Splanchnic bed metabolism of glucose in preterm neonates[1–3]

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ABSTRACT

Background: Glucose is a major oxidative substrate for intestinal energy generation in neonatal animals; however, few data in preterm infants are available. Early administration of enteral nutrition, including glucose, may be an effective strategy to support intestinal adaptation to extrauterine life in preterm neonates.

Objective: The purpose of the present study was to quantify the first-pass uptake and oxidation of glucose by the splanchnic tissues (intestine and liver) in human neonates.

Design: Eight preterm infants [birth weight ($\bar{x}$ ± SD): 1.19 ± 0.22 kg, gestational age: 29 ± 1 wk] were studied while they received 2 different enteral intakes (A: 40% enteral, 60% parenteral, total glucose intake = 7.5 ± 0.5 mg · kg^{-1} · min^{-1}, and B: 100% enteral, total glucose intake = 7.8 ± 0.4 mg · kg^{-1} · min^{-1}). Splanchnic and whole-body glucose kinetics were measured by use of dual-tracer techniques.

Results: During both feeding periods, approximately one-third of dietary glucose intake was utilized during the first pass by the splanchnic tissues. More than three-quarters of this utilized glucose was oxidized in both periods (79 ± 36% with A and 84 ± 45% with B). Whole-body glucose oxidation was substantial under both circumstances: 72 ± 5% and 77% ± 6% of the glucose flux was oxidized during partial (A) and full (B) enteral feeding, respectively.

Conclusions: Approximately one-third of dietary glucose is utilized during the first pass by the splanchnic tissues, irrespective of the dietary intake. Most of the utilized glucose is used for energy generation. *Am J Clin Nutr* 2004;79:831–7.

KEY WORDS Enteral nutrition, first-pass glucose uptake, intestine, oxidation, parenteral nutrition, preterm infants, stable isotopes

INTRODUCTION

In utero, the fetus receives nutrients continuously via the umbilical vein. After birth, newborns undergo several physiologic adaptations to adjust to their extrauterine environment. In particular, they must adapt to a shift from glucose as the major energy source to a carbohydrate-fat mixture as the energy source (1, 2). Therefore, neonates have to mobilize stores of carbohydrates, proteins, and lipids in adequate amounts to meet their substantial metabolic needs. Energy expenditure in neonates is ≈3 times higher per unit of body mass than in adults (3).

Studies in several mammalian species have shown that the portal-drained viscera (the intestines, pancreas, spleen, and stomach) account for 35% of whole-body energy expenditure, whereas they contribute < 5% of total body weight (4–6). In contrast, no studies in humans have been performed to quantify the substrates that are used as fuel sources by the intestine. This information is critical, especially in situations in which the intestine is damaged, eg, by infection, chemotherapy, necrotizing enterocolitis, or asphyxia. Moreover, identifying the substrates used to favor this high oxidative activity is important when the intestine is atrophied, eg, after periods of prolonged total parenteral nutrition or directly postpartum in preterm neonates. Knowing the required oxidative substrates can help to quickly reestablish gut function, because the appropriate substrates can be applied.

The extent to which orally administered nutrients are absorbed by the intestine and are metabolized within the splanchnic tissues (intestine and liver) or transported to the systemic circulation can be determined by the use of dual-stable-isotope-tracer methods. Recently, using this technique in neonatal pigs, we showed that under normal feeding conditions, the portal-drained viscera extract 6% of the dietary glucose intake (7). Studies in healthy adults showed that a similar fraction of the oral glucose load (10%) is utilized by the splanchnic tissues, and that 90% of the dietary glucose is available for the peripheral tissues (8). In preterm neonates, however, little is known about first-pass glucose uptake by the splanchnic tissues.

We found in neonatal pigs that intestinal energy production during a normal protein intake is largely derived from the oxidation of glucose and amino acids (7, 9, 10). During protein restriction, the intestines maintain their high rate of energy metabolism, although amino acid oxidation is significantly reduced and intestinal glucose oxidation becomes more important.

