol/l, at 2 h after the meal. The arterial lactate concentration rose from basal, 0.35 ± 0.04, to a maximum of 0.74 ± 0.06 mmol/l at 90 min after the meal. The splanchnic uptake of lactate was reduced to zero at 45 min after the meal (Fig. 8). The blood concentrations of glycerol decreased after glucose. The arterial insulin concentration rose immediately after glucose ingestion; the splanchnic release of insulin increased 10-fold, with peak levels of 43 ± 14 and 49 ± 16 mU/min at 15 and 30 min, respectively, after glucose ingestion.

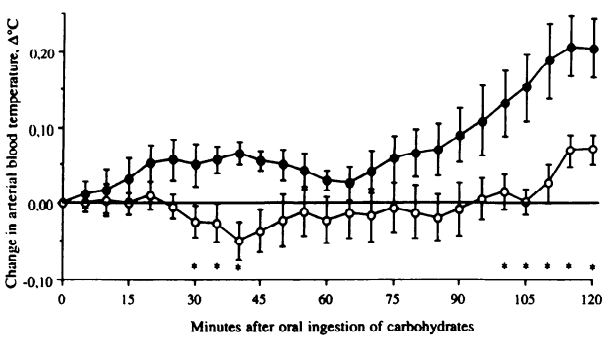

Fig. 6. Change in arterial blood temperature after oral ingestion of 375-ml water solution of 75 g fructose (n = 6) or glucose (n = 6). Symbols as in Fig. 4.

DISCUSSION

It was recently shown that almost one-half of the rise in energy expenditure that follows ingestion of a mixed meal occurs in the splanchnic organs (10, 11). Beside its thermogenic effects, the mixed meal was found to increase cardiac output, splanchnic blood flow, blood temperature, and the dissipation of heat across the abdominal wall. The aim of the present work was to examine the specific changes in whole body and splanchnic energy expenditure and blood flow that could be elicited by the ingestion of either fructose or glucose without interference from other nutrients.

The results show that splanchnic oxygen consumption does not increase significantly above its basal level during 2 h after oral ingestion of 75 g of either glucose or fructose. At the same time the rise in whole body energy expenditure was of a magnitude that agrees well with previous reports (43, 44). It may thus be concluded that the entire rise in energy expenditure after ingestion of fructose or glucose occurs exclusively in the extrasplanchnic tissues and that there were no measurable net splanchnic energy costs for the absorption, processing, or storage during 2 h after carbohydrate administration. The explanation for this unexpected finding is not immediately apparent, but the following possibilities may be considered. The energy required for splanchnic handling of the carbohydrates may have been generated via anaerobic glycolysis rather than by oxidative metabolism. In the case of fructose, the triose phosphates formed from fructose 1-phosphate may be metabolized along the gluconeogenic pathway to form hepatic glycogen as well as via the glycolytic pathway, resulting in the formation of pyruvate and subsequently lactate. The energy required for glycogen synthesis from fructose (3 ATP/mol fructose) may thus in part be generated by the formation of pyruvate and lactate (4 ATP/mol fructose). After consideration of the observed splanchnic release of fructose, lactate, and pyruvate during 2 h after fructose ingestion (Table 4), it can be estimated that glycolytic metabolism may have generated ~225 mmol ATP, sufficient to support the conversion of 75 mmol fructose to glycogen. All

Table 3. *Blood temperatures and blood-drained splanchnic heat*

Blood Temperatures, °C	Basal	Minutes After Carbohydrate Meal					
		15	30	45	60	90	120
Aorta, 36°C							
Fructose	369±0.127	386±0.126	403±0.125	395±0.114	383±0.122	424±0.116	525±0.113
Glucose	422±0.057	422±0.061	399±0.068	388±0.064	399±0.065	414±0.056	498±0.070
Water controls	479±0.136	463±0.132	449±0.123	425±0.122	426±0.146	496±0.101	544±0.106
Hepatic vein, 36°C							
Fructose	522±0.144	561±0.147	602±0.138	615±0.134	575±0.134	605±0.133	673±0.122
Glucose	571±0.072	558±0.079	531±0.086	535±0.068	552±0.067	559±0.058	631±0.072
Water controls	684±0.142	646±0.130	659±0.123	624±0.125	646±0.149	693±0.100	756±0.095
Blood-drained splanchnic heat, W							
Fructose	13±2	17±2	18±1	18±2	16±2	16±1	14±1
Glucose	12±2	18±1	19±3	14±2	14±2	13±2	12±1
Water controls	13±2	13±1	14±0	15±2	14±2	14±2	15±2
Blood-drained splanchnic heat/splanchnic oxygen uptake, J/ml							
Fructose	12±1	16±2	15±1	16±1	15±2	17±1	13±1
Glucose	11±1	15±1	15±1	13±1	13±1	13±2	13±2
Water controls	12±1	13±1	15±1	15±2	15±2	14±1	14±2

Values are means ± SE from 24 male volunteers before and at timed intervals after oral ingestion of 375-ml water solution of 75 g fructose (n = 6) or glucose (n = 6) or 375 ml water only (n = 7).

