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ORIGINAL ARTICLE

A potential role for muscle in glucose homeostasis: in vivo kinetic studies in glycogen storage disease type 1a and fructose-1,6-bisphosphatase deficiency

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Abstract

Background A potential role for muscle in glucose homeostasis was recently suggested based on characterization of extrahepatic and extrarenal glucose-6-phosphatase (glucose-6-phosphatase- β). To study the role of extrahepatic tissue in glucose homeostasis during fasting glucose kinetics were studied in two patients with a deficient hepatic and renal glycogenolysis and/or gluconeogenesis.

Design Endogenous glucose production (EGP), glycogenolysis (GGL), and gluconeogenesis (GNG) were quantified with stable isotopes in a patient with glycogen storage disease type 1a (GSD-1a) and a patient with fructose-1,6-bisphosphatase (FBPase) deficiency. The [$6,6\text{-}^2\text{H}_2$]glucose dilution method in combination with the

deuterated water method was used during individualized fasting tests.

Results Both patients became hypoglycemic after 2.5 and 14.5 h fasting, respectively. At that time, the patient with GSD-1a had EGP 3.84 $\mu\text{mol/kg}$ per min (30% of normal EGP after an overnight fast), GGL 3.09 $\mu\text{mol/kg}$ per min, and GNG 0.75 $\mu\text{mol/kg}$ per min. The patient with FBPase deficiency had EGP 8.53 $\mu\text{mol/kg}$ per min (62% of normal EGP after an overnight fast), GGL 6.89 $\mu\text{mol/kg}$ per min GGL, and GNG 1.64 $\mu\text{mol/kg}$ per min.

Conclusion EGP was severely hampered in both patients, resulting in hypoglycemia. However, despite defective hepatic and renal GNG in both disorders and defective hepatic GGL in GSD-1a, both patients were still able to produce glucose via both pathways. As all necessary enzymes of these pathways have now been functionally detected in muscle, a contribution of muscle to EGP during fasting via both GGL as well as GNG is suggested.

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Abbreviations

EGP	Endogenous glucose production
GGL	Glycogenolysis
GNG	Gluconeogenesis
GSD	Glycogen storage disease
FBPase	Fructose-1,6-bisphosphatase

Introduction

Endogenous glucose production (EGP) during fasting is predominantly derived from hepatic gluconeogenesis (GNG) and glycogenolysis (GGL), with a minor contribution from renal GNG (Ekberg et al. 1999). Recently, a potential additional role for muscle in EGP has been

suggested based on characterization of an isoform of glucose-6-phosphatase, glucose-6-phosphatase- β (Glc-6-Pase- β) expressed in muscle and other extrahepatic tissue (Martin et al. 2002; Shieh et al. 2003). Glc-6-Pase- β has been shown to have structural and functional properties in muscle comparable with glucose-6-phosphatase- α expressed in liver, kidney, and intestine (EC 3.1.3.9; Glc-6-Pase- α) (Shieh et al. 2004). As patients with glycogen storage disease 1a (GSD-1a; OMIM #232200) are deficient for Glc-6-Pase- α , resulting in defective hepatic and renal GNG and GGL, Glc-6-Pase- β activity in muscle might explain the residual EGP previously observed in these patients (Kalhan et al. 1982; Schwenk et al. 1986; Tsalikian et al. 1984; Weghuber et al. 2007). In order to investigate the potential role of extrahepatic and extrarenal tissue in glucose homeostasis during fasting in vivo, we performed whole-body kinetic studies in a patient with GSD-1a and a patient with fructose-1,6-bisphosphatase (FBPase) deficiency (OMIM #229700), an inborn error of hepatic and renal GNG. For the first time, differential contributions of GGL and GNG to EGP during fasting were quantified in these disorders using the [6,6- $^2\text{H}_2$]glucose isotope dilution method combined with the deuterated water method (Landau et al. 1996; Wolfe et al. 2005).

