The Disposal of an Oral Glucose Load in Healthy Subjects

A Quantitative Study

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SUMMARY

Although it is an established concept that the liver is important in the disposition of glucose, the quantitative contribution of the splanchnic and peripheral tissues, respectively, to the disposal of an oral glucose load is still controversial. In the present investigation, we have employed the hepatic venous catheter technique in combination with a double-tracer approach (in which the glucose pool is labeled with ^{3}H-glucose and the oral glucose load is labeled with ^{14}C-glucose) to quantitate the four determinants of oral glucose tolerance: rate of oral glucose appearance, splanchnic glucose uptake, peripheral glucose uptake, and suppression of hepatic glucose production. Studies were carried out in 11 normal volunteers in the overnight-fasted state and for 3.5 h after the ingestion of glucose (1 g/kg body wt; range, 55–93 g).

In the postabsorptive state, the rate of endogenous (hepatic) glucose production, evaluated from the ^{3}H-glucose infusion, was 2.34 ± 0.06 mg/min · kg. Glucose ingestion was accompanied by a prompt reduction of endogenous glucose output, which reached a nadir of 0.62 ± 0.23 mg/min · kg at 45 min and remained suppressed after 3.5 h (0.85 ± 0.22 mg/min · kg). The average inhibition of hepatic glucose output during the absorptive period was 53 ± 5%. The appearance of ingested glucose in arterial blood, as derived from the ^{14}C-glucose measurements after correction for recycling ^{14}C-C radioactivity, reached a peak after 15–30 min, and ^{14}C-glucose continued to enter the systemic circulation throughout the observation period. The rate of appearance of ingested glucose was 2.47 ± 0.45 mg/min · kg at 3.5 h. A total of 73 ± 4% of the oral load was recovered in the systemic circulation within 3.5 h. The cumulative net output of glucose from the splanchnic area, measured directly with the hepatic vein catheter technique, was 46 ± 5 g over 3.5 h. This net splanchnic glucose balance resulted from the appearance of 50 ± 5 g of the glucose load plus a residual hepatic production of 15 ± 2 g, minus a splanchnic glucose uptake of 19 ± 4 g. Splanchnic fractional extraction of glucose (basal = 2.7 ± 0.7%) failed to increase in response to glucose ingestion. Splanchnic glucose uptake, however, was significantly ($P < 0.001$) higher during the absorptive period (19 ± 4 g/3.5 h) than in the basal state (5 ± 1 g/3.5 h). Peripheral glucose uptake (48 ± 6 g/3.5 h) was also enhanced by glucose ingestion ($P < 0.001$ versus a basal value of 27 ± 2 g/3.5 h) and accounted for over 70% of total glucose disposal.

It is concluded that, after the ingestion of a glucose load in healthy subjects: (1) endogenous glucose production is suppressed by approximately 50%, (2) both splanchnic and peripheral uptake of glucose are stimulated, (3) the rise in splanchnic uptake is achieved primarily by augmented glucose availability rather than by increased splanchnic fractional extraction of glucose, and (4) peripheral glucose uptake accounts for the majority of total glucose disposal. DIABETES 1985; 34:580–88.

In man, glucose tolerance after glucose ingestion is determined by four factors: the rate of appearance of oral glucose, splanchnic glucose uptake, peripheral glucose uptake, and suppression of hepatic glucose production. Although these factors have been evaluated individually in separate studies, no single investigation has attempted to simultaneously quantitate changes in these physiologic parameters in the same individual.

It is generally stated in most textbooks that the liver is the major site of glucose deposition after oral glucose administration.[1] Studies in the rat,[2] in the dog,[3,4] and in man,[5-7] using a variety of experimental approaches, have provided support for this concept. However, in none of these studies was

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splanchnic glucose uptake directly quantitated. In contrast, other reports have emphasized the predominant role of peripheral tissues in the disposal of an oral glucose load.[8–12]

In man, the central role of the liver in glucose homeostasis after glucose ingestion derives primarily from the studies of Felig et al.[7] Using the hepatic venous catheter technique, these authors surmised that approximately 60 g of a 100-g oral glucose load was retained within the splanchnic area. However, these studies have been challenged by experiments performed in dogs in which less than one-quarter of an administered glucose load was shown to be taken up by the liver.[11,12] Recently, we have reexamined this question in 22 healthy, young volunteers undergoing hepatic vein catheterization. During a 4-h period after the ingestion of a 92-g glucose load, the cumulative splanchnic glucose output amounted to 69 g or 75% of the ingested load.[13] These results indicate a quantitatively less important role for the liver in the disposal of oral glucose.

It is important to point out that the hepatic vein catheter technique measures only the *net* balance of glucose across the splanchnic region. The net splanchnic glucose balance (SGB) is comprised of two separate components, splanchnic glucose uptake (SGU) and hepatic glucose production (HGP), and is represented by the following equation: net SGB = HGP − SGU. Thus, unless hepatic venous catheterization (to measure net SGB) and tracer techniques (to measure HGP) are performed simultaneously in the same subject, SGU cannot be assessed. To our knowledge, no one has provided quantitative information on splanchnic glucose uptake in man. Radziuk, using a double-tracer technique, showed that HGP was suppressed by approximately 60% during the 4 h after the ingestion of a 100-g oral glucose load.[14] However, these studies were not performed in combination with hepatic vein catheterization, so that SGU could not be determined.

