Role of human liver, kidney, and skeletal muscle in postprandial glucose homeostasis

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Meyer, Christian, Jean M. Dostou, Stephen L. Welle, and John E. Gerich. Role of human liver, kidney, and skeletal muscle in postprandial glucose homeostasis. Am J Physiol Endocrinol Metab 282: E419–E427, 2002; 10.1152/ajpendo.00032.2001.—Recent studies indicate a role for the kidney in postabsorptive glucose homeostasis. The present studies were undertaken to evaluate the role of the kidney in postprandial glucose homeostasis and to compare its contribution to that of liver and skeletal muscle. Accordingly, we used the double isotope technique along with forearm and renal balance measurements to assess systemic, renal, and hepatic glucose release as well as glucose uptake by kidney, skeletal muscle, and splanchic tissues in 10 normal volunteers after ingestion of 75 g of glucose. We found that, during the 4.5-h postprandial period, 22 ± 2 g (30 ± 3% of the ingested glucose) were initially extracted by splanchic tissues. Of the remaining 53 ± 2 g that entered the systemic circulation, 19 ± 3 g were calculated to have been taken up by skeletal muscle and 7.5 ± 1.7 g by the kidney (26 ± 3 and 10 ± 2%, respectively, of the ingested glucose). Endogenous glucose release during the postprandial period (16 ± 2 g), calculated as the difference between overall systemic glucose appearance and the appearance of ingested glucose in the systemic circulation, was suppressed 61 ± 3%. Surprisingly, renal glucose release increased twofold (10.6 ± 2.5 g) and accounted for ~60% of postprandial endogenous glucose release. Hepatic glucose release (6.7 ± 2.2 g), the difference between endogenous and renal glucose release, was suppressed 82 ± 6%. These results demonstrate a hitherto unappreciated contribution of the kidney to postprandial glucose homeostasis and indicate that postprandial suppression of hepatic glucose release is nearly twofold greater than had been calculated in previous studies (42 ± 4%), which had assumed that there was no renal glucose release. We postulate that increases in postprandial renal glucose release may play a role in facilitating efficient liver glycogen repletion by permitting substantial suppression of hepatic glucose release.

gluconeogenesis; glycogenolysis; glucose disposal

CONSIDERABLE INFORMATION has recently accumulated regarding postprandial glucose homeostasis. It appears that about one-third of ingested carbohydrate is immediately taken up by splanchic tissues (5, 22, 33–35, 37, 38, 44, 60). Of the remaining two-thirds of the ingested carbohydrate that enters the systemic circu-

lation, some is extracted by the liver (23), but most is taken up by peripheral tissues. Limb balance measurements indicate that skeletal muscle is the predominant site for this peripheral glucose disposal, being responsible for about one-fourth of the ingested carbohydrate (5, 26, 33–35, 37, 38, 44). The fate of the remaining 40% of the ingested carbohydrate is less clear.

In addition to tissue uptake of ingested carbohydrate, another important factor for postprandial glucose homeostasis is suppression of the release of glucose endogenously produced by gluconeogenesis and breakdown of stored glycogen (18, 33, 44). Until recently, this was thought to occur almost exclusively in the liver (51). Most (7, 8, 39–42, 45, 49, 50, 52) but not all (21) recent studies indicate that, in postabsorptive normal volunteers, the kidney may account for 15–25% of all glucose released into the circulation. However, it should be pointed out that bias in the handling of data in some of these studies (39–42, 45, 49, 50, 52) may have led to an overestimation of renal glucose release (28). Recent studies also indicate that renal release of glucose, like that of the liver, is regulated by insulin (9, 40) and counterregulatory hormones (10, 39, 49). These findings suggest that the kidney may also be involved in postprandial glucose homeostasis.

Changes in renal glucose metabolism after carbohydrate ingestion have not, to our knowledge, been previously investigated. Certain considerations, however, indicate that the kidney may play a role. Normally, renal glucose fractional extraction in the postabsorptive state is 1–2% (7, 8, 21, 39–42, 49, 50, 52). Should this persist postprandially, the kidney could be a site of considerable glucose disposal. Moreover, previous studies have estimated postprandial hepatic glucose release merely as the difference between total systemic glucose appearance and the appearance of ingested glucose in the systemic circulation, ignoring the potential contribution of the kidney (5, 22, 26, 33–35, 37, 38, 44). Consequently, postprandial hepatic glucose release has been overestimated, and the importance of its suppression may also have been overestimated if there were concomitant suppression of renal glucose release.

