Blood-to-Brain Glucose Transport and Cerebral Glucose Metabolism Are Not Reduced in Poorly Controlled Type 1 Diabetes

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To test the hypothesis that blood-to-brain glucose transport is reduced in poorly controlled type 1 diabetes, we studied seven patients with a mean (± SD) HbA$_{1c}$ level of 10.1 ± 1.2% and nine nondiabetic subjects during hyperinsulinemic, mildly hypoglycemic (~3.6 mmol/l, ~65 mg/dl) glucose clamps. Blood-to-brain glucose transport and cerebral glucose metabolism were calculated from rate constants derived from blood and brain time-activity curves—the latter determined by positron emission tomography (PET)—after intravenous injection of [1-^{11}C]glucose using a model that includes a fourth rate constant to account for regional egress of ^{11}C metabolites. Cerebral blood flow and cerebral blood volume were determined with intravenous H$_2$^{15}O and inhaled C^{15}O, respectively, also by PET. At plateau plasma glucose concentrations of 3.6 ± 0.0 and 3.7 ± 0.1 mmol/l, rates of blood-to-brain glucose transport were similar in the two groups (23.7 ± 2.2 and 21.6 ± 2.9 µmol · 100 g^{-1} · min^{-1}, P = 0.569, in the control subjects and the patients, respectively). There were also no differences in the rates of cerebral glucose metabolism (16.8 ± 0.8 and 16.3 ± 1.2 µmol · 100 g^{-1} · min^{-1}, P = 0.693, respectively). Plasma epinephrine (1,380 ± 340 vs. 450 ± 170 pmol/l, P = 0.0440) and glucagon (26 ± 5 vs. 12 ± 1 pmol/l, P = 0.0300) responses to mild hypoglycemia were reduced in the patients with type 1 diabetes. We conclude that neither blood-to-brain glucose transport nor cerebral glucose metabolism is measurably reduced in people with poorly controlled type 1 diabetes. *Diabetes* 47:1444–1450, 1998

S urvival requires a continuous supply of glucose to the brain via the circulation. Because of its detrimental, and potentially devastating, effects on the brain, hypoglycemia is the limiting factor in the management of diabetes (1). Therefore, pending development of methods that provide perfect insulin replacement, strategies that minimize the risk of iatrogenic hypoglycemia

are needed urgently if people with diabetes are to reap the benefits of glycemic control safely (2). Much has been learned about the physiology of glucose counterregulation—the prevention or correction of hypoglycemia—and its pathophysiology in type 1 diabetes (1), but development of methods that effectively prevent, correct, or compensate for compromised glucose counterregulation awaits better insight into the fundamental mechanisms of that pathophysiology.

Falling plasma glucose concentrations normally elicit a characteristic series of physiological responses. These include, in sequence, decrements in insulin secretion, increments in glucose counterregulatory hormone (glucagon, epinephrine, growth hormone, and cortisol) secretion and autonomic nervous system activation, symptoms of hypoglycemia, and cognitive dysfunction (3–5). Glycemic thresholds for these responses (when quantitated with the same experimental methods, including the hyperinsulinemic stepped hypoglycemia clamp technique, arterialized venous sampling, and definition of the threshold as the plasma glucose concentration at which a given parameter first deviates from the 95% CI for that parameter at the same time point during otherwise identical euglycemic control studies) are remarkably reproducible from laboratory to laboratory in healthy humans (3–5). Nonetheless, these thresholds are dynamic rather than static. For example, the glycemic thresholds for autonomic responses, including epinephrine, and symptomatic responses to falling glucose levels lie at higher plasma glucose concentrations in people with poorly controlled type 1 diabetes (6,7) and at lower plasma glucose concentrations in those with well-controlled (and therefore frequently hypoglycemic) type 1 diabetes (7). Recent antecedent iatrogenic hypoglycemia plays an important role in the development of the latter shifts of glycemic thresholds to lower plasma glucose concentrations (8–11), which, in turn, play central roles in the pathogenesis of the clinical syndromes of defective glucose counterregulation and hypoglycemia unawareness that lead to substantially increased risk for severe hypoglycemia in type 1 diabetes (1,9,12–16).

