0021-972X/01/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 86, No. 5
Printed in U.S.A.

Blood-Brain Barrier Transport and Brain Metabolism of Glucose during Acute Hyperglycemia in Humans*

STEEN G. HASSELBALCH, GITTE M. KNUDSEN, BRUNELLA CAPALDO, ALFREDO POSTIGLIONE, AND OLAF B. PAULSON

Neurobiology Research Unit, Department of Neurology, and the PET and Cyclotron Unit, University Hospital, Rigshospitalet (S.G.H., G.M.K., O.B.P.), DK-2100 Copenhagen, Denmark; and Institute of Internal Medicine and Metabolic Diseases, Universita Degli Studi Di Napoli Federico II (B.C., A.P.), 80131 Naples, Italy

ABSTRACT

It is controversial whether transport adaptation takes place in chronic or acute hyperglycemia. Blood-brain barrier glucose permeability and regional brain glucose metabolism (CMR_{glc}) was studied in acute hyperglycemia in six normal human subjects (mean age, 23 yr) using the double indicator method and positron emission tomography and [^{18}F]fluorodeoxyglucose as tracer. The Kety-Schmidt technique was used for measurement of cerebral blood flow (CBF). After 2 h of hyperglycemia (15.7 ± 0.7 mmol/L), the glucose permeability-surface area product from blood to brain remained unchanged (0.050 ± 0.008 *vs.* 0.059 ± 0.031 mL/100 g·min). The unidirectional clearance of [^{18}F]fluorodeoxyglucose (K_1*) was reduced from 0.108 ± 0.011 to 0.061 ± 0.005 mL/100 g·min ($P < 0.0004$). During hyperglycemia, global CMR_{glc} remained constant (21.4 ± 1.2 *vs.* 23.1 ± 2.2 μmol/100 g·min, normo- and hyperglycemia, respectively). Except for a significant increase in white matter CMR_{glc}, no regional difference in CMR_{glc} was found. Likewise, CBF remained unchanged.

The reduction in K_1* was compatible with Michaelis-Menten kinetics for facilitated transport. Our findings indicate no major adaptational changes in the maximal transport velocity or affinity to the blood-brain barrier glucose transporter. Finally, hyperglycemia did not change global CBF or CMR_{glc}. (*J Clin Endocrinol Metab* **86:** 1986–1990, 2001)

UNDER NORMAL physiological conditions, glucose is the major metabolic fuel in the brain, and therefore, adequate glucose supply is essential for the maintenance of cerebral energy production. Experimental and human data support the idea that a sustained decrease in blood glucose for several days induces an increase in blood-brain barrier (BBB) transport capacity (1–3). Conversely, experimental studies have indicated that chronic hyperglycemia may down-regulate glucose transport and thereby protect the brain from excessive high brain glucose concentrations (4–7). Other experimental studies have failed to confirm the down-regulation of glucose transport in both acute and chronic hyperglycemia (8, 9). Pelligrino and co-workers (2) found evidence for an increase in BBB transport in chronic hyperglycemia. Very few human studies on BBB glucose transport during hyperglycemia are available (10–12), and to date, no studies during acute hyperglycemia have been performed in humans. Excessive amounts of glucose in the brain tissue may lead to additional cell damage after acute stroke (13); therefore, it is of importance to clarify whether the human brain possesses adaptational mechanisms that down-regulate BBB glucose transport within minutes to hours, possibly protecting the brain in case of acute increases in glucose.

Received November 6, 2000. Revision received January 18, 2001. Accepted February 5, 2001.

Address all correspondence and requests for reprints to: Steen G. Hasselbalch, M.D., Neurobiology Research Unit, Building 9201, National University Hospital, Rigshospitalet, 9 Blegdamsvej, DK-2100 Copenhagen Ø, Denmark. E-mail: sgh@pet.rh.dk.