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The present studies were therefore undertaken to quantitate the contribution of the kidney to postprandial glucose homeostasis and to reassess the magnitude of postprandial suppression of hepatic glucose release. Moreover, we also simultaneously evaluated muscle glucose uptake and its net release of potential gluconeogenic precursors so as to obtain a more complete view of postprandial glucose homeostasis.

METHODS

**Subjects.** Informed written consent was obtained from 10 healthy volunteers after the protocol had been approved by The University of Rochester Institutional Review Board. The subjects (5 men, 5 women 49 ± 2 yr of age) had normal physical examinations, routine laboratory tests, and glucose tolerance (World Health Organization criteria) (59), as well as no family history of diabetes mellitus. For 3 days before the study, all had been on a weight-maintaining diet containing ≥200 g carbohydrate and had abstained from alcohol.

**Protocol.** Subjects were admitted to the University of Rochester General Clinical Research Center between 6:00 and 7:00 PM the evening before experiments, consumed a standard meal between 6:30 and 8:00 PM, and fasted thereafter. At ~5:30 AM, an antecubital vein was cannulated, and primed continuous infusions of [6-3H]glucose (~75 μCi, ~0.75 μCi/min; Amersham Biosciences, Arlington Heights, IL) was started. At ~8:00 AM, an infusion of p-aminohippuric acid (12 mg/min) was started for determination of renal blood flow (RBF). In addition, five subjects also received an infusion of [9,10-3H]palmitate; their baseline data have been previously reported (41). Between 8:00 and 9:00 AM, a renal vein was catheterized under fluoroscopy and the position of the catheter tip ascertained by injecting a small amount of iodinated contrast material. At ~9:00 AM, a dorsal hand vein was cannulated and kept in a thermoregulated Plexiglas box at 65°C for sampling arterialized venous blood, and a large antecubital vein was cannulated retrogradely in the contralateral arm for sampling of the deep venous system of the forearm, as previously described (34). About 1 h later, simultaneous blood sampling was started from the dorsal hand vein, the renal vein, and the antecubital vein at 30-min intervals for the next 5.5 h. After the 60-min baseline period, each subject ingested 75 g of glucose as an oral glucose solution (Dextrol, American Scientific Products, McGaw Park, IL) containing 3 g of [6,6-2H2]glucose for determination of the rate of appearance of the ingested glucose in the systemic circulation.

**Analytical procedures.** Blood samples were collected for glucose, lactate, alanine, and glycerol concentrations, [6-3H]glucose specific activities, and [6,6-2H2]glucose enrichments in oxalate-fluoride tubes for free fatty acid (FFA) concentrations in EDTA tubes and for insulin and glucagon concentrations in EDTA tubes containing a protease inhibitor. Whole blood glucose was immediately determined in triplicate with a glucose analyzer (Yellow Springs Instrument, Yellow Springs, OH) with a coefficient of variation (CV) of 0.9%. For other determinations, samples were placed immediately in a 4°C ice bath, and plasma was separated within 30 min by centrifugation at 4°C. [6-3H]glucose specific activities were determined using 4 ml of plasma in duplicate by HPLC (46) with a CV of 0.5%. Plasma [6,6-2H2]glucose enrichments were determined by gas chromatography-mass spectroscopy (GC-MS) as previously described (14). Plasma lactate, alanine, glycerol, and FFA concentrations were determined by standard microfluorometric assays (36, 43, 56). Plasma insulin and glucagon were determined by standard radioimmunoassays, as previously described (53). Plasma p-aminohippuric acid concentrations were determined by a colorimetric method (4). Forearm blood flow (FBF) was determined at each blood sampling at baseline and at 1-h intervals after oral glucose ingestion (30, 90, 150, 210 and 270 min) by means of electrocapacitance plethysmography (34) after the procedure described by Jackson et al. (31).