The mechanism(s) of these shifts in glycemic thresholds is unknown. One hypothesis, based on the reported (17–19), albeit debated (20), finding of decreased brain glucose uptake in chronically hyperglycemic rodents, is that chronic hyperglycemia causes decreased blood-to-brain glucose transport, which, in turn, causes autonomic and symptomatic responses at higher-than-normal plasma glucose concentrations as glucose levels fall. This hypothesis has not been supported in several studies in humans (21–24), but questions can be raised about each of those. Using positron emission tomography (PET), Brooks et al. (21) found no significant difference in brain [^{11}C]3-*O*-methylglucose extrac-

tion in four patients with poorly controlled type 1 diabetes compared with four nondiabetic control subjects, each studied at a plasma glucose level of 3.8 mmol/l. However, the mean rate of blood-to-brain glucose transport was 18% lower in the diabetic patients, an apparent difference that was not significant statistically in their small sample. Furthermore, the behavior of a glucose analog, not glucose, was studied. The interpretation of data obtained with a glucose analog assumes implicitly that any change in blood-brain barrier glucose transport in type 1 diabetes does not involve a change in affinity of the transporter for the analog relative to glucose. Also using PET, Gutniak et al. (22) found no significant difference in blood-to-brain [U-^{11}C]glucose transport (with a correction for egress of ^{11}C metabolites) in six patients with well-controlled type 1 diabetes compared with eight nondiabetic controls studied during euglycemia (~6.0 mmol/l) and hypoglycemia (~2.8 mmol/l). They reported the unprecedented finding of significantly lower rates of cerebral glucose metabolism in the patients with type 1 diabetes with their corrected method. Although rates of glucose transport and metabolism were not reported, Eastman et al. (23), also using PET, observed no apparent differences in brain utilization of the fluorinated glucose analog [^{18}F]2-deoxyglucose in four patients with type 2 diabetes compared with nondiabetic control subjects. Finally, using nuclear magnetic resonance and [1-^{13}C]glucose, Novotny et al. (24) found no significant difference in calculated brain glucose concentrations in four patients with well-controlled type 1 diabetes compared with seven nondiabetic control subjects. That method provided no direct measure of blood-to-brain glucose transport or cerebral glucose metabolism. Thus, in the only reported study that examined patients with poorly controlled diabetes, rates of blood-to-brain transport of a glucose analog tended to be reduced (21).

Using a recently developed method (25), we tested the hypothesis that blood-to-brain glucose transport is reduced in people with poorly controlled type 1 diabetes. Blood-to-brain glucose transport and cerebral glucose metabolism were calculated from rate constants derived from blood and brain time-activity curves, the latter determined by PET, after intravenous injection of [1-^{11}C]glucose using a model that includes a fourth rate constant to account for regional egress of all ^{11}C metabolites.

RESEARCH DESIGN AND METHODS

Subjects. Seven patients with type 1 diabetes (four women, three men) with a mean ($\pm$ SD) age of 35 $\pm$ 8 years, a mean BMI of 25.7 $\pm$ 4.8 kg/m^2, and a mean HbA$_{1c}$ of 10.1 $\pm$ 1.2% and nine nondiabetic control subjects (four women and five men) with a mean age of 29 $\pm$ 7 years and a mean BMI of 23.6 $\pm$ 2.0 kg/m^2 were studied. The patients were selected for a HbA$_{1c}$ level of >9.0% on initial screening; for the absence of untreated proliferative retinopathy (funduscopic examination), autonomic neuropathy (cardiovascular reflex tests), and nephropathy (serum creatinine and urine protein); and for the absence of a history of severe hypoglycemia during the year before study. Their mean ($\pm$ SD) duration of diabetes was 20.7 $\pm$ 6.9 years and their mean insulin dose was 33 $\pm$ 5 U/day. All had background retinopathy, but none had proliferative retinopathy. Some had microalbuminuria, but none had urinary protein excretion >300 mg/24 h or a serum creatinine concentration >1.5 mg/dl. All were aware of their hypoglycemic episodes.

This study was approved by the Washington University Human Studies and Radioactive Drug Research Committees and was conducted at the Washington University General Clinical Research Center with the consent of each participating subject.

Protocol. Patients with type 1 diabetes were instructed to avoid hypoglycemia carefully for 3 days prior to the study and were admitted to the center the day before the study. Their plasma glucose concentrations were intentionally held high overnight to preclude hypoglycemia. After an overnight fast, at about 8:00 A.M., the

patients and the nondiabetic control subjects, who arrived at the center that morning, were transferred to the PET suite, positioned in the PET chair, and prepared for study, including insertion of a sampling line in a radial artery. After baseline observations (–30 and 0 min), insulin was infused intravenously (12.0 pmol · kg^{-1} · min^{-1}, 2.0 mU · kg^{-1} · min^{-1}). Plasma glucose concentrations were lowered to ~3.6 mmol/l (~65 mg/dl) and clamped at that level with variable intravenous 20% glucose infusions through 240 min. Plateau glucose levels were achieved by at least 90 min. PET studies (see below) included intravenous [1-^{11}C]glucose injection at 150 min with blood and brain time-activity determinations through 210 min. Blood samples for hormone and metabolic intermediate levels were drawn and symptoms were assessed at 30-min intervals. Heart rate and blood pressure were measured at 15-min intervals.