* This work was supported by grants from the Lundbeck Foundation, the Danish Medical Research Council, the Foundation of 17-12-1981, and the Simon F. Hartmann Family Foundation.

Using the iv double indicator method, we studied BBB glucose transport during acute hyperglycemia. Furthermore, we studied the regional cerebral glucose metabolism ($rCMR_{glc}$) before and during acute hyperglycemia using positron emission tomography with [^{18}F]fluorodeoxyglucose as the tracer (PET-FDG). The questions to be addressed were the following. Does BBB glucose transport change during acute hyperglycemia? Is CMR_{glc} affected by marked acute elevations in blood glucose levels?

Materials and Methods

Six healthy subjects (mean age, 23 yr; range, 20–27 yr; five men and one woman) were studied. Informed consent was obtained from the subjects after the investigational program was explained, and the study was conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the ethic committee system in Denmark.

Under local analgesia, catheters were inserted percutaneously low on the neck into the internal jugular vein, in the radial artery, and in two antecubital veins as previously described (3). BBB transport of glucose was studied twice during hyperglycemia using the double indicator method; one measurement was performed approximately 15 min after a constant level of hyperglycemia had been obtained, and the other was performed after 2 h of steady state hyperglycemia. Due to technical difficulties, BBB permeability could not be determined in one subject. BBB permeability during hyperglycemia was compared with BBB permeability studied in a normoglycemic control group of age-matched subjects (3). Regional CMR_{glc} was studied twice with PET-FDG in the same subject on 2 separate days: in a normoglycemic control condition and in a hyperglycemic condition.

Hyperglycemic clamp

The hyperglycemic, normoinsulinemic clamp was induced by a constant iv infusion of somatostatin (0.6 mg/kg·h) and insulin (0.15 mIU/kg·min), dissolved in isotonic saline, and infused in an antecubital vein

by two separate pumps at the rate of 10 mL/h. The desired plasma glucose level of approximately 15 mmol/L was reached within 45–85 min by a variable infusion of 20% glucose, and plasma glucose was clamped at this level.

In the control condition, somatostatin and insulin were infused at the same rate as during the hyperglycemic condition, and plasma glucose was kept constant by a variable infusion of 20% glucose.

BBB permeability measurements

The iv double indicator method was used for estimation of BBB transfer variables. The iv approach was developed in our laboratory and has been described in detail previously (14). In brief, a 5- to 10-mL bolus containing the test substance [7 megabecquerels (MBq) [^{3}H]glucose] and three BBB-impermeable reference substances [7 MBq $^{24}Na^+$, 40 MBq [^{99m}Tc]diethylenetriamine pentaacetic acid ([^{99m}Tc]DTPA), and 0.4 MBq $^{36}Cl^-$] was injected iv through an antecubital catheter. Starting 2–3 s before injection, 1-mL blood samples were continuously collected from the radial artery and jugular vein for 50 s by means of a sampling machine (Ole Dich Instrumentmakers, Hvidovre, Denmark) at a fixed interval of 1.3 s. Blood samples were centrifuged, and after at least 3 weeks 3 mL scintillation fluid (Picofluor 40, Packard, Downers Grove, IL) was added to 300-μL plasma samples, and β-emission was counted (Packard PA 800-CA) with spillover and quench corrections by external standardization.

To correct for differences in the brain input of test and reference substances due to iv injection, a five-parameter Dirac impulse response for passage through the cerebrovascular bed was computed from the input and output of the reference substance. This response was then combined with the single membrane (well mixed) model of the brain (14) and convolved with the arterial input curve of the test substance to yield a theoretical test output curve, which was iteratively compared with the actual test output curve. When cerebral blood flow (CBF) was known, the model variables could be obtained by minimizing the sum of square of the differences between the theoretical and the measured outflow test curve by means of the simplex method. CBF was measured using the Kety-Schmidt technique for measurement of global CBF as previously described (15).