Materials and methods

Study individuals

Patient 1 presented with severe hypoglycemia (plasma glucose 0.3 mmol/L) and hepatomegaly at the age of 4 months. GSD-1a was diagnosed on the basis of a complete deficiency of glucose-6-phosphatase activity in a fresh liver biopsy. This diagnosis was later confirmed by mutation analysis revealing two mutations known to completely abolish Glc-6-Pase- α activity (Table 1) (Rake et al. 2000). Patient 2 was admitted at 11 months because of convulsions due to hypoglycemia. At this time, she exhibited severe metabolic acidosis with hyperlactatemia

and a marked hepatomegaly. She was diagnosed with FBPase deficiency by repeated demonstration of undetectable enzyme activity in leucocytes (Table 1) (Baker et al. 1970).

The in vivo stable isotope studies were approved by the Institutional Review Board. Both patients and their parents gave informed consent prior to the studies.

Study protocol

Fasting tests were performed at the age of 17.9 and of 16.7 years, respectively. Both patients were admitted 1 day before the test. An intravenous catheter was inserted into antecubital veins of both arms after topical application of lidocaine cream. One catheter was used to administer [6,6- $^2\text{H}_2$]glucose and the other for blood sampling. At baseline, a blood sample was collected to determine background enrichment of deuterated water in plasma. Fasting was started at a time considered safe based on previous experience with fasting in the patients. Prior to fasting, both patients consumed their regular evening meal. Patient 1 received nocturnal nasogastric drip feeding without glucose polymers. This drip feeding was discontinued 2 h prior to initiation of [6,6- $^2\text{H}_2$]glucose infusion and substituted by an unlabeled glucose infusion at a rate of 5 mg/kg per min, which was continued until the start of the [6,6- $^2\text{H}_2$]glucose infusion. Both patients remained fasted throughout the test and maintained bed rest (Fig. 1).

Twelve hours prior to [6,6- $^2\text{H}_2$]glucose infusion, both patients drank deuterium-enriched water (99% pure; Cambridge Isotope Laboratories, Cambridge, MA, USA) at a dose of 5 g/kg body water divided in five doses within 120 min (Ackermans et al. 2001). The total amount of body water (kg) was estimated as 60% of body weight (kg) (Friis-Hansen 1961). Thereafter, patients were only allowed to drink tap water enriched to 0.5% with deuterated water until the end of the test. At the start of the fasting test in patient 1, after 10 h of fasting in patient 2, and after collection of a blood sample to determine background enrichment of

Table 1 Patient characteristics

	Sex	Age (years)	Height (m)	Weight (kg)	Inborn error of metabolism	Enzyme activity (normal range)	DNA analysis
Patient 1	M	17.9	1.76 (-1 SD)	75.0 (+1.5 SD)	Glucose-6-phosphatase deficiency (GSD 1a)	0.0 (10–30) nmol/min/mg protein ^a	R170X Δ F327 ^b
Patient 2	F	16.7	1.50 (-2 SD)	60.0 (+2 SD)	Fructose-1,6-bisphosphatase deficiency	<0.1 (3–20) nmol/min/mg protein ^c	ND

ND not determined

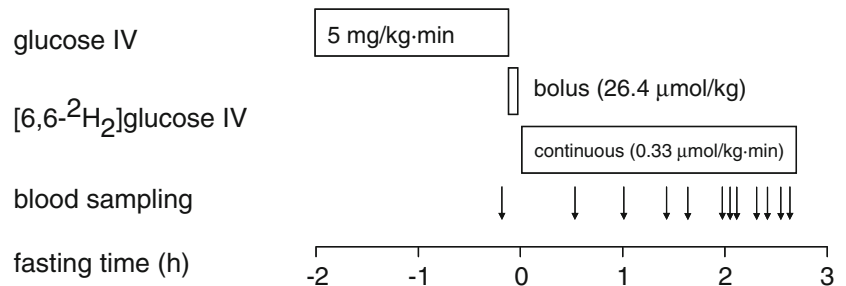
^a In hepatocytes

^b Rake JP et al 2000

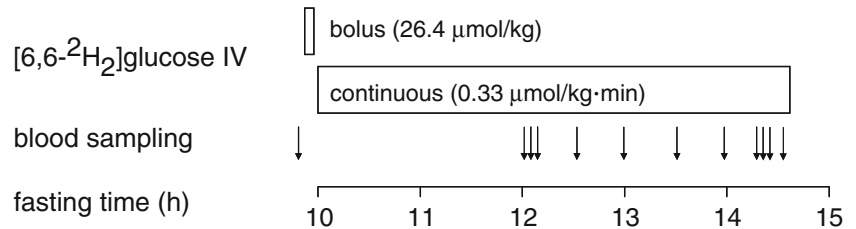
^c In leucocytes, repeated measurements; Baker L et al. 1970