PET. Blood-to-brain glucose transport and cerebral glucose metabolism were calculated from rate constants derived from blood and brain time-activity curves, the latter determined by PET, after intravenous injection of [1-^{11}C]glucose, using a model that includes a fourth rate constant to account for regional egress of all ^{11}C metabolites (25).

Subjects were positioned in a Siemens ECAT 961 EXACT HR PET scanner (Siemens Medical Systems, Hoffman Estates, IL) such that the head was in the approximate center of the field of view. Individual attenuation measurements were made with [68]Ge-^{68}Ga-rotating rod sources. Emission data were acquired in the 2-D mode. Cerebral blood flow was measured with a 40 s emission scan after rapid intravenous injection of 35–50 mCi of H$_2$[15]O in saline (26,27). Regional cerebral blood volume was measured for 5 min beginning 2 min after brief inhalation of 50–100 mCi of [^{15}O]carbon monoxide (C[15]O) (26,28). During these two studies, arterial blood was withdrawn at 5 ml/min from the radial artery catheter through an extension tube to a lead-shielded scintillation detector. Positron emissions from the arterial blood were counted with 1 s temporal resolution. The blood radioactivity measurements were corrected for delay and dispersion in the catheter using previously determined parameters.

Measurements of blood-to-brain glucose transport and cerebral glucose metabolism were performed after slow intravenous injection of 3–15 mCi of [1-^{11}C]glucose (25). Dynamic PET acquisition was carried out for 1 h. Forty-four separate frames were collected: 16 at 30 s, 8 at 60 s, 16 at 120 s, and 4 at 180 s. During this scan, arterial blood samples of 0.1–0.2 ml were drawn frequently from the arterial catheter. Hematocrits were determined by microcentrifugation. All radiopharmaceuticals were produced in the Washington University School of Medicine cyclotron facility (29,30).

PET images were reconstructed with filtered back projection using the individual attenuation measurements and scatter correction with a ramp filter cut off at the Nyquist frequency to produce images with resolutions of 4.4 mm full-width half-maximum in all three dimensions. Physiological data were calculated for the cerebral hemispheres in the following manner. Individual slice templates were created from the H$_2$[15]O image filtered with a Gaussian filter to resolution of 23 mm full-width half-maximum in all three dimensions. A threshold of 42% of the maximum pixel value in the slice was applied to each slice. Previously, in a study of nine normal subjects with co-registered magnetic resonance images of the brain, we determined that this algorithm accurately identifies the edge of the brain. These individual slice templates were applied to the unfiltered H$_2$[15]O and C[15]O and dynamic [1-^{11}C]D-glucose images for those slices below the superior saggital sinus and above the transverse sinus (as identified from the cerebral blood volume image). Mean pixel values summed over the templated slices were used for calculation of physiological data. [1-^{11}C]Glucose PET time-radioactivity curves were generated from the dynamic PET data using a previously determined conversion factor relating PET radioactivity measurements to blood radioactivity measured by the scintillation counter. PET and arterial whole blood time-activity data were processed using a modified Marquardt parameter estimation routine and a four-compartment model (25). Compartment 1 represents the intravascular compartment of the brain (arterial, capillary, and venous) containing free glucose that can exchange with free glucose in the brain. Compartment 2 represents free glucose in the brain. Compartment 3 represents glucose metabolites in the brain. Compartment 4 represents the vascular space to which metabolites go after they leave the brain. The volume of compartment 1 was fixed equal to the measured cerebral blood volume. In general, five parameters were estimated—four rate constants (k^*_{21}, k^*_{12}, k^*_{32}, and k^*_{43}) and the time shift (T_0). The initial estimate for T_0 was the difference between the arrival of radioactivity at the radial artery and at the brain as determined during the H$_2$[15]O scan by observing the sudden increase in total coincidence events in the head as recorded at 1 s intervals by the scanner. In four cases (two type 1 diabetes and two nondiabetic subjects), no unique solution could be obtained for the five-parameter estimation. In these cases, T_0 was fixed equal to the initial estimate and the four rate constants were estimated. Because the parameter estimation was based on time-radioactivity data from whole blood, we calculated the glucose concentration of whole blood (Glc$_{wb}$) as the plasma glucose concentration (1.00–0.30 $\times$ hematocrit) (31). Implicit in these calculations is the assumption that there exists rapid equilibration between plasma and intra-erythrocyte glucose. This has been demonstrated
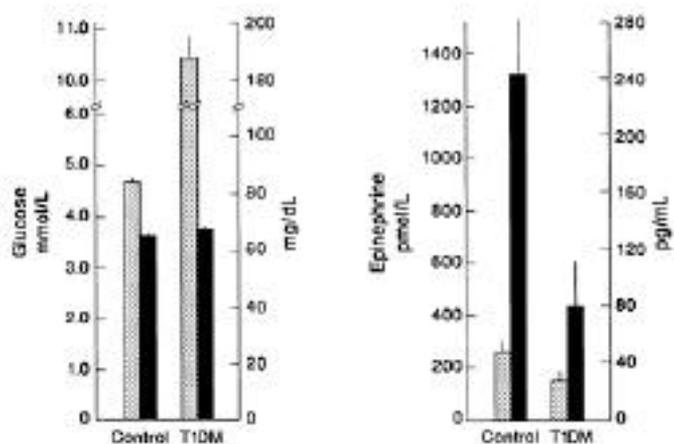
FIG. 1. Mean (± SE) plasma glucose and epinephrine concentrations at baseline (▨) and during hyperinsulinemic, mildly hypoglycemic (3.6 mmol/l) clamps (■) in nondiabetic control subjects and patients with poorly controlled type 1 diabetes (T1DM).

