Acute effects on insulin sensitivity and diurnal metabolic profiles of a high-sucrose compared with a high-starch diet\textsuperscript{1–3}

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ABSTRACT  Decreased insulin sensitivity is associated with diabetes mellitus, ischemic heart disease, and hypertension, both independently and in association as what is called the metabolic syndrome. Although the negative effects of obesity, sedentary lifestyles, and high-fat diets on insulin sensitivity are well established, the influence of type and quantity of dietary carbohydrate is more controversial. This study aimed to assess the acute (24 h) effects of a high-sucrose compared with a high-starch diet on insulin sensitivity and to identify changes in blood metabolites that might lead to altered insulin sensitivity. Eight healthy adults consumed high-sucrose or high-starch diets (50% of dietary energy) in a randomized, crossover trial. Insulin sensitivity was assessed by a short insulin tolerance test the following morning. No differences were detected in insulin sensitivity, either for glucose metabolism [K\textsubscript{ittglucose} (the rate constant for the decline in blood glucose concentrations) for sucrose diet = 3.86 ± 245 mmol · L/min) than with the high-sucrose diet (6290 ± 283 mmol · L/min) (P < 0.001). Plasma fatty acid concentrations showed a late postprandial rise with the sucrose-rich diet relative to the starch-rich diet, which was mirrored with a fractionally later peak in triacylglycerol concentrations.  Am J Clin Nutr 1998;67:1186–96.

KEY WORDS  Insulin sensitivity, dietary carbohydrate, sucrose, starch, glucose metabolism, fatty acids, triacylglycerol, lipid metabolism

INTRODUCTION

Decreased insulin sensitivity is recognized as a major metabolic feature of type 2 diabetes and is one of the earliest detectable abnormalities in some people who go on to develop type 2 diabetes. An association among cardiovascular risk factors (type 2 diabetes, hyperlipidemia, glucose intolerance, and obesity) was described by Avogaro and Crepaldi (1); Reaven (2) extended this with a description of the metabolic syndrome, or syndrome X, in which decreased insulin sensitivity is a key feature.

Obesity and exercise are associated with decreased and increased insulin sensitivity, respectively (3, 4). Himsworth (5) was one of the first to explore the effects of diet on insulin sensitivity, contrasting high-carbohydrate and low-carbohydrate diets. Since then animal work has clearly shown the capacity of high-fat, high-sucrose, or high-fructose diets to reduce insulin sensitivity (6–13), but this has not been evident at the lower dietary concentrations of sucrose or fructose usually given in human studies. Some human studies have shown a positive effect (improvement in insulin sensitivity) of a high-complex-carbohydrate, low-fat diet (14, 15), but others have shown no change with such a diet (16, 17). Work on the type of dietary carbohydrate has also been inconclusive, with several studies showing no effect on insulin sensitivity (18–22), some showing an adverse effect of sucrose or fructose reflected by a rise in fasting serum insulin concentrations (23, 24), and one showing an adverse effect of fructose as measured by the insulin tolerance test (25). By contrast, Koivisto and Yki-Jarvinen (26) reported a beneficial effect of fructose on insulin sensitivity and a recent study showed an increase in insulin sensitivity with a diet with a high glycemic index (27), but only with the high-dose insulin step of a hyperinsulinemic, euglycemic clamp.

The present study was designed to establish whether insulin sensitivity is affected acutely by major manipulation of the type of dietary carbohydrate, and whether the metabolic profiles associated with this intervention could provide information on possible mechanisms underlying altered sensitivity. Previous work has been done on the postprandial metabolic profiles of sucrose and fructose, both in healthy individuals and patients with diabetes. Coulston et al (28) examined the effects of a sucrose-rich diet on glucose, insulin, and triacylglycerol profiles in people...
with diabetes and found small rises in the postprandial triacylglycerol areas under the curve with this diet compared with a high-starch diet (in which other macronutrient contributions were fixed). Work has also been done comparing fructose-rich with sucrose-rich diets in both patients with diabetes (19) and those without (29), but no information on postprandial triacylglycerol profiles was reported. Raised triacylglycerol concentrations may have some association with altered insulin sensitivity; therefore, the present study sought to extend the knowledge in this area by examining in detail a 24-h metabolic profile of glucose, insulin, fatty acids (NEFAs), triacylglycerols, and carbohydrate metabolite concentrations in healthy subjects consuming a sucrose-rich compared with a starch-rich diet.

