Characterization of hepatic and brain metabolism in young adults with glycogen storage disease type 1: a magnetic resonance spectroscopy study

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Weghuber D, Mandl M, Krššák M, Roden M, Nowotny P, Brehm A, Krebs M, Widhalm K, Bischof MG. Characterization of hepatic and brain metabolism in young adults with glycogen storage disease type 1: a magnetic resonance spectroscopy study. Am J Physiol Endocrinol Metab 293: E1378–E1384, 2007. First published September 4, 2007; doi:10.1152/ajpendo.00658.2006.—In glycogen storage disease type 1 (GSD1), children present with severe hypoglycemia, whereas the propensity for hypoglycemia may decrease with age in these patients. It was the aim of this study to elucidate the mechanisms for milder hypoglycemia symptoms in young adult GSD1 patients. Four patients with GSD1 [body mass index (BMI) 23.2 ± 6.3 kg/m², age 21.3 ± 2.9 yr] and four healthy controls matched for BMI (23.1 ± 3.0 kg/m²) and age (24.0 ± 3.1 yr) were studied. Combined 1H/31P nuclear magnetic resonance spectroscopy (NMRS) was used to assess brain metabolism. Before and after administration of 1 mg glucagon, endogenous glucose production (EGP) was measured with [6,6-2H2]glucose and hepatic glucose metabolism was examined by 1H/13C/31P NMRS. At baseline, GSD1 patients exhibited significantly lower rates of EGP (0.53 ± 0.04 vs. 1.74 ± 0.03 mg·kg⁻¹·min⁻¹; P < 0.01) but an increased intrahepatic glycogen (502 ± 89 vs. 236 ± 11 mmol/l; P = 0.05) and lipid content (16.3 ± 1.1 vs. 1.4 ± 0.4%; P < 0.001). After glucagon challenge, EGP did not change in GSD1 patients (0.53 ± 0.04 vs. 0.59 ± 0.24 mg·kg⁻¹·min⁻¹; P = not significant) but increased in healthy controls (1.74 ± 0.03 vs. 3.95 ± 1.34; P < 0.0001). In GSD1 patients, we found an exaggerated increase of intrahepatic phosphomonoesters (0.23 ± 0.08 vs. 0.86 ± 0.19 arbitrary units; P < 0.001), whereas inorganic phosphate decreased (0.36 ± 0.08 vs. -0.43 ± 0.17 arbitrary units; P < 0.01). Intracerebral ratios of glucose and lactate to creatine were higher in GSD1 patients (P < 0.05 vs. control). Therefore, hepatic defects of glucose metabolism persist in young adult GSD1 patients. Uptregulation of the glucose and lactate transport at the blood-brain barrier could be responsible for the amelioration of hypoglycemic symptoms.

endogenous glucose production; glucose-6-phosphate; intrahepatocellular lipid content; hypoglycemia

GLYCOGEN STORAGE DISEASE (GSD) type 1 is an inherited defect of endogenous glucose production (EGP) occurring approximately once in every 100,000 live births (44). Two forms of GSD1 are known at present: GSD1a, caused by a defect of the glucose-6-phosphatase hydrolase, and GSD1b, caused by non-functioning mutations of the glucose-6-phosphatase translocase. Both known defects of GSD1 inactivate the multienzyme complex of glucose-6-phosphatase, which is necessary for the terminal step of gluconeogenesis, the conversion of glucose-6-phosphate (G6P) to glucose. Thus G6P is trapped inside the cell and cannot be released into the circulation, resulting in susceptibility to hypoglycemia during periods of fasting. Mutation search in liver biopsies is the gold standard for diagnosis of this disease. In healthy subjects, glucagon stimulates glycogen breakdown and gluconeogenesis, and thus insufficient increase of plasma glucose after injection of glucagon has been used as an alternative, noninvasive diagnostic test for impaired hepatic glucose production (40, 41).