for human blood (32,33). The parameter estimation results were used to calculate the following biological quantities:

$$K_1 = V_1 \cdot k^*_{21} \qquad \text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$$
$$\text{CTXGlc} = K_1 \cdot \text{Glc}_{wb} \qquad \mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$$
$$K = V_1 \cdot (k^*_{21} \cdot k^*_{32})/(k^*_{12} + k^*_{32}) \qquad \text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$$
$$\text{CMRGlc} = K \cdot \text{Glc}_{wb} \qquad \mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$$

Blood-to-brain glucose transport is represented as CTXGlc and cerebral glucose metabolism as CMRGlc.

Other analytical methods. Plasma epinephrine and norepinephrine were measured with a single isotope derivative (radioenzymatic) method (34); and plasma pancreatic polypeptide (35), free insulin (36), C-peptide (36), glucagon (37), growth hormone (38), and cortisol (39) were measured with radioimmunoassays. Plasma glucose was measured with a glucose oxidase method (Beckman Glucose

Analyzer 2); serum nonesterified fatty acids with an enzymatic colorimetric method (40); and blood lactate (41), β-hydroxybutyrate (42), and alanine (43) with enzymatic techniques. Neurogenic and neuroglycopenic symptom scores were determined by asking the subjects to score (from 0, none, to 6, severe) six neurogenic (heart pounding, shaky/tremulous, nervous/anxious, sweaty, hungry, and tingling) and six neuroglycopenic (difficulty thinking/confused, tired/drowsy, weak, warm, faint, and dizzy) symptoms (44).
Statistical analysis. Data are expressed as the means ± SE except where SD is specified. Student's t tests were used to compare data from the two study groups at baseline and during the hyperinsulinemic, mildly hypoglycemic (~3.6 mmol/l) clamps.

RESULTS

Mean (± SE) plasma glucose concentrations were reduced from 4.7 ± 0.1 mmol/l (84 ± 1 mg/dl) at baseline to 3.6 ± 0.0 mmol/l (65 ± 0 mg/dl) during the clamps in the nondiabetic control subjects, and from 10.4 ± 0.3 mmol/l (187 ± 6 mg/dl) at baseline to 3.7 ± 0.1 mmol/l (66 ± 1 mg/dl) during the clamps in the patients with type 1 diabetes (Fig. 1). These glucose reductions caused increments in plasma epinephrine concentrations from 280 ± 50 pmol/l (50 ± 9 pg/ml) to 1,380 ± 340 pmol/l (253 ± 63 pg/ml) in the control subjects, and from 150 ± 30 pmol/l (28 ± 7 pg/ml) to 450 ± 170 pmol/l (82 ± 31 pg/ml) in the patients (Fig. 1). At virtually identical mildly hypoglycemic glucose levels (~3.6 mmol/l), plasma epinephrine levels were significantly (P = 0.0440) lower in the patients with type 1 diabetes.

