Editorial

Does Tight Glucose Control Enhance Brain Sensitivity to Low Glucose?

Aggressive insulin-treatment regimens are associated with a significant increase in the incidence of hypoglycemia, and this often limits our ability to institute tight glucose control in patients with insulin-dependent diabetes mellitus (1). This is not surprising in view of the fact that an adequate supply of glucose is essential to maintain normal cerebral cognitive function. Approximately 60% of total-body glucose metabolism can be ascribed to cerebral metabolism, and >90% of cerebral metabolic demands are met by the oxidative metabolism of glucose (2). Data from both human and animal experiments and clinical observations are consistent with the conclusion that the cerebral and peripheral counterregulatory responses to hypoglycemia may vary in insulin-treated diabetic subjects depending on the overall ambient glucose concentration, suggesting that adaptive mechanisms exist to maintain the cerebral glucose supply under conditions of both hypo- and hyperglycemia (3–8).

The means by which glucose enters neuronal tissue is unknown, but glucose-transporter protein can be identified in nonneuronal tissue throughout the brain, particularly in the luminal and abluminal membranes of microvessel endothelial cells and glial cells (9). Glucose normally crosses the blood-brain barrier down a concentration gradient by a process of facilitated diffusion. The gradient is maintained by the rapid phosphorylation of glucose to glucose-6-phosphate by the enzyme hexokinase (2). Under euglycemic conditions, the rate of glucose transport across the blood-brain barrier exceeds the rate of glucose phosphorylation, which is the rate-limiting step in the process of glucose metabolism (2). During modest reductions in the plasma glucose concentration, there is a reduction in the rate of glucose transport across the blood-brain barrier. However, the normal rate of cerebral glucose metabolism will be preserved as long as sufficient glucose can be delivered to maintain the phosphorylation reaction. There are data in humans both from the measurement of cerebral A-V differences (10) and studies that used positron emission tomography (3) that, in response to a fall in the plasma glucose level, the brain extracts for metabolism an increased fraction of the glucose presented to it. Thus, the normal physiological arrangement whereby the rate of cerebral glucose transport exceeds the rate of glucose phosphorylation ensures that, during acute hypoglycemia, cerebral glucose metabolism is preserved as the result of an increase in the fractional utilization of glucose. However, if the glucose level falls to a point where delivery is no longer sufficient to allow the hexokinase reaction to proceed at the normal rate, a fall in the rate of cerebral glucose metabolism will occur and presumably result in cerebral dysfunction.

Although it has not yet been possible to measure the threshold glucose level at which the normal rate of cerebral glucose metabolism falls, indirect evidence is consistent with the notion that this threshold may vary with the overall level of glucose present before the induction of hypoglycemia. Animal studies of chronic hypoglycemia due to implantation of insulin-producing tumors have shown that there is an increase in unidirectional flux of glucose into the brain (5). Over time and with restoration of euglycemia, these changes revert to normal. Conversely, decreased blood-brain glucose transfer has been found in rats with chronic hyperglycemia, and this returns toward normal when euglycemia is restored (6,7). The cellular and molecular mecha-

nisms underlying these changes are still unclear. The activity of blood-brain barrier glucose transporters and glucose-transporter concentration in vivo is decreased in experimental diabetes, together with a decrease in cerebral blood flow and prolongation of capillary transit time (7). There was an increase in glucose-transporter mRNA in diabetic rat brain capillaries, suggesting that the downregulation of glucose-transporter activity is by a posttranscriptional mechanism (11). Although insulin can be shown to influence the expression of glucose-transporter mRNA, there is no evidence that it plays a direct role in the enhanced glucose-extraction or increased glucose-distribution volume at the whole-organ level. Thus, on the basis of these observations, it could be predicted that a diabetic subject who experiences frequent hypoglycemia may be able to maintain a normal rate of cerebral glucose metabolism in the face of lower plasma glucose levels through numerous potential mechanisms including enhanced cerebral blood flow and increased fractional glucose clearance, which may be mediated by increased glucose-transporter activity. Conversely, in a chronically hyperglycemic subject, the critical fall in cerebral glucose metabolism may be expected to occur at a higher plasma glucose concentration as a result of the chronic suppression in cerebral glucose uptake.