Several techniques have been employed to quantitate the contribution of peripheral tissues to the disposal of an oral glucose load in man. By extrapolation from forearm to total body glucose uptake, Butterfield and Whichelow concluded that approximately 70–80% of the ingested glucose could be accounted for by peripheral glucose uptake.[8,9] Using a similar approach, Jackson et al. estimated that peripheral tissues could account for the disposal of approximately 40% of the glucose load.[6] In a more recent study by these same authors,[15] it would appear that significantly >40% of the ingested glucose could be accounted for by peripheral glucose removal. Employing leg catheterization, with extrapolation to total body glucose uptake, we estimated that 71% of an ingested glucose load was disposed of by peripheral tissues.[13] These results are in agreement with our recent hepatic vein catheterization studies and suggest that peripheral, not splanchnic tissues, play the predominant role in the disposal of an oral glucose load.

To provide a quantitative measurement of the four physiologic variables (rate of oral glucose appearance, splanchnic glucose uptake, suppression of hepatic glucose production, and peripheral glucose uptake) that determine overall glucose tolerance, the present study was performed. This was accomplished by employing hepatic venous catheterization in combination with a double-tracer technique[10,16,17] to quantitate the rates of appearance of oral and endogenous glucose and to allow direct quantitation of splanchnic glucose uptake.

MATERIALS AND METHODS

Subjects. The subjects were 11 healthy, young volunteers (6 women, 5 men). Their mean age was 29 ± 3 yr (range 20–48 yr), and their body weight 66 ± 4 kg (range 48–93 kg), corresponding to an age-adjusted relative obesity of 98 ± 4% (range 81–119%, according to the Society of Actuaries, Build and Blood Pressure Study, Chicago, 1959). All subjects consumed a weight-maintaining diet containing at least 200 g of carbohydrate per day for 3 days before the study. None of them was taking any medication or had a family history of diabetes mellitus. The nature, purpose, and potential risks of the study were explained to all subjects, and their voluntary consent was obtained before their participation. The study protocols were reviewed and approved by the Ethics Committee of the Karolinska Institute and the Committee on Human Investigation at Yale University School of Medicine.

Experimental protocols. The subjects were studied in the recumbent position at 8 a.m. after a 12–14-h overnight fast. The double-tracer technique employed has been described in detail previously.[17] In brief, after catheterization of a brachial artery and an antecubital vein, a primed-constant infusion of D-3-^{3}H-glucose (New England Nuclear, Cambridge, Massachusetts) was started and continued throughout the study via the antecubital vein. The constant infusion rate was approximately 0.6 μCi/min, and the ratio of the priming dose to the constant infusion rate was about 100. A period of 120 min was allowed for equilibration of ^{3}H-glucose; the end of this equilibration period was designated time zero. At this time, the subjects ingested 1 g of glucose/kg body wt (as a 45% aqueous solution) over 5 min. The glucose solution contained approximately 100 μCi of D-1-^{14}C-glucose (New England Nuclear). Arterial blood samples were collected every 5 min for 20 min before time zero and then every 15 min for 210 min after glucose ingestion. Urine was collected at the end of the experiment for determination of urinary glucose loss. In 10 of the normal subjects, the double-tracer study was combined with hepatic vein catheterization. A Cournand catheter (no. 7 or 8) was introduced percutaneously into an antecubital vein or a femoral vein and manipulated under fluoroscopic control to a right-sided main hepatic vein. The tip of the catheter was placed 3–4 cm from the wedge position, and the catheter was kept open by intermittent flushing with isotonic saline. Hepatic blood flow was estimated by a continuous infusion of indocyanine green,[13,18,19] which was started 45 min before time zero and continued throughout the study. Blood was sampled simultaneously from the artery and the hepatic vein for cold and tracer glucose determination.

Analytic procedures. Blood glucose was measured by the glucose-oxidase method.[20] Indocyanine green and plasma insulin were assayed as described earlier.[21] Plasma samples were divided into four aliquots. One aliquot was used for the measurement of glucose concentration by the glucose-oxidase method using a glucose analyzer (Beckman Instruments Co., Palo Alto, California). The second aliquot was deproteinized with barium hydroxide-zinc sulphate. The deproteinized supernatant was then evaporated to dryness to

remove ^3H_2O, reconstituted with water, and counted. In the third aliquot, ^{14}C-glucose was measured as ^{14}C-gluconic acid after reaction with glucose oxidase and column chromatography.[22] The fourth aliquot was used to measure ^{14}C radioactivity in position 6 of the glucose molecule according to the method of Reichard et al.[22] Aliquots of the infused (3-^{3}H-glucose) and the ingested (1-^{14}C-glucose) glucose tracer were run along with the plasma samples for the precise determination of the ^{3}H-glucose infusion rate and the specific activity of the glucose drink, respectively. Counting was performed in a two-channel, liquid scintillation counter (TriCarb, Packard, Downers Grove, Illinois). Results were expressed as dpm/ml of plasma after correction for counting efficiency and for spillover of ^{14}C counts into the ^{3}H channel. The hematocrit was measured on every blood sample with the use of capillary tubes.

Data analysis. Hepatic plasma flow was calculated by dividing the green dye infusion rate by the arterio-hepatic venous difference of serum-green dye concentration. Hepatic blood flow was then obtained by dividing plasma flow by (1 − hematocrit). Splanchnic glucose output (SGO) was calculated as the product of hepatic blood flow and the arterial-hepatic venous blood glucose concentration difference.