**Calculations.** Systemic release and uptake of glucose were determined with steady-state equations under basal conditions (58) and subsequently after glucose ingestion with the non-steady-state equations of DeBodo et al. (16) and Finegood et al. (25), with a pool fraction of 0.65 and a volume of distribution of 200 ml/kg. The rate of appearance of the oral glucose in the systemic circulation was calculated from [6,6-2H2]glucose data with the equation of Chiasson et al. (13). Endogenous glucose release was calculated as the difference between the overall rate of glucose appearance and the rate of appearance of exogenous glucose. Hepatic glucose release was calculated as the difference between endogenous glucose release and renal glucose release (RGR).

Initial splanchnic glucose uptake of the ingested glucose was calculated as the difference between the amount of glucose ingested and the total appearance of the ingested glucose in the systemic circulation during the 4.5-h postprandial period, on the assumption that absorption of the ingested glucose had been completed as has been reported by Radziuk et al. (48).

Renal plasma flow (RPF) was determined by p-aminohippuric acid clearance technique (4), and RBF was calculated as RPF/(1 – hematocrit). Renal net balances of glucose and lactate were calculated as (arterial concentration – renal venous concentration) × RBF; analogous equations were applied to calculate renal net balances of alanine, glycerol, and FFA, except that RPF was used because tissue exchange of these substrates occurs via plasma.

Renal glucose fractional extraction (FX) was calculated as:

\[
\text{FX} = \frac{\text{[6-3H]glucose specific activity } \times \text{ arterial } \text{glucose concentration} - \text{[6-3H]glucose specific activity } \times \text{ renal vein glucose concentration}}{\text{[6-3H]glucose specific activity } \times \text{ arterial } \text{glucose concentration}}
\]

and

\[
\text{FX} = \frac{\text{[6,6-2H2]glucose specific activity } \times \text{ arterial } \text{glucose concentration}}{\text{[6,6-2H2]glucose specific activity } \times \text{ arterial } \text{glucose concentration}}
\]

In ~15% of the sampling times, negative values for FX were obtained. These values most likely represent random analytical error (28); nevertheless, to avoid potential bias, these values were used for calculations.

Renal glucose uptake (RGU) was calculated as RBF × arterial glucose × FX. RGU derived from the ingested glucose was calculated as the product of overall RGU and the fraction of the arterial glucose derived from the ingested glucose. The latter was determined from the ratio of the systemic appearance of the ingested glucose to the overall rate of glucose appearance in the systemic circulation. RGR was calculated as RGU – renal glucose net balance. Assumptions and methodological limitations of the combined net balance and isotopic approach for determining glucose release by liver and kidney have been previously discussed in detail (41, 52).

Forearm balances of glucose, lactate, alanine, and glycerol were calculated analogously to their renal balances, except that FBF or plasma flow was used. Forearm data per 100 ml of tissue were converted to values per kilogram of forearm muscle as previously described (34), on the assumption that 80% of the measured FBF perfused muscle (15) and that that muscle compromised 60% of the forearm volume (1). On the assumption that forearm muscle was representative of muscle elsewhere in the body, these values were multiplied by total body skeletal muscle mass, which was calculated from midarm circumference.
and triceps skinfold thickness by use of the equation of Heymsfield et al. (30). Muscle uptake of glucose derived from the ingested glucose was calculated as the product of overall muscle glucose uptake and the fraction of the arterial glucose derived from the ingested glucose.

Statistical analysis. Unless stated otherwise, data are expressed as means ± SE. Paired two-tailed Student’s t-tests were used to compare the mean baseline data with the mean data obtained after oral glucose ingestion. A P value <0.05 was considered statistically significant.

RESULTS

Arterial glucose, insulin, and glucagon concentrations. Postabsorptive arterial glucose, insulin, and glucagon concentrations averaged 4.7 ± 0.1 mM, 56 ± 5 pM, and 69 ± 5 ng/l, respectively (Fig. 1). After glucose ingestion, arterial glucose increased to peak values (7.8 ± 0.3 mM) at 90 min and returned to postabsorptive levels (4.7 ± 0.2 mM) by 240 min. Arterial insulin followed a similar pattern, reaching a peak concentration (325 ± 45 pM) at 90 min and returning to postabsorptive values (50 ± 8 pM) by 270 min. Plasma glucagon decreased to a nadir (48 ± 4 ng/l) at 120 min and returned to postabsorptive values (63 ± 6 ng/l) at 270 min.