Numerous clinical observations are consistent with the above formulation. Thus, it was originally reported by Wyke (12) and subsequently confirmed by others that chronically hyperglycemic diabetic subjects may experience symptoms and signs of hypoglycemia in response to a falling but still normal plasma glucose level. Boyle et al. (13) have shown that the glycemic threshold for the symptoms of hypoglycemia is higher in subjects with poorly controlled diabetes than in nondiabetic control subjects. Conversely, subjects who are enrolled in aggressive insulin-treatment programs that result in plasma glucose concentrations that are repeatedly in the mildly hypoglycemic range appear to have lower thresholds for the release of counterregulatory hormones and a greater incidence of hypoglycemic unawareness (8). Trials that use insulin-pump therapy have reported that as many as 28% of subjects have severe insulin reactions, with a rate of 54 episodes/100 subject-yr (1). Numerous cross-sectional and prospective studies have examined the effects of strict glucose control on glucose counterregulation and have shown that the magnitude of hormonal responses and the threshold at which the responses occur are decreased (4,8). It has been postulated that this results from an adaptive alteration that allows for a more efficient maintenance of cerebral glucose metabolism in response to hypoglycemia (14). If this were true, it could be predicted that these subjects should also be protected from the adverse effects of hypoglycemia and may show cognitive and other cerebral dysfunction at lower levels than chronically euglycemic or hyperglycemic diabetic patients.

However, the data reported by Amiel et al. (this issue, p. 109) are not consistent with this hypothesis. In this study, the authors examined symptomatology, counterregulatory responses, and EEG changes in a cross-sectional study of subjects with mild chronic hypoglycemia, either due to aggressive insulin treatment of diabetes or insulinoma, compared with poorly controlled diabetic subjects and nondiabetic control subjects. Their study confirms previous reports that chronic mild hypoglycemia is associated with reduced hormonal responses to acute hypoglycemia, and also finds that symptoms were not perceived until lower glucose levels had been reached in well-controlled diabetic subjects or subjects with insulinoma. However, rather than being protected from the EEG abnormalities of chronic hypoglycemia, these subjects were more likely to have EEG changes compatible with hypoglycemia than poorly controlled diabetic subjects or control subjects. These data provide an explanation as to why hypoglycemia can lead to confusion and coma without any warning symptoms in subjects in the best of glucose control.

This provocative study highlights the need for additional studies to clarify the metabolic and molecular alterations in the brain that occur in response to a falling glucose level. However, the full clinical implications of these findings should be interpreted with caution and should await additional prospective studies that define the extent to which they are generally applicable to a broad spectrum of subjects with insulin-dependent diabetes mellitus. Only four diabetic subjects were included in this study, and the validity of including subjects with insulinoma in the same group as well-controlled diabetic subjects is open to question in view of the potential differences in the counterregulatory mechanisms. Furthermore, the duration of diabetes was different in the two diabetic patient groups, and this factor may independently affect counterregulatory responses to and symptoms of hypoglycemia. The findings of δ-waves on the EEG is compatible with but not specific for hypoglycemia, and the significance of this sign as a predictor of long-term clinically significant cognitive impairment is uncertain.

Several studies have shown that cortical responses to insulin-induced hypoglycemia, assessed by reaction time, P300 latencies, or other psychological tests, differ widely among people with or without diabetes (15–17). Some individuals show significant impairment when the glucose level is <2.8 mM, whereas others show minimal changes. These characteristics may ultimately be the most important determinants of an individual's experience with hypoglycemia and of the potential for adverse cerebral effects of tight glucose control. Likewise, there may be a subgroup of subjects in whom EEG changes develop at higher glucose levels or who adapt differently to the cerebral effects of the recurrent hypoglycemia. Because of this individual heterogeneity, a larger group of representative subjects should be prospectively studied to determine whether the conclusion of this study depends on the specific characteristics of a small number of subjects. The issue is of the utmost importance because it could potentially influence the

selection of diabetic subjects for different treatment regimens. Furthermore, it is possible that, with a greater understanding of the molecular and cellular physiology of cerebral hypoglycemia, novel strategies could be developed to protect the brain from the adverse effects of low glucose. The study by Amiel et al. (this issue, p. 109) underscores the need for a careful and critical assessment of the relationship between blood glucose management and the recurrent problem of hypoglycemia in insulin-treated patients.

KEVAN C. HEROLD, MD
KENNETH S. POLONSKY, MD

From the Department of Medicine, Section of Endocrinology, The University of Chicago, Chicago, Illinois.

Address correspondence and reprint requests to Kevan C. Herold, MD, Department of Medicine, Box 435, The University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637.

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