In the basal state, the rate of appearance of glucose in the systemic circulation (R_a) was measured as the ratio of ^{3}H-glucose infusion rate (dpm/min) to the steady-state plasma ^{3}H-glucose specific activity (dpm/mg, mean of 4–5 determinations between −20 min and time zero). After glucose ingestion, the glucose system is driven out of steady state. Rates of glucose appearance (R_a) and disappearance (R_d) during non-steady state were computed from the ^{3}H-glucose data with the use of a two-compartment model for the glucose system[16] previously described in detail.[17] It should be noted that the rates of glucose appearance calculated from the infused tracer (^{3}H-glucose) are total rates of appearance, including endogenous as well as exogenous glucose. Likewise, the rates of glucose disappearance include all pathways of glucose loss from the systemic circulation. The use of tritiated glucose to evaluate rates of glucose appearance and disappearance has previously been validated in both steady-state and non-steady-state conditions.[16] Additional validation of this technique has been provided with the glucose clamp technique.[23] Urinary glucose loss (which was minimal) was measured at the end of the study and subtracted from the rate of glucose disappearance integrated over 3.5 h to obtain total tissue glucose disposal during the entire test.

The ^{14}C-glucose data were used to calculate the appearance of oral glucose (RaO). To obtain the ^{14}C-glucose counts appearing directly from the absorption of the oral load, correction for recycling in the Cori cycle was instituted. Recycling was determined by analyzing plasma ^{14}C counts in position 6 of the glucose molecule and multiplying this value by five. This gives an estimate of total recycled glucose.[24] These total recycled counts were then subtracted from the total ^{14}C-glucose counts (measured as ^{14}C-gluconic acid) to obtain the ^{14}C-glucose counts appearing directly from the absorption of the oral load. It should be noted that in no subject did recycled ^{14}C radioactivity account for more than 10% of the total number of ^{14}C counts (mean = 7 ± 1%). The contribution to the plasma glucose concentration made by the ingested glucose was estimated by dividing the measured plasma ^{14}C-glucose counts by the ^{14}C specific activity in the glucose drink. These "calculated" plasma glucose concentrations represent the glucose profile that would exist if the only source of glucose entry into the body was from the ingested glucose load and they will, of course, be lower than the actually measured plasma glucose concentrations. Using these "calculated" (i.e., from the ^{14}C-glucose data) plasma glucose concentrations and the measured plasma ^{3}H-3-glucose counts, the rate of peripheral appearance of oral glucose was computed using the two-compartmental model of glucose kinetics. The rate of appearance of endogenous glucose (RaE) was subsequently obtained as the difference between the rates of appearance for total and oral glucose. All rates of glucose turnover were averaged over 15-min intervals.

In the subjects undergoing hepatic vein catheterization, ^{3}H-glucose activities were measured in simultaneously drawn arterial and hepatic venous plasma samples. The splanchnic extraction ratio of ^{3}H-glucose was calculated as the ratio of the arterio-hepatic venous concentration difference to the arterial concentration of ^{3}H-glucose. The splanchnic extraction ratio of cold glucose (SERglu) was calculated from the following equation:[24]

$$\text{SERglu} = ([F \times Ga + Rao] - [F \times Ghv - Rae])/(F \times Ga + Rao) \quad \text{(eq. 1)}.$$

In this equation, F is the hepatic blood flow, and Ga and Ghv are blood glucose levels in the artery and hepatic vein, respectively. RaO and RaE represent the rates of appearance of oral and endogenous glucose, respectively.

Since (F × Ga) − (F × Ghv) is equal to the splanchnic glucose output (SGO), the above equation can be rewritten as follows:

$$\text{SERglu} = (\text{RaO} + \text{RaE} - \text{SGO})/(F \times Ga + \text{RaO}) \quad \text{(eq. 2)},$$

where the absolute value of SGO is used in the calculation.

The rate of appearance of ingested glucose (RaO) was used as a minimal estimate of the rate of glucose absorption from the gastrointestinal tract, which cannot be independently measured. It is important to point out that RaO will underestimate gut glucose absorption by an amount equal to the quantity of glucose that is removed by the splanchnic tissues (gut and liver) at each transsplanchnic passage. The quantitative impact of this assumption is elaborated on in detail in DISCUSSION.

Splanchnic glucose uptake (SGU) in the basal state was obtained as the difference between the rate of glucose appearance (R_a) and net splanchnic glucose output (SGO). Splanchnic glucose uptake after the oral glucose load was calculated as the sum of the appearance rates for oral and endogenous glucose (RaO + RaE) minus net splanchnic glucose output (SGO), which equals the numerator in equation 2.

Total, whole-body glucose uptake was obtained as R_d/(1 − SERglu) (R_d is the total glucose removal from the *systemic* circulation and excludes the first transsplanchnic passage of glucose). Peripheral glucose uptake was obtained

as the difference between total and splanchnic glucose uptake.

Integration was performed by the trapezoidal rule. Mean values were compared by the unpaired or the paired *t*-test as appropriate. Correlation analysis was performed by standard techniques. All data are given as the mean ± SEM.

RESULTS

Arterial glucose and net splanchnic glucose output. The arterial glucose concentration was 74 ± 2 mg/dl in the basal state and rose to 160 ± 7 mg/dl at 45 min after ingestion of the glucose load. Subsequently, arterial glucose gradually declined but had not returned to the basal level at 3.5 h. The net splanchnic glucose output (SGO) in the basal state was 2.0 ± 0.3 mg/min · kg. After ingestion of glucose, it rose to a peak value of 6.1 ± 0.6 mg/min · kg at 30 min, then fell rather rapidly so that from 90 min onward it was no longer significantly different from the basal value (Figure 1). The rise in SGO after glucose ingestion was the result of an increase in both splanchnic blood flow and arterial-hepatic venous glucose differences (Figure 1).