Fig. 1 Study protocols in patients 1 [glycogen storage disease type 1a (GSD-1a)] and 2 [fructose-1,6-bisphosphatase (FBPase)] deficiency

Patient 1 (GSD-1a)



Patient 2 (FBPase deficiency)



[6,6-²H₂]glucose in plasma, a primed continuous infusion of [6,6-²H₂]glucose (99% pure; Cambridge Isotope Laboratories) was started (bolus 26.4 μmol/kg; continuous infusion 0.33 μmol/kg per min) to reach an estimated 2% plasma enrichment (Bier et al. 1977). Blood samples were drawn every 5 min at the beginning and end of the test when patients became hypoglycemic, and every 30 min during the test (Fig. 1). Samples were centrifuged at 3,000 rpm for 10 min, after which plasma was collected and stored at -20°C. Blood samples to determine fractional GNG were immediately deproteinized by adding an equal amount of 10% perchloric acid. These samples were centrifuged at 4,000 rpm for 20 min, after which the supernatant was collected and stored at -20°C. Blood glucose levels were monitored every hour and more frequently when glucose levels dropped <3.5 mmol/L. The test was terminated when clinical symptoms of hypoglycemia occurred, after which patients were immediately given carbohydrate-rich drinks and a meal.

Analytical methods

Plasma glucose concentration Plasma glucose levels were analyzed with the hexokinase method on a Roche MODULAR P800 analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

Hormones Plasma insulin and cortisol concentrations were determined on an Immulite 2000 system (Diagnostic Products Corporation, Los Angeles, CA, USA). Insulin

was measured with a chemiluminescent immunometric assay, and cortisol was measured with a chemiluminescent immuno assay. Glucagon was determined by RIA (Linco Research, St. Charles, MO, USA). Plasma free fatty acid (FFA) levels were measured by an enzymatic method (NEFAC; Wako Chemicals GmbH, Neuss, Germany).

Plasma [6,6-²H₂]glucose enrichment Plasma glucose enrichments were determined as described previously (Ackermans et al. 2001). Briefly, plasma was deproteinized with methanol and evaporated to dryness. The extract was derivatized with hydroxylamine and acetic anhydride (Reinauer et al. 1990). The aldonitrile pentaacetate derivative of glucose was extracted into methylene chloride and evaporated to dryness. The extract was reconstituted in ethyl acetate and injected into a gas chromatograph/mass spectrometer (HP 6890 series GC system and 5973 Mass Selective Detector, Agilent Technologies, Palo Alto, CA, USA). Separation was achieved on a J&W DB17 column (30 m × 0.25 mm, d_f 0.25 μm; J&W Scientific, Folsom, CA). Glucose ions were monitored at *m/z* 187, 188 and 189. The isotopic enrichment of glucose was determined by dividing the peak area of *m/z* 189 by the peak area of *m/z* 187 after correction for background enrichment of [6,6-²H₂]glucose.

Deuterium enrichment in glucose at position C5 and in plasma water Glucose was converted to hexamethylene tetra-amine (Ackermans et al. 2001; Landau et al. 1996). Hexamethylene tetra-amine was injected into a gas chromatograph/

mass spectrometer (HP 6890 series GC system and 5973 Mass Selective Detector, Agilent Technologies). Separation was achieved on an AT-amine column (30 m × 0.25 mm, d_f 0.25 μ m; Alltech Associates Inc, Deerfield, IL, USA). Hexamethylene tetra-amine ions were monitored at m/z 140 and 141. Deuterium enrichment in plasma was determined by a method adapted from Previs et al. (Previs et al. 1996).

Calculations and statistical analysis

Rate of glucose appearance The rate of glucose appearance in plasma (R_a glucose), reflecting whole-body endogenous glucose production (EGP) during fasting, was calculated with Steele's non-steady-state equation (Steele 1959). The fraction of the total extracellular glucose pool was assumed to be equal to the extracellular water compartment, which was between 20% and 25% of body weight in the patients studied (Friis-Hansen 1961). Calculated rates of EGP were compared to rates of EGP after overnight fasting in healthy individuals of the same age, as reported previously (Bier et al. 1977).

