cylindrical lenses. The deflector is composed of a glass substrate with ultrasonic transducers bonded to one end. The oscillator signal is transduced into planar acoustic wave fronts that traverse the length of the glass. The compressions from the peaks and troughs of the waves impose a periodic variation in refractive index throughout the material. In effect, a thick grating with the capability of diffracting visible light is created. A laser beam is introduced, at a small angle, into the aperture and is efficiently diffracted (70 to 90 percent) out at a new angle. The beam steering is accomplished by changing the input oscillator frequency to create a new grating spacing and a different exit angle (*11*).

11. R. Adler, *IEEE Spectrum* **4**, 42 (1967).
12. T. Lewis, *J. Physiol. (London)* **49**, 36 (1915).
13. B. F. Hoffman and P. F. Cranefield, *Electrophysiology of the Heart* (McGraw-Hill, New York, 1960), p. 79.

14. Tyrode's solution (*p*H 7.4) consists of (m*M*) NaCl, 137; KCl, 2.7; $CaCl_2$, 1.8; $MgCl_2$, 0.7; NaH_2PO_4, 0.4; $NaHCO_3$, 12; glucose, 11; and water.

15. We are extremely grateful for the generous gift of WW-781 dye from A. Waggoner.

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Blood-Brain Glucose Transfer: Repression in Chronic Hyperglycemia

Abstract. *Diabetic patients with increased plasma glucose concentrations may develop cerebral symptoms of hypoglycemia when their plasma glucose is rapidly lowered to normal concentrations. The symptoms may indicate insufficient transport of glucose from blood to brain. In rats with chronic hyperglycemia the maximum glucose transport capacity of the blood-brain barrier decreased from 400 to 290 micromoles per 100 grams per minute. When plasma glucose was lowered to normal values, the glucose transport rate into brain was 20 percent below normal. This suggests that repressive changes of the glucose transport mechanism occur in brain endothelial cells in response to increased plasma glucose.*

Glucose is transported across the cerebral capillary endothelium by facilitated diffusion (*1*). It has been shown for other nutrients, for example, β-hydroxybutyrate, that the membrane constituent responsible for facilitated diffusion is subject to induction (*2*).

In 1959, Wyke (*3*) described a group of patients with "relative cerebral hypoglycemia" in whom symptoms indicative of hypoglycemia existed at normal plasma glucose concentrations. The condition of the patients improved upon elevation of the plasma glucose, suggesting insufficient capacity for glucose transport from blood to brain, compensated by the increased plasma glucose.

Diabetics with markedly elevated plasma glucose concentrations respond to rapid normalization of plasma glucose with symptoms of hypoglycemia, including hypothalamic excitation and increased sympathetic discharge, often referred to as "resetting of the glucostat" (*4*).

These clinical observations suggest an influence of chronically elevated plasma glucose concentrations on the transport capacity of the blood-brain barrier. The present study was undertaken to determine the influence of chronic hyperglycemia on the rate of glucose transfer from blood to brain. The study revealed a reduction of the maximum transport capacity that may be explained by mechanisms known from variation of gene expression (induction or repression).

Ninety-three rats were divided in two groups. The experimental group was rendered hyperglycemic by a single intraperitoneal injection of streptozotocin (50 mg per kilogram of body weight). The two groups were housed and handled in the same way for 3 weeks. Unidirectional blood-brain glucose transfer and blood and plasma flow rates of the parietal cortex were measured in both groups at different plasma glucose concentrations reached after administration of glucose or insulin.

Details of the glucose and insulin treatments and the determination of kinetic constants for glucose transport across the blood-brain barrier were given previously (*5*). The determination of kinetic constants was based on the equation

$$E^* = 1 - e^{-PS/F} \quad (1)$$

where E^* is the unidirectional extraction of labeled glucose, and

$$PS = \frac{T_{max}}{K_t + C_a} \quad (2)$$

and F is the plasma flow to brain. The notations T_{max} and K_t are used for the maximum reaction rate and the half-saturation constant of a transport process, respectively, and replace the symbols V_{max} and K_m commonly used for proper enzymatic reactions. C_a is the arterial plasma glucose concentration (*6*). We measured E^*, the fraction extracted in brain, by an integral method (*7*). According to this method

$$E^* = \frac{M^*(T)}{F \int_0^T C_a^*(t)\, dt} \quad (3)$$

in which $M^*(T)$ is the amount of labeled glucose in a sample of brain (excluding glucose in plasma), F the plasma flow rate into the sampled region, and $C_a^*(t)$ the arterial tracer glucose concentration. The integral was determined by withdrawal of arterial blood at a constant rate. The animals were decapitated 20

