Sweet and Low: Measuring Brain Glucose During Hypoglycemia

Elizabeth R. Seaquist[1] and Gülin Öz[2]

In insulin-treated diabetes, the brain is exposed to extremes in glycemia that may have important effects on cerebral function. Consequently, understanding how the brain handles glucose delivered via the circulation under a range of glucose concentrations is important to patients with diabetes. In this issue of *Diabetes*, van de Ven et al. (1) report a new method to measure the kinetics of glucose transport under hypoglycemic conditions in human subjects. Their observations, coupled with the findings of others (2–4) provide firm evidence that a linear relationship exists between brain and blood glucose concentrations across the entire spectrum of glucose concentrations experienced by humans with uncomplicated type 1 diabetes. As a result, the brain is exposed to the same relative change in glucose concentration as the rest of the body during acute episodes of hypo- and hyperglycemia.

In the brain, glucose is transported across the blood-brain barrier by facilitated diffusion using GLUT1 (5). Once in the brain, glucose enters neurons via GLUT3 or astrocytes via GLUT1 (Fig. 1). It is then phosphorylated and used in pathways important in the generation of cellular energy, neurotransmitters, and other metabolites. Cerebral glucose content is regulated by a balance between the rate-limiting steps of glucose transport and metabolism.

The successful measurement of the kinetics of glucose transport and metabolism in living humans has generally required the use of noninvasive methods because invasive approaches, such as microdialysis, impose significant risk. Using ^{1}H-labeled nuclear magnetic resonance (^{1}H-NMR), we (3,4) and others (2) have examined the relationship between blood and brain glucose concentrations under conditions of hyperglycemia. These experimental conditions were necessary in the past because the NMR signal for glucose virtually disappears with progressive hypoglycemia. In the brain, glucose concentrations have generally been found to be 20–30% of those measured in the plasma. Consequently, when plasma glucose concentrations are reduced to hypoglycemic levels, the concentration in the brain falls below 1 mmol/L, a level at which the glucose spectra cannot be distinguished from the noise of the measurement. When collected under a range of hyperglycemic levels, kinetic constants for transport and metabolism can be derived from the reversible Michaelis-Menten model. However, whether the transport parameters derived from this model under hyperglycemia also hold under hypoglycemic conditions has been uncertain. van de Ven et al. (1) overcame the technical difficulties of measuring brain glucose concentration during hypoglycemia by infusing ^{13}C-glucose during euglycemic and hypoglycemic clamps while collecting the ^{13}C-NMR data from a large volume of interest in occipital brain tissue. Even though blood glucose concentration was successfully reduced to 3 mmol/L, they were able to maintain sufficient isotopic enrichment in both blood and brain to examine the relationship between glucose concentrations in these spaces. The kinetic constants derived from their data are the same as those derived from data collected under hyperglycemic conditions using ^{1}H-NMR.

Why is this finding important to the readers of *Diabetes*? The study by van de Ven et al. (1) did not find any differences in the glucose transport kinetics measured between patients with well-controlled type 1 diabetes and controls. This is good news for patients with diabetes who have symptoms of hypoglycemia when their glucose levels drop. However, this may not apply to patients who experience recurrent hypoglycemia. Clinically, patients with recurrent episodes of hypoglycemia are known to develop hypoglycemia unawareness and the perturbation in the counterregulatory responses to hypoglycemia that has been labeled hypoglycemia-induced autonomic failure (HAAF) (6). There is now abundant indirect evidence to support the hypothesis that brain glucose transport is increased in response to recurrent episodes of hypoglycemia. Years ago, Simpson et al. (7) demonstrated that the number of GLUTs identified at the blood-brain barrier in rats was higher in animals subjected to recurrent hypoglycemia than in controls. Using ^{1}H-NMR, we have shown that brain glucose concentrations are 17% higher in patients with type 1 diabetes and hypoglycemia unawareness than in controls without these conditions studied under the same levels of glycemia (8). Both observations provide indirect evidence that either glucose transport is increased or glucose metabolism is decreased in these patients. Future investigation of humans with HAAF using the methods of van de Ven should help determine if brain glucose transport is increased in these patients. These investigations will go a long way in helping us understand why patients with HAAF are unable to detect their hypoglycemia until they develop neuroglycopenia.

From the [1]Division of Endocrinology and Diabetes, Department of Medicine, University of Minnesota, Minneapolis, Minnesota; and the [2]Center for Magnetic Resonance Research, Department of Radiology, University of Minnesota, Minneapolis, Minnesota.
Corresponding author: Elizabeth R. Seaquist, seaqu001@umn.edu.
DOI: 10.2337/db12-0571

See accompanying brief report, p. 1974.