At baseline, plasma free insulin concentrations were higher (P = 0.0123) in the patients with type 1 diabetes (Table 1), which was as expected because they were receiving insulin peripherally. In the nondiabetic subjects, plasma C-peptide levels were 0.46 ± 0.20 nmol/l at baseline and fell to 0.03 ± 0.00 during the hypoglycemic clamps. C-peptide levels were unmeasurably low (<0.01 nmol/l) in the type 1 dia-

TABLE 1
Plasma insulin, glucagon, pancreatic polypeptide, growth hormone, and cortisol; blood lactate, serum nonesterified fatty acid (NEFA), β-hydroxybutyrate (β-OHB), and alanine; and plasma norepinephrine concentrations, neurogenic and neuroglycopenic symptom scores, heart rates, and systolic and diastolic blood pressures at baseline and during hyperinsulinemic, mildly hypoglycemic (3.6 mmol/l) clamps in nondiabetic control subjects (n = 9) and patients with poorly controlled type 1 diabetes (T1DM) (n = 7)

| Parameter | Baseline (–30 to 0 min) | | | Clamp (120 to 240 min) | | |
	Control subjects	P	Type 1 diabetic subjects	Control subjects	P	Type 1 diabetic subjects
Insulin (pmol/l)	30 ± 5	0.0123	220 ± 50	520 ± 30	0.0120	690 ± 60
Glucagon (pmol/l)	20 ± 2	NS	14 ± 1	26 ± 5	0.0300	12 ± 1
Pancreatic polypeptide (pmol/l)	22 ± 3	NS	17 ± 2	34 ± 9	NS	16 ± 2
Growth hormone (pmol/l)	4.7 ± 3.6	NS	2.9 ± 1.0	18.8 ± 5.1	0.0001	5.1 ± 1.2
Cortisol (nmol/l)	310 ± 60	NS	235 ± 25	410 ± 35	0.0300	300 ± 30
Lactate (μmol/l)	600 ± 75	NS	780 ± 120	950 ± 75	0.0220	710 ± 40
NEFA (μmol/l)	480 ± 75	0.0018	150 ± 25	80 ± 20	NS	65 ± 15
β-OHB (μmol/l)	210 ± 55	NS	110 ± 20	90 ± 10	NS	100 ± 20
Alanine (μmol/l)	315 ± 30	NS	390 ± 55	265 ± 15	NS	275 ± 35
Norepinephrine (nmol/l)	1.21 ± 0.14	NS	1.39 ± 0.21	1.55 ± 0.21	NS	1.65 ± 0.24
Neurogenic symptom score	2.7 ± 0.8	NS	2.5 ± 1.0	4.5 ± 1.3	NS	3.5 ± 1.5
Neuroglycopenic symptom score	2.7 ± 1.0	NS	1.2 ± 0.5	2.7 ± 0.9	NS	2.5 ± 1.1
Heart rate (beats/min)	55 ± 4	0.0120	74 ± 5	72 ± 3	NS	72 ± 5
Systolic blood pressure (mmHg)	138 ± 5	NS	153 ± 7	144 ± 5	NS	163 ± 9
Diastolic blood pressure (mmHg)	71 ± 6	NS	87 ± 7	63 ± 2	NS	74 ± 5

Data are means ± SE. To convert insulin to microunits per milliliter, divide by 6.0; to convert glucagon to picograms per milliliter, divide by 0.2871; to convert pancreatic polypeptide to picograms per milliliter, divide by 0.239; to convert growth hormone to nanograms per milliliter, divide by 44.15; to convert cortisol to micrograms per deciliter, divide by 27.59; and to convert norepinephrine to picograms per milliliter, divide by 0.005911.
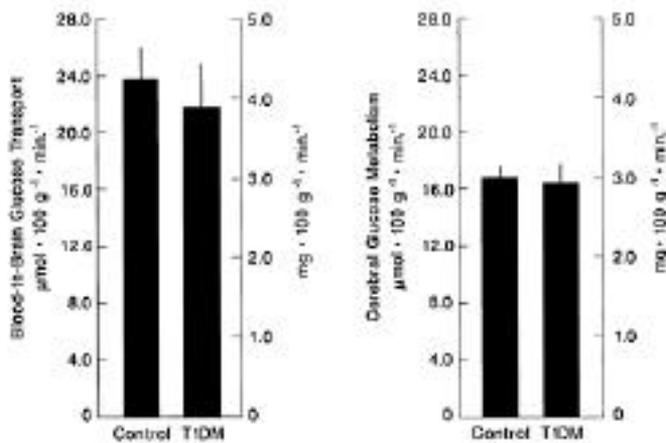
FIG. 2. Mean (± SE) rates of blood-to-brain glucose transport and rates of cerebral glucose metabolism during hyperinsulinemic, mildly hypoglycemic (3.6 mmol/l) clamps in nondiabetic control subjects and patients with poorly controlled type 1 diabetes (T1DM).