Interestingly, there is only limited information on EGP in GSD1. Most studies have been performed in children, where glucose production was found to be ~50% lower than normal (29, 40). However, these results are questionable because determinations of EGP by stabile tracer techniques have used fixed priming and short equilibration periods, thus overestimating EGP. In adolescent patients with GSD1, the propensity for hypoglycemia seems to decrease (18), possibly due to an increase in EGP. Even less is known about EGP in adult patients with GSD1. Powell et al. (31) reported on two adults with GSD1 who maintained plasma glucose concentrations of ~60 mg/dl even after three-day fasts in the face of normal glucose utilization, but EGP was not determined. Using hepatic vein catheters, Havel et al. (18) reported splanchnic glucose output to be ~60% of normal. However, these measurements do not take into account renal glucose production, and thus EGP has yet to be measured in adult GSD1 patients.

Invasive liver biopsies revealed increased (9, 29) or unchanged (19) hepatocellular G6P concentrations. These divergent results could be due to limitations inherent to invasive tissue sampling (36, 39). Nuclear magnetic resonance spectroscopy (NMRS) overcomes these limitations (33) and allows detection of increased hepatocellular concentrations of phosphomonoesters (PME) (28) and intrahepatocellular lipids (1). However, the PME peak derived from liver tissue contains the resonances of phosphorylated carbohydrates, including hexose, pentose, and triose phosphates as well as phosphocholine and phosphoethanolamine (12), and thus it has not yet been proven that the increased concentration of PME results from elevation of G6P.

Another organ likely to be affected by GSD1 is the brain (26). Similar to the mechanisms leading to impaired hormonal counterregulation during hypoglycemia in type 1 diabetes (8), recurrent hypoglycemia also potentially increases the expression of Endocrinology and Metabolism, Dept. of Internal Medicine III, Medical Univ. of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria (e-mail: martin.bischof@meduniwien.ac.at).
sion of glucose transporters in the brain of GSD1 patients. Thus the reduced propensity for hypoglycemia symptoms in older GSD1 patients might not only be due to changes in systemic glucose metabolism but could also result from more efficient cerebral glucose uptake (14) or adaptations of intracerebral energy metabolism (4, 7). Remarkably, brain metabolism of GSD1 patients has not yet been examined.

The present study was therefore designed to 1) assess EGP during steady state after a long equilibration period, 2) convincingly demonstrate intrahepatic accumulation of G6P by inducing glycolysis with glucagon, 3) determine the amount of intrahepatoendothelial lipid (HCL) accumulation, and 4) elucidate the mechanisms for milder hypoglycemia symptoms in young adult GSD1 patients by examining intracerebral energy and glucose metabolism.

MATERIALS AND METHODS

Experimental subjects. Four patients (3 female, 1 male) with genetically diagnosed GSD1 and four healthy control subjects (3 female, 1 male) were included in the study. To be eligible, they had to be at least 18 years old; exclusion criteria were any acute illness within 2 wk or donation of blood within 30 days before the study, clinically relevant anemia, pregnancy, metal medical devices or fragments in the body, and claustrophobia. Written informed consent was obtained from the participants. The study was performed in accordance with the Declaration of Helsinki (1964), including current revisions, and was approved by the Ethics Committee of the Medical University of Vienna.

