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Brain glucose concentrations in poorly controlled diabetes mellitus as measured by high-field magnetic resonance spectroscopy

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Abstract

Hyperglycemia and diabetes alter the function and metabolism of many tissues. The effect on the brain remains poorly defined, but some animal data suggest that chronic hyperglycemia reduces rates of brain glucose transport and/or metabolism. To address this question in human beings, we measured glucose in the occipital cortex of patients with poorly controlled diabetes and healthy volunteers at the same levels of plasma glucose using proton magnetic resonance spectroscopy. Fourteen patients with poorly controlled diabetes (hemoglobin A_{1c} = 9.8% ± 1.7%, mean ± SD) and 14 healthy volunteers similar with respect to age, sex, and body mass index were studied at a plasma glucose of 300 mg/dL. Brain glucose concentrations of patients with poorly controlled diabetes were lower but not statistically different from those of control subjects (4.7 ± 0.9 vs 5.3 ± 1.1 μmol/g wet wt; P = .1). Our sample size gave 80% power to detect a difference as small as 1.1 μmol/g wet wt. We conclude that chronic hyperglycemia in diabetes does not alter brain glucose concentrations in human subjects.

1. Introduction

The effects of chronic hyperglycemia on the brain have been difficult to define. Reduced cognitive function, particularly with respect to memory and attention, has been identified in patients with poorly controlled diabetes [1-3], and epidemiological studies demonstrate a link between dementia and a diagnosis of diabetes [4,5]. Investigators have identified specific abnormalities in central nerve conduction that are more common in diabetes [6-8], but it is unclear if these abnormalities are linked to metabolic changes that occur as a result of chronic hyperglycemia or are caused by the vascular disease so common in patients with diabetes.

Overall levels of glycemia have been proposed to play a role in determining brain glucose uptake and metabolism [9]. Because normal glucose sensing in the brain relies in part on rates of brain glucose uptake and metabolism, abnormalities in glucose sensing should be expected in subjects with aberrations in glucose homeostasis. Observations made in human subjects with diabetes suggest that these anticipated changes in glucose sensing do indeed occur. Subjects with recurrent hypoglycemia demonstrate a decrease in the blood glucose concentration at which they develop symptoms of hypoglycemia or mount a counterregulatory response to hypoglycemia [10-13]. Conversely, chronic hyperglycemia has been associated with an increase in the blood glucose concentration at which the symptoms of hypoglycemia (increased heart rate, release of counterregulatory hormones, etc) occur [14]. One plausible mechanism that has been proposed and investigated is that brain glucose uptake is changed in such a way as to compensate for the altered glucose delivery to the brain [9]. Glucose transport at the blood-brain barrier is predominantly mediated by the ubiquitous glucose transporter, GLUT1 [15-18]. In the setting of chronic hypoglycemia, glucose transporters at the blood-brain barrier have been found to be increased by some [19,20] but not all [21] investigators. After chronic hyperglycemia, glucose transporters

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at the rodent blood-brain barrier have been found to be reduced [19,22-24]. Together, these studies suggest that glucose transport may be one mechanism through which the brain can compensate for alterations in global glucose metabolism.

If altered expression of GLUT1 occurs as a result of aberrations in glucose homeostasis, brain glucose concentrations in subjects with such aberrations should be different from those in control subjects with chronic normoglycemia. Assuming a fixed glucose transport capacity on a per GLUT1 molecule basis, the decrease in transporter density that has been shown to occur in chronic hyperglycemia [19,22-24] would be expected to lead to a decreased permeability surface area, which in turn would lead to a decreased apparent maximal glucose transport rate, T_{max}. Without a major adaptive change in brain energy metabolism, which almost entirely relies on blood glucose and its transport across the blood-brain barrier, a decrease in T_{max} would be expected to lead to decreased brain glucose content at a given plasma glucose concentration, which would imply that glucose transport could become rate limiting for metabolism at higher plasma glucose concentrations. Regardless of the mechanism, it would appear that a change in brain glucose concentration at a given plasma glucose concentration is central to the hypothesis that brain glucose transport is a critical element underlying how the brain copes with changes in glucose availability.

Brain glucose concentrations can be directly measured using in vivo magnetic resonance spectroscopy (MRS) [25,26], whereas positron emission tomography can provide precise measurements of the glucose phosphorylation in the brain and, to some extent, of the unidirectional glucose transport from the operational parameter, k_1. Positron emission tomography studies thus far have not reported a reduction in glucose transport or an increase in glucose metabolism in patients with poorly controlled diabetes [27,28], possibly because small but clinically significant differences may have been beyond the precision of these important studies. However, we have recently demonstrated that patients with type 1 diabetes and hypoglycemia unawareness have steady-state brain glucose concentrations that are 13% higher than those in healthy volunteers studied under the same metabolic conditions using proton MRS [29]. Proton MRS may be able to identify the small differences in brain glucose concentrations that are expected to result from an alteration in glucose transport if the hypothesis that antecedent hyperglycemia in poorly controlled patients with diabetes reduces brain glucose transport is true. Therefore, the aim of the current study was to examine in human beings whether chronic hyperglycemia alters glucose content by measuring brain glucose concentrations in patients with poorly controlled diabetes and healthy volunteers at the same levels of plasma glucose using proton MRS.

2. Methods

2.1. Study participants

Subjects with diabetes were recruited for study participation from the Endocrine Clinic of the University of Minnesota. To be included in the study, subjects were required to be older than 18 years, have a hemoglobin A_{1c} ($HgbA_{1c}$) of greater than 8.5% within 3 months of enrollment (for healthy subjects, the range is from 4.5% to 6.0%), have no recent episodes of hypoglycemia, and fulfill the requirements for a magnetic resonance study, which, in addition to the usual magnetic resonance exclusion criteria, precluded subjects weighing more than 300 lb. Control subjects were recruited from the University of Minnesota and Fairview-University Medical Center communities and were similar to the patients with respect to age, body mass index, and sex. The study protocol was conducted according to procedures approved by the institutional review board.

2.2. Protocol

All subjects with diabetes were asked to monitor their blood glucose values at home before each meal and at bedtime for the week before the study. Subjects with hypoglycemia (blood glucose, <70 mg/dL with or without symptoms) within 24 hours before the study were excluded from participation. Patients with self-reported diagnosis of type 1 diabetes were admitted to the General Clinical Research Center of the University of Minnesota the night before the experiment. Their evening dose of long-acting insulin was held and they were maintained on an intravenous infusion of insulin overnight to maintain their glycemia between 100 and 180 mg/dL. The insulin infusion was discontinued at 7:30 AM and the patients were then transported to the Center for Magnetic Resonance Research for the experiment. Subjects with a self-reported diagnosis of type 2 diabetes were asked to discontinue their oral medications 3 days before study and to hold their insulin the night before the experiment. Medications used alone or in combination by the 6 subjects with type 2 diabetes included troglitazone, insulin (n = 4), metformin (n = 2), glyburide (n = 3), pioglitazone (n = 2), and glipizide.

All subjects were studied in the Center for Magnetic Resonance in the morning after an overnight fast. In preparation for the experiment, an intravenous catheter was placed retrograde into one foot for the acquisition of blood samples and 2 additional intravenous catheters were placed into the upper extremities for the delivery of somatostatin, insulin, and glucose. The leg used for blood sampling was wrapped in heated towels and hot packs to arterialize the venous blood [30], and baseline samples were obtained for glucose, insulin, and ketones. A somatostatin infusion was then begun and advanced slowly to a rate of 0.16 mg/(kg min) over 30 minutes to suppress endogenous insulin secretion [31]. An intravenous insulin infusion