In an oxidation study in parenterally fed preterm infants during the first weeks of life, we also showed that, on a whole-body level, glucose is an important fuel source that accounts for 30–40% of energy expenditure, whereas protein oxidation accounts for 10–15%. The remaining 40–50% was probably due to lipid

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TABLE 1
Characteristics of the subjects included in the study[1]

	Value
Gestational age (wk)	29 ± 1
Birth weight (kg)	1.19 ± 0.22
CRIB score[2]	1 ± 1
Postnatal age (d)	
Period A	6 ± 1
Period B	13 ± 2
Study weight (kg)	
Period A	1.11 ± 0.18
Period B	1.18 ± 0.21

[1] All values are $\bar{x}$ ± SD; $n = 8$.
[2] Critical risk index for babies; range: 0–23 (14).

oxidation (11, 12). Whether glucose is catabolized by the intestinal and hepatic tissues in neonates has not yet been studied.

In the present study, the dual-stable-isotope-tracer technique was used to examine splanchnic and whole-body glucose kinetics in preterm infants. We hypothesized that, as in piglets, dietary glucose would be an important source of energy for the neonatal gut, especially when dietary protein intake is limited. Specifically, the study was designed to determine first-pass glucose uptake and oxidation by the splanchnic tissues during the provision of 2 different enteral formulas.

SUBJECTS AND METHODS

Subjects

Patients eligible for the present study were premature infants with birth weights ranging from 750 to 1500 g who were appropriate for gestational age according to the charts of Usher and McLean (13). Exclusion criteria were congenital anomalies, gastrointestinal or liver diseases, and maternal diabetes. The study protocol was approved by the Erasmus University Institutional Review Board, and written informed consent was obtained from the infants' parents.

Eight preterm infants were included in the study (**Table 1**). CRIB scores (the critical risk index for babies, an indication of illness; range: 0–23; 14) on the first day of life were all < 2. The infants received a nutrient regimen according to our feeding protocol; a combination of breast or formula feeding (Nenatal; Nutricia, Zoetermeer, Netherlands; 0.024 g protein/mL, 0.077 g carbohydrate/mL, and 0.044 g fat/mL) and parenteral nutrition containing glucose (10% glucose), amino acids (10% Primene; Clintec Benelux NV, Brussels), and lipids (20% Intralipid; Fresensius Kabi, Den Bosch, Netherlands). Nenatal was given as sole enteral nutrition 12 h before the start of the study and during the study days.

Protocol

To investigate the influence of enteral intake and postnatal age on splanchnic glucose uptake, the study was implemented in 2 periods on 2 consecutive study days. During period A (age: 6 ± 1 d), the infants received 40% enteral feeding and 60% parenteral feeding continuously through intragastric and intravenous catheters, respectively. During period B (age: 13 ± 2 d), they received full enteral feeding through an intragastric catheter (**Figures 1** and **2**). During period A, the infants were implanted with both an arterial and an intravenous catheter for the infusion of tracers and the withdrawal of blood samples. During period B, a peripheral intravenous catheter was available for the infusion of tracers, and blood samples were collected by heel stick. To collect breath samples from these infants, we used the method described by Perman et al (15), who used a nasal tube. This method has been used in children (15) and preterm infants for the collection of expiratory carbon dioxide after the administration of ^{13}C-labeled substrates (16, 17). We validated this technique for use in oxidation studies in preterm infants (18). Briefly, a 6 French gastric tube (6 Ch Argyle; Sherwood Medical, Tullamore, Ireland) was placed 1-1.5 cm into the nasopharynx, and a 15-mL sample of end-tidal breath was taken slowly with a syringe. Duplicate aliquots of expired air from each sampling point were stored in evacuated tubes for analysis.

Isotope infusion

Three different stable-isotope infusions were performed during each study day. First, a primed 2-h infusion of [^{13}C]bicarbonate (99.0 mol% ^{13}C; Cambridge Isotopes, Woburn, MA) dissolved in