Study protocol. On the first study day, patients arrived at the metabolic ward of the Division of Endocrinology and Metabolism, Department of Internal Medicine III, at 10:00 pm. Catheters were inserted into antecubital veins of the left and right arms for blood sampling and glucose infusion, respectively. To avoid hypoglycemia from prolonged fasting, plasma glucose was kept at ~70 mg/dl by a variable infusion of 5% glucose throughout the experiment in GSD1 patients. At 4:00 a.m., a bolus [3.5 mg/kg × body wt (kg) × [fasting blood glucose (mg/dl)/70 mg/dl]] followed by a continuous [0.035 mg/kg × body wt (kg) per min] infusion of D-16,6-[2H2]glucose (Cambridge Isotope Laboratories, Andover, MA) was started. To ensure stable plasma enrichments, the variable glucose infusion was enriched with 5% [1H2]glucose according to the hot glucose infusion protocol in patients with GSD1, whereas no glucose infusion was needed to maintain euglycemia in controls (16). On the second trial day, participants were transferred to the magnetic resonance unit and NMRS was performed between 8:00 a.m. and 1:00 p.m. At 11:00 a.m., 1 mg glucagon dissolved in 20 ml saline was injected intravenously. Blood samples for assessment of fasting serum triglycerides, total cholesterol, and uric acid as well as EGP (3 during steady-state, i.e., ~7 h after start of glucose infusion and 1 after administration of glucagon), glucoregulatory hormones, free fatty acids (FFA), lactate, and [1H3]glucose were used to directly and noninvasively assess liver and brain metabolism with the use of a 3.0-T/80-cm NMR Medspec spectrometer and 10-cm-diameter circular [1H4/C4/P4] triple-tuned surface coil (both Bruker Biospin, Ettlingen, Germany) (Fig. 1). The volunteers remained in supine position inside the magnet bore. At first, [1H3/P3] NMRS of the brain was performed as previously described (4, 7). Briefly, [31P] spectra were obtained by a pulse-and-acquire method (repetition time 5 s) from the occipital lobe of the brain. For this measurement, an automatic shimming routine on the signal from the sensitive volume of the coil was applied. Signal from brain tissue was localized, and signal from superficial tissues and the skull was suppressed by adjusting flip angle of 250–µs rectangular excitation pulses to ~180° in the coil plane. Peak positions and intensities were read manually from the spectra by using the software supplied by the system manufacturer (Bruker Biospin). For acquisition of [1H] spectra (Bruker), the volume of interest (VOI) 4 × 1 × 4 cm3 was selected in the occipital lobe of the brain with the stimulated echo acquisition mode (STEAM) localization technique [repetition time (TR)/echo time (TE)/middle time (TM) = 6,000/9/50 ms] (17). Manual shimming was applied on the [1H] water signal from the VOI, reaching the line width (full-width half maximum) of 7–11 Hz. The water signal was suppressed by the modified SWAP (sequence for water suppression with adiabatic modulated pulses) method (27). The relative peak areas were obtained by using the LCModel software package (created by S. W. Provencher, Oakville, ON, Canada) (32). Simulated spectral basis containing spectra of alanine, aspartate, creatine, phosphocreatine, γ-aminoxylic acid, glucose, glutamine, glutamate, choline compounds, myo-inositol, scyllo-inositol, N-acetyl aspartate (NAA), N-acetyl aspartylglutamate (NAAG), taurine, macromolecules, and lipids in the spectral range from 0.2 to 4.0 ppm was included into the analysis. The intraindividual CVs calculated from the integrated peak areas of creatine were ~<5–6%, which was comparable with our previous studies (4). Thereafter, the surface coil was placed over the lateral lobe of the liver. Interleaved measurement of these three nuclei allowed for simultaneous sampling of PME, glycogen, and HCL concentrations as described previously (37): the time course of the changes in PME and inorganic phosphate concentration was measured from external volume-suppressed [31P] spectra (TR = 2.5 s, no. of acquisitions = 64) by using the β-ATP signal as an internal reference for the quantitation. Haptic glyceroll concentration was determined at baseline, during, and after glucagon challenge from [31C] spectra (5) (TR = 150 ms, NA = 2,500), where the signal from superficial muscle and adipose tissue was also suppressed by one-dimensional image selected in vivo spectroscopy by comparison with the spectra of an external standard solution (150 mmol/l glycogen + 50 mmol/l KCl). HCL content was assessed from methylene and methyl resonance to that of water in localized breath-hold STEAM [1H] spectra (VOI = 3 × 3 × 3 cm3; TM = 30 ms; TE = 15, 20, 30, 50, 70 ms; NA = 1 for each TE) and following the individual spin-spin relaxation correction of water and methylene resonance expressed as percent of total tissue signal (water + methylene + methyl) (1). Gas chromatography-mass spectrometry was applied for determination of [2H] enrichment as previously described (5).