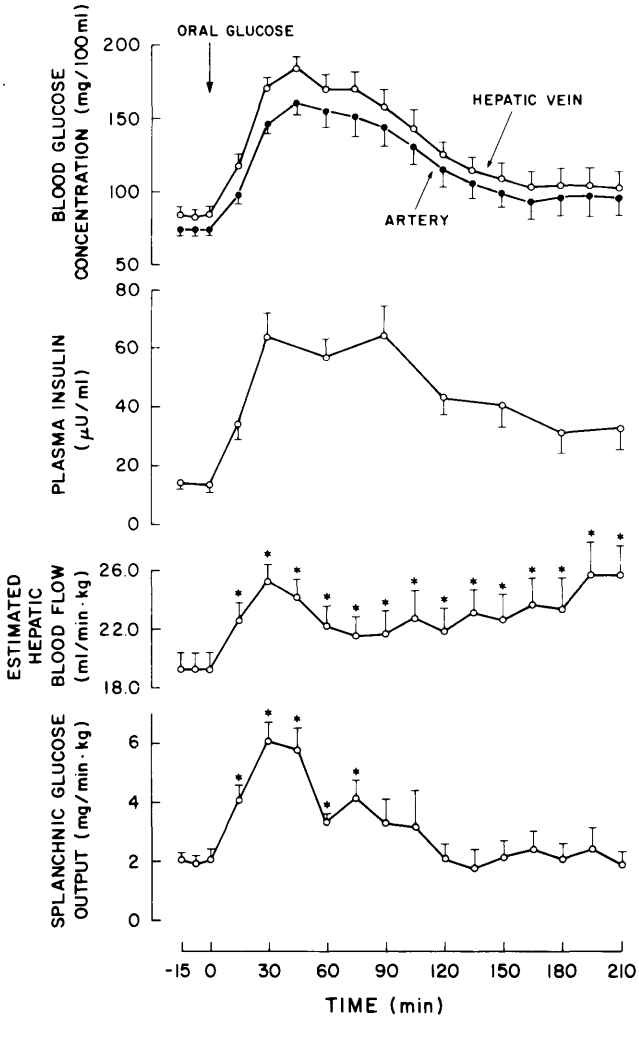

FIGURE 1. Time course of blood glucose concentration, plasma insulin response, estimated hepatic blood flow, and net splanchnic glucose output in 10 normal subjects after the ingestion of 1 g/kg of glucose. The vertical bars indicate 1 SEM, and the asterisks denote mean values significantly ($P < 0.05$ or less) different from the mean basal values (paired *t*-test).

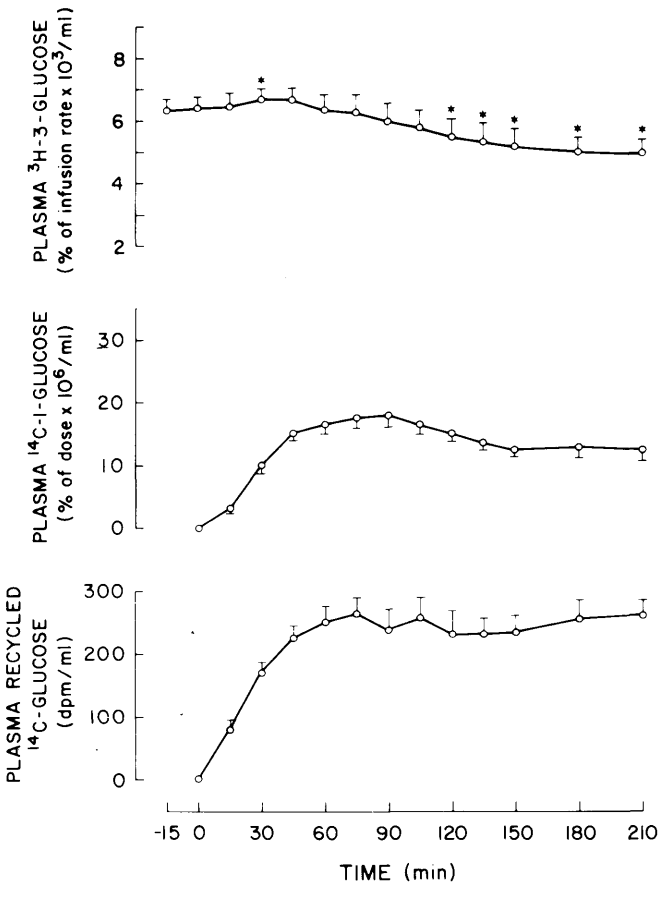

FIGURE 2. Plasma levels of ^{3}H-3-glucose, ^{14}C-1-glucose, and recycled ^{14}C-glucose in 11 normal subjects. Symbols as in Figure 1.

Cumulative net splanchnic glucose output over the 3.5 h of the study was 46 ± 5 g of glucose (66 ± 7% of the ingested load). The corresponding values over 3 h were 41 ± 5 g or 61 ± 6% of the oral load. The cumulative splanchnic glucose output above the basal rate was 18 ± 6 g (25 ± 8% of the oral load).

Insulin data. The fasting plasma insulin concentration was 13 ± 2 μU/ml (Figure 1). Thirty minutes after glucose ingestion, it rose to a peak value of 64 μU/ml. The mean value during the 3.5-h study period was 42 ± 5 μU/ml. It should be noted that, at the end of the study, the plasma insulin concentration was still significantly higher than in the post-absorptive state (Figure 1).

Isotopic data. Plasma ^{3}H-glucose concentration showed an initial, small rise at 30 min, then fell gradually throughout the period of glucose absorption, so that it was 25% below basal at 210 min ($P < 0.005$) (Figure 2). Plasma ^{14}C-glucose concentrations rose progressively, reaching a maximum value at 90 min and then declining slightly. The appearance of recycled glucose approximately paralleled that of total ^{14}C-glucose counts, but at no time did it account for >10% of the total ^{14}C counts (Figure 2).