FIG. 3. Mean (± SE) rates of cerebral blood flow and cerebral blood volumes during hyperinsulinemic, mildly hypoglycemic (3.6 mmol/l) clamps in nondiabetic control subjects and patients with poorly controlled type 1 diabetes (T1DM).

betic patients. Plasma glucagon, pancreatic polypeptide, growth hormone, and cortisol levels were comparable at baseline in the two groups (Table 1). During the mildly hypoglycemic clamps, glucagon ($P = 0.0300$), growth hormone ($P = 0.0001$), and cortisol ($P = 0.0300$) levels, like the epinephrine levels, were lower, and pancreatic polypeptide levels tended to be lower, in the patients with type 1 diabetes (Table 1). Serum nonesterified fatty acid levels were lower ($P = 0.0018$) at baseline in the patients with type 1 diabetes but were suppressed comparably during the hyperinsulinemic, mildly hypoglycemic clamps (Table 1). Blood β-hydroxybutyrate and alanine levels were similar in the two groups under both conditions (Table 1). Blood lactate levels were similar at baseline but lower ($P = 0.0220$) in the patients with type 1 diabetes during the mildly hypoglycemic clamps (Table 1). Plasma norepinephrine concentrations did not differ between the two groups under either condition, nor did neurogenic or neuroglycopenic symptom scores (Table 1). Aside from higher ($P = 0.0120$) heart rates at baseline in the patients, heart rates, systolic blood pressures, and diastolic blood pressures did not differ between the two groups (Table 1).

Mean (± SE) rates of blood-to-brain glucose transport were 23.7 ± 2.2 µmol · 100 g^{-1} · min^{-1} in the nondiabetic control subjects and 21.6 ± 2.9 µmol · 100 g^{-1} · min^{-1} in the patients with poorly controlled type 1 diabetes ($P = 0.5690$) (Fig. 2) at mean clamped plasma glucose concentrations of 3.6 ± 0.0 and 3.7 ± 0.1 mmol/l, respectively (Fig. 1). There were also no differences in the rates of cerebral glucose metabolism (16.8 ± 0.8 and 16.3 ± 1.2 µmol · 100 g^{-1} · min^{-1}, respectively, $P = 0.693$) (Fig. 2) or cerebral blood flow (60.2 ± 4.8 and 55.3 ± 3.8 ml · 100 g^{-1} · min^{-1} respectively, $P = 0.461$) (Fig. 3) between the two groups. Cerebral blood volume was slightly higher in the nondiabetic control subjects (3.6 ± 0.1 and 3.3 ± 0.1 ml/100 g, respectively, $P = 0.0360$) (Fig. 3). Finally, there was no difference in the ratio of blood-to-brain glucose transport to cerebral glucose metabolism (1.42 ± 0.12 in the controls and 1.31 ± 0.10 in the patients) between the two groups. Calculation of confidence intervals demonstrated that a reduction of blood-to-brain glucose transport in patients with type 1 diabetes of 30% can be excluded with 80% probabil-
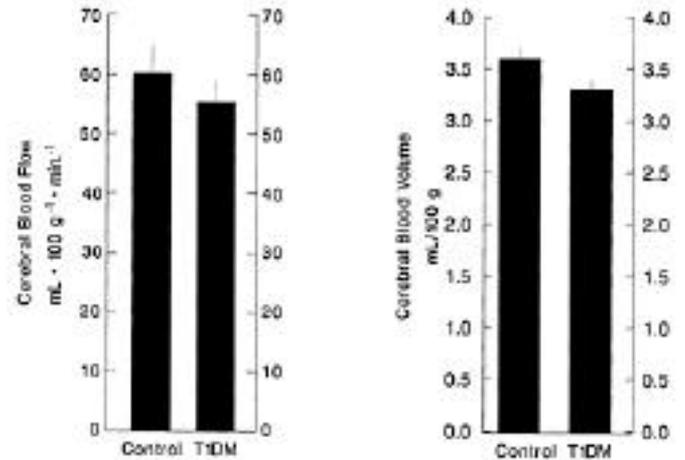
ity, and a reduction of 25% can be excluded with 70% probability. For the ratio of blood-to-brain glucose transport to cerebral glucose metabolism, a reduction of 23% can be excluded with 80% probability, and a reduction of 20% can be excluded with 70% probability.