Plasma metabolites and hormones. Plasma glucose concentrations were measured by the glucose oxidase method (glucose analyzer II; Beckman Instruments, Fullerton, CA). Time courses of plasma lactate, FFA, β-hydroxybutyrate, insulin, C-peptide, and glucagon were quantified as described previously (6). Uric acid, triglycerides, cholesterol, and transaminases were routinely determined in the Institute of Medical and Chemical Laboratory Diagnostics of the Vienna General Hospital.

Calculation and statistical evaluation. Rates of EGP were calculated as the tracer infusion rate divided by the mean [2H] MPEs of plasma glucose at steady-state conditions and according to the Steele equation (42) in nonsteady state and are given as milligrams per minute per kilogram body weight per minute. Rates of disappearance (Rd) were estimated as being equal to EGP in controls (steady state) and the sum of EGP and glucose infusion rate in GSD1.

Statistical analysis. Data are given as means ± SE. Changes of sequential data (time curves) within experiments were analyzed by ANOVA for repeated measurements. In addition, the ANOVA for repeated measurements was used to assess differences of a variable within defined time periods. Differences were considered statistically significant at P values <0.05.

RESULTS

Patient characteristics. Four patients with GSD1 [1 male, 3 female, body mass index (BMI) 23.2 ± 6.3 kg/m2, age 21.3 ± 2.9 yr] and four healthy controls (1 male, 3 female, BMI...
23.1 ± 3 kg/m, age 24 ± 3.1 yr) were studied. There were no differences in regard to age or BMI between healthy and GSD1 subjects. GSD1 patients tended to have higher baseline levels of uric acid, serum triglycerides, total cholesterol, and liver-function parameters (Table 1).

Glucose metabolism. Plasma glucose concentrations of GSD1 patients were lower before glucagon challenge compared with controls (mean 67.9 ± 3.0 vs. 86.7 ± 7.3 mg/dl, respectively, P < 0.01). An average glucose infusion rate of 1.4 mg·kg⁻¹·min⁻¹ was necessary to maintain basal glucose concentration in GSD1 patients, whereas no glucose infusion was needed to maintain euglycemia in controls. After glucagon infusion, plasma glucose increased in healthy subjects but remained stable throughout the entire experiment in GSD1 patients (Fig. 2D).

GSD1 patients exhibited significantly lower levels of EGP than healthy controls at baseline (P < 0.01). After challenge with glucagon, levels of EGP did not change in GSD1 patients but increased in healthy controls compared with baseline values (P < 0.0001, Fig. 3). During steady state, R4 was similar (P = 0.48) in GSD1 patients (1.92 ± 0.87 mg·kg⁻¹·min⁻¹) and healthy controls (1.74 ± 0.04 mg·kg⁻¹·min⁻¹).

Plasma concentrations of metabolites and hormones. Whereas plasma lactate levels were higher in GSD1 patients throughout the experiment (P < 0.02 vs. controls at baseline and 1 h after glucagon; P < 0.03 after 2 h), plasma concentrations of FFA were increased in GSD1 only at baseline (Table 2). Both groups showed comparable levels of butyrate at baseline and after glucagon administration. Plasma concentrations of glucagon and insulin were similar in both groups.