Estimates for the following parameters were obtained: PS_1, the permeability surface area product from the blood to the brain, and E, the average unidirectional extraction. PS_2/V_e, the PS product from the brain to the blood divided by the tracer distribution space was usually also obtained, but in hyperglycemia, PS_2 approached zero, and values are not reported here. The unidirectional clearance, K_1, was calculated from E $\times$ CBF. In application of the iv double indicator technique, it is assumed that the iv injected bolus mixes completely with blood before arrival at the brain capillaries, so that systemically measured arterial blood substrate concentrations equal those of the brain capillaries. This assumption seems acceptable because the bolus must pass through the venous system to the heart and the lungs before arriving at the carotid artery, and during this long passage it is likely that the bolus completely mixes with systemic blood. In a previous study this has also been experimentally verified (3).

Determination of CMR_{glc} by PET-FDG

We used a PC4096+pet camera (General Electric Medical Systems, Milwaukee, WI) yielding 15 consecutive slices with a slice thickness of 6.7 mm and a spatial resolution in the image plane of 6.7 mm. Slices were placed parallel to the canthomeatal line (CM line: a line through the lateral canthus of the eye and the external meatus of the ear) with midslice planes from approximately 10–103 mm above the CM line. After placement of the subject in the scanner, a transmission scan was performed immediately before the activity scan for attenuation correction. At the start of the scanning, 185–210 MBq FDG in 10 mL saline were injected as a bolus over 20 s through an antecubital catheter followed by 5–10 mL saline at the same infusion rate. One-milliliter blood samples were drawn simultaneously from the jugular vein and the radial artery at 10-s intervals from 0–3 min, at 20-s intervals from 3–5 min, at 1-min intervals from 5–10 min, at 2-min intervals from 10–20 min, and at 5-min intervals for the rest of the scanning period. FDG blood samples were immediately placed one ice and centrifuged, and 500 μL plasma were taken for γ-counting (COBRA 5003, Packard Instruments, Downers Grove, IL). Dynamic scanning was started at time zero with the following scan sequence: 10 6-s scans (0–1 min), 3 20-s scans (1–2 min), 8 1-min scans (2–10 min), 5 2-min scans (10–20 min), and 8 5-min scans (20–60 min). Regional CMR_{glc} was calculated pixel by pixel from the time-activity curves in brain and blood using the Patlak Plot method supplied with the standard GE 4096 software. The absolute time interval from 10–45 min was used to calculate the net clearance of FDG (K*). The transfer coefficients for FDG BBB transport (K_1* and k_2*, inward and outward transports, respectively) and phosphorylation (k_3*) were estimated as described by Sokoloff and co-workers (16). CMRglc was calculated from $CMR_{glc} = (C_p/LC) \times K^*$, where C_p is the mean plasma glucose concentration during the scan period, LC is the FDG lumped constant, and K* is the slope of the Patlak plot described above. LC was calculated as $LC = (k_3^*/k_3) + ((K_1^*/K_1) - (k_3^*/k_3))\,(K^*/K_1^*)$ (17), where the transport coefficient (K1*/K1) was set at 1.48, and the phosphorylation coefficient (k_3^*/k_3) was set at 0.39 (15, 18).

Mean CMR_{glc} values for several cortical and subcortical regions were determined using a computerized brain atlas (19). With this software, the last scan in the dynamic sequence (55–60 min) was resliced by linear and nonlinear transformation into standard brain slices, and slices from approximately 50–90 mm above the CM line were used for the regional analysis. Global CMR_{glc} was calculated from whole slice regions of interest weighted with their area corrected for 2.5% cerebrospinal fluid space (20).