Overall systemic glucose appearance and disappearance. Arterial glucose concentrations, [6-3H]glucose specific activity and radioactivity, 6,6-dideuteroglucose enrichments, and arterial-renal vein differences are given in Table 1. Overall postabsorptive systemic glucose appearance (the sum of hepatic and renal glucose release) averaged 9.2 ± 0.5 µmol·kg⁻¹·min⁻¹ (Fig. 2). After glucose ingestion, it increased to a peak rate (20.9 ± 1.7 µmol·kg⁻¹·min⁻¹) at 60 min and subsequently decreased to postabsorptive rates (9.2 ± 0.8 µmol·kg⁻¹·min⁻¹) at 270 min. Overall systemic glucose disappearance followed a similar pattern but reached peak rates at 90

![Fig. 1. Plasma glucose, insulin, and glucagon concentrations.](http://ajpendo.physiology.org/)

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Table 1. Arterial and arterial-renal venous differences for glucose concentrations, specific activities, radioactivities, and arterial dideuterated glucose enrichments

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Glucose concentration</th>
<th>Glucose specific activity</th>
<th>Glucose radioactivity</th>
<th>Arterial glucose enrichment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.7 ± 0.1</td>
<td>6.65 ± 0.02</td>
<td>102.4</td>
<td>0.00</td>
</tr>
<tr>
<td>30</td>
<td>6.65 ± 0.02</td>
<td>102.4</td>
<td>16.0</td>
<td>0.00</td>
</tr>
<tr>
<td>60</td>
<td>8.1 ± 0.1</td>
<td>16.0</td>
<td>26.7</td>
<td>0.00</td>
</tr>
<tr>
<td>90</td>
<td>11.4</td>
<td>26.7</td>
<td>102.4</td>
<td>0.00</td>
</tr>
<tr>
<td>120</td>
<td>9.2 ± 0.5</td>
<td>102.4</td>
<td>69 ± 5</td>
<td>0.00</td>
</tr>
<tr>
<td>180</td>
<td>5.9 ± 0.3</td>
<td>69 ± 5</td>
<td>56 ± 5</td>
<td>0.00</td>
</tr>
<tr>
<td>210</td>
<td>7.8 ± 0.3</td>
<td>56 ± 5</td>
<td>10.9</td>
<td>0.00</td>
</tr>
<tr>
<td>240</td>
<td>4.7 ± 0.2</td>
<td>10.9</td>
<td>6.3</td>
<td>0.00</td>
</tr>
<tr>
<td>270</td>
<td>3.2 ± 0.2</td>
<td>6.3</td>
<td>4.7</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Values are means ± SE. a-v, Arteriovenous.
min and was still slightly above postabsorptive rates at 270 min (11.4 ± 0.5 μmol·kg⁻¹·min⁻¹).

Systemic appearance of ingested glucose and renal and hepatic glucose release. Postprandial systemic glucose appearance consists of the appearance of endogenous glucose released from liver and kidney and the appearance of ingested glucose. The appearance of ingested glucose into the systemic circulation was evident by 30 min and peaked at 90 min (15.6 ± 1.5 μmol·kg⁻¹·min⁻¹) (Fig. 3). Over the 4.5-h postprandial period, 53.0 ± 2.2 g of the 75 g ingested glucose appeared in the systemic circulation. The ingested glucose accounted for an average of 77.7 ± 2.4% of the circulating glucose during this interval, a value similar to the 75% found by Kelley et al. (34) and Fery et al. (24) under comparable experimental conditions. Although the rate of appearance of the ingested glucose was still above zero at 270 min, this probably represented ingested glucose initially incorporated into hepatic glycogen (54) rather than ongoing intestinal absorption (33, 34). Therefore, with the assumption of complete absorption of the ingested glucose, net splanchnic sequestration would have amounted to 22.0 ± 2.2 g (29.3 ± 2.9% of the ingested load).