Intrahepatic glucose metabolism. Healthy volunteers and GSD1 patients displayed a different pattern of hepatic response to the glucagon injection (Fig. 2, A–C). In GSD1 patients, baseline hepatic glycogen concentrations (Fig. 2B) were ~100% higher (P = 0.05 vs. control) and decreased only during the first 15–20 min, whereas an increase in hepatic glycogen concentrations was observed during the rest of the experiment. After glucagon challenge, PME markedly increased, whereas inorganic phosphate levels decreased. In healthy subjects, hepatic glycogen decreased throughout the experiment. Both PME and inorganic phosphate (Fig. 2, A and C) were found to increase after glucagon injection.

HCL content was significantly higher in GSD1 patients than in controls at baseline (16.3 ± 1.1 vs. 1.4 ± 0.4%), HCL levels
not being different after glucagon challenge in both groups (Fig. 4).

**Brain metabolism.** Analysis of energy-rich phosphates revealed no difference between both groups. Phosphocreatine/ATP as well as inorganic phosphate/ATP ratios were not different between GSD1 patients and healthy controls. 1H NMRS revealed increased concentrations of intracerebral glucose and lactate in GSD1 patients. /H9252-Hydroxybutyrate could only be detected in few GSD1. The intracerebral concentrations of glutamine, glutamate, glycerophosphocholine, myo-inositol, and NAA (as ratios to creatine) were comparable between groups (Table 3).

**DISCUSSION**

Employing noninvasive NMRS and stable-isotope tracer techniques in GSD1 patients, we found 1) a 70% decrease in EGP; 2) a marked increase in PME, reflecting G6P formation, in response to glucagon challenge; 3) an 11-fold amount of HCL content, and 4) higher concentrations of intracerebral glucose and lactate compared with healthy controls.

Reduced EGP is the major metabolic abnormality of GSD1 (43). There is some evidence that the propensity for hypoglycemia decreases with age in GSD1, and because Rd was shown to be normal in these patients (18), an increase in EGP compared with children with GSD1 would be expected. Employing state-of-the-art techniques, we found that EGP remained at $\sim 30\%$ of normal even in young adults with GSD1. This is markedly lower than the previously reported EGP in children (22, 43) and adults (18) with GSD1. Rd was not different between GSD1 patients and healthy controls, which is in agreement with previous studies (31). Thus we found no evidence that glucose metabolism is normalized in adult GSD1 patients.

In comparison with healthy volunteers, we found hepatic glycogen content of GSD1 patients to be twofold higher at basal conditions. This is in good agreement with previous data resulting from liver biopsies (38) and magnetic resonance spectroscopy (35).

This study also followed the time course of hepatic glucose metabolism after intravenous application of a glucagon bolus. In healthy volunteers, glucagon stimulated hepatic glycogen breakdown and increased EGP. The intrahepatic concentrations of both PME and inorganic phosphate showed a trend toward increase from baseline conditions. Patients with GSD1 displayed a pathological alteration of hepatic glucose metabolism after glucagon challenge: hepatic glycogen only decreased during the first 15 min and then started to increase again. We could not find an increase in EGP as seen in healthy volunteers. Furthermore, there was a strong increase in PME during the first 30 min, while at the same time inorganic phosphate decreased.

\begin{table}
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Uric acid, mg/dl</td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>4.8±0.9</td>
</tr>
<tr>
<td>GSD1</td>
<td>7.4±2.5</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>73±26</td>
</tr>
<tr>
<td>GSD1</td>
<td>742±423</td>
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<tr>
<td>Total cholesterol, mg/dl</td>
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<tr>
<td>Healthy</td>
<td>162±13</td>
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<tr>
<td>GSD1</td>
<td>280±80</td>
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<tr>
<td>ALT, U/l</td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>21±3</td>
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<tr>
<td>GSD1</td>
<td>122±101</td>
</tr>
<tr>
<td>GGT, U/l</td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>17±1</td>
</tr>
<tr>
<td>GSD1</td>
<td>117±103</td>
</tr>
</tbody>
</table>

All data are given as means ± SD. GSD1, glycogen storage disease type 1; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutaryltransferase.