Determination of CBF

Global CBF was measured by the Kety-Schmidt technique (21) in the desaturation mode, using ^{133}Xe as the flow tracer. Cerebral venous blood and arterial blood were sampled from the internal jugular vein and the radial artery, respectively, as previously described in detail (22). In brief, the brain was saturated by an iv infusion of ^{133}Xe dissolved in saline at a constant rate of approximately 15 MBq/min for 30 min. Blood samples were obtained at -2, -1, 0, 0.5, 1, 2, 3, 4, 6, 8, and 10 min, where 0 denotes the time when the infusion was terminated and placed in sealed vials for counting in a well counter (COBRA 5003, Packard Instrument). The measured CBF values were corrected for the systematic overestimation of flow values due to incomplete tracer washout at the end of the measurement period (22). Assuming a constant rate of cerebral oxygen metabolism during the experiment, CBF was corrected to the time of the BBB measurements as previously described (18).

Results

BBB parameters

During hyperglycemia, glucose was infused at a mean rate of 125 mL/h (range, 54–275 mL/h), and the plasma glucose concentration increased to a mean steady state level of 15.5 $\pm$ 0.7 mmol/L. CBF measured during acute hyperglycemia was 47.3 $\pm$ 5.8 mL/100 g·min. No significant differences in any of the measured BBB parameters or in the unidirectional influx were observed between the first and second BBB measurements (Table 1). The mean unidirectional clearance of FDG (K_1*) obtained by dynamic PET decreased by 45% from 0.110 $\pm$ 0.013 in normoglycemia to 0.061 $\pm$ 0.006 in hyperglycemia ($P < 0.0002$, by paired t test; Table 2).

Cerebral glucose metabolism

Regional CMR_{glc} was measured in several cortical and subcortical regions (Table 2). CMR_{glc} was significantly increased in white matter in centrum semiovale, whereas glucose metabolism in cortical, and subcortical gray matter regions remained unchanged. Despite the changes in white matter glucose metabolism, global CMR_{glc} was constant in hyperglycemia (Table 3).

TABLE 1. BBB permeability for glucose measured with the double indicator method

	Hyperglycemia, 15 min (n = 5)	Hyperglycemia, 126 min (n = 5)	Normoglycemia (n = 8)	*P*
Plasma glucose (mmol/L)	15.3 ± 0.6 [14.8–15.8]	15.1 ± 0.6 [14.6–15.6]	5.4 ± 0.9 [4.6–6.0]	
PS_1	0.050 ± 0.008 [0.042–0.057]	0.059 ± 0.031 [0.032–0.086]	0.076 ± 0.010 [0.069–0.083]	NS
E	0.095 ± 0.011 [0.085–0.105]	0.112 ± 0.052 [0.066–0.158]	0.159 ± 0.029 [0.138–0.180]	0.012
K_1	0.047 ± 0.008 [0.040–0.054]	0.055 ± 0.027 [0.032–0.079]	0.066 ± 0.011 [0.044–0.087]	NS
J_{in}	0.758 ± 0.132 [0.642–0.873]	0.885 ± 0.434 [0.504–1.266]	0.407 ± 0.098 [0.339–0.475]	0.027

Values are the mean ± SD. Values in *brackets* are the 95% confidence intervals. Normoglycemic values are taken from an age-matched control group (3). PS_1 (milliliters per 100 g/min), permeability-surface area products for transport of glucose from blood to brain determined from double indicator experiments; E, unidirectional extraction fraction from blood to brain (fraction); J_{in}, unidirectional clearance from blood to brain (micromoles per 100 g/min) calculated as plasma glucose concentration times PS_1.

TABLE 2. Global FDG transfer coefficients and lumped constant measured by dynamic PET-FDG

	Normoglycemia	Hyperglycemia	*P*
K_1* (mL/100g·min)	0.110 ± 0.013	0.061 ± 0.006	<0.0002
k_2* (min^{-1})	0.151 ± 0.026	0.161 ± 0.022	NS
k_3* (min^{-1})	0.097 ± 0.034	0.032 ± 0.003	0.01
V_p (%)	4.5 ± 0.4	4.3 ± 0.5	NS
K* (mL/100 g·min)	0.042 ± 0.007	0.010 ± 0.001	<0.0002
LC	0.81 ± 0.06	0.57 ± 0.02	<0.0005