Absolute gluconeogenesis and glycogenolysis Absolute GNG was calculated by multiplying R_a glucose by the fractional GNG. Fractional GNG was calculated as follows (Landau et al. 1996): 100% · (deuterium enrichment in glucose at position C5/deuterium enrichment in plasma water). Absolute GGL was calculated by subtracting absolute GNG from R_a glucose.

Results

Plasma glucose, FFA, and glucoregulatory hormones

Plasma glucose In patient 1, after exogenous glucose supplementation was stopped, plasma glucose decreased from 6.3 mmol/L to 1.1 mmol/L within 2.5 h (Fig. 2). In patient 2, plasma glucose decreased from 3.7 mmol/L to 2.5 mmol/L at 12–14.5 h of fasting (Fig. 3).

Plasma FFA Plasma FFA concentration was 1.64 mmol/L in patient 1 and 2.16 mmol/L in patient 2 at the end of the test. This may have been inaccurate in patient 1, as the hypertriglyceridemia could have interfered with the enzymatic assay.

Glucoregulatory hormones At the end of the test in both patients, plasma insulin levels were undetectable. Plasma glucagon was 190 ng/L in both patients, and plasma

cortisol was 666 nmol/L in patient 1 and 792 nmol/L in patient 2.

Glucose kinetics

Patient 1 (GSD-1a) After 2 h of fasting, EGP was 5.09 μ mol/kg per min, normal after an overnight fast 13.23 μ mol/kg per min (Bier et al. 1977). The test was terminated at 2.6 h of fasting (EGP was 3.84 μ mol/kg per min). GGL decreased from 4.39 to 3.09 μ mol/kg per min between 2 and 2.6 h of fasting, representing 86.2–80.5% of EGP, respectively. GNG was low but detectable: 0.60 and 0.78 μ mol/kg per min (13.7–19.6% of EGP) at 2–2.6 h of fasting (Fig. 2).

Patient 2 (FBPase deficiency) After 12 h of fasting, EGP was 13.27 μ mol/kg per min, corresponding with the predicted EGP after an overnight fast for this age (13.77 μ mol/kg per min) (Bier et al. 1977). EGP decreased to 8.53 μ mol/kg per min during the subsequent 2.5 h (14.5 h of fasting). At 12 h of fasting, GGL was 10.44 μ mol/kg per min (78.7% of EGP), decreasing to 6.88 μ mol/kg per min (80.7% of EGP) during the subsequent 2.5 h of fasting. GNG was 2.83 μ mol/kg per min (21.3% of EGP) at 12 h of fasting, decreasing to 1.65 μ mol/kg per min (19.3% of EGP) during the subsequent 2.5 h (Fig. 3).

Discussion

We report for the first time the contribution of both GGL and GNG to EGP during fasting in a patient with Glc-6-Pase- α deficiency (GSD-1a) and a patient with FBPase deficiency. Our data on glucose kinetics show a persistent EGP from both GGL and GNG in both patients, despite their undetectable enzyme activities. On the basis of these results, a potential role of muscle in glucose homeostasis via both GGL and GNG in vivo is suggested. In patient 1, Glc-6-Pase- α activity was completely deficient, which was confirmed by mutation analysis (Table 1) (Rake et al. 2000). This excludes any contribution from liver, kidney, or small intestine to EGP. However, EGP in this patient was still 30% of the predicted EGP in healthy individuals of the same age after an overnight fast (Bier et al. 1977). This is in line with previous studies showing residual EGP, even up to 60% of normal, in patients with GSD-1 (Kalhan et al. 1982; Schwenk et al. 1986; Tsalikian et al. 1984; Weghuber et al. 2007).