DISCUSSION

These data demonstrate that blood-to-brain glucose transport and cerebral glucose metabolism are not measurably reduced in patients with poorly controlled type 1 diabetes compared with nondiabetic control subjects all studied at the same, mildly hypoglycemic plasma glucose concentration (~3.6 mmol/l, 65 mg/dl).

We determined rates of blood-to-brain glucose transport and cerebral glucose metabolism with a newly developed PET method using glucose, rather than a glucose analog, and with that glucose labeled with the positron-emitting isotope ^{11}C in the 1-position of the glucose molecule (25). Others have used the glucose analogs [^{11}C]3-*O*-methyl-glucose (21), [^{18}F]2-deoxyglucose (23), or randomly labeled [^{11}C]glucose—the latter method requiring a correction factor for egress of ^{11}C metabolites (22)—and PET to estimate these kinetic parameters; or they used [1-^{13}C]glucose and nuclear magnetic resonance to estimate brain glucose concentrations (24). We also used a mathematical model that includes a fourth rate constant to account for regional egress of ^{11}C metabolites (25). This method has been validated in macaques (25), in which blood-to-brain glucose transport was shown to be related to the arterial plasma glucose extraction by Michaelis-Menten kinetics and net glucose extraction measured with the PET method correlated with that determined by arteriovenous glucose differences.

Although blood-to-brain glucose transport has been estimated in previous studies of people with diabetes (21–23), only that of Brooks et al. (21) specifically examined patients with poorly controlled type 1 diabetes. The rodent data (17–19) suggest that marked chronic hyperglycemia, i.e., poorly controlled diabetes, rather than diabetes per se is associated with decreased blood-to-brain glucose transport. With respect to the hypothesis we tested (blood-to-brain glucose transport is reduced in patients with poorly controlled

type 1 diabetes), the mean absolute rate of blood-to-brain glucose transport reported by Brooks et al. (21) was 18% lower in their patients compared with their control subjects. That apparent difference was not significant statistically with their sample size of four patients and four control subjects, but the data do not refute the hypothesis convincingly. Indeed, from their data it appears that the lower 90% CI would include a reduction of 40%. In a larger sample and using a different method, we found similar rates of blood-to-brain glucose transport in nine nondiabetic control subjects (23.7 ± 2.2 $\mu mol \cdot 100 \ g^{-1} \cdot min^{-1}$) and seven patients with poorly controlled (mean $\pm$ SD HbA_{1c}, $10.1 \pm 1.2\%$) type 1 diabetes ($21.6 \pm 2.9 \ \mu mol \cdot 100 \ g^{-1} \cdot min^{-1}$). This 9% difference in mean values was not statistically significant ($P = 0.569$). Studies in experimental animals with uncontrolled diabetes that have found reduced blood-to-brain glucose transport reported values in the range of 22–33% lower than in control animals (17–19). Based on our data, a difference of that magnitude in chronically hyperglycemic humans can be excluded with 70–80% confidence. Thus, we conclude that blood-to-brain glucose transport is not measurably reduced in poorly controlled type 1 diabetes.

We also found similar rates of cerebral glucose metabolism in nondiabetic control subjects and patients with poorly controlled type 1 diabetes (16.8 ± 0.8 and $16.3 \pm 1.2 \ \mu mol \cdot 100 \ g^{-1} \cdot min^{-1}$, $P = 0.693$, respectively). This finding differs from that of Gutniak et al. (22), who reported significantly reduced (by 29% during euglycemia) rates of cerebral glucose metabolism in their patients with well-controlled type 1 diabetes. It is perhaps relevant that the latter investigators used a [U-^{11}C]glucose PET method, which does not account adequately for egress of labeled ^{11}C metabolites (22). On the basis of the present data, we conclude that cerebral glucose metabolism is also not measurably reduced in patients with poorly controlled type 1 diabetes.