Values are the mean ± SD (n = 6). K_1*, k_2*, k_3*, Transfer coefficients for FDG [K_1*, unidirectional clearance from blood to brain; k_2*, fractional clearance from brain to blood; k_3*, fractional rate of phosphorylation; V_p, plasma volume in brain; K*, net clearance of FDG (K_1* × k_3*)/(k_2* + k_3*), determined from dynamic PET-FDG; LC, lumped constant determined from LC = (k_3*/k_3) + ((K_1*/K_1) − (k_3*/k_3)] (K*/K_1*) (17), where the transport coefficient (K_1*/K_1) was set at 1.48, and the phosphorylation coefficient (k_3*/k_3) was set at 0.39 (15, 18).

Discussion

BBB transport of glucose

No significant differences were found between the two BBB permeability studies performed at the start and at the end of the hyperglycemic clamp, suggesting that BBB glucose transport capacity does not change within hours of acute hyperglycemia. It should be noted that the acute hyperglycemic condition used in the present study was unphysiological in the sense that insulin secretion was suppressed to control for other variables during the study. Because of the small number of subjects and the variation in the data, the possibility of a type 2 error must also be considered. Further, variation in the data could have been induced by the use of a separate control group. On the other hand, the absolute value for PS_1 during acute hyperglycemia was fully compatible with that obtained from literature values for Michaelis-Menten parameters. Using mean values from Ref. 23 for T_{max} (maximal transport velocity) and K_t (the half-saturation constant), and assuming K_d to be 0.01 mL/100 g·min, the excepted value for PS_1 calculated on the basis of T_{max} and K_t was not significantly different from the determined PS_1 at 2 h of hyperglycemia (0.042 ± 0.001 *vs.* 0.059 ± 0.032 mL/100 g·min; $P > 0.05$, by paired *t* test).

BBB transport of FDG obtained with PET (K_1*) decreased by 45% compared with normoglycemia. Because BBB hexose transport follows Michaelis-Menten kinetics for facilitated diffusion, increases in blood glucose induce a decrease in K1* because of the competitive inhibition of the glucose transporter. The PS_1 obtained during hyperglycemia by the double indicator method in the present study was, however, not significantly different from PS_1 values previously obtained in normoglycemia [0.076 ± 0.010 mL/100 g·min (3)]. We ascribe the discrepancy in the unchanged PS_1 values and the decrease in K_1* to the fact that the sample size was small. Although Michaelis-Menten parameters for glucose BBB transport were not determined in this study, the decrease in K1* could be fully explained by the increase in blood glucose without implying changes in the Michaelis-Menten parameters. We acknowledge, however, that this negative conclusion is inferred from previous data and should be corroborated in future studies, in which other methods may allow for repeated measurements, *i.e.* functional magnetic resonance

TABLE 3. CMR_{glc} measured by PET-FDG

Region of interest	Normoglycemia (n = 6)	Hyperglycemia (n = 6)	Difference (%)	*P*
Frontal cortex	27.1 ± 1.9	27.1 ± 2.8	0	NS
Temporal cortex	25.2 ± 1.4	26.1 ± 2.6	+4	NS
Parietal cortex	25.8 ± 1.9	25.5 ± 2.7	−1	NS
Occipital cortex	23.6 ± 1.5	24.7 ± 3.4	+4	NS
Nucleus caudatus	25.8 ± 1.4	25.0 ± 4.3	−3	NS
Putamen	27.6 ± 2.0	26.0 ± 2.5	−6	NS
Thalamus	25.4 ± 2.3	24.8 ± 4.1	−2	NS
Hippocampus	16.9 ± 1.9	18.4 ± 3.9	+9	NS
Centrum semiovale	11.7 ± 1.2	16.5 ± 2.0	+42	0.005
Global	21.4 ± 1.2	23.1 ± 2.2	+8	NS

Values are in micromoles per 100 g/min (mean ± SD). Regional values are weighted mean values derived from several slices (50–90 mm above the CM line). Global CMR_{glc} is calculated from whole slice roi values corrected for 2.5% CSF space, as described in *Materials and Methods*. The statistical test was the paired *t* test; $P < 5\%$ was considered significant.