Three different explanations for the presence of EGP in GSD-1 have been proposed. First, it has been suggested that

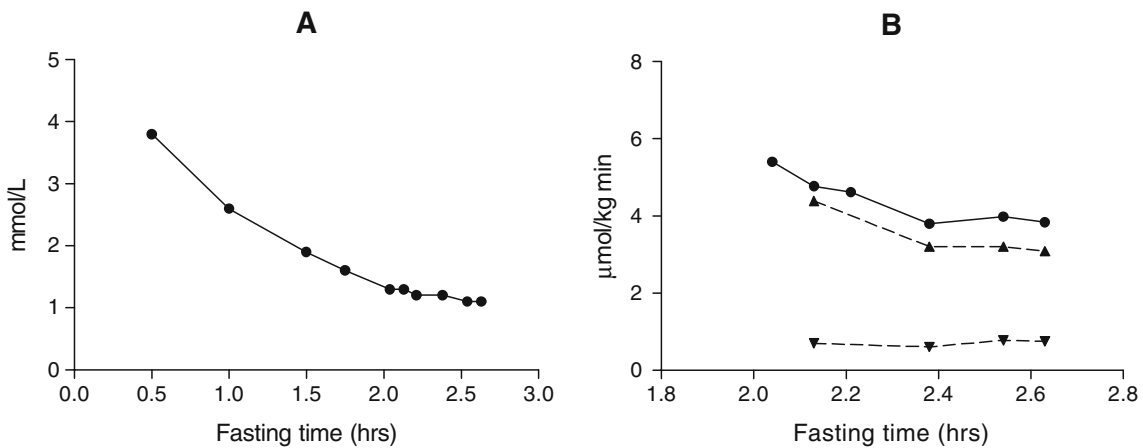


Fig. 2 Glucose kinetics in relation to plasma glucose concentration and fasting duration in a patient with glucose-6-phosphatase deficiency (GSD-1a). Plasma glucose concentrations are depicted

in the *left panel* (A). Endogenous glucose production (EGP; ●), glycogenolysis (GGL; ▲) and gluconeogenesis (GNG; ▼) are depicted in the *right panel* (B)

EGP is based on increased cycling through hepatic glycogen via action of amylo-1,6-glucosidase. However, this was ruled out by *in vivo* kinetic stable isotope studies (Rother et al. 1995). Second, EGP might be due to lysosomal digestion of hepatic glycogen through α -1,4-glucosidase activity. However, this is very unlikely (Kalderon et al. 1989a; Tsalikian et al. 1984), as α -1,4-glucosidase is not susceptible to substrate or hormonal regulation, and EGP in patients with GSD-1 is influenced by exogenous glucose supplementation (Schwenk et al. 1986; Tsalikian et al. 1984). Third, EGP in GSD-1 may be derived through muscular GGL and/or GNG. This hypothesis was made plausible by recent characterization of muscular Glc-6-Pase- β (Shieh et al. 2003, 2004). Although Glc-6-Pase- β has an approximately eightfold lower glucose-6-phosphatase activity than Glc-6-Pase- α (Shieh et al. 2003), the ubiquitous expression of Glc-6-Pase- β could still result in a significant cumulative glucose-6-phosphatase activity.

The observed wide range in residual EGP between GSD-1a patients of the same age and with completely abolished enzyme activity, which is reflected by the interindividual differences in fasting tolerance in patients with GSD-1 (Kalderon et al. 1989b; Labrune et al. 1993; Moses 2002), may then be explained by differences in muscle mass and/or muscular glycogen content.

In the patient with GSD-1a studied by us, GGL contributed more than 80% to the observed EGP. In addition, GNG still contributed up to 19% to EGP in this patient (Fig. 2b). This contrasts with data from Kalderon et al., who excluded GNG as a source for EGP in GSD-1 based on a lack of carbon recycling from [U-¹³C]glucose (Kalderon et al. 1989a, b). Their method, however, only provides an indirect and nonquantitative assessment of GNG, whereas GNG determined with the deuterated water method, as used in our study, is a direct method to quantify