The absolute rates of cerebral glucose metabolism (e.g., $16.8 \pm 0.8 \ \mu mol \cdot 100 \ g^{-1} \cdot min^{-1}$ in nondiabetic control subjects) reported here are lower than the usually reported normal whole-brain values of about 25 to 29 $\mu mol \cdot 100 \ g^{-1} \cdot min^{-1}$ based on the Kety-Schmidt technique (45). However, Madsen et al. (46) have pointed out that the Kety-Schmidt technique overestimates cerebral glucose metabolism. Furthermore, we based our measurements on whole-blood, rather than plasma, glucose concentrations, which reduces arteriovenous differences by 10–12%. Also, the contribution of cerebrospinal fluid reduces calculated whole hemisphere values by 5–10% (47). Finally, we performed our PET measurements at clamped plasma glucose concentrations of ~3.6 mmol/l, the plasma glucose concentration at which the Kety-Schmidt data of Boyle et al. (48) indicate that glucose metabolism is decreased, presumably because glucose transport becomes limiting to brain glucose metabolism. This glucose level also approximates the glycemic thresholds for neuroendocrine responses to hypoglycemia (3–5) in normal humans. Indeed, several such responses were elicited in the present study.

The relationship between blood-to-brain glucose transport and cerebral glucose metabolism is perhaps most relevant biologically. At clamped plasma glucose levels of ~3.6 mmol/l, the ratios of glucose transport to brain glucose metabolism approached unity but, again, there was no significant difference ($P = 0.520$) between the nondiabetic control subjects and the patients with poorly controlled type 1 diabetes.

Because recent antecedent hypoglycemia might increase blood-to-brain glucose transport (1,17,48), we instructed our patients with poorly controlled type 1 diabetes to make every effort to avoid hypoglycemia for 3 days before their admission and intentionally held their plasma glucose concentrations high during the day and through the night before study. As a result, baseline glucose levels were higher in the patients than in the control subjects (10.4 ± 0.3 vs. 4.7 ± 0.1 mmol/l, respectively). Glucose levels were then lowered to ~3.6 mmol/l over <90 min and held at that level through 240 min, with the PET measurements started at 150 min to allow ample time (at least 60 min) for glucose equilibration. We think it most unlikely that the greater absolute reductions in plasma glucose obliterated pre-existing reduced blood-to-brain glucose transport rates in the patients, because hypoglycemia did not occur and the time interval between initiation of glucose-lowering and the measurements (2 1/2 to 3 1/2 h) was much shorter than that required for hypoglycemia to increase blood-to-brain glucose transport (days) in rodents (17) and humans (48). Finally, our data do not allow us to exclude decreased blood-to-brain glucose transport in discrete areas of the brain (e.g., the hypothalamus). However, the rodent data that provided the premise of the hypothesis that we tested (17–19) used measures of global brain glucose uptake.

During hypoglycemia, the plasma concentrations of the key glucose counterregulatory hormones glucagon and epinephrine were significantly lower in the patients with type 1 diabetes than in the control subjects. Although glycemic thresholds for several responses to falling glucose levels, including the epinephrine response, are shifted to higher-than-normal plasma glucose concentrations in patients with poorly controlled type 1 diabetes (1,6,7), an absent pancreatic α-cell glucagon response and a reduced adrenomedullary epinephrine response to a given level of hypoglycemia are the rule in established (C-peptide negative) type 1 diabetes (1,6,7,12–16). The lower blood lactate levels observed in the patients might well have been a biological reflection of the lower plasma epinephrine levels. The plasma cortisol response to hypoglycemia was also reduced in the patients, implying a reduced pituitary adrenocorticotropin response. The pituitary growth hormone response was also reduced. Finally, the plasma pancreatic polypeptide response, a marker of the parasympathetic nervous system response to hypoglycemia, tended to be reduced in the patients.

We tested the hypothesis that blood-to-brain glucose transport is decreased in patients with poorly controlled type 1 diabetes. We did not test the converse hypothesis that blood-to-brain glucose transport is increased in patients with well-controlled (and thus frequently hypoglycemic) type 1 diabetes (1,9,11). Nonetheless, given the similar blood-to-brain glucose transport rates under the conditions of the present study, increased blood-to-brain glucose transport cannot explain the observed reduced counterregulatory hormone (e.g., epinephrine) response to mild hypoglycemia (3.6 mmol/l) in these patients with type 1 diabetes. Clearly, this second hypothesis requires direct examination.

With a mean blood glucose of approximately 250 mg/dl, estimated from their HbA_{1c} levels (49), the insulin-treated patients with type 1 diabetes we studied were undoubtedly less hyperglycemic than the diabetic rodents studied earlier (17–19). Furthermore, one could suggest that, despite efforts to avoid them, episodes of antecedent hypoglycemia might

have occurred and negated an effect of hyperglycemia to decrease blood-to-brain glucose transport. In any event, the present data indicate that neither blood-to-brain glucose transport nor cerebral glucose metabolism is measurably reduced in people with poorly controlled type 1 diabetes.

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