![Fig. 2. Intrahepatic concentrations of PME (A), glycogen (B), and P (C) after injection of 1 mg glucagon. Plasma glucose concentrations of GSD1 (○) and healthy subjects (●) are given in D (arrow indicates glucagon challenge). *P < 0.0001 vs. healthy subjects; §P < 0.001 vs. healthy subjects.](http://ajpendo.physiology.org/ by 10.220.33.5 on July 8, 2017)
There is controversial data on glucose metabolism in GSD1 more than 40 years ago, needle-biopsy studies suggested increased hepatocellular G6P concentrations in GSD1 patients (9, 29), which was contradicted by other reports (19). Even at 3 T, in vivo NMRS cannot directly quantify G6P because the PME peak contains the resonances of hexose, pentose, and triose phosphates as well as phosphocholine and phosphoethanolamine (12). Thus, to convincingly demonstrate accumulation of G6P, we induced glycogenolysis by injecting glucagon. Because this hormone stimulates glycogenolysis only in the liver (21), a contamination of the PME signal by overlying intercostal muscles can be ruled out. The conversion of G6P to free glucose is blocked in GSD1, and thus the early increase of PME most likely results from hepatocellular G6P. Our results clearly show that patients with GSD1 exhibit three- to fivefold increased hepatocellular G6P concentrations in GSD1 patients more than 40 years ago, needle-biopsy studies suggested increased hepatocellular G6P concentrations in GSD1 patients (9, 29), which was contradicted by other reports (19). Even at 3 T, in vivo NMRS cannot directly quantify G6P because the PME peak contains the resonances of hexose, pentose, and triose phosphates as well as phosphocholine and phosphoethanolamine (12). Thus, to convincingly demonstrate accumulation of G6P, we induced glycogenolysis by injecting glucagon. Because this hormone stimulates glycogenolysis only in the liver (21), a contamination of the PME signal by overlying intercostal muscles can be ruled out. The conversion of G6P to free glucose is blocked in GSD1, and thus the early increase of PME most likely results from hepatocellular G6P. Our results clearly show that patients with GSD1 exhibit three- to fivefold higher concentrations of hepatic G6P than controls, paralleled by a decrease of hepatic inorganic phosphate, which is used to synthesize G6P. The intracellular trapping of glucose increases glycolysis and augments lactate formation (22).

Hyperlipidemia, as seen in our patients, is a characteristic feature of GSD1 (15) and is associated with storage of neutral lipids in the liver (25), being more than 11 times higher compared with healthy controls. De novo lipogenesis and cholesterobiogenesis is increased in GSD1, possibly due to increased production of acetyl-CoA and signaling actions of G6P (3). Furthermore, increased splanchnic uptake of FFA (2) as well as inhibition of hepatic fatty-acid oxidation by increased malonyl-CoA could also contribute to the pathogenesis of steatosis. We found plasma β-hydroxybutyrate to be similar in GSD1 and healthy subjects, indicating no impairment in hepatic fatty-acid oxidation. Thus the high hepatic lipid content

Table 2. Plasma concentrations of metabolites and hormones before, 1 h, and 3 h after glucagon