In the basal state, the total rate of glucose appearance (R_a) averaged 2.34 ± 0.06 mg/min · kg. After glucose administration, total glucose appearance displayed a biphasic time

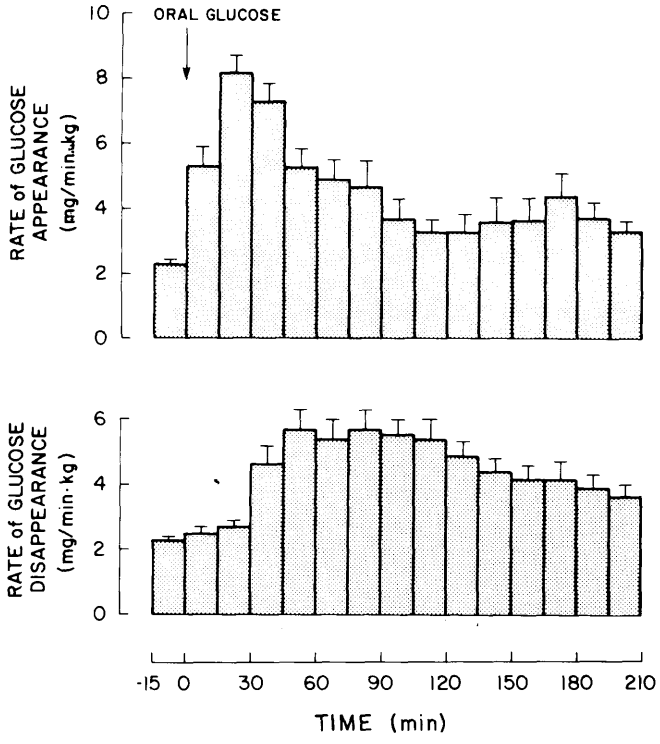

FIGURE 3. Rates of total glucose appearance and disappearance in 11 normal subjects after the ingestion of 1 g/kg of glucose. Symbols as in Figure 1.

course, with an initial peak at 15–30 min and a smaller secondary rise at 165–180 min (Figure 3). The rate of glucose disappearance from peripheral plasma (R_d) was promptly stimulated after glucose ingestion; it reached a plateau between 45 and 120 min and then declined slightly over the last hour of the study (Figure 3).

The rate of appearance of oral glucose paralleled the time course of total R_a (Figure 4). At the end of 210 min, a total of 50 ± 4 g of the ingested dose had been released to the systemic circulation, but ^{14}C-glucose still continued to appear in arterial plasma at an average rate of 2.47 ± 0.45 mg/min · kg at the end of the study ($P < 0.001$ versus time zero).

Glucose ingestion was followed by a gradual decline in calculated endogenous glucose production, which became significantly lower than in the basal state at 30–45 min. Endogenous glucose production then plateaued at 0.6–0.7 mg/kg · min from 45 to 135 min. Thereafter, it rose slightly to a value, 0.85 ± 0.22 mg/min · kg, at the end of the study that was still significantly lower than in the basal state (by 62 ± 10%, $P < 0.001$). The average suppression of endogenous glucose production during 3.5 h after glucose ingestion was 53 ± 5% (Figure 4).

Total glucose removal from peripheral plasma (R_d) averaged 64 ± 4 g over 3.5 h. This amount represents true tissue uptake of glucose, since glucosuria was negligible. Using the values of SERglu obtained from equation 2, the whole-body glucose uptake for the 10 subjects undergoing hepatic catheterization was calculated to be 67 ± 4 g over 3.5 h (see also Data Analysis). Peripheral glucose uptake (whole body minus splanchnic glucose uptake) was 48 ± 6 g, or 70% of total glucose uptake. The mean rate of peripheral glucose utilization during the entire absorption period (3.36 ± 0.34 mg/min · kg) was significantly ($P < 0.001$) higher than the postabsorptive rate (1.92 ± 0.12 mg/min · kg).

Splanchnic extraction and uptake of glucose. In the fasting state, splanchnic extraction ratio of ^{3}H-glucose in the 10 normal subjects undergoing hepatic vein catheterization was 2.7 ± 0.7%. After oral glucose, the extraction ratio of ^{3}H-glucose failed to increase significantly above the postabsorptive values (Figure 5) and averaged 2.4 ± 0.9% over the 3.5 h of the study. When equation 2 (cf. Data Analysis) was used to calculate the splanchnic extraction ratio for cold glucose (SERglu), the values and time course paralleled those obtained from the ^{3}H-glucose data, except at two early (15 and 30 min) time points (Figure 5). The mean SERglu for the entire absorptive period was 4.6 ± 0.9%, a value that was slightly, but not significantly higher than that in the basal state. Splanchnic glucose uptake (SGU) in the basal state was 0.38 ± 0.10 mg/kg · min (Figure 6). There was significant stimulation of SGU at 15 and 30 min after glucose administration to levels of 2–3 mg/kg · min. SGU subsequently declined but increased again during the last hour of the test. The cumulative SGU over 3.5 h was found to be 19 ± 4 g, a value fourfold above that in the basal state (5 ± 1 g/3.5 h, $P < 0.001$, Figure 6).