(24). No other studies in humans have to date confirmed our findings in acute hyperglycemia. Studies performed in diabetic subjects have not shown changes in BBB glucose transport: With [*methyl*-^{11}C]glucose and PET, Brooks and co-workers (10) studied glucose transport in four diabetic subjects and found no changes in BBB parameters during normoglycemia and chronic hyperglycemia compared with normal controls. In accordance with these results, using [^{11}C]glucose and PET, Gutniak and co-workers (11) demonstrated no differences in unidirectional glucose clearances from blood to brain in six insulin-dependent diabetic subjects or in control subjects. Finally, Fanelli and co-workers found BBB transport unchanged in poorly controlled diabetic subjects compared with that in normal subjects (12). In two experimental studies in rats, BBB glucose transport was evaluated during acute hyperglycemia and was unchanged (8, 9). Thus, although experimental data for glucose transport during acute hyperglycemia are scarce, the findings are in agreement with the present results. However, the possibility that the negative conclusion of the present study was due to a small number of subjects and variation in the data must be borne in mind.

The unidirectional influx of glucose increased during hyperglycemia (J_{in}), but as the net uptake of glucose remained unchanged, the glucose efflux from the brain must have increased as well. The physiological significance of this presumed increase in glucose flux across the BBB remains unclear.

Cerebral glucose metabolism

CMR_{glc} measured by PET-FDG was unchanged during acute hyperglycemia. The estimation of CMR_{glc} by PET-FDG depends on the lumped constant, LC, which is the conversion factor between FDG and glucose net uptake. LC decreases during hyperglycemia because of changes in the brain distribution volumes of glucose and FDG (25, 26). In line with this observation, we found a 30% decrease in LC during hyperglycemia. We calculated LC directly from the FDG transfer coefficients and found a value of 0.81 in normoglycemia, which is higher than the standard value of 0.52 normally applied in human PET-FDG (27). Direct estimation of LC from global net uptake of FDG and glucose suggests, however, that this value is considerably underestimated, and the value of 0.81 agrees with previously obtained values for LC in our laboratory (15). The calculation of LC depends on the assumption that the transport and phosphorylation coefficients are constant with changes in blood glucose concentration and, further, that they are uniform throughout the brain tissue. Both assumptions have been verified for the transport coefficient (18), and it is reasonable to assume that they are also valid for the phosphorylation coefficient, as previously argued by Sokoloff and co-workers (16). Thus, we conclude that CMR_{glc} did not change during acute hyperglycemia, and experimental studies support this conclusion; using the deoxyglucose method in rats, Orzi and co-workers (28) and Brøndsted and Gjedde (29) found no change in CMR_{glc} during acute hyperglycemia. Likewise, using labeled glucose in rats, Duckrow and co-workers could not demonstrate changes in CMR_{glc} during acute hyperglycemia (8). No studies of brain glucose metabolism during acute hyperglycemia have been performed in humans. In poorly controlled diabetic subjects, CMR_{glc} has been found to be unchanged, suggesting that chronic elevated blood glucose levels do not change CMR_{glc} (12), in line with our observations in acute hyperglycemia.

The regional analysis of CMR_{glc} surprisingly showed that white matter CMR_{glc} increased during hyperglycemia. At present, we have no explanation for this finding, which should be corroborated in future studies.