SUBJECTS AND METHODS

Subjects

The experimental protocol was approved by the joint ethics committees of Newcastle and North Tyneside Health authorities, University of Newcastle upon Tyne, and University of Northumbria at Newcastle, and each subject gave his or her informed, written consent to participate. All studies were conducted in the Wellcome Research Laboratories, Royal Victoria Infirmary, Newcastle upon Tyne.

Eight healthy, weight-stable volunteers (four men and four women) were recruited from the student and staff populations of the University of Newcastle upon Tyne and from the staff of the Royal Victoria Infirmary, Newcastle upon Tyne. None had diabetes mellitus (or a first-degree relative with diabetes), ischemic heart disease, hypertension, or any other disease associated with altered insulin sensitivity. None were taking any drugs known to alter insulin sensitivity or to affect carbohydrate or lipid metabolism. All were nonsmokers and had habitual alcohol intakes of <21 units per week [one unit = 8 g alcohol (30)].

Experimental protocol

Each subject (n = 8) took part in two experimental periods of 24 h each in a randomized crossover design, such that four subjects received the high-starch diet first and four received the high-sucrose diet first. Subjects were admitted at 0700, having fasted from 2200 the previous evening. Alcohol and strenuous exercise were avoided for 24 h before each experimental period. Study periods were separated by a minimum of 1 wk (men), with 1 mo for females to keep as close as possible to a fixed point in the menstrual cycle because concentrations of blood lipids can vary with stage of the menstrual cycle (31, 32). Each dietary period was followed immediately by an insulin tolerance test. Frequent measurements of blood glucose, serum insulin, plasma NEFA, serum triacylglycerol, and other blood metabolite (pyruvate, lactate, and glycerol) concentrations were made during each 24-h study.

Percentage body fat was calculated by the equations of Siri (33) from estimates of body density derived from skinfold thickness measurements (using a Holtain/Tanner-Whitehouse skin caliper; Holtain, Crosswell, United Kingdom) at four separate sites (34). Body composition was also estimated by bioelectrical impedance analysis (Holtain Body Composition Analyzer).

Insulin sensitivity and metabolic profiles

Insulin sensitivity was assessed by using a modified insulin tolerance test (35). After the injection of 0.05 units of insulin per kg body mass, blood samples were taken for measurement of plasma glucose and NEFA concentrations at 1-min intervals from 3 to 15 min. Arterial blood samples were taken from a retrograde intravenous cannula in a dorsal hand vein, 15 min before the test. This hand was kept in a heated box at 55 °C to facilitate arterial blood sampling. Rate constants for the decrease in substrate concentrations (Kitt) were derived from plasma glucose concentrations at 3–15 min and for plasma NEFA concentrations at 6–15 min, by regression analysis of the natural logarithm of glucose and NEFA concentrations, respectively. A typical insulin tolerance test analysis, with the log-transformed curves for glucose and NEFA concentrations, is shown in Figure 1. The R² values for the regression lines from which the rate constants were derived are also shown.

Blood samples for the metabolic profile were taken over a 22-h period from an antecubital vein at 30-min intervals for 2 h after

![Figure 1](https://example.com/figure1.png)

**Figure 1.** An example of the modified insulin tolerance test. After the injection of 0.05 units of insulin per kg body mass, plasma glucose and fatty acid (NEFA) concentrations were measured at 1-min intervals from 3 to 15 min. Shown are the log-transformed curves for glucose and NEFA, with R² values for the regression lines from which the rate constants were derived.
each of the four meals and then hourly, except overnight when sampling was every 2 h. Blood glucose (and plasma glucose for the insulin tolerance test) was analyzed with a glucose analyzer (Yellow Springs International, Yellow Springs, OH) with use of the glucose oxidase method (interassay CV: 1.7%). Serum insulin was estimated by using an enzyme-linked immunosorbent assay specific for insulin (interassay CV: 2.9%; Dako Diagnostics Ltd, Ely, United Kingdom), plasma NEFAs were estimated by using an enzymatic colorimetric method (interassay CV: 3.2%; Wako Chemicals GmbH, Neuss, Germany), and triacylglycerols were estimated by enzymatic hydrolysis of triacylglycerols with subsequent enzymatic assay for glycerol (interassay CV: 3.9%; Wako Chemicals GmbH). Blood metabolites [pyruvate (intraassay CV: 4.9%), lactate (intraassay CV: 3.5%), and glycerol (intraassay CV: 4.3%)] were measured by using a centrifugal analyser fitted with a fluorimetric attachment (36).