RGR before glucose ingestion averaged 1.12 ± 0.25 μmol·kg⁻¹·min⁻¹ and accounted for 11.4 ± 2.3% of overall systemic glucose appearance. It is of interest that treating data as had been done in previous studies (28) would have resulted in a value of 14.2 ± 1.5%. After glucose ingestion, RGR increased approximately fourfold at 30 min and remained elevated for the next 2 h. During the 4.5-h postprandial period, it averaged 2.34 ± 0.54 μmol·kg⁻¹·min⁻¹ and accounted for 61.0 ± 13.4% of endogenous glucose release. Net renal glucose balance became markedly more negative (basal: −20 ± 14 μmol/min vs. an average of −107 ± 35 μmol/min, P = 0.02) during the initial 90-min postprandial period, consistent with changes in tracer-determined RGR. Subsequently, renal glucose net balance became positive, indicating net RGU. Hepatic glucose release before glucose ingestion averaged 8.34 ± 0.34 μmol·kg⁻¹·min⁻¹. After glucose ingestion, it decreased to nadir at 210 min (0.21 ± 1.16 μmol·kg⁻¹·min⁻¹). During the 4.5-h postprandial period, it was suppressed an average of 81.6 ± 5.7%.

RGU and other substrate net balances. RBF and renal FX both increased transiently, reaching peak values at 150 min and 210 min, respectively (P = 0.02 and P = 0.05, respectively) (Fig. 4).

RGU before glucose ingestion averaged 0.89 ± 0.17 μmol·kg⁻¹·min⁻¹ and accounted for 9.4 ± 1.7% of systemic glucose disposal. After glucose ingestion, RGU increased more than threefold to a peak value...
(2.83 ± 0.58 μmol·kg⁻¹·min⁻¹, *P* < 0.01) at 90 min and returned to postabsorptive rates at 240 min. During the 4.5-h postprandial period, glucose uptake by the kidney (10.0 ± 2.4 g) accounted for 13.3 ± 2.6% of systemic glucose disposal and 9.9 ± 2.3% of the disposal of the ingested glucose (7.5 ± 1.7 g).

Arterial lactate (Fig. 5) and alanine (Fig. 6) concentrations increased significantly after glucose ingestion, whereas arterial glycerol (Fig. 7) concentrations decreased. Renal lactate net uptake increased (average over 4.5 h: 213 ± 15 vs. 166 ± 12 μmol/min postabsorptive average, *P* = 0.04), whereas glycerol net uptake decreased (average during 4.5 h: 30 ± 2 vs. 62 ± 5 μmol/min postabsorptive average, *P* < 0.001). There was no change in renal alanine net uptake.

Arterial FFA averaged 287 ± 31 μmol during the postprandial period, a 62% reduction from postabsorptive values (761 ± 96 μmol, *P* < 0.001). Renal FFA net uptake averaged 25 ± 16 μmol/min during the postprandial period, a 65% reduction from baseline (73 ± 22 μmol/min, *P* < 0.001).

Muscle glucose uptake and other substrate net balances. Muscle glucose uptake averaged 1.91 ± 0.23 μmol·kg⁻¹·min⁻¹ before glucose ingestion and accounted for 22.0 ± 3.7% of systemic glucose disposal. After glucose ingestion, muscle blood flow increased about 10% (*P* = 0.03) (Fig. 4). Muscle glucose FX also increased, reaching a peak threefold greater than baseline (9.7 ± 1.9 vs. 3.1 ± 0.4, *P* < 0.001) at 60 min before returning to baseline at 210 min. During the initial 2 h after glucose ingestion, muscle glucose uptake increased approximately fivefold. Over the 4.5-h postprandial period, it averaged 5.72 ± 0.79 μmol·kg⁻¹·min⁻¹ and accounted for 38.3 ± 5.6% of systemic glucose disposal (25.9 ± 3.5 g) and 25.9 ± 3.4% of the disposal of the ingested glucose (19.4 ± 2.6 g).

Before glucose ingestion, there was net release of lactate (47 ± 29 μmol/min; Fig. 5), alanine (60 ± 16 μmol/min; Fig. 6), and glycerol (2 ± 3 μmol/min; Fig. 7). After glucose ingestion, there was a transient net uptake of lactate and reduced net release of alanine, as previously found (32, 34, 47). However, over the 4.5-h
postprandial period, there was no significant change in net release of lactate (23 ± 23 μmol/min, \( P = 0.085 \)), alanine (44 ± 14 μmol/min, \( P = 0.063 \)), and glycerol (−2 ± 3 μmol/min, \( P > 0.9 \)).