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Baseline</th>
<th>1 h</th>
<th>3 h</th>
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<tbody>
<tr>
<td>FFA, mmol/l</td>
<td>330±227</td>
<td>134±132</td>
<td>651±179</td>
</tr>
<tr>
<td>GSD1</td>
<td>783±74§</td>
<td>512±329</td>
<td>894±229</td>
</tr>
<tr>
<td>Lactate, mg/dl</td>
<td>949±224</td>
<td>1,136±146</td>
<td>1,173±302</td>
</tr>
<tr>
<td>GSD1</td>
<td>8,675±3,095</td>
<td>10,429±3,796</td>
<td>8,829±4,416§</td>
</tr>
<tr>
<td>Butyrate, µmol/l</td>
<td>29±14.5</td>
<td>18.3±32.3</td>
<td>32.3±5.4</td>
</tr>
<tr>
<td>GSD1</td>
<td>22.8±8.7</td>
<td>24.8±12.4</td>
<td>25.8±12.1</td>
</tr>
<tr>
<td>Glucagon, pg/ml</td>
<td>76.3±9.7</td>
<td>566±339.3</td>
<td>77.3±7.9</td>
</tr>
<tr>
<td>GSD1</td>
<td>65.5±21</td>
<td>1,391±1,155.1</td>
<td>125.1±61.3</td>
</tr>
<tr>
<td>Insulin, µU/ml</td>
<td>6.5±0.7</td>
<td>8.4±1.9</td>
<td>7.0±2.4</td>
</tr>
<tr>
<td>GSD1</td>
<td>9.2±1.4</td>
<td>12.2±1.5</td>
<td>4.8±0.7</td>
</tr>
<tr>
<td>C-peptide, µU/ml</td>
<td>2.7±0.4</td>
<td>4.0±0.4</td>
<td>2.0±0.3</td>
</tr>
<tr>
<td>GSD1</td>
<td>1.5±0.3†</td>
<td>1.8±0.4†</td>
<td>1.5±0.7†</td>
</tr>
</tbody>
</table>

Data are given as means ± SD. FFA, free fatty acids. *P < 0.001 vs. healthy; †P < 0.01 vs. healthy; ‡P < 0.02 vs. healthy; §P < 0.03 vs. healthy.
is most likely due to increased hepatic FFA uptake and lipogenesis.

Intracerebral glucose and lactate concentrations were also increased in GSD1 patients. The increase of intracerebral glucose most likely results from increased glucose uptake due to recurrent hypoglycemia as described in well-controlled type 1 diabetic patients (8). A very similar mechanism has also been described for upregulation of monocarboxylic acid transporters at the blood-brain barrier and possibly glial and neuronal membranes (24). In addition, the abundant supply of lactate in GSD1 patients could contribute to the high intracerebral lactate concentrations. In the light of a persistent defect in EGP and normal $R_g$, it is tempting to assume that both increased uptake of lactate and glucose are responsible for the amelioration of hypoglycemia symptoms in GSD1 patients.

The glycogen content of the human brain is estimated at $\sim$3.5 $\mu$mol/g and thus represents a substantial glucose store relative to free glucose (30). Indeed, there is evidence that glycogen is depleted under conditions of severe glucose deprivation and that increased storage of glycogen after acute severe hypoglycemia potentially contributes to hypoglycemia unawareness (11). Because we were not able to detect glycogen in pilot studies and thus have not included $^{13}$C-NMR in our experimental protocol, we can only speculate whether brain glycogen content is affected by GSD1. However, because prolonged chronic hypoglycemia, which is very similar to the condition of GSD1, did not have any effect of brain glycogen content (23) and a significant contribution of brain glycogen to cerebral glucose metabolism is only found under severe metabolic stress (10), it seems unlikely that any of our observations are caused or exacerbated by alterations of brain glycogen storage or metabolism.

Both the intracerebral concentrations of the neuronal marker NAA (20) as well as the astrocyte marker myo-inositol (13) were similar in healthy and GSD1 subjects, making a major structural alteration of the brain unlikely.

A limitation of our study is the small number of subjects studied. Because the number of young adult patients with GSD1 is small, we were not able to include more subjects in this study. We did not adjust for multiple comparisons, and GSD1 is small, we were not able to include more subjects in our study. Because the number of young adult patients with structural alteration of the brain unlikely.

In summary, we found that the hepatic defects of glucose metabolism, i.e., low EGP that is insufficiently stimulated by glucagon, persist in young adult GSD1 patients. This is paralleled by a marked increase in $G_6P$, which gives way to significantly enhanced HCL accumulation. Moreover, increased uptake of glucose and lactate could be responsible for the amelioration of hypoglycemic symptoms in these patients.

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