DISCUSSION

In the present study, the influence of an oral glucose load on total body and regional glucose exchange has been evaluated from the net splanchnic balance data (catheter technique) as well as from the ^{3}H-glucose and the ^{14}C-glucose results, measuring whole body glucose turnover and the rate of appearance of the oral glucose load, respectively. The results allow us to estimate the splanchnic uptake of glucose in a manner not previously possible in man. The findings demonstrate that after the ingestion of a glucose load,

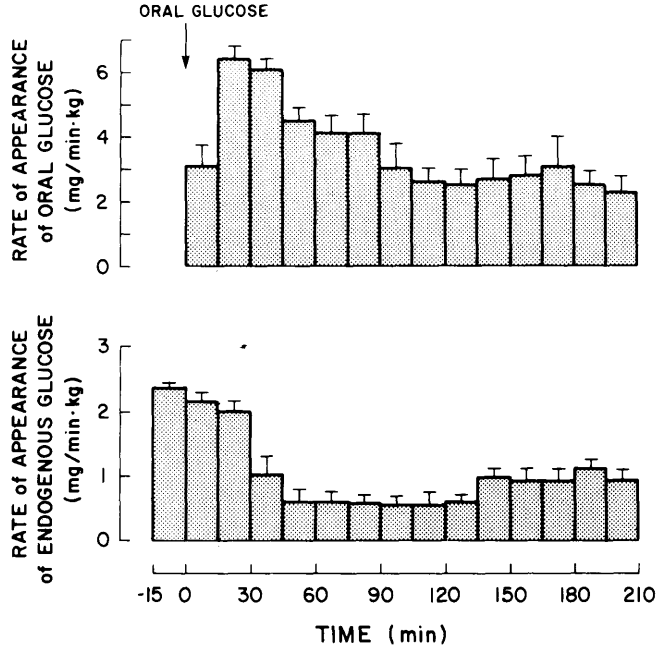

FIGURE 4. Time course of the appearance of oral glucose and endogenous glucose in 11 normal subjects. Symbols as in Figure 1.

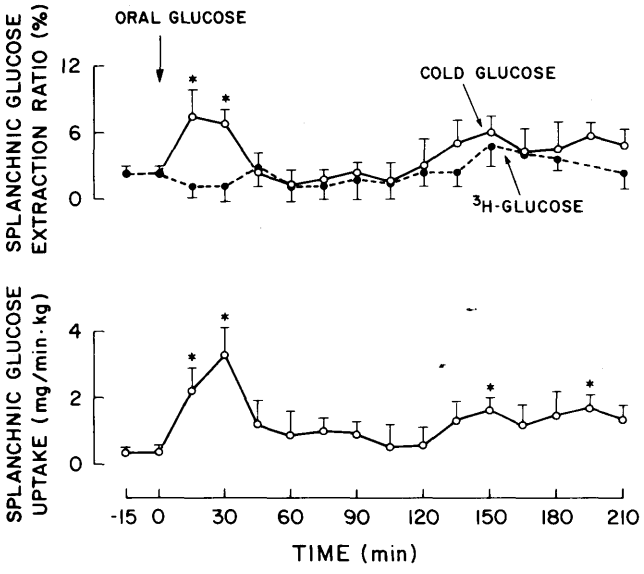

FIGURE 5. Time course of splanchnic glucose extraction ratio and splanchnic glucose uptake in 10 normal subjects after the ingestion of 1 g/kg of glucose. The splanchnic glucose extraction ratio was measured from ^{3}H-glucose data (dotted line) and from "cold" glucose data (equation 2, solid line), respectively. Symbols as in Figure 1.

splanchnic glucose uptake increases substantially above the basal level, particularly during the first 30 min after glucose administration (Figure 5); the cumulative splanchnic glucose uptake during the 3.5-h absorptive period was 19 ± 4 g (corresponding to a mean value of 1.35 ± 0.22 mg/kg · min) or three times the basal rate (Figure 6). It is noteworthy that the former value is very similar to that observed during hyperglycemia induced by i.v. glucose administration in man.[21,23]

With regard to the mechanism(s) of stimulation of splanchnic glucose uptake, higher blood flow and raised glucose levels during absorption combined to augment glucose delivery to the splanchnic area (31.2 ± 2.6 mg/min · kg versus a basal value of 14.2 ± 0.8, $P < 0.001$). In contrast, the fractional extraction of glucose across the splanchnic vascular bed showed no significant increase after the ingestion of glucose when calculated on the basis of the ^{3}H-glucose measurements. Furthermore, only a small and transient rise was estimated according to equation 2, i.e., by combining the tracer results with the net balance data obtained by catheter (Figure 5). These data indicate that hyperglycemia, not hyperinsulinemia, is the major factor regulating glucose uptake by the splanchnic tissues and are in keeping with previously published results.[23,24]

The current measurements thus suggest that the efficiency of the splanchnic tissues in extracting circulating glucose is only minimally stimulated by the ingestion of a glucose load. This is at variance with previously presented data of Felig et al.,[7] from which we *calculated* values for splanchnic glucose uptake and fractional extraction.[25] As discussed in an earlier publication,[13] the reason for this discrepancy is that the indirect estimates in the previous studies were obtained under the assumption that all of the ingested glucose load is absorbed within 3 h,[7,25] an assumption that is not supported by the ^{14}C-glucose data in the present study (see subsequent discussion).