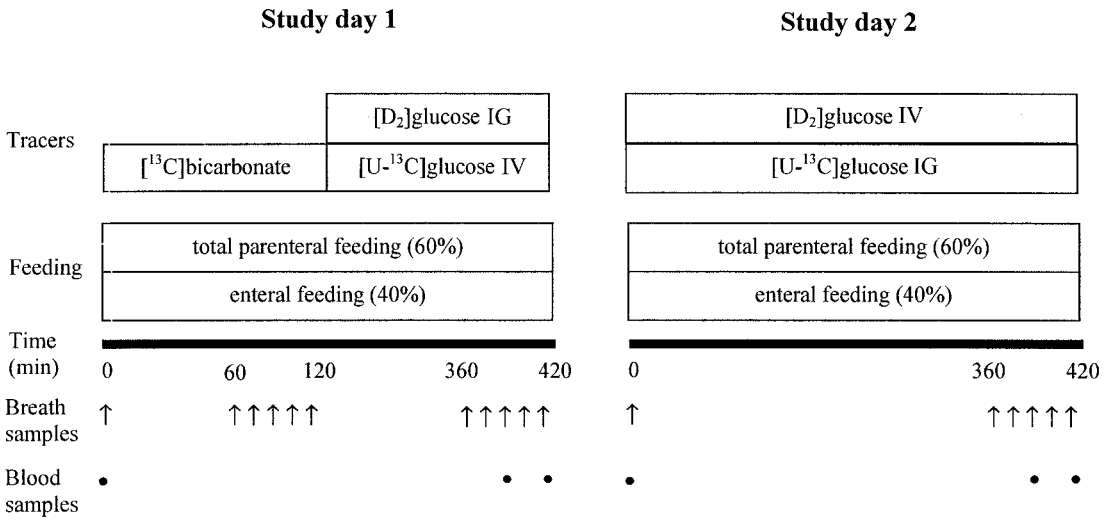

FIGURE 1. Overview of study period A during study days 1 and 2. IG, intragastric; IV, intravenous.

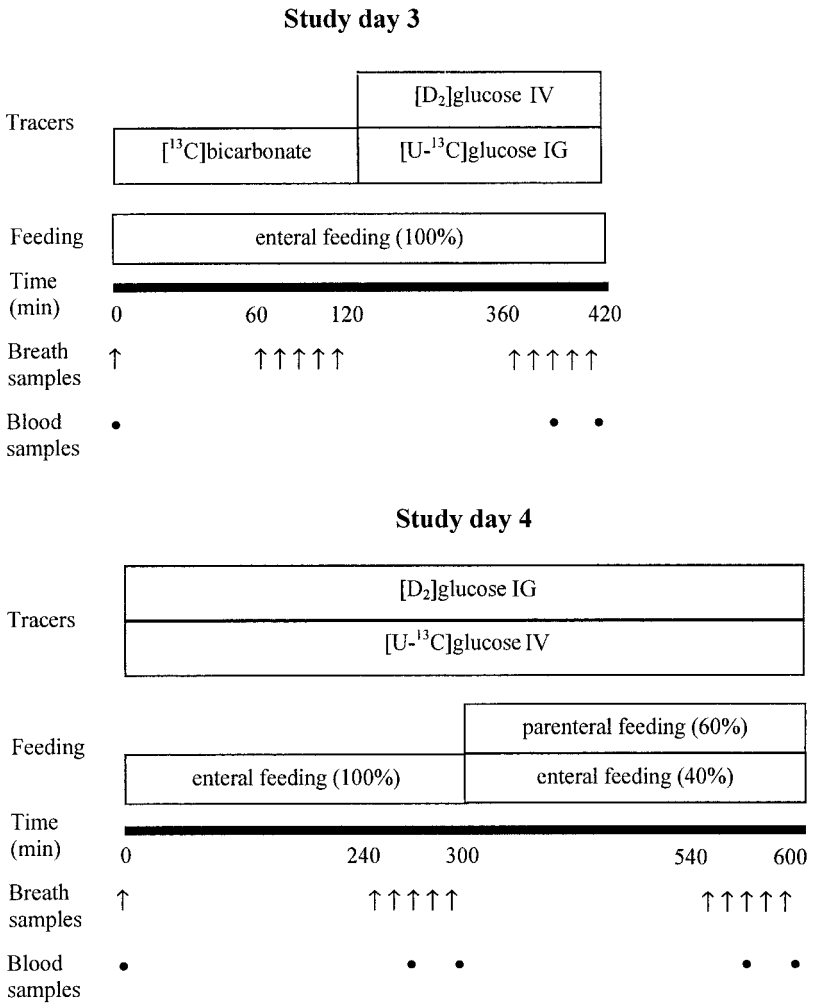

FIGURE 2. Overview of study period B during study days 3 and 4. IG, intragastric; IV, intravenous.