**DISCUSSION**

Our study attempted to quantitate the fate of an ingested glucose load. Before the results of our experiments are discussed, certain limitations of the methods employed need to be taken into consideration to understand the precision with which such quantification can be made (45). First, splanchnic, muscle, and renal net balance measurements depend on detection of relatively small differences in arteriovenous concentrations and variability in blood flow calculations. The precision of these measurements depends on the inherent variability of the analytical procedures as well as on the reproducibility of the results of the people making these measurements. In our hands, the CVs for glucose concentrations and skeletal/renal blood flow measurements are ~1.5 and 5%, respectively. Second, there is analytic imprecision in specific activity measurements. In our hands, the CV for glucose specific activity measured by HPLC is ~0.5%.

Another source of variation is the use of the “hot hand” procedure to obtain arterialized blood as opposed to the use of arterial blood, because there may be venous contamination. In our studies, \( O_2 \) saturation in samples exceeded 90%, thus indicating little or no contamination. With hepatic and renal venous sampling, one assumes that sampling from one kidney or one hepatic vein is representative of both kidneys and the whole liver, respectively. However, there can be considerable variation between simultaneously sampled hepatic veins (3), and there can be contamination of renal vein sampling. In our studies, monitoring of para-amin hippuric acid levels indicating >90% clearance suggests that there was little or no contamination. There are several other sources for imprecision such as using plasma values for substrates corrected to whole blood values based on hematocrit (45); these have been discussed in detail previously (45).

Regardless of the foregoing discussion of methods, our data provide clear-cut evidence for a hitherto unappreciated contribution of the kidney to postprandial glucose homeostasis and indicate that there is considerably greater postprandial suppression of hepatic glucose release than was previously thought.

In the present study, the kidney accounted for ~10% of the disposal of a 75-g ingested glucose load. To put this into perspective, the uptake of glucose by skeletal muscle, based on simultaneously measured forearm glucose uptake, was estimated to account for ~25% of the ingested glucose load. Although extrapolations to total body skeletal muscle from regional measurements should be viewed with caution, the value that we obtained is similar to the average (27 ± 2%) found in eight previous studies whose data permitted this calculation (5, 26, 33–35, 37, 38, 44).

Renal uptake of glucose has been previously shown to increase during hyperglycemia (6, 19) and to be stimulated by insulin (9, 40). In the present study, increases in renal glucose fractional extraction and renal blood flow both contributed to the increased postprandial renal glucose uptake. These changes may have resulted, at least in part, from postprandial hyperinsulinemia, because insulin has been shown to increase renal blood flow and glucose fractional extraction in normal postabsorptive humans (7, 40). Had these changes in blood flow and fractional extraction not occurred, the observed renal glucose uptake would have been reduced by ~50%. Thus the mass action effects of hyperglycemia and changes in blood flow and fractional extraction contributed similarly to the postprandial renal glucose uptake.

The magnitude of the postprandial renal glucose uptake may seem surprising because the kidney, in contrast to liver and muscle, does not normally store appreciable glycogen (2). However, all of the glucose taken up by the kidney could be accounted for by its being released as lactate and its being oxidized, as a substitute for FFA.

Lipid is normally the major oxidative fuel of the kidney (57). In the present study, postprandial renal FFA net uptake was reduced by 65% (i.e., by 48 μmol/min). Substitution of glucose for these FFA to provide equivalent ATP via oxidation would have required 163 μmol/min, or 7.9 g, over the 4.5-h postprandial period. This would account for 79% of the glucose taken up by the kidney postprandially (10.0 g). These considerations provide further, albeit indirect, evidence in favor of a renal glucose-fat acid cycle, as has been recently postulated (41) and analogous to the situation for skeletal muscle postulated by Taylor et al. (54). These investigators observed no net glycogen accumulation in skeletal muscle for nearly 2 h after ingestion of a meal containing 290 g of carbohydrate. Because muscle glucose uptake would have increased substantially during this period, as demonstrated in the present and other studies (5, 26, 33–35, 37, 38, 44, 47), it was postulated that the glucose taken up was oxidized in place of FFA.