ACKNOWLEDGMENTS

This work was supported by a Distinguished Clinical Scientist Award from the American Diabetes Association (to E.R.S.) and National Institutes of Health Grant R01-NS-035192 (to E.R.S. and G.O.).

No potential conflicts of interest relevant to this article were reported.

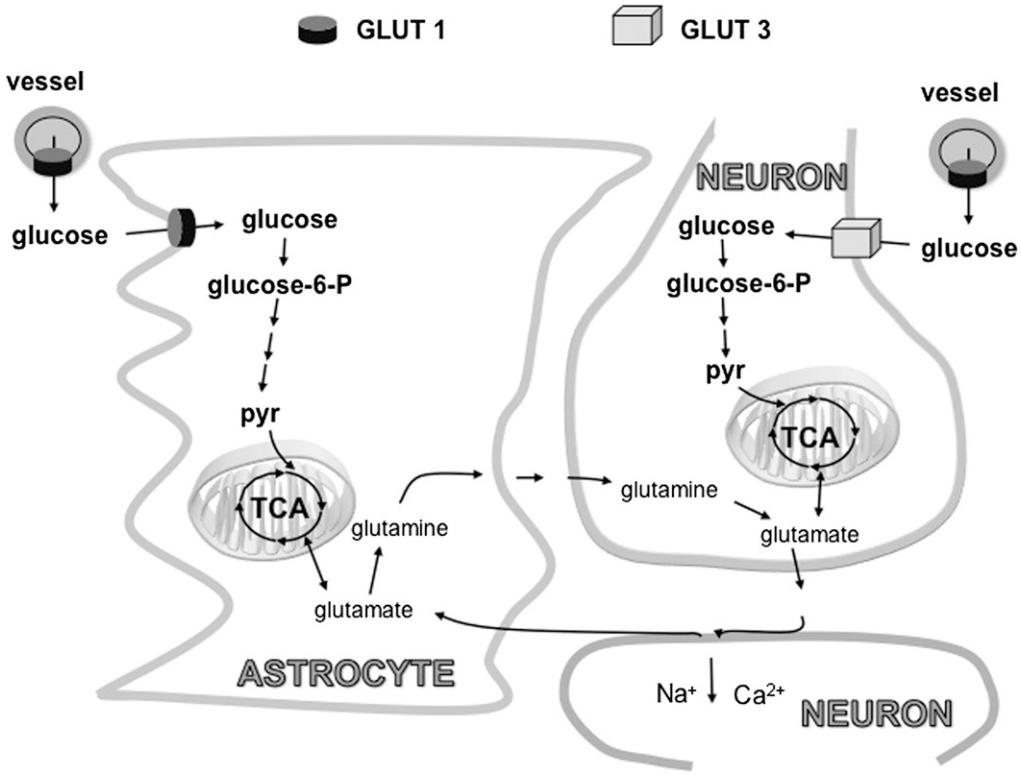

FIG. 1. Brain glucose metabolism. Glucose crosses the blood-brain barrier and enters astrocytes and neurons via specific GLUTs. In the cell, glucose is metabolized to provide energy and support neurotransmission. TCA, tricarboxylic acid cycle; pyr, pyruvate.

REFERENCES

1. van de Ven KCC, van der Graaf M, Tack CJ, Heerschap A, de Galan BE. Steady-state brain glucose concentrations during hypoglycemia in healthy humans and patients with type 1 diabetes. Diabetes 2012;61:1974–1977
2. de Graaf RA, Pan JW, Telang F, et al. Differentiation of glucose transport in human brain gray and white matter. J Cereb Blood Flow Metab 2001;21:483–492
3. Gruetter R, Ugurbil K, Seaquist ER. Steady-state cerebral glucose concentrations and transport in the human brain. J Neurochem 1998;70:397–408
4. Seaquist ER, Damberg GS, Tkac I, Gruetter R. The effect of insulin on in vivo cerebral glucose concentrations and rates of glucose transport/metabolism in humans. Diabetes 2001;50:2203–2209
5. Simpson IA, Carruthers A, Vannucci SJ. Supply and demand in cerebral energy metabolism: the role of nutrient transporters. J Cereb Blood Flow Metab 2007;27:1766–1791
6. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. Diabetes 2005;54:3592–3601
7. Simpson IA, Appel NM, Hokari M, et al. Blood-brain barrier glucose transporter: effects of hypo- and hyperglycemia revisited. J Neurochem 1999;72:238–247
8. Criego AB, Tkac I, Kumar A, Thomas W, Gruetter R, Seaquist ER. Brain glucose concentrations in patients with type 1 diabetes and hypoglycemia unawareness. J Neurosci Res 2005;79:42–47