sterile saline (10.02 μmol/kg and 10.02 μmol $\cdot$ kg^{-1} $\cdot$ h^{-1}, concentration measured after administration) was administered at a constant rate. The [^{13}C]bicarbonate infusion was immediately followed by 2 primed 5-h infusions (10.0 μmol/kg and 5.0 μmol $\cdot$ kg^{-1} $\cdot$ h^{-1}) of [U-^{13}C]glucose (99.0 mol% ^{13}C; Cambridge Isotopes) and [D_2]glucose (98.0 mol% ^{13}C; Cambridge Isotopes), which were designed to assess whole-body and splanchnic glucose kinetics. During both period A and period B, we administered the tracers in the following order (Figures 1 and 2): on study days 1 and 4, [U-^{13}C]glucose was given via an intravenous catheter and [D_2]glucose via the intragastric catheter. On study days 2 and 3, the intravenous and intragastric routes were switched. All isotopes were tested and were found to be sterile and pyrogen-free before use in our studies. To quantify the effect of postnatal age on whole-body and splanchnic glucose kinetics, we performed a separate study on the fourth study day (Figure 2). The first 5 h, the infants received full enteral feeding simultaneously with 2 labeled glucose tracers intravenously and intragastrically; the next 5 h the infants received 40% enteral and 60% parenteral feeding simultaneously with 2 labeled glucose tracers intravenously and intragastrically. At time zero, baseline blood and breath samples were collected. During the last hour of each tracer infusion, breath samples were collected at 15-min intervals, and blood samples were obtained at 390 and 420 min. The total amount of blood withdrawn during a study day was 1.5 mL, which is $<$ 2% of blood volume in a 1000-g infant. Blood was centrifuged immediately (10 min, 0 °C, and 8000 $\times$ g) and was stored at $-$70 °C for further analysis.

Analytic methods

Blood samples were prepared for mass spectrometry with the penta-acetate derivative of glucose: 50 μL plasma was mixed with 200 μL ice-cold acetone. After being kept refrigerated for 10 min, the solution was centrifuged through a 10-kDa cutoff filter for 10 min at 0 °C and 8000 $\times$ g. The filtrate was dried under vacuum, and 50 μL acetic anhydride:pyridine (2:1, by vol) was added. Thereafter, gas chromatography–mass spectrometry was performed. The analyses were performed with a 6890 series gas chromatograph linked to a model 5973 quadrupole mass spectrometer (Hewlett-Packard, Palo Alto, CA). Breath samples were analyzed for enrichment of $^{13}CO_2$ on an isotope ratio mass spectrometer (ABCA; Europa Scientific, Van Loenen Instruments, Leiden, Netherlands) (19).

Calculations

Plasma enrichments of glucose were used to calculate the rate of glucose turnover. The rate of glucose turnover was calculated by measuring the tracer dilution at steady state as modified for

stable isotope tracers, as previously described (20, 21).

Glucose flux was calculated according to the following equation:

$$Q_{IV} = I_{IV\ tracer} \times [(IE_{inf}/IE_{IV}) - 1] \quad (1)$$

where Q_{IV} is the flux of the intravenous glucose tracer (μmol · kg^{-1} · h^{-1}), $I_{IV\ tracer}$ is the intravenous glucose tracer infusion rate in μmol · kg^{-1} · h^{-1}, IE_{inf} is the isotopic enrichment [mole percent excess (MPE)] of the infusate, and IE_{IV} is the plasma isotopic enrichment (MPE) of the glucose tracer at steady state.

First-pass glucose uptake by the splanchnic tissues was calculated according to the expression (22, 23):

$$\text{First-pass uptake} = [(IE_{IV} - IE_{IG})/IE_{IV}] \times \text{enteral intake} \quad (2)$$

where first-pass glucose uptake is expressed in μmol · kg^{-1} · h^{-1}, IE_{IG} is the plasma isotopic enrichment of the intragastric glucose tracer at steady state, and enteral intake is expressed in μmol · kg^{-1} · h^{-1}.

Under steady-state conditions, the rate of glucose appearance is equal to the rate of glucose disappearance. Glucose can enter the glucose pool by intravenous or enteral glucose infusion and by glucose production from other substrates (eg, glycerol, glycogen, and amino acids). The glucose production rate can be calculated as follows:

$$GPR = Q_{IV} - \text{total glucose intake} \quad (3)$$

where GPR is the glucose production rate in μmol · kg^{-1} · h^{-1} and total glucose intake (enteral and intravenous) is also in μmol · kg^{-1} · h^{-1}.

Whole-body carbon dioxide production was estimated as follows:

$$\text{Whole-body } CO_2 \text{ production} = I_{bicarbonate} \times [(IE_{bicarbonate\ infusate}/IE_{breath}) - 1] \quad (4)$$

where $I_{bicarbonate}$ is the infusion rate of $NaH^{13}CO_3$ (μmol · kg^{-1} · h^{-1}), $IE_{bicarbonate\ infusate}$ is the enrichment (MPE) of [^{13}C]bicarbonate in the bicarbonate infusate, and IE_{breath} is the breath $^{13}CO_2$ enrichment at plateau during the $NaH^{13}CO_3$ infusion (MPE).