Not only did the kidney play a role in the disposal of the ingested glucose, it also influenced postprandial glucose homeostasis by increasing its release of glucose. Thus, in contrast to liver, whose postprandial release of glucose was markedly decreased, there was a more than twofold increase in renal glucose release, so that it on average actually exceeded that of the liver during the 4.5-h postprandial period. This finding was surprising, because hyperglycemia and hyperinsulinemia would have been expected to suppress renal glucose release (6, 19, 40).

Several factors could explain the reciprocal changes in hepatic and renal glucose release. First of all, the liver is exposed to higher (i.e., portal) insulin concentrations than is the kidney. Second, suppression of hepatic glycogenolysis, which we postulate to have largely accounted for the suppression of hepatic glucose release, is known to be more sensitive to insulin than is hepatic gluconeogenesis (12). Third, suppres-
sion of glucagon secretion may have played a role, because glucagon supports hepatic glucose release (11) but has no effect on renal glucose release (50). Fourth, glucose ingestion increases sympathetic nervous system activity (55), which may have preferentially augmented renal glucose release. In support of this view is the observation that infusion of epinephrine causes a sustained increase in renal glucose release while increasing hepatic glucose release transiently and to a lesser extent (49).

From a teleological point of view, this increased postprandial release of glucose by the kidney would permit greater suppression of hepatic glycogenolysis so that there could be more efficient glucagon replenishment. Because the kidney increases its release of glucose, calculation of postprandial hepatic glucose release as the difference between the overall appearance of glucose in the systemic circulation and the appearance of the ingested glucose substantially underestimates the suppression of hepatic glucose release. In nine previous studies in which hepatic glucose release was calculated in this manner, the mean value for its postprandial suppression was 42 ± 4% (5, 22, 26, 33–35, 37, 38, 44). In the present studies, calculation of hepatic glucose release as the difference between overall systemic glucose release and the sum of ingested and renal glucose release indicated a suppression of 82 ± 6%. To put this into perspective, 82% suppression of hepatic glucose release would amount to ~30 g less glucose entering the circulation during the 4.5-h postprandial period. A suppression of 42% would have led to only ~10 g less glucose entering the circulation.

It is worth noting that the initial net splanchnic sequestration (presumably representing hepatic glucose uptake) found in the present study (~22 g) accounted for 30 ± 3% of the ingested glucose load. This is remarkably similar to the mean of 33 ± 4% found in the nine previous reports (5, 22, 26, 33–35, 37, 38, 44, 60). Although this in itself is substantial, it underestimates total postprandial hepatic glucose uptake, since the liver also extracts glucose from the systemic circulation (23). Nevertheless, taking into consideration only the initial net hepatic uptake of ingested glucose (22 g) and the glucose conserved via suppression of hepatic glucose release (30 g), one can assign to the liver management of ~50 g of postprandial “glucose traffic.” Muscle, the next most important tissue for postprandial glucose disposal (see below), was responsible for uptake of 26 g (~20 g ingested glucose + 6 g endogenous glucose). These considerations suggest that the liver is the more important organ for postprandial glucose homeostasis and that hepatic abnormalities would be expected to have a substantial impact on postprandial glucose metabolism, as has been demonstrated in people with impaired glucose tolerance and those with type 2 diabetes (18, 27).

Quantification of postprandial renal glucose uptake and release in the present study not only refines our appreciation of the contribution of the liver but also provides a more complete view of postprandial glucose disposal than has been previously available. According to the results of the present and previous studies (5, 22, 26, 33–35, 37, 38, 44, 60), ~25–35% of an ingested 100-g carbohydrate load would be initially extracted by the liver. Of the remaining 65–75% of the ingested glucose that enters the systemic circulation, ~40% would be taken up by skeletal muscle (5, 26, 33–35, 37, 38, 44) and ~10% would be taken up by the kidney and liver. These three tissues could thus account for ~75–85% of the disposal of the ingested glucose. Brain glucose uptake in postabsorptive volunteers has been reported to be ~80 mg/min (17, 20, 29). On the assumption that this rate would remain constant postprandially and that ingested glucose represented 75% of circulating glucose, as was found in the present and previous studies (24, 34), it can be calculated that brain would take up ~15–20% of the ingested glucose. Therefore, uptake of glucose by liver, muscle, brain, and kidney could account for at least 90% of the disposal of an ingested glucose load.

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