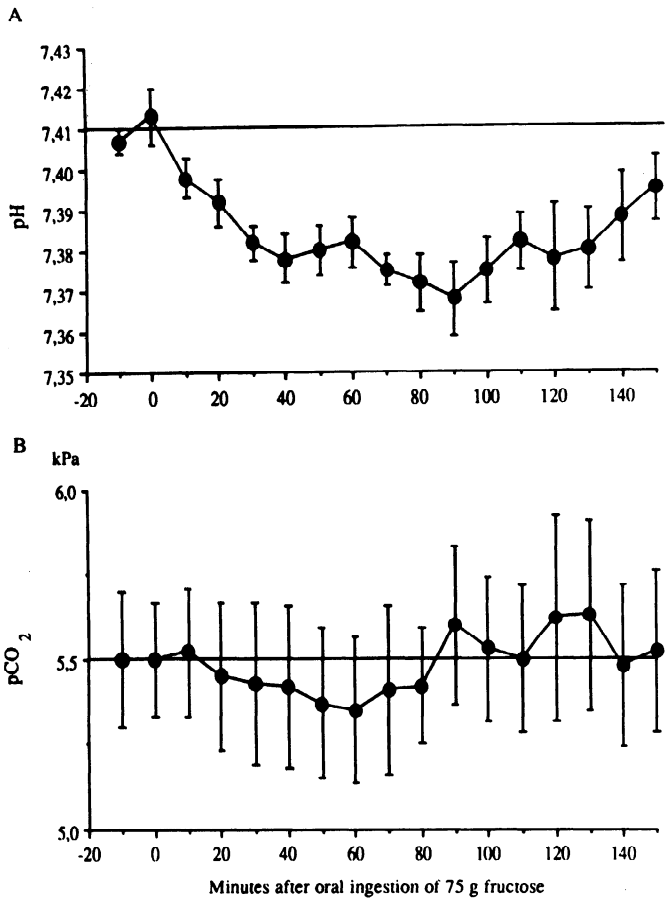

Fig. 7. Change in arterial blood pH (A) and arterial blood P_{CO_2} (B) after oral ingestion of 375-ml water solution of 75 g fructose (n = 6).

in all, a total of 165 mmol fructose or as much as 40% of the ingested load could be accounted for by this calculation. In addition, fructose administration is known to reduce hepatic ATP levels, as demonstrated in human liver biopsy samples (25) and later confirmed by magnetic resonance spectroscopy (35). Hence, it is possible that partial depletion of the hepatic ATP pool may have further supported hepatic glycogen synthesis from fructose. The data do not allow a more precise evaluation of the fate of the fructose load since the completeness of intestinal absorption after 2 h is unknown. Moreover, the extent to which fructose is metabolized by the intestinal wall rather than by the liver in humans is not known. Despite the above shortcomings of the calculations, the data suggest that anaerobic glycolysis may be a significant source of energy production for hepatic glycogen synthesis from fructose. This hypothesis is compatible with the finding that splanchnic oxygen uptake was unchanged after ingestion of fructose.

It may be argued that, if there was significant ATP generation via anaerobic glycolysis in the liver and subsequent ATP utilization in the formation of hepatic glycogen, these processes would be expected to result in extra heat generation in the splanchnic area. However, no significant increase in the amount of heat drained by the hepatic veins was observed, probably due to the variable heat leakage across the abdominal wall previously observed after a mixed meal (10). Moreover, the relation between aerobic splanchnic metabolism and hepatic venous heat drainage was similar in the fructose and glucose groups. In view of these considerations and findings, it is apparent that measurements of hepatic venous heat drainage are unlikely to be helpful in the evaluation of splanchnic carbohydrate metabolism.

Calculations of splanchnic ATP formation similar to those above for fructose cannot readily be made for glucose, but it is apparent that the splanchnic output of lactate and pyruvate was less marked after glucose compared with fructose (Tables 4, 5) and that ATP generation from anaerobic glycolysis is likely to have been smaller. Glucose ingestion was accompanied by a much larger increase in splanchnic release and arterial concentration of insulin compared with fructose administration. The more pronounced rise in insulin may have exerted several effects of importance for splanchnic and whole

Table 4. *Substrate balance before and at timed intervals after oral ingestion of 75 g fructose in 375 ml water*

	Basal	Minutes After Fructose Meal					
		15	30	45	60	90	120
Fructose, μmol/l							
Artery	4±4	473±91	601±91	681±56	521±65	485±58	445±75
Hepatic vein	35±16	673±123	927±109	900±76	694±68	619±92	587±134
hv-a difference	31±15	200±78	326±70	220±41	173±40	133±46	142±64
Splanchnic release, μmol/min	43±20	270±104	473±107	278±45	222±46	191±64	267±55
Glucose, μmol/l							
Artery	4,470±296	5,155±348	5,258±303	5,312±326	5,168±346	4,885±370	4,785±299
Hepatic vein	5,160±304	5,948±318	5,953±268	5,940±341	5,663±317	5,440±291	5,427±212
hv-a difference	690±121	793±83	695±128	628±87	495±89	555±115	642±239
Splanchnic release, μmol/min	923±185	1,142±162	1,003±197	830±135	657±129	807±188	937±403
Lactate, μmol/l							
Artery	529±70	1,578±362	2,215±377	2,506±284	2,189±222	1,980±118	1,690±260
Hepatic vein	438±106	2,091±549	2,972±577	3,246±392	2,754±395	2,416±168	2,002±419
hv-a difference	−90±42	513±228	757±231	740±197	566±212	435±62	312±163
Splanchnic release, μmol/min	−111±52	769±327	1,069±306	944±242	700±278	604±76	470±258
Pyruvate, μmol/l							
Artery	61±10	179±42	273±43	288±29	238±24	226±23	162±33
Hepatic vein	69±22	318±81	444±73	475±48	386±47	349±28	238±55
hv-a difference	12±12	105±48	171±40	187±36	148±37	123±31	76±24
Splanchnic release, μmol/min	19±16	190±71	241±51	239±44	185±42	164±37	113±38
Glycerol, μmol/l							
Artery	49±4	44±4	34±3	32±3	33±6	25±3	30±5
Hepatic vein	11±5	11±2	14±3	9±2	7±2	5±2	14±10
a-hv difference	38±5	20±5	20±5	25±4	19±3	19±3	25±6
Splanchnic uptake, μmol/min	48±5	45±5	28±6	33±5	37±10	28±7	37±9
Insulin, mU/l							
Artery	4±2	16±4	17±2	15±2	14±2	16±4	14±3
Hepatic vein	8±2	22±4	24±2	22±2	20±1	20±2	20±3
hv-a difference	3.7±1.7	6.4±1.6	6.9±1.4	6.8±1.5	6.4±2.0	4.4±1.6	6.3±1.5
Splanchnic release, mU/min	4.9±2.1	8.7±2.4	9.8±2.0	8.8±1.8	8.6±2.0	6.2±1.8	9.2±2.2

Values are means ± SE from 6 healthy male volunteers. hv-a, hepatic venous − arterial difference; a-hv, arterial − hepatic venous difference.

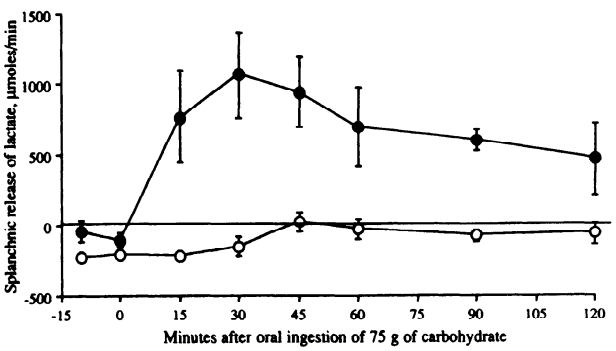

Fig. 8. Splanchnic release of lactate before and after oral ingestion of 375-ml water solution of 75 g fructose (n = 6) or glucose (n = 6). Symbols as in Fig. 4.

body energy expenditure. Thus a 10-fold increase in insulin concentration, as observed after glucose, is likely to inhibit hepatic gluconeogenesis (14). In addition, the elevated insulin levels are likely to reduce protein degradation and amino acid oxidation (33), resulting in diminished plasma amino acid levels. The latter change may, in turn, serve to retard tissue protein synthesis (32). Hepatic gluconeogenesis, protein breakdown, and synthesis are all energy-requiring processes. We may thus consider the possibility that the unchanged level of oxygen consumption in splanchnic tissues after glucose may reflect the net balance of diminished gluconeogenesis and protein metabolism and augmented costs for absorption and processing of the glucose load. However, irrespective of the mechanisms involved, the results demonstrate that ingestion of either of the two most common dietary carbohydrates results in no net rise in splanchnic oxygen consumption and, consequently, no splanchnic contribution to the rise in whole body oxygen uptake.

In view of the magnitude of the error of the method for determination of splanchnic oxygen uptake (coefficient of variation 6.5%, calculated from duplicate determinations in the same individual), it is clear that a small rise in splanchnic oxygen consumption may escape detection with the present methodology. However, it is unlikely that a major proportion of the whole body rise in oxygen uptake after fructose or glucose (Table 2) could be localized to the splanchnic area without being detected.

Fructose ingestion was accompanied by a more marked rise in the respiratory exchange ratio than that seen after glucose, in agreement with previous observations (43, 44). This finding indicates that fructose stimulated carbohydrate oxidation more readily than glucose. The explanation for the difference between fructose and glucose in this regard is not immediately apparent. However, the possibility should be considered that the greater lactate production after fructose may have contributed. The splanchnic release of lactate during 2 h after fructose ingestion exceeded that seen after glucose by an average of 63 mmol. Moreover, the estimated amount of lactate present in the extracellular compartment at the end of the 2-h study period was 13 mmol greater after fructose than after glucose. It may thus be assumed that lactate metab-

Table 5. *Substrate balance before and at timed intervals after oral ingestion of 75 g glucose in 375 ml water*

	Basal	Minutes After Glucose Meal					
		15	30	45	60	90	120
Glucose, μmol/l							
Artery	4,400±250	7,180±570	8,830±540	9,610±420	9,270±440	7,820±230	6,700±410
Hepatic vein	5,020±210	8,592±665	10,200±646	11,115±474	10,673±575	8,978±226	7,487±410
hv-a difference	620±87	1,412±147	1,368±178	1,502±140	1,405±170	1,157±100	783±43
Splanchnic release, μmol/min	715±91	2,502±198	2,387±342	2,200±181	2,055±274	1,625±164	1,096±135
Lactate, μmol/l							
Artery	351±40	305±29	448±30	604±76	686±94	738±60	618±55
Hepatic vein	163±22	176±18	353±55	610±119	664±138	680±61	134±55
hv-a difference	189±21	129±13	95±41	−6±52	22±51	59±30	54±49
Splanchnic uptake, μmol/min	217±23	229±21	156±69	−19±73	30±74	82±45	63±80
Pyruvate, μmol/l							
Artery	44±3	44±2	69±11	96±18	101±18	99±9	73±6
Hepatic vein	29±2	32±2	72±19	118±34	136±42	121±19	80±12
hv-a difference	−18±2	−14±1	3±8	27±16	42±23	27±11	10±8
Splanchnic release, μmol/min	−20±2	−24±2	6±16	43±25	62±34	39±16	15±13
Glycerol, μmol/l							
Artery	66±11	31±8	23±4	24±4	24±3	23±3	26±3
Hepatic vein	9±3	8±3	6±2	8±3	6±2	6±2	5±2
a-hv difference	57±10	23±4	17±2	16±2	17±1	17±1	21±2
Splanchnic uptake, μmol/min	66±11	42±7	30±3	24±1	25±2	23±2	29±5
Insulin, mU/l							
Artery	5±2	42±5	55±8	59±7	57±8	42±6	34±7
Hepatic vein	8±2	65±11	85±15	86±8	81±14	58±8	43±8
hv-a difference	3±1	23±7	29±9	27±3	24±6	16±2	9±3
Splanchnic release, mU/min	4±2	43±14	49±16	40±4	36±9	22±3	14±4

Values are means ± SE from 6 healthy male volunteers.

olism after fructose exceeded that after glucose by 50 mmol. With the assumption that all of this lactate was oxidized to CO_2 and water, ~100 mmol CO_2 would be produced and expired. This amount of CO_2 equals the total difference in CO_2 production between the fructose and glucose groups (Table 2). It is thus possible that a major part of the marked increase in respiratory exchange ratio after fructose, as compared with glucose, may be accounted for by an augmented lactate oxidation. Moreover, it may be argued that the lactate accumulation after fructose ingestion, and the ensuing metabolic acidosis, may elicit hyperventilation and augmented CO_2 expiration due to compensatory mechanisms in the regulation of the acid-base balance. However, the bicarbonate available in the extracellular space would cover only a limited proportion of the extra CO_2 expired after fructose ingestion. There were no signs of alveolar hyperventilation. No significant fall in arterial P_{CO_2} accompanied the reduced arterial blood pH after fructose. It thus seems probable that the observed fructose-induced rise in respiratory quotient reflects a true increase in carbohydrate oxidation rather than a change in the CO_2 pool size.

Although absorbed from the intestine somewhat more slowly than glucose (23, 45), fructose has been shown to induce a significantly greater total thermogenic response than equivalent amounts of glucose (44). Accordingly, in the present study, the rise in energy expenditure after fructose was consistently greater than after glucose, although the difference did not attain statistical significance. This seeming discrepancy might be due to the fact that our postprandial study period was only one-half of that in the earlier less invasive studies (43, 44). For practical and safety reasons, we had to limit our postprandial study period to 2 h, covering the onset, rise, and maximum of the thermogenesis, and 1 h of relative postprandial steady-state conditions.

The current results indicate that the carbohydrate-induced rise in energy expenditure occurs exclusively in extrasplanchnic tissues. Previous studies have indicated that carbohydrate ingestion increases oxidative metabolism in skeletal muscles and, in addition, stimulates efferent sympathoadrenal activity in humans (2-4, 6, 28). However, the present findings do not allow conclusions as to which extrasplanchnic tissues are the dominating sites for the carbohydrate-induced thermogenesis.

Earlier studies have shown increased cardiac output after food ingestion (17, 18). Increased total and splanchnic blood flows have recently been demonstrated after mixed meals containing glucose (10, 11). The present study showed considerable increments in both total and splanchnic blood flow after oral ingestion of glucose, but no such effect was observed after fructose. The literature gives little information about this difference in circulatory effects between glucose and fructose. The mechanism whereby glucose stimulates both total and regional splanchnic blood flow is not known. Carbohydrate administration has been shown to elicit central nervous sympathoadrenal activity (2, 3, 6, 28). The subsequent stimulation of β-adrenergic receptors would be expected to reduce regional vascular resistance, thereby allowing for increased blood flow in, e.g., splanchnic tissues and skeletal muscles. However, after fructose, which is known to stimulate the sympathoadrenal system as well as glucose (43, 44), we were unable to demonstrate any significant effects on either cardiac output or splanchnic blood flow. This indicates that the blood flow stimulation ob-

served already within 15 min after glucose ingestion may have been dominated by mechanisms other than the increased sympathoadrenal activity. The secretion of insulin that follows glucose administration may be such a possible mechanism. Insulin, even in doses insufficient to cause measurable hypoglycemia, has been shown to increase muscular blood flow in humans by stimulating β-adrenergic receptors (13). Possible blood flow stimulating effects of insulin might explain why glucose causes enhanced total and regional blood flow, whereas fructose, which is a less potent stimulator of insulin secretion (38), does not. Further studies will be required to evaluate the quantitative importance of each of the possible mechanisms that may mediate the marked circulatory effects of glucose.

Fructose ingestion was accompanied by a significant increase in arterial blood temperature during the second postprandial hour, whereas no such rise was seen after glucose. Thus fructose caused a considerable accumulation of heat in the body, in magnitude almost similar to that seen after mixed meals (10, 11). The reason why glucose, eliciting a thermogenic response of essentially the same magnitude as fructose, failed to increase blood temperature and cause heat accumulation may be secondary to its effect on blood flow. Increased blood flow, especially in skin and subcutaneous tissue, may facilitate heat dissipation to the environment. Consequently, increased loss of heat after glucose ingestion would prevent net accumulation of heat in spite of a simultaneously increased thermogenesis.

It was found that the ingestion of water without carbohydrate caused a small but statistically significant increase in energy expenditure, a finding that does not seem to have been described earlier. The effect was not due to muscular activity associated with ingestion of the fluid, since a distinct rise in oxygen consumption was observed also when water was administered via a gastric tube. A control group without water would be needed to assess whether or not the results represent a true thermogenic effect of water. One possible mechanism causing thermogenic effects of water might be the energy-consuming process of cell shrinkage, which has been shown to follow the cell swelling that accompanies exposure to water and hypotonic cell environment (20). However, the thermogenic effect observed after water administration, amounting to 2–3% of basal energy expenditure during 2 h after ingestion of 375 ml water at 36.5°C, may have biological significance. This effect should be taken into account when calculating total thermic effects of nutrients ingested in the form of water solutions. With the carbohydrates fructose and glucose, such subtraction would, in the present study, reduce the thermic effects of the sugars by 20–30%.

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