**Diets**

Subjects received a standard diet providing 55% of energy as carbohydrate, 35% as fat (in a 1:1:1 ratio of saturated to monounsaturated to polyunsaturated fatty acids), and 10% as protein, with 50% of the energy in one period as starch and 50% of the energy in the other as sucrose. Both diets consisted of similar foods with the carbohydrate source in each being the main difference. Dietary fiber differed between the two diets (14.2 g in the high-starch diet compared with 6.8 g in the high-sucrose diet). Menus are shown in **Table 1**. Major food items were bought in bulk to minimize variability between batches. Each item was weighed to the nearest 0.1 g during meal preparation. Four meals (breakfast, lunch, dinner, and supper) were served throughout the day at 0800, 1200, 1700, and 2000 and the distribution of macronutrients during the day was similar for both diets (**Table 2**). Water was allowed freely during the study period and one cup of instant decaffeinated coffee or tea was allowed with each meal.

Diets were devised with the aid of the computer software MICRODIET (37), using UK national food tables (38). Energy requirements for the test diets were based on calculated basal metabolic rates by using the factors age, sex, and body mass (39) multiplied by a physical activity level of 1.5 (40). Each food item was adjusted according to each individual’s calculated requirements, so that nutrient proportions remained constant.

**Habitual dietary intakes of subjects**

Subjects’ habitual food intakes were estimated by using a 7-d food record and food portion sizes were quantified with the aid of a photographic food atlas (41). The food record was validated by comparing estimated food nitrogen intake with 24-h urinary nitrogen excretion and the completeness of the urine collection was assessed through urinary recovery of a 240-mg oral dose of p-aminobenzoic acid (42).

**Statistical analysis**

Statistical analysis was carried out with the aid of SPSS for Windows (SPSS Inc, Chicago) and Microsoft Office EXCEL (Microsoft Corporation, Redmond, WA). Where appropriate, all paired data [indexes of insulin sensitivity (Kitt$_{SBS}$ and Kitt$_{glucose}$), areas under the curve, and fasting hormone and metabolite concentrations] were compared with two-tailed paired $t$ tests. Differences between diets, where the data are expressed as change between diets at each time point, were assessed with 99% CIs about the zero difference, with a higher CI used to examine the statistical effects of multiple testing. Glucose area under the curve analyses were calculated by multiplying the mean glucose concentration at a pair of adjacent time points by the intervening time interval, and summing each of these products to give the total area under curve. Data are presented as means ± SEMs or SDs as appropriate.

**RESULTS**

**Subject characterization**

The volunteers for this study were healthy, young (mean age: 25 y; range: 20–31 y) men and women with body mass indexes (in kg/m²) < 25 (**Table 3**). Body fat content as estimated by bio-electrical impedance analysis correlated strongly with skinfold thickness measurements ($r = 0.96$), but values for percentage body fat were $≈2%$ higher with bioelectrical impedance analysis than with the skinfold thickness method. Blood lipid concentrations were below values associated with increased cardiovascular risk. The subjects’ habitual dietary intakes of fat were lower