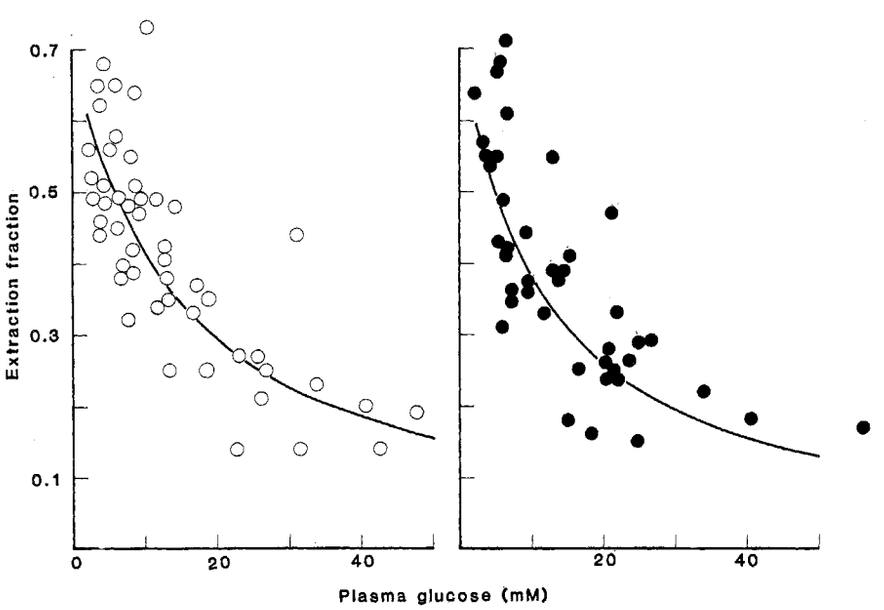

Fig. 1. Extraction of labeled glucose from the brains of control rats (○) and rats rendered hyperglycemic for 3 weeks by single intraperitoneal injection of streptozotocin (●). The extraction fractions were measured 20 seconds after a single intravenous injection of labeled glucose and labeled flow indicator (butanol), at the plasma glucose concentrations of arterial blood shown in the abscissa.

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seconds (T) after an intravenous injection of radioactively labeled glucose and butanol. The plasma flow to brain was calculated from Eq. 3, with E^* for butanol being assumed to be a function of the blood flow rate (*7*).

The kinetic constants were estimated by fitting Eqs. 1 and 2 to simultaneous measurements of F and E^* for glucose at different values of C_a by direct nonlinear least-squares regression analysis (*8*).

The average plasma glucose concentrations of the groups prior to study are given in Table 1, as are the extractions of radioactively labeled glucose measured in the control animals. The labeled glucose extracted from the two groups at glucose concentrations reached after administration of glucose or insulin appear in Fig. 1. The two groups did not differ with respect to cerebral blood flow, mean arterial blood pressure, arterial oxygen tension, or arterial carbon dioxide tension.

The values of T_{max} estimated from the values of E^* shown in Fig. 1 are given in Table 1. The values of K_t did not differ significantly, being 8.6 mmole/liter in control animals and 6.4 mmole/liter in the chronically hyperglycemic animals. From the values of T_{max} and K_t, we calculated the curves describing the relations between E^* and C_a, using Eqs. 1 and 2. The curves are shown in Fig. 1.

The flux of glucose in the direction blood to brain was estimated from Eq. 4, which is derived from Eq. 2

$$J \simeq PS\ C_a = \frac{T_{max}}{K_t + C_a} C_a \qquad (4)$$

where J is the unidirectional glucose flux in the direction blood to brain. The curves describing the relations between J and C_a in the two groups are shown in Fig. 2.

It is apparent from Fig. 2 that the transport capacity of the blood-brain barrier for glucose changes such as to reduce the flux of glucose from blood to brain at any concentration. At glucose concentrations of 20 mmole/liter, the chronically hyperglycemic rats transported glucose in the direction blood to brain no faster than did control rats at 10 mmole/liter. Thus, the adjustment tended to prevent the brain glucose content from increasing.

Although no overt hypoglycemic symptoms were present in the animal preparation used here, the results offer an explanation of why hypoglycemic symptoms may appear at normal plasma glucose concentrations in chronically hyperglycemic subjects. In adapted rats, the average glucose flux from blood to brain when the plasma glucose was 10 mmole/liter was 20 percent below normal.

Table 1. Chronic hyperglycemia in rats. The animals received single intraperitoneal injection of streptozotocin 3 weeks before the measurements were made. Experimental and control animals were otherwise treated in the same way. Values are expressed as means ± standard error.

Variable (unit)	Control group (N = 50)	Chronic hyperglycemia for 3 weeks (N = 43)
Body weight (g)	316 ± 6	281 ± 5
Plasma glucose (mmole/liter)	9.0 ± 0.4	25.2 ± 1.2
Arterial pH	7.41 ± 0.01	7.46 ± 0.01
Labeled glucose extraction	0.44 ± 0.02*	0.25 ± 0.02†
Maximum transport capacity for glucose (μmole/100 g-min)	400 ± 29	286 ± 24‡

*N = 18. †N = 13. ‡P < .001.