Cerebral blood flow

In experimental studies both acute and chronic hyperglycemia have been found to be associated with a decrease in CBF (30–32). This flow reduction could not be explained by changes in CMR_{glc} (30). The decreased CBF has been suggested to have significant pathophysiological consequences in experimental hyperglycemia, and if these findings apply to humans, they may further increase the ischemic brain damage in hyperglycemic stroke patients. In the present study the mean CBF value of 47.3 ± 5.8 mL/100 g·min was identical to previously obtained values in normoglycemia (15, 22). Studies in humans also found no change in CBF in poorly controlled diabetes (12), suggesting that neither acute nor chronic hyperglycemia *per se* induces major changes in CBF.

Acknowledgments

We thank the technicians Karin Stahr and Gerda Thomsen for valuable help. The John and Birthe Meyer Foundation is gratefully acknowledged for the donation of the Cyclotron and PET scanner.

References

1. **Christensen TG, Diemer NH, Laursen H, Gjedde A.** 1981 Starvation accelerates blood-brain glucose transfer. Acta Physiol Scand. 112:221–223.
2. **Pelligrino DA, Segil LJ, Albrecht RF.** 1990 Brain glucose utilization and transport and cortical function in chronic vs. acute hypoglycemia. Am J Physiol. 259:E729–E735.
3. **Hasselbalch SG, Knudsen GM, Jakobsen J, Hageman LP, Holm S, Paulson OB.** 1995 Blood brain barrier permeability of glucose and ketone bodies during short-term starvation in humans. Am J Physiol. 268:E1161—E1166.
4. **Gjedde A, Crone C.** 1981 Blood-brain glucose transfer: repression in chronic hyperglycemia. Science. 214:456–457.
5. **McCall AL, Millington WR, Wurtman RJ.** 1982 Metabolic fuel and amino acid transport into the brain in experimental diabetes mellitus. Proc Nat Acad Sci USA. 79:5406–5410.
6. **Pardridge WM, Triguero D, Farrell CR.** 1990 Downregulation of blood-brain barrier glucose transporter in experimental diabetes. Diabetes. 39:1040–1044.
7. **Mooradian AD, Morin AM.** 1991 Brain uptake of glucose in diabetes mellitus: the role of glucose transporters. Am J Med Sci. 301:173–177.
8. **Duckrow RB, Bryan RMJ.** 1987 Regional cerebral glucose utilization during hyperglycemia. J Neurochem. 48:989–993.
9. **Harik SI, Gravina SA, Kalaria RN.** 1988 Glucose transporter of the blood-brain barrier and brain in chronic hyperglycemia. J Neurochem. 51:1930–1934.
10. **Brooks DJ, Gibbs JS, Sharp P, et al.** 1986 Regional cerebral glucose transport in insulin-dependent diabetic patients studied using [11C]3-*O*-methyl-D-glucose and positron emission tomography. J Cereb Blood Flow Metab. 6:240–244.
11. **Gutniak M, Blomqvist G, Widén L, Stone-Elander S, Hamberger B, Grill V.** 1990 D-[U-^{11}C]glucose uptake and metabolism in the brain of insulin dependent diabetic subjects. Am J Physiol. 258:E805–E812.
12. **Fanelli CG, Dence CS, Markham J, Videen TO, Paramore DS, Cryer PE, Powers WJ.** 1998 Blood to brain glucose transport and cerebral glucose metabolism are not reduced in poorly controlled type 1 diabetes. Diabetes. 9:1444–1450.
13. **Kushner M, Nencini P, Reivich M, et al.** 1990 Relation of hyperglycemia early in ischemic brain infarction to cerebral anatomy, metabolism, and clinical outcome. Ann Neurol. 28:129–135.
14. **Knudsen GM.** 1994 Application of the double-indicator technique for measurement of blood-brain barrier permeability in humans. Cerebrovasc Brain Metab Rev. 6:1–30.