<table>
<thead>
<tr>
<th>Meal</th>
<th>High-sucrose diet (8.4 MJ)</th>
<th>High-starch diet (8.4 MJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breakfast</strong></td>
<td>Yogurt, low fat, natural (125 g)</td>
<td>Puffed rice cereal (30 g)</td>
</tr>
<tr>
<td></td>
<td>Cream, whipping (30 g)</td>
<td>Semiskim milk (225 g)</td>
</tr>
<tr>
<td></td>
<td>Sugar (45 g)</td>
<td>White bread (35 g)</td>
</tr>
<tr>
<td></td>
<td>Strawberries (25 g)</td>
<td>Polyunsaturated margarine</td>
</tr>
<tr>
<td></td>
<td>Semiskim milk (25 g)</td>
<td>(10 g)</td>
</tr>
<tr>
<td><strong>Lunch</strong></td>
<td>Roast beef (50 g)</td>
<td>Roast beef (25 g)</td>
</tr>
<tr>
<td></td>
<td>Carrots (50 g)</td>
<td>Carrots (50 g)</td>
</tr>
<tr>
<td></td>
<td>Broccoli (75 g)</td>
<td>Broccoli (75 g)</td>
</tr>
<tr>
<td></td>
<td>Meringues (30 g)</td>
<td>White rice, raw weight (85 g)</td>
</tr>
<tr>
<td></td>
<td>Polyunsaturated margarine (30 g)</td>
<td>Red peppers (20 g)</td>
</tr>
<tr>
<td></td>
<td>Sugar (65 g)</td>
<td>White bread (35 g)</td>
</tr>
<tr>
<td></td>
<td>Semiskim milk (50 g)</td>
<td>Butter (7 g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sunflower oil (18 g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vinegar (8 g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semiskim milk (25 g)</td>
</tr>
<tr>
<td><strong>Dinner</strong></td>
<td>Turkey (41 g)</td>
<td>Turkey (26 g)</td>
</tr>
<tr>
<td></td>
<td>Cucumber (50 g)</td>
<td>Cucumber (50 g)</td>
</tr>
<tr>
<td></td>
<td>Lettuce (30 g)</td>
<td>Lettuce (30 g)</td>
</tr>
<tr>
<td></td>
<td>Onion (10 g)</td>
<td>Onion (10 g)</td>
</tr>
<tr>
<td></td>
<td>Tomato (70 g)</td>
<td>Tomato (70 g)</td>
</tr>
<tr>
<td></td>
<td>Olive oil (5 g)</td>
<td>Sunflower oil (18 g)</td>
</tr>
<tr>
<td></td>
<td>Sunflower oil (14 g)</td>
<td>Vinegar (8 g)</td>
</tr>
<tr>
<td></td>
<td>Vinegar (7 g)</td>
<td>White rice, raw weight (85 g)</td>
</tr>
<tr>
<td></td>
<td>Sugar-free jelly (200 g)</td>
<td>White bread (47 g)</td>
</tr>
<tr>
<td></td>
<td>Sugar (90 g)</td>
<td>Butter (7 g)</td>
</tr>
<tr>
<td></td>
<td>Cream, whipping (15 g)</td>
<td>Semiskim milk (25 g)</td>
</tr>
<tr>
<td></td>
<td>Semiskim milk (50 g)</td>
<td></td>
</tr>
<tr>
<td><strong>Supper</strong></td>
<td>Cocoa powder (4 g)</td>
<td>Potatoes, baked, no skins</td>
</tr>
<tr>
<td></td>
<td>Semiskim milk (200 g)</td>
<td>(156 g)</td>
</tr>
<tr>
<td></td>
<td>Sugar (20 g)</td>
<td>Butter (12 g)</td>
</tr>
<tr>
<td></td>
<td>Meringues (10 g)</td>
<td>Semiskim milk (25 g)</td>
</tr>
<tr>
<td></td>
<td>Polyunsaturated margarine (5 g)</td>
<td></td>
</tr>
</tbody>
</table>
than amounts in the average UK diet and met current guidelines produced by the UK Department of Health (40). The subjects’ habitual diets were high in carbohydrate, low in total fat, low in saturated fat, and moderate in protein intake (Table 4). We were able to validate the food diaries by measuring urinary nitrogen for seven of eight volunteers, and there was a significant although modest correlation (r = 0.49) between mean daily nitrogen intake estimated by the food diaries and urinary nitrogen excretion measured over a single 24-h period.

**Insulin sensitivity**

No significant differences were detected in insulin sensitivity as assessed by the modified insulin tolerance test for glucose metabolism (K_{ITT glucose} = 3.86%/min and 3.72%/min for the high-sucrose and high-starch diets, respectively; pooled SEM: 0.23). There were also no significant differences for lipid metabolism (K_{ITT NEFA} = 12.9%/min and 11.4%/min, respectively; pooled SEM: 1.18).

**Metabolic profiles**

There were marked differences in the blood glucose and serum insulin concentration profiles between the diets (Figure 2 and Figure 3). With the high-sucrose diet, blood glucose rose more rapidly to a higher peak after each of the four meals. Serum insulin concentrations also rose more rapidly after each meal with the high-sucrose diet. After these postprandial peaks, blood glucose concentrations fell more rapidly with the high-sucrose diet, dipping below the fasting value after each meal except supper. This is in contrast with results for the high-starch diet, with which mean blood glucose concentrations never went below the mean fasting value. The area under the glucose curve was significantly greater for the high-starch diet than for the high-sucrose diet (x–SD: 6780 ± 245 compared with 6290 ± 283 mmol · L/min; P < 0.001).

Consumption of a high-sucrose meal substantially suppressed plasma NEFA concentrations (Figure 4), which returned to fasting levels before the next meal, except after dinner, for which the interval before supper was relatively short (3 h). The high-starch breakfast produced a response similar to that seen with the high-sucrose breakfast, but with subsequent high-starch meals changes in plasma NEFA concentrations were less marked.

Triacylglycerol concentrations rose gradually with both diets after breakfast, with a further increase in the first hour after lunch (Figure 5). After this time point (1300), however, triacylglycerol concentrations began to diverge. With the high-starch diet, triacylglycerol...

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**Table 3**

Anthropometric characteristics and fasting blood lipid concentrations of the volunteers

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 4)</th>
<th>Women (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>25.5 ± 6.4</td>
<td>23.8 ± 1.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.4 ± 1.4</td>
<td>21.7 ± 1.3</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skinfold thickness</td>
<td>18.6 ± 2.3</td>
<td>28.1 ± 4.2</td>
</tr>
<tr>
<td>Impedance</td>
<td>21.2 ± 5.2</td>
<td>30.1 ± 4.1</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.84 ± 0.06</td>
<td>0.74 ± 0.05</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/L)</td>
<td>(4.01 ± 0.45)²</td>
<td>(4.01 ± 0.45)²</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>(1.32 ± 0.19)</td>
<td>(1.32 ± 0.19)</td>
</tr>
<tr>
<td>Serum triacylglycerol (mmol/L)</td>
<td>(0.73 ± 0.19)</td>
<td>(0.73 ± 0.19)</td>
</tr>
</tbody>
</table>

¹ x ± SD.
² Pooled value for men and women in parentheses.

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**Table 4**

Habitual daily dietary intakes of energy and macronutrients of eight volunteers

<table>
<thead>
<tr>
<th></th>
<th>Intake</th>
<th>Percentage of total energy</th>
<th>Percentage of nonethanol energy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/d (MJ/d)</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Energy</td>
<td>(10.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Protein</td>
<td>78</td>
<td>13.3</td>
<td>14.1</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>305</td>
<td>48.6</td>
<td>51.5</td>
</tr>
<tr>
<td>Starch</td>
<td>180</td>
<td>28.8</td>
<td>30.7</td>
</tr>
<tr>
<td>Sucrose</td>
<td>63</td>
<td>9.8</td>
<td>10.4</td>
</tr>
<tr>
<td>Fat</td>
<td>86</td>
<td>32.1</td>
<td>34.4</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>28</td>
<td>10.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Nonstarch polysaccharides</td>
<td>19</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alcohol</td>
<td>20</td>
<td>6.0</td>
<td>—</td>
</tr>
</tbody>
</table>

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1 Both diets provided a total of 8.4 MJ/d.
2 Available carbohydrate (39).
concentrations gradually declined toward fasting values. With the high-sucrose diet, concentrations continued to climb to a peak concentration at 1730, 0.5 h after dinner. Triacylglycerol concentrations then rapidly declined until supper (2000), after which concentrations gradually returned to fasting values at 0600. Glycerol concentrations rose higher at midnight with the sucrose diet, but by 0600 concentrations with both diets were similar (Figure 6).

Glycolytic products showed particularly marked differences between diets. Blood lactate and pyruvate concentrations peaked <1 h after each of the three meals of the day, with postprandial concentrations that were up to threefold higher with the high-sucrose diet than with the high-starch diet (Figure 7 and Figure 8).

**DISCUSSION**

Feeding high-sucrose and high-fructose diets to rats is associated with reduced insulin sensitivity (6–13), but the evidence from human studies is often inconclusive or conflicting (18–27). The aims of this study were to establish whether insulin sensitivity is affected acutely by major manipulation of the dietary carbohydrate source and whether the metabolic profiles associated with such an intervention could provide information on possible mechanisms underlying the altered sensitivity.

The acute effects of feeding high-sucrose compared with high-starch diets on insulin sensitivity in healthy young adults are clear. No significant differences between diets in insulin-stimulated glucose or NEFA clearance rates were detected. The modified insulin tolerance test used in this study has been well validated as an assay of insulin sensitivity through a comparison of this test with the euglycemic clamp for glucose metabolism (35). Although use of the rate of decrease in plasma NEFA concentrations after insulin administration has yet to be validated as an index of insulin sensitivity by an independent method, the present results suggest that these diets do not differ in this aspect of insulin action. Although marked between-diet differences were seen for postprandial glucose and insulin responses, fasting concentrations before the insulin tolerance test, ie, on the morning after the dietary intervention, were not significantly different.

**FIGURE 2.** Diurnal profile of blood glucose concentrations with the high-starch and high-sucrose diets. x ± SEM; n = 8.

**FIGURE 3.** Diurnal profile of serum insulin concentrations with the high-starch and high-sucrose diets. x ± SEM; n = 8.
between diets [by paired t testing of geometrically transformed
data (Table 5)]. This finding is consistent with the lack of effect
of these diets on insulin sensitivity. There were minor differences
in the macronutrient compositions of the two diets (Table 2), but
these were unlikely to have been sufficient to affect the results.
Since Crapo et al's (43) early work on postprandial glucose
and insulin responses to different carbohydrates, there have been
many reports on postprandial responses to single test meals
(44–47). However, an inherent problem of a single test meal is
that the interpretation of the data is restricted to effects of the
food after fasting, so that possible later effects are ignored. Other
workers have sought to examine the possible effects when more
than one test meal is used. Ercan et al (48) used an identical two-
meal study, with one meal consumed in the fasting state and one
later in the fed state. One observation was that the glucose
response curve was greater after the second meal; thus,
responses in the fed and fasted states were different. However,
such differences after multiple meals need not only reflect the
differing extremes of the fed or fasted state. Nestler et al (49)
used breakfasts of differing rates of absorption and found that
although the glycemic response curve was retarded after a slowly
absorbed breakfast, this was offset by a greater glucose response
curve after lunch. This likely reflects an extended fed state after
the slowly absorbed breakfast before the second meal. In the
present study we tried to replicate a more normal eating pattern
and thus examine effects in both the fed and fasted states.
Most of the characteristic metabolic effects of high-sucrose
diets (ie, those not shared by high-starch diets), either immedi-
ately after the consumption of a test meal or with longer-term
exposure to sucrose-rich diets, are thought to be caused by the
fructose component of these diets (50). After absorption, a high
proportion of fructose is taken up by the liver, with low concen-
trations being detected in the blood after sucrose or fructose con-
sumption. Hepatic fructokinase, a highly active ketohexokinase
with a strong specificity for fructose, catalyzes the phosphoryla-
tion of fructose to fructose-1-phosphate. This step bypasses
phosphofructokinase, one of the key regulatory enzymes in gly-
colysis, which explains the rapid metabolism of fructose
compared with glucose by the liver. Because pyruvate kinase is
stimulated by fructose-1-phosphate, there is a strong drive for

**FIGURE 4.** Diurnal profile of fatty acid (NEFA) concentrations with the high-starch and high-sucrose diets. $\bar{x}$ ± SEM; n = 8.

**FIGURE 5.** Diurnal profile of serum triacylglycerol concentrations with the high-starch and high-sucrose diets. $\bar{x}$ ± SEM; n = 8.
production of pyruvate and then other metabolic intermediates such as lactate, acetyl-CoA, and malonyl-CoA. Experimental work supports this theory of rapid metabolism of fructose. Increased production of lactate and pyruvate has been shown with the acute administration of fructose. Brundin and Wahren (51) found large differences in lactate and pyruvate concentrations after the acute ingestion of a 75-g fructose load compared with a 75-g glucose load in human volunteers.

Fructose is also known to have acute effects on lipid metabolism by inducing a rapid production of the precursors necessary for lipid synthesis. The glycolysis product dihydroxyacetone phosphate is readily converted to glycerol-3-phosphate, which is required for the esterification of long-chain acyl-CoA in triacylglycerol synthesis. Acetyl-CoA, derived from pyruvate, is converted to malonyl-CoA, which is then synthesized into long-chain fatty acids. Fructose again differs from glucose at this point because high lactate and pyruvate concentrations in the liver (seen with fructose ingestion) promote the formation of malonyl-CoA, and the capacity of high concentrations of these glycolytic products to increase malonyl-CoA has been shown in hepatocytes in vitro (52). Malonyl-CoA further affects lipogenesis through inhibition of carnitine O-palmitoyltransferase, the rate-limiting enzyme in the oxidation of fatty acids, shifting the balance in favor of esterification. Thus, there are three mechanisms by which fructose can increase triacylglycerol secretion from the liver; indeed, liver perfusion experiments in rats (53) with fructose and insulin have shown increased VLDL secretion.

Fructose is also involved in gluconeogenesis, but this involvement varies between the fed and fasting states, with direct gluconeogenesis from fructose predominating over production via lactate in the fasting state. Experiments on catheterized humans suggest that in the fasting state up to 66% of fructose is converted into glucose (54).

Changes in blood concentrations of, and especially in areas under the curve for, metabolites and hormones have been widely interpreted as reflections of changes in the rates of appearance or disappearance of these metabolites and hormones from the bloodstream. However, changes in the rate of flux of a substance are not necessarily reflected in altered circulating concentrations, so the latter must be interpreted with care. In the context of

**FIGURE 6.** Diurnal profile of blood glycerol concentrations with the high-starch and high-sucrose diets. $\bar{x} \pm$ SEM; $n = 8$.

**FIGURE 7.** Diurnal profile of blood pyruvate concentrations with the high-starch and high-sucrose diets. $\bar{x} \pm$ SEM; $n = 8$. 
postprandial glycemia, the area under the glucose concentration by time curve is certainly related to the rate and extent of glucose absorption, but cannot be used unequivocally as an index of either kinetic variable. Because only half of the sucrose molecule is glucose and only part of the fructose moiety is converted to glucose (54), we would expect lower glucose availability from the gut with a high-sucrose diet and hence a lower area under the curve. In addition, a significant proportion of the fructose is likely to be used for lipogenesis.

The dietary differences in blood lipid concentrations can be explained by a combination of the factors described so far and by the unique features of fructose metabolism. The differences in blood lipid concentrations between the diets together with 99% CIs about the zero difference are shown in Figure 9 and Figure 10 (a 99% CI was used to reduce the risk of a type I statistical error resulting from the multiple t testing used to derive the interval). The two main troughs, immediately after lunch and after dinner, were a result of the greater peaks in insulin secretion with the high-sucrose diet, thus suppressing mobilization of NEFAs from adipose tissue. Three significant peaks are apparent 3–5 h after each meal for plasma NEFAs, representing higher concentrations with the high-sucrose diet than with the high-starch diet. The late postprandial increases in NEFA concentrations with the high-sucrose diet may have been a consequence of the lower insulin concentrations at these time points, thus facilitating NEFA release from adipose tissue. A further explanation could be that there was simply less available carbohydrate in the high-sucrose diet (as a result of the incomplete conversion of fructose to glucose), necessitating mobilization of fatty acids for oxidation. The nighttime peak may have been the result of lowered carbohydrate availability with the high-sucrose diet compared with the high-starch diet.

The clearest difference in triacylglycerol profiles between the two diets was seen late in the afternoon, with concentrations rising late after the midday meal with the high-sucrose diet and continuing to rise until the surge of insulin produced by the next meal. The most plausible explanation in the context of this short period of time is that VLDL triacylglycerol synthesis increases in the liver from the metabolism of fructose (50). The absence of a similar rise in triacylglycerol concentrations in the late postprandial period after the high-sucrose breakfast may simply have been a factor of time because the peak difference between the diets was seen 5.5 h after lunch, whereas the postprandial period in the morning was only 4 h. However, it is also possible that the different response to the two meals was a consequence of the different states in which they were consumed. Breakfast was eaten after an overnight fast, whereas lunch was consumed only 4 h after a previous meal. The greater triacylglycerol concentrations after lunch with the high-sucrose diet may have been a result of increased synthesis, encouraged by the fed state in which the meal was consumed. One possible mechanism could be the increased concentrations of malonyl-CoA in the fed state, which would promote esterification.