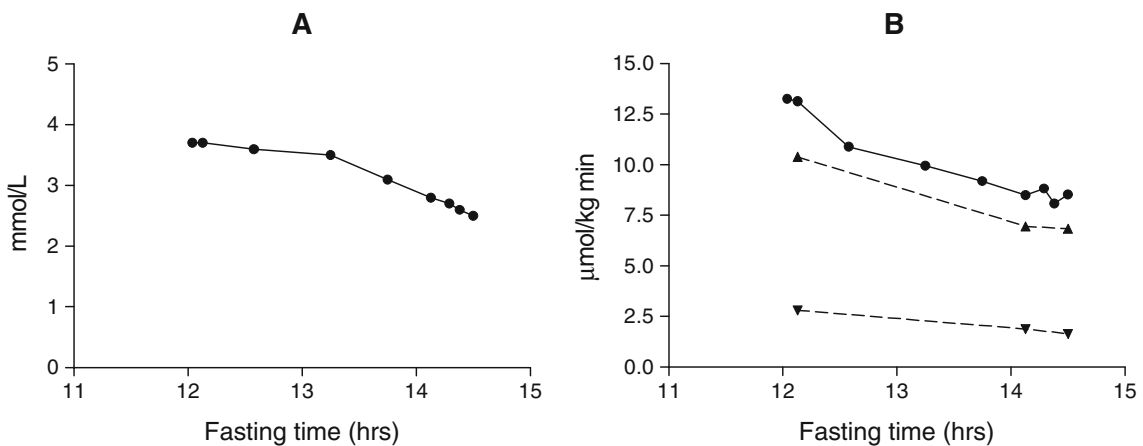


Fig. 3 Glucose kinetics in relation to plasma glucose concentration and fasting duration in a patient with fructose-1,6-bisphosphatase (FBPase) deficiency. Plasma glucose concentrations are depicted in

the *left panel* (A). Endogenous glucose production (EGP; ●), glycogenolysis (GGL; ▲) and gluconeogenesis (GNG; ▼) are depicted in the *right panel* (B)

GNG, yielding accurate results (Wolfe et al. 2005). Possibly, in experiments by Kalderon et al., the ^{13}C label from $[\text{U-}^{13}\text{C}]$ glucose was diluted beyond detection in the triose phosphate and oxaloacetate carbon pools (Kelleher 1986). The observed GNG may also be of muscular origin. Apart from Glc-6-Pase- β , a specific isoform of FBPase, another key enzyme in GNG, is functionally expressed in muscle (Tejwani 1983; Tillmann et al. 1998). Based on the formerly presumed lack of glucose-6-phosphatase activity in muscle, this muscle-specific FBPase was previously considered not to be involved in GNG (Adams et al. 1990; Dzugaj 2006). Alternatively, the observed residual EGP in the patient with GSD-1a might also be explained by renal GGL and/or renal and intestinal GNG, as Glc-6-Pase- β is also expressed in kidney and small intestine (Martin et al. 2002). However, expression of Glc-6-Pase- β is much lower in kidney and small intestine than in muscle (Martin et al. 2002) and has yet to be shown to be functionally active in these tissues. Furthermore, muscle has by far the largest body reservoir of glycogen (Shieh et al. 2004) and is therefore the most likely candidate tissue for extrahepatic and extrarenal glucose production.

A potential role for muscle in GNG is further supported by results of our study in the patient with liver- and kidney-specific FBPase (EC 3.1.3.11) isoform deficiency. Although liver FBPase activity was not assayed and molecular investigation on the FBPase gene was not performed because, until now, only mixed results on disease-causing mutations have been reported in FBPase deficiency (Kikawa et al. 2002), the clinical presentation, in combination with repeated confirmation of absent FBPase activity in leucocytes, is highly suggestive of complete absence of liver- and kidney-specific FBPase isoform in patient 2. We detected that GNG still contributed up to 20% to EGP in this patient (Fig. 3). This might be explained by muscle-specific FBPase isoform activity in combination with Glc-6-Pase- β activity.

It should be mentioned that a transaldolase exchange reaction may have contributed to deuterium labeling of glucose at position C5 (Landau et al. 1966). This would lead to an overestimation of gluconeogenesis as calculated from the ratio of deuterium labeling at glucose position C5 over deuterium labeling at glucose position C2. However, this alternative pathway cannot explain the results in the patient with GSD-1a, as functional hepatic glucose-6-phosphatase is still needed to release deuterium-labeled glucose in plasma. In addition, the contribution of this pathway to glucose C5 deuterium labeling in vivo remains to be determined, and therefore, the deuterated water method is currently one of the two best available methods to quantify gluconeogenesis and glycogenolysis in vivo (Bock et al. 2008).

Although we report a significant endogenous glucose production from gluconeogenesis and glycogenolysis in a

patient with GSD-1a and a patient with FBPase deficiency, it should be noted that EGP in these patients was clearly not sufficient to maintain normoglycemia. Therefore, EGP originating from extrahepatic and extrarenