Brain Glycogen Content and Metabolism in Type 1 Diabetes

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Introduction

Glycogen is the sole glucose reservoir in the brain and is mobilized to support cerebral energy metabolism during hypoglycemia (1, 2, 3). Furthermore, its levels rebound to higher than normal after a hypoglycemic episode, a phenomenon termed "supercompensation" (1, 2), suggesting it may provide energy for the brain during subsequent periods of hypoglycemia. Glycogen supercompensation was suggested to contribute to the development of hypoglycemia unawareness (HU) (1, 2), a condition frequently encountered in type 1 diabetes (T1D) as a result of insulin use and recurrent episodes of hypoglycemia (4). Hence, recurrent hypoglycemia may lead to maintenance of higher than normal levels of brain glycogen, perhaps to provide sufficient fuel to maintain cerebral energy metabolism during future hypoglycemic episodes. To test the hypothesis that subjects with T1D and HU have higher levels of brain glycogen than controls, we measured brain glycogen content and turnover using ^{13}C MRS.

Methods and Subjects

Subjects were administered IV glucose over 50h at a rate titrated to maintain a blood glucose concentration of 125 mg/dl. Subjects with T1D were withdrawn from their insulin and administered IV insulin, first at a rate of 0.5 mU/kg/min and then adjusted as necessary to ensure that ≥ 2 mg/kg/min of glucose could be infused while still maintaining target blood glucose. Controls were matched to subjects with T1D and given insulin at the same rate as their T1D subject. Studies began with the administration of a 20g bolus of 75% [1-^{13}C]glucose followed by an infusion of 50% [1-^{13}C]glucose for the next ~32 hrs, and unlabelled dextrose thereafter. Samples for blood glucose, insulin, and fractional enrichment were obtained every 10-60 minutes. ^{13}C glycogen levels in the occipital lobe were measured at 5, 8, 13, 23, 32, 37 and 50 h using methods described before (2, 5). Briefly, measurements were performed on a 4 T/90 cm magnet (Oxford/Varian). A quadrature 14 cm ^{1}H surface coil with a 9 cm diameter linear ^{13}C coil was used. Localization was achieved by 3D outer volume suppression combined with 1D ISIS. Since ventricle enlargement was noted in some patients, all ^{13}C glycogen levels were corrected for the cerebrospinal fluid (CSF) content of the voxel as described before (5). Five patients with T1D and HU (1F/4M, age 57±4, BMI 25±4 kg/m^2) and 5 healthy volunteers (1F/4M, age 57 ± 3, BMI 24±2 kg/m^2) participated in the study. A steady–state model of glycogen metabolism (6) was fitted to the time courses of the newly synthesized glycogen using the software SAAM II (The SAAM Institute, Seattle, WA).

Results and Discussion

Average blood glucose and insulin levels were matched between the patients and controls (Table, p = 0.2 for both glucose and insulin). On the other hand, newly synthesized glycogen levels ([1-^{13}C]glycogen concentrations divided by the plasma glucose isotopic enrichments) were higher on average in controls than patients (Figure). Metabolic modeling of these data revealed a similar glycogen turnover rate in the two groups (p = 0.6), but a strong trend for lower brain glycogen content in patients than controls (p = 0.05, Table).

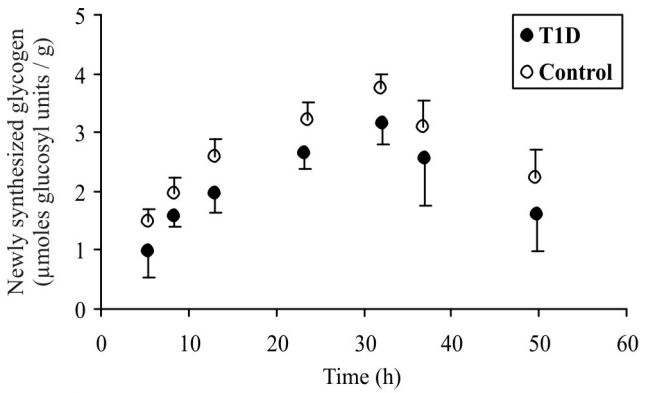

Fig. ^{13}C incorporation into and washout from glycogen C1 over time in patients and controls. Average (±SD) values of 5 subjects in each group are shown. Data were corrected for the CSF content of the voxel and the isotopic enrichment of plasma glucose.

Patients with T1D and HU have higher brain glucose concentrations compared to controls at the same blood glucose levels (7), likely due to upregulated glucose transport in these subjects (8). Lower glycogen levels in T1D and HU in the presence of higher brain glucose levels than controls are surprising, considering that glucose is the main regulator of glycogen content. Therefore these data suggest that the regulatory mechanisms of glycogen synthase and phosphorylase are altered in patients with T1D and HU. In conclusion, while this first investigation of brain glycogen metabolism in T1D indicated that the maintenance of higher brain glycogen content does not appear to contribute to the syndrome of hypoglycemia unawareness in T1D, it demonstrated a potential difference in the regulation of glycogen metabolism. Patients with T1D and HU may not need to maintain glycogen levels similar to controls because they have more glucose available for metabolism than controls at the same plasma glucose levels. It remains to be determined if patients with T1D and HU mobilize glycogen at rates similar to controls during hypoglycemia (2).

	Blood glucose (mg/dl)	Serum insulin (mU/l)	Brain glycogen turnover rate (μmol/g/h)	Brain glycogen content (μmol/g)
Subjects with T1D and HU	131 ± 10	53 ± 21	0.3 ± 0.2	3.9 ± 1.2
Controls	122 ± 14	105 ± 65	0.3 ± 0.1	5.0 ± 1.2

* Values shown are averages ± SD over the 5 subjects in each group.

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