The results reveal a remarkable plasticity of the facilitated diffusion mechanism for glucose in the blood-brain barrier. Whether the repression is the result of increased plasma glucose or decreased plasma insulin is unknown. The long-term decrease in circulating insulin has been thought to influence the number of insulin receptors on cells, and plasma insulin decreases by 80 percent in streptozotocin-induced diabetes in rats. Although the decrease appears unable to influence the number of peripheral insulin receptors in this condition (*9*), the possibility should be kept in mind. However, we tend to interpret the alteration as being secondary to the increase in plasma glucose concentration in analogy with our earlier finding of induction processes of the brain endothelium after the concentration of ketone in the body is increased (*2*).

The cerebral capillary endothelium has been characterized as a "tight" epithelium (*10*), and it is well known that transport mechanisms in epithelia are subject to adaptive changes (*11*) in response to lasting changes of the surrounding fluid. The present findings are in accordance with this generalization. It is tempting to speculate that the brain endothelium is endowed with regulatory functions that may damp variations of the glucose concentration of brain interstitial fluid, as has been shown for potassium (*12*).

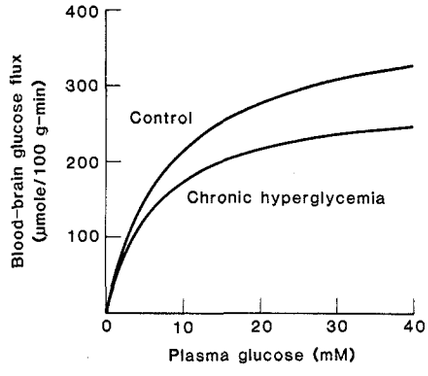

Fig. 2. Unidirectional blood-brain glucose flux into parietal cortex of normal rats and rats rendered chronically hyperglycemic. The curves were calculated from kinetic constants given in the text and in Table 1.

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References and Notes

1. C. Crone, *J. Physiol. (London)* **181**, 103 (1965).
2. A. Gjedde and C. Crone, *Am. J. Physiol.* **229**, 1165 (1975); T. J. Moore, A. P. Lione, M. C. Sugden, D. M. Regen, *ibid.* **230**, 619 (1976); G. Dahlquist and B. Persson, *Pediatr. Res.* **10**, 910 (1976); P. M. Daniel, E. R. Love, S. R. Moorhouse, O. E. Pratt, *J. Neurol. Sci.* **34**, 1 (1977).
3. B. D. Wyke, *Electroenceph. Clin. Neurophysiol.* **11**, 602 (1959); *Principles of General Neurology* (Elsevier, London, 1969), p. 586.
4. K. G. M. Alberti, A. Dornhorst, A. S. Rowe, *Isr. J. Med. Sci.* **11**, 571 (1975); R. A. DeFronzo, R. Andres, T. A. Bledsoe, G. Boden, G. A. Faloona, J. D. Tobin, *Diabetes* **26**, 445 (1977); R. A. DeFronzo, R. Hendler, N. Christensen, *ibid.* **29**, 125 (1980); U. Lilavivathane, R. G. Brodows, P. D. Woolf, R. C. Campbell, *ibid.* **28**, 873 (1979); A. McCall, W. Millington, S. Temple, R. J. Wurtman, *ibid.*, p. 381; B. Zinman, E. F. Stokes, A. M. Albisser, A. K. Hanna, H. L. Minuk, A. N. Stein, B. S. Leibel, E. B. Marliss, *Metabolism* **28**, 511 (1979).
5. A. Gjedde, *Acta Physiol. Scand.* **108**, 331 (1980).
6. C. Crone, *ibid.* **58**, 292 (1963); H. Lund-Andersen, *Physiol. Rev.* **59**, 305 (1979).
7. A. Gjedde, A. J. Hansen, E. Siemkowicz, *Acta Physiol. Scand.* **108**, 321 (1980); A. Gjedde and M. Rasmussen, *J. Neurochem.* **35**, 1382 (1980).
8. V. J. Cunningham and G. S. Sarna, *J. Neurochem.* **33**, 433 (1979).
9. R. S. Bar and J. Roth, *Arch. Int. Med.* **137**, 474 (1977); S. Gammeltoft, L. Ø. Kristensen, M. Folke, L. Sestoft, in *Insulin: Chemistry, Structure and Function of Insulin and Related Hormones,* D. Brandenburg and A. Wollmer, Eds. (de Gruyter, Berlin, 1980), pp. 271–275.
10. C. Crone and A. M. Thompson, in *Capillary Permeability, Alfred Benzon Symposium 2,* C. Crone and N. A. Lassen, Eds. (Munksgaard, Copenhagen, 1970), pp. 447–453; C. Crone, in *Water Transport Across Epithelia, Alfred Benzon Symposium 15,* H. H. Ussing, N. Bindslev, N. A. Lassen, O. Sten-Knudsen, Eds. (Munksgaard, Copenhagen, 1981), pp. 258–267.
11. N. Bindslev, *J. Physiol. (London)* **288**, 449 (1979).
12. M. Bradbury, *The Concept of a Blood-Brain Barrier* (Wiley, Chichester, England, 1979).
13. We thank M. Frank, B. Mertz, E. Munch, and B. Ree for technical assistance. Supported by grants 512-8173, 512-15355, and 512-20605 from the Medical Research Council (Denmark).

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