Splanchnic and whole-body glucose oxidation rates were determined by assuming that carbon dioxide production during the $NaH^{13}CO_3$ infusion was equal to carbon dioxide production during the [U-^{13}C]glucose infusion. By determining the increase in $^{13}CO_2$ enrichment of each individual infant during both the $NaH^{13}CO_3$ infusion and the [U-^{13}C]glucose infusion, variance can be diminished and there is no need for a correction factor (24) to account for [^{13}C]bicarbonate sequestration in the whole body (11, 25).

As described previously, glucose oxidation was calculated by multiplying the recovery of the ^{13}C label in the expiratory air with the rate of appearance of glucose (11). The fraction of glucose oxidized was measured according to the following equation:

$$\text{Fraction of glucose oxidized} = [IE_{IV} \times I_{bicarbonate}]/[IE_{breath} \times I_{IVtracer} \times 6] \quad (5)$$

where IE_{breath} is the $^{13}CO_2$ breath enrichments (MPE) at steady state during the $NaH^{13}CO_3$ infusion. The denominator is multiplied by a factor of 6 to account for the number of labeled carbon atoms.

Whole-body glucose oxidation was then calculated as follows:

$$\text{Whole-body glucose oxidation} = \text{Equation } 5 \times \text{Equation } 1 \quad (6)$$

The calculation of the metabolism of enterally administered [U-^{13}C]glucose to carbon dioxide is complicated by the fact that some of the intragastric glucose tracer is absorbed and transferred to the systemic circulation and thereby labels the arterial pool. Thus, the non-first-pass oxidation of [^{13}C]glucose that was administered enterally but was absorbed and entered the body on the following study day can be calculated as follows:

$$\text{Non-first-pass oxidation of the enteral administered [U-}^{13}\text{C] glucose} = (IE_{IG}/IE_{IV}) \times \text{Equation } 6 \quad (7)$$

where IE_{IG} is the tracer enrichment (MPE) in plasma during the intragastric [^{13}C]glucose infusion on study days 2 and 3, and IE_{IV} is the tracer enrichment (MPE) in plasma during the intravenous [^{13}C]glucose infusion on study days 1 and 4.

Total glucose oxidation on study days 2 and 3 is calculated as described previously:

$$\text{Total glucose oxidation} = \text{recovery (Equation } 5) \times Q_{IV\ D2} \quad (8)$$

where $Q_{IV\ D2}$ is the flux of the intravenous [D_2]glucose tracer (μmol · kg^{-1} · h^{-1}).

First-pass glucose oxidation by the splanchnic tissues can thus be calculated with the following equation:

$$\text{First-pass glucose oxidation} = \text{Equation } 8 - \text{Equation } 7 \quad (9)$$

Statistics

Data are expressed as the mean values (± SEM) obtained from samples taken over the last hour of each tracer infusion. All analyses were conducted by using SPSS 10/PC (SPSS Inc, Chicago). Statistical comparisons were performed with a paired Student's *t* test whenever the results were normally distributed. In cases of apparent nonnormality, a Mann-Whitney *U* test was performed. *P* values < 0.05 were considered statistically significant.

RESULTS

All infants were appropriate for gestational age because of the inclusion criteria (mean gestational age: 29 ± 1 wk; Table 1). Two infants were mechanically ventilated during both periods, and 6 infants received supplemental oxygen through a nasal prong. All infants received caffeine, therapeutic plasma concentrations of which were within the normal range, and all infants were clinically stable at the time of the study. The infants did not receive any vasopressors that could influence splanchnic blood flow. Seven infants had received antenatal steroids. The results of routine blood chemistry and hematology tests (measurements of electrolytes, calcium, glucose, acid base, hematocrit, thrombo-

TABLE 2
Glucose and energy intakes during periods A (partial enteral feeding) and B (full enteral feeding)[1]

	Period A	Period B
Total glucose intake ($mg \cdot kg^{-1} \cdot min^{-1}$)	7.5 ± 0.5	7.8 ± 0.4
Enteral	2.7 ± 0.3	7.1 ± 0.3
Parenteral	5.0 ± 0.4	0.7 ± 0.1
Total energy intake ($kcal \cdot kg^{-1} \cdot d^{-1}$)	100 ± 4[2]	111 ± 5
Enteral	41 ± 5	107 ± 5
Parenteral	58 ± 6	4 ± 1

[1] All values are $\bar{x}$ ± SD; $n = 8$.
[2] Significantly different from period B, $P < 0.05$ (Student's t test).

cyte count, and white blood cell count) were all within normal limits for preterm infants, and there were no significant changes in these variables for 24 h before and after the study.