It should be noted that the glucose extraction ratio obtained from the measurements of arterial and hepatic venous ^{3}H-glucose concentrations and that calculated from equation 2 measure two somewhat different processes. While the former only traces glucose in the systemic circulation, the latter takes into account not only the circulating glucose but also the glucose absorbed via the gut. Thus, when the splanchnic glucose extraction ratio was calculated according to equation 2, a slightly (although not significantly) greater average value was obtained during the absorptive period (4.6 ± 0.9%) than that derived from ^{3}H-glucose measurements. As can be seen in Figure 5, except for the 15- and 30-min time points, the curves are virtually identical. It should also be pointed out that equation 2 does not take into account the glucose that may have been utilized or stored by the splanchnic tissues during absorption. Equation 2 therefore provides a minimal estimate of the splanchnic glucose extraction ratio because its calculation is based on the rate of appearance in the *systemic* circulation of oral glucose (RaO). To obtain a maximal estimate of the splanchnic glucose extraction ratio, one can enter the entire glucose load into equation 2 instead of RaO. This yields a calculated average extraction ratio of 8.4 ± 1.1%, a value significantly ($P < 0.01$) greater than basal. According to these considerations, the magnitude of the true extraction ratio should therefore be somewhere in between these minimal and maximal (4.6–8.4%) values. In this context, it is of interest that, whereas the gut can take up glucose both from the circulation and from the intestinal lumen during absorption, the liver is only exposed to circulating glucose. This raises the possibility that the difference in extraction ratios obtained with the two approaches may, at least in part, reflect a relatively greater efficiency of intestinal cells to take up glucose during absorption as compared with that of the liver to extract circulating glucose. As suggested by Field et al.[26] and also by Cherrington (Lilly Lecture, American Diabetes Association Annual Meeting, Las Vegas, 1984), it is possible that an increase in portal venous glucose concentration may have a specific effect to enhance hepatic glucose uptake.

The experimental approach employed in the present study allowed us to quantitate the relative contribution of the splanchnic and the peripheral tissues to the total disposal of

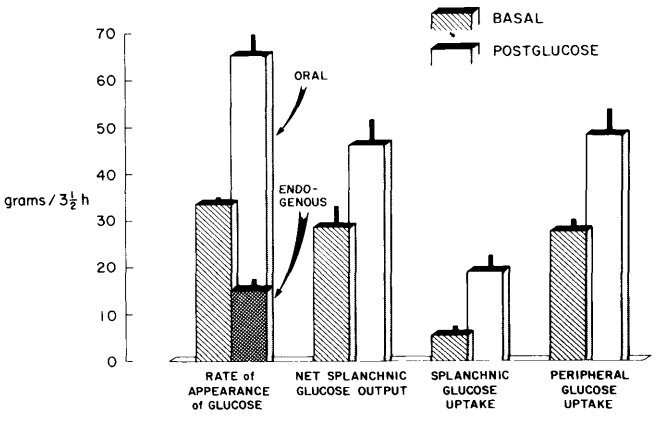

FIGURE 6. Rate of appearance of glucose, splanchnic glucose output, and splanchnic and peripheral glucose uptake in the basal state and after glucose ingestion. Cumulative values for 3.5 h are presented.

the oral glucose load (Figure 6). The subjects ingested 68 ± 3 g of glucose, 50 ± 4 g of which had appeared in the systemic circulation after 3.5 h, whereas the remaining 18 ± 4 g were unrecovered. The endogenous (hepatic) glucose production during the absorptive period was suppressed by approximately one-half, resulting in a residual cumulative hepatic glucose production of 15 ± 2 g during 3.5 h. This value is in agreement with previously published data by Radziuk.[27,28] The appearance in the systemic circulation of ingested glucose (50 g) plus endogenous glucose (15 g) amounted to 65 g. Total glucose uptake by splanchnic tissues may now be estimated at 19 ± 4 g by subtracting the cumulative net splanchnic glucose output (46 ± 5 g) from the total appearance of glucose. These data thus indicate that the splanchnic tissues can retain no more than one-third of the oral glucose load even if one assumes that 10–15% of the ingested glucose was not absorbed. This value is significantly less than the 60% contribution indicated for the splanchnic organs by previous investigators[5–7] and is consistent with results recently published by our laboratory.[13] In contrast, the peripheral, extra-splanchnic tissues (both insulin-dependent and non-insulin-dependent) take up slightly >70% of the ingested glucose load (Figure 6). The discrepancy between the present results and those of Felig et al.[7] have been discussed in detail in a previous publication[13] and will be reviewed subsequently.

The contribution of peripheral tissues to the disposal of an oral glucose load can be viewed in several ways. First, the total quantity of glucose that was disposed of by the peripheral tissues (both insulin-dependent and non-insulin-dependent) amounted to 48 g as evaluated by ^{3}H-glucose determination, and to 46 g as measured by the net balance technique (Figure 6). Second, the amount of glucose that escaped from the splanchnic area and was made available to the peripheral tissues for extra, above-basal glucose consumption was no more than 18 g during the 3.5-h period after the load. Finally, one can examine separately the effect of glucose ingestion on glucose disposal by insulin-dependent peripheral tissues. In the postabsorptive state, it can be estimated that approximately 25% of glucose utilization takes place in insulin-dependent peripheral tissues, since 75–80% occurs in the brain and other tissues with an obligatory need for glycolytic metabolism.[29,30] After glucose administration, however, the majority of the increment in peripheral glucose disposal occurs in insulin-dependent tissues. In the present study, basal glucose utilization averaged 2.3 mg/min · kg, which extrapolates to 33 g over 3.5 h and of this approximately 7 g represent insulin-dependent uptake. During the 3.5-h period after the oral load, peripheral tissues took up 48 g (Figure 6). If one assumes that basal glucose disposal by the brain and other glycolytic tissues (26 g) remains unchanged, then glucose uptake by insulin-dependent tissues increased by more than 300%. In previous studies employing femoral venous catheterization, we have shown that after both oral[13] and i.v.[23] glucose administration over 70–80% of the administered glucose load is taken up by peripheral (primarily muscle) tissues. Thus, even if glucose uptake by the brain and other non-insulin-dependent tissues increased after ingestion of the glucose load, from a qualitative standpoint this would not alter our conclusions. These considerations further emphasize the contribution of peripheral tissues in maintaining normal glucose tolerance after glucose ingestion. Thus, glucose uptake by both splanchnic and peripheral tissues plays an important role in the disposal of an oral glucose load. However, from a quantitative standpoint the peripheral tissues may be viewed as making the greater contribution.