Whitley et al (55) showed a late rise in triacylglycerol concentrations after a test meal rich in simple carbohydrate compared with a high-fat meal. The same Oxford Lipid Metabolism group investigated effects of sequential meals and reported an early rise in triacylglycerol and NEFA concentrations after lunch, apparently related to consumption of fat in the breakfast (56). Compared with the Oxford studies, increases in plasma triacylglycerol in the present study were delayed.

Both the raised NEFA and triacylglycerol concentrations with the high-sucrose diet have a potential role to play in decreasing insulin sensitivity. Studies in rats have shown a close associa-

TABLE 5
Mean fasting blood concentrations at the end of each dietary period

<table>
<thead>
<tr>
<th>Dietary period</th>
<th>Blood glucose mmol/L</th>
<th>Serum insulin pmol/L</th>
<th>Plasma NEFAs mmol/L</th>
<th>Serum triacylglycerol mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-sucrose diet</td>
<td>4.62 ± 0.31</td>
<td>38.3 ± 13.5</td>
<td>0.25 ± 0.039</td>
<td>0.73 ± 0.16</td>
</tr>
<tr>
<td>High-starch diet</td>
<td>4.95 ± 0.28</td>
<td>36.2 ± 19.7</td>
<td>0.22 ± 0.079</td>
<td>0.76 ± 0.18</td>
</tr>
</tbody>
</table>

1 x ± SD. No significant differences were detected with paired t test comparisons of data (geometrically transformed for fasting insulin concentrations).
tion between decreased insulin sensitivity with high-sucrose or high-fructose diets and fasting hypertriglyceridemia (5, 7, 9). Some human studies have reported a rise in fasting triacylglycerol concentrations with more moderate intakes of sucrose or fructose, and an association between these increased concentrations and raised fasting insulin concentrations may reflect decreased insulin sensitivity (57, 58). Although the link between raised fasting and raised postprandial concentrations of triacylglycerol or NEFAs and insulin resistance is not established, the potential role of raised NEFA or triacylglycerol concentrations in decreasing insulin sensitivity is suspected and has been shown experimentally (59, 60). Furthermore, altered postprandial lipid profiles have been identified as a cardiovascular risk factor (61).

We also examined the effects of the two diets on glycolytic products. The marked increases in blood lactate and pyruvate concentrations after each meal with the high-sucrose but not the high-starch diet can be explained most plausibly by the rapid metabolism of fructose in the liver.

In conclusion, in young, healthy adults 24-h exposure to a sucrose-rich diet compared with a high-starch diet, with all other major dietary components held constant, produced no detectable effect on insulin sensitivity as assessed by a modified insulin tolerance test. However, this lack of effect cannot be extrapolated to the population at large. More sedentary, obese persons who are insulin resistant may be more sensitive to alterations in the type of carbohydrate in the diet, a possibility we are addressing in fur-
ther work. Blood glucose and serum insulin concentrations followed the pattern expected for these diets, with increased areas under the curve for glucose with the high-starch diet, a probable consequence of the greater availability of glucose with this diet. Similarly, the greater rise postprandially in plasma fatty acids with the high-sucrose diet may have resulted from a combination of less available carbohydrate and lower insulin concentrations. Markedly increased late postprandial triacylglycerol concentrations with the high-sucrose diet may represent increased hepatic synthesis. These last two findings may be involved in the pathogenesis of reduced insulin sensitivity, which has been associated with long-term consumption of such diets.

The detection of such between-diet differences in fit, healthy, insulin-sensitive persons gives rise to the possibility that such changes would be exaggerated in a more insulin-resistant population. The observation that responses to the experimental diets differed with different meals during the day, particularly for triacylglycerol concentrations, emphasizes the limitations in assessing the postprandial effects of a nutrient with a single test meal. Finally, the key to the differences between these diets may not be relative proportions of disaccharides and polysaccharides, but rather the presence of fructose within the sucrose diet.

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