Intakes of glucose and energy are shown in **Table 2**. By study design, no significant differences were found in protein and carbohydrate intakes during periods A and B, respectively (protein: 3.4 ± 0.1 and 3.2 ± 0.2 $g \cdot kg^{-1} \cdot d^{-1}$; glucose: 7.5 ± 0.5 and 7.8 ± 0.4 $mg \cdot kg^{-1} \cdot min^{-1}$). Fat intake was significantly higher during full enteral feeding (4.7 ± 0.3 $g \cdot kg^{-1} \cdot d^{-1}$ during period A compared with 5.8 ± 0.3 $g \cdot kg^{-1} \cdot d^{-1}$ during period B; $P <$ 0.05), which resulted in a slightly but significantly higher energy intake (11% greater) during period B.

Isotopic plateau

Glucose kinetics were calculated from the plateau enrichment values in breath and plasma. Details of the isotopic enrichments of plasma glucose at baseline and at plateau during periods A and B are given in **Table 3**. The background (baseline) recovery of the ^{13}C label in expiratory air was not significantly different between the periods: period A, 1.0918 ± 0.0007 APE; period B, 1.0883 ± 0.0018 APE. The $^{13}CO_2$ enrichment in breath during [^{13}C]sodium bicarbonate infusion rose rapidly during the first hour of infusion in both periods to become constant in all infants by 120 min, with <3% variation in plateau values: period A, 1.6 ± 0.5%; period B, 2.0 ± 1.1%. The CV ($\bar{x}$ ± SD) of breath [^{13}C]glucose enrichment above baseline at plateau was 1.2 ± 0.8% during period A and 1.9 ± 1.0% during period B.

TABLE 4
First-pass (FP) glucose uptake and oxidation by the splanchnic tissues during periods A (partial enteral feeding) and B (full enteral feeding)[1]

	Period A	Period B
FP uptake ($\mu mol \cdot kg^{-1} \cdot h^{-1}$)	398 ± 65	825 ± 253
Fractional FP uptake (%)	44 ± 8	32 ± 9
FP oxidation ($\mu mol \cdot kg^{-1} \cdot h^{-1}$)	323 ± 136	573 ± 273
Fractional FP oxidation of FP uptake (%)	79 ± 36	84 ± 45

[1] All values are $\bar{x}$ ± SEM; $n = 8$. Absolute and fractional FP uptake and oxidation were not significantly different between periods (Mann Whitney U test).

Glucose kinetics

First-pass glucose kinetics in the intestine and liver during partial and full enteral feeding are summarized in **Table 4**. First-pass glucose uptake expressed as a percentage of dietary intake, ie, fractional first-pass uptake, did not differ significantly between the 2 feeding periods. More than one-third of dietary intake was utilized by the splanchnic tissues during both partial and full enteral feeding. Postnatal age did not influence first-pass glucose uptake. Postnatal age also did not significantly influence first-pass glucose uptake when enteral intake was restricted: at a postnatal age of 5 d and a restricted intake, 44 ± 8% of dietary intake was utilized; at a postnatal age of 13 d and a restricted intake, 39 ± 8% was utilized. During restricted enteral intake, the splanchnic tissues oxidized dietary glucose at a rate of 323 ± 136 $\mu mol \cdot kg^{-1} \cdot h^{-1}$. During full enteral feeding, glucose oxidation by the splanchnic tissues was 573 ± 273 $\mu mol \cdot kg^{-1} \cdot h^{-1}$. Taken together, the first-pass glucose oxidation was not significantly different between the 2 feeding periods, and accounted for more than three-quarters of the utilized glucose.