With regard to the net splanchnic balance data, it is noteworthy that the cumulative net output of glucose after the oral load observed in the present study was significantly greater than previously reported values.[7] Thus, in the current study the total glucose output during 3 h after the load corresponded to 61 ± 6% (or 41 ± 5 g) of the ingested glucose (68 ± 3 g) as compared with 40 ± 3% (cumulative output 40 ± 3 g, oral load 100 g) in a previous report by Felig et al.[7] Among possible explanations for this discrepancy is that a commercial glucose preparation, containing approximately 90 g (not 100 g) only, was used in the earlier study.[7] More importantly, the duration of that study (2.5–3 h) was shorter, and it is likely that a considerable amount of the oral load was not absorbed. As discussed in a previous publication,[13] incomplete absorption would significantly overestimate the contribution of the splanchnic bed to total glucose disposal. If only 70% of the administered 90-g oral glucose load were absorbed (see subsequent discussion), only 36% of the ingested glucose $(0.70 \times 90 - 40/0.70 \times 90) \times (100)$ was retained within the splanchnic region. This result is more consistent with the present data.

It has been demonstrated that net splanchnic glucose output in man is inhibited by 80% within 45 min after i.v. infusion of glucose at a low rate (2 mg/min · kg), which resulted in a rise in arterial glucose of 10 mg/dl and only in a doubling of arterial plasma insulin levels.[31] In view of this, it is of interest that oral administration of glucose, resulting in greater elevations in both arterial glucose and insulin levels, is accompanied by a smaller inhibition (approximately 50%) of endogenous glucose production (Figure 4) than is i.v. glucose infusion. Comparable results with oral glucose have been previously reported with the use of a similar isotope technique.[14,27,28] The reason for the different suppression of endogenous glucose production after i.v. versus oral administration is not clear.

In the present study, the appearance of ^{14}C-glucose in the systemic circulation provides a minimal estimate of gastrointestinal absorption of the glucose load. After 3.5 h, no more than 75% of the ingested load could be accounted for as having appeared in arterial plasma. Furthermore, at 210 min ^{14}C-glucose continued to appear at a rate corresponding to 2.5 mg/min · kg of glucose (Figure 4). While some of this could conceivably represent glucose that was initially taken up by the liver and subsequently released, studies using oral ingestion of glucose labeled both with tritium in the 2 position and ^{14}C in the 1 position suggest that this process is quantitatively small.[14,32] Therefore, although the possibility that some of the ^{14}C-glucose may have originated from glycogen labeled with ^{14}C early during the absorptive period cannot be excluded, the major part of the ongoing appearance of ^{14}C-glucose in the systemic circulation at the end of the study most probably reflects continuing absorption of glucose from the intestine.

The question arises as to what proportion of the ingested load would eventually appear in the systemic circulation if

measurements were taken for a longer time. Our ^{14}C-glucose data extrapolate to 57 g of ingested glucose over 4 h, or 86% of the glucose load. Radziuk et al.[14] estimated that within 4 h approximately 90% of the ingested glucose is accounted for. With the use of a different approach, Jacot et al.[33] estimated that 10–15% of an oral glucose load is not absorbed after 4 h. Furthermore, studies in the dog[3,12] measuring glucose recovery in the portal vein have shown that only 75–80% of an intraduodenal or oral glucose load is absorbed as such within 3–4 h. Finally, recent work has shown that some glucose may indeed escape intestinal absorption and be efficiently metabolized by the colonic flora.[34] The available evidence is thus concordant in indicating that ingested glucose is never recovered completely as glucose in the circulation.

The fate of the ingested glucose that is absorbed from the gut but fails to appear in the systemic circulation cannot be established from our data. Any combination of the following three possibilities could explain the incomplete glucose recovery: (1) glucose is used locally by gut tissues as an energy-providing substrate; (2) in the process of absorption some glucose is converted to three-carbon compounds, which are then released into the portal blood; or (3) glucose is taken up by the liver. Because of the difficulties inherent in portal vein catheterization, these processes cannot be evaluated in man. In the dog, however, roughly 4% of the ingested glucose is directly oxidized by the gut and an additional 10% is recovered over 4 h in the portal blood as lactate and alanine.[3,12]

Last, it is of interest to examine the implications of the present results with respect to the mechanism by which the liver repletes its glycogen content. In the postabsorptive state, the liver produces glucose at the rate of about 2.0 mg/min · kg. For a 70-kg man, this amounts to 8.4 g/h or approximately 80 g from the time of the evening meal until breakfast the next morning. The present results, in which subjects ingested 1 g/kg of glucose, indicate that only one-quarter of this 80 g could be accounted for by direct glucose uptake. It seems likely, therefore, that sources other than glucose must serve as the precursors for glycogen repletion. A similar conclusion has been reached by Radziuk.[28] In 1974, Nilsson and Hultman demonstrated that fructose infusion resulted in a fourfold greater increase in liver glycogen content compared with an equivalent amount of glucose.[35] Since fructose can be transformed to glycogen only after conversion to three-carbon compounds, these data suggest that the majority of glycogen repletion occurs via the gluconeogenic pathway. Similar conclusions have been reached by Shikama and Ui[36] and by Boyd et al.[37] Most recently, Newgard, Foster, McGarry, and co-workers have provided additional support that the majority of live glycogen repletion occurs via three-carbon compound flux through the gluconeogenic pathway.[38,39]

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