15. **Hasselbalch SG, Madsen PL, Knudsen GM, Holm S, Paulson OB.** 1998 Calculation of the FDG lumped constant by simultaneous measurements of global glucose and FDG metabolism in humans. J Cereb Blood Flow Metab. 18:154–160.
16. **Sokoloff L, Reivich M, Kennedy C, et al.** 1977 The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem. 28:897–916.
17. **Kuwabara H, Evans AC, Gjedde A.** 1990 Michaelis-Menten constraints improved cerebral glucose metabolism and regional lumped constant measurements with [18F]fluorodeoxyglucose. J Cereb Blood Flow Metab. 10:180–189.
18. **Hasselbalch SG, Knudsen GM, Holm S, et al.** 1996 Transport of D-glucose and 2-fluorodeoxyglucose across the blood- brain barrier in humans. J Cereb Blood Flow Metab. 16:659–666.
19. **Greitz T, Bohm C, Holte S, Eriksson L.** 1991 A computerized brain atlas: construction, anatomical content, and some applications. J Comp Assisted Tomography. 15:26–38.
20. **Schwartz M, Creasey H, Grady CL.** 1985 Computed tomographic analysis of brain morphometrics in 30 healthy men, aged 21 to 81 years. Ann Neurol. 17:146–157.
21. **Kety SS, Schmidt CF.** 1948 The nitrous oxide method for quantitative determinations of cerebral blood flow in man: theory, procedure, and normal values. J Clin Invest. 27:476–483.
22. **Madsen PL, Hasselbalch SG, Hagemann LP, et al.** 1995 Persistent resetting of the cerebral oxygen/glucose uptake ratio by brain activation: evidence obtained with the Kety-Schmidt technique. J Cereb Blood Flow Metab. 15:485–491.
23. **Blomqvist G, Gjedde A, Gutniak M, et al.** 1991 Facilitated transport of glucose from blood to brain in man and the effect of moderate hypoglycaemia on cerebral glucose utilization. Eur J Nucl Med. 18:834–837.
24. **Gruetter R, Novotny EJ, Boulware SD, Rothman DL, Shulman RG.** 1996 1H NMR studies of glucose transport in the human brain. J Cereb Blood Flow Metab. 16:427–438.
25. **Schuier F, Orzi F, Suda S, Lucignani G, Kennedy C, Sokoloff L.** 1990 Influence of plasma glucose concentration on lumped constant of the deoxyglucose method: effects of hyperglycemia in the rat. J Cereb Blood Flow Metab. 10:765–773.
26. **Dienel GA, Cruz NF, Mori K, Holden JE, Sokoloff L.** 1991 Direct measurement of the λ of the lumped constant of the deoxyglucose method in rat brain: determination of lambda and lumped constant from tissue glucose concentration or equilibrium brain/plasma distribution ratio for methylglucose. J Cereb Blood Flow Metab. 11:25–34.
27. **Reivich M, Alavi A, Wolf A, et al.** 1985 Glucose metabolic rate kinetic model parameter determination in humans: the lumped constants and rate constants for [^{18}F]fluorodeoxyglucose and [^{11}C]deoxyglucose. J Cereb Blood Flow Metab. 5:179–192.
28. **Orzi F, Lucignani G, Dow Edwards D, et al.** 1988 Local cerebral glucose utilization in controlled graded levels of hyperglycemia in the conscious rat. J Cereb Blood Flow Metab. 8:346–356.
29. **Brondsted HE, Gjedde A.** 1990 Glucose phosphorylation rate in rat parietal cortex during normoglycemia, hypoglycemia, acute hyperglycemia, and in diabetes-prone rats. Acta Neurol Scand. 81:233–236.
30. **Duckrow RB, Beard DC, Brennan RW.** 1987 Regional cerebral blood flow decreases during chronic and acute hyperglycemia. Stroke. 18:52–58.
31. **Harik SI, LaManna JC.** 1988 Vascular perfusion and blood-brain glucose transport in acute and chronic hyperglycemia. J Neurochem. 51:1924–1929.
32. **Knudsen GM, Tedeschi E, Jakobsen J.** 1992 The influence of haematocrit and blood glucose on cerebral blood flow in normal and in diabetic rats. NeuroReport. 3:987–989.