Whole-body glucose oxidation and glucose production rates are shown in **Table 5**. There was no significant difference in the amount of glucose oxidized by the whole body between the 2 feeding periods. During both intakes, whole-body glucose oxidation accounted for ≈75% of glucose flux: period A, 72 ± 5%; period B, 77 ± 6%. Postnatal age did not influence whole-body glucose oxidation: at a postnatal age of 13 d and a restricted enteral intake, 69 ± 5% of the glucose flux was oxidized. The glucose production rate was ≈1500 $\mu mol \cdot kg^{-1} \cdot h^{-1}$ in both

TABLE 3
Baseline and steady-state plasma isotopic enrichments on study days 1 and 2 during period A (partial enteral feeding) and on study days 3 and 4 during period B (full enteral feeding)[1]

	[U-^{13}C]Glucose		[D_2]Glucose	
Period and study day	Baseline	Plateau	Baseline	Plateau
	mol %		*mol %*	
Period A				
Day 1	0.0192 ± 0.0043	0.1308 ± 0.0610	2.7115 ± 0.0519	2.7729 ± 0.0702
Day 2	0.0199 ± 0.0039	0.1135 ± 0.0629	2.7347 ± 0.0720	2.7883 ± 0.0715
Period B				
Day 3	0.0199 ± 0.0073	0.1309 ± 0.0644	2.6702 ± 0.0735	2.8245 ± 0.0955
Day 4	—	0.1895 ± 0.0497	—	2.7621 ± 0.0604
Period A				
Day 4	0.0166 ± 0.0032	0.1739 ± 0.0262	2.6725 ± 0.0258	2.7780 ± 0.0430

[1] All values are $\bar{x}$ ± SD; $n = 8$. The baseline enrichments on the different study days were not significantly different (Student's t test). On study days 1 and 4, [U-^{13}C]glucose was administered intravenously and [D_2]glucose intragastrically; on study days 2 and 3, [U-^{13}C]glucose was given intragastrically and [D_2]glucose intravenously.

TABLE 5
Whole-body (WB) glucose kinetics in preterm infants during periods A (partial enteral feeding) and B (full enteral feeding)[1]

	Period A		Period B
	6 d old	13 d old	13 d old
	$\mu mol \cdot kg^{-1} \cdot h^{-1}$		$\mu mol \cdot kg^{-1} \cdot h^{-1}$
IV flux	3405 ± 220	3108 ± 295	2885 ± 233
WB oxidation	2522 ± 331	2305 ± 163	2161 ± 101
WB oxidation of flux (%)	72 ± 5	69 ± 5	77 ± 6
GPR	1433 ± 255	1343 ± 146	1781 ± 221

[1] All values are $\bar{x}$ ± SEM; $n = 8$. IV, intravenous; GPR, glucose production rate. WB glucose kinetics was not significantly different between periods (Student's *t* test).

periods, and accounted for 40 ± 3% and 62 ± 6% of the glucose flux in periods A and B, respectively.

DISCUSSION

To our knowledge, this is the first study to provide insight into both splanchnic glucose uptake and splanchnic oxidative capacity in preterm infants. Our data indicate that the splanchnic tissues (which include both the intestine and the liver) utilize one-third of oral glucose intake, irrespective of the level of enteral feeding. Approximately 80% of the utilized glucose is oxidized, presumably to sustain the high rate of visceral metabolism. Whole-body glucose oxidation accounted for three-quarters of the glucose turnover. Given that splanchnic glucose oxidation was substantial in the early weeks of life, early administration of enteral nutrition, including glucose, may be an effective strategy to support intestinal adaptation to extrauterine life in preterm neonates. These data show that the splanchnic tissues extract a disproportionate amount of dietary glucose to serve mainly as a fuel source in the early life of preterm neonates.

Neonates depend on the gastrointestinal tract for the acquisition of nutrients through the processes of propulsion, digestion, and absorption of ingested food. Studies in adults showed < 500 mg of residual glucose in gastric washings obtained 3 h after the ingestion of 100 g oral glucose (26). Furthermore, ≥ 98% of glucose is removed from the intestinal lumen before it reaches the ileum (27). However, glucose was not the sole source of carbohydrates in the present study; the formula also contained lactose, maltose, and glucose polymers. Others have shown that glucose polymers are well absorbed by young infants (28, 29). Kien et al (30) showed that lactose digestion from formula was ≈79%, although there was a significant linear correlation between lactose digestion and postconceptional age. Thus, most of the dietary milk carbohydrates are absorbed by the intestinal mucosa at a postnatal age of 1 wk. Therefore, glucose that does not appear in the systemic circulation is utilized by the intestine and liver and is not lost via the feces before being used for synthetic purposes.

The substantial dietary glucose uptake observed during both partial and full enteral feeding reflects the use of absorbed glucose for different splanchnic metabolic fates, at least under clinically stable conditions and in the absence of significant intestinal diseases. Splanchnic glucose extraction equals the sum of intestinal and hepatic glucose extraction. Any combination of the following 4 possibilities could explain the lower systemic availability of the dietary glucose: *1*) glucose is used by mucosal tissue as a energy-providing substrate; *2*) glucose is used for the synthesis of intestinal glycoproteins; *3*) in the process of absorption, some glucose is converted into three-carbon compounds, which are then released into the portal vein; and *4*) glucose is taken up and metabolized by the liver. It should be emphasized quite clearly that catheterization of the portal vein was not ethically feasible in the small infants we studied. Consequently, it was not possible to quantify the net hepatic uptake of dietary glucose and the relative contributions of intestinal and hepatic tissues to the splanchnic glucose oxidation.

By using dual-stable-isotope methodology, we were able to measure first-pass glucose oxidation by the intestine and liver, and we found that more than three-quarters of the intestinally absorbed glucose was oxidized. Thus, it seems that dietary glucose is an important energy source for the splanchnic mucosa. The present data on intestinal glucose oxidation agree with our previous observations in protein-restricted piglets, in which we found that intestinal glucose oxidation accounts for ≈50% of the total visceral carbon dioxide production (7). Similarly, in vitro studies with human enterocytes reported that the respiratory fuels of human enterocytes include glucose, glutamine, and, to a lesser extent, ketone bodies as indicated in the proportion of oxygen consumption attributed to these fuels (31).

A second metabolic fate of the glucose utilized during the first pass might be mucin synthesis. Intestinal mucins are key components of the first line of host defense against intestinal pathogens. These large glycoproteins secreted by specialized goblet cells form viscous gels that trap microorganisms and limit their diffusion to the intestinal epithelium. Isolated mucin has high concentrations of carbohydrates, representing 65% of the mucin by weight (32, 33). Recently, we found in preterm infants that > 80% of the dietary threonine intake was utilized in the first pass, which was not used for oxidative purposes but for synthetic purposes (SRD van der Schoor, unpublished observations, 2003). Therefore, we speculate that preterm neonates have a high visceral need for threonine, presumably for the synthesis of (glyco)proteins, and, consequently, that neonates may have a high need for glucose as well.

After its splanchnic release into the systemic circulation, glucose can be oxidized in the peripheral tissues, metabolized to lactate and recycled to glucose via gluconeogenesis, stored as glycogen, or used in various synthetic processes. Because glucose represents the main source of energy for preterm infants during most of the neonatal period, it is important to determine the extent of whole-body glucose oxidation and its contribution to total glucose use. This knowledge assists in the clinical determination of the optimal rate of glucose infusion for preterm infants, which is the rate that is appropriate to the neonate's capacity to oxidize glucose. In the present study, we quantified the whole-body oxidation of glucose and the glucose production rate in relation to an increasing enteral intake. Our results show that > 70% of the glucose turnover is oxidized, and these observations are similar to other studies, except for the study done by Cowett et al (34). In preterm infants, we and others previously showed that 50–65% of the whole-body glucose turnover was oxidized (10, 35, 36). Cowett et al (34) studied glucose oxidation in preterm infants of different postnatal ages and found that the fraction of glucose oxidized decreased with postnatal age. We did not find a significant effect of postnatal age on whole-body glucose oxidation, which might be because the infants we studied differed in age by only 7 d. However, the purpose of this part of

the study was to show that glucose metabolism did not differ by postnatal age or feeding pattern.

In conclusion, we showed that the splanchnic tissues extract one-third of the dietary glucose intake in preterm infants in their first weeks of life. A significant amount of this utilized glucose is used for oxidative purposes by the intestine and liver. Our results also show that neither the amount of enteral feeding nor postnatal age significantly affects glucose uptake and oxidation by the splanchnic tissues. Taken together, these results highlight the critical importance of the splanchnic tissues in actively regulating glucose flow to the peripheral tissues in the first weeks of life in preterm neonates.

SRDvdS collected and analyzed the data and wrote the manuscript; BS and DLW analyzed the data; HAB, DT, and DGB provided helpful comments in writing the manuscript; and JBvG designed the study and provided helpful comments in writing the manuscript. None of the authors had any financial or personal interest in any company or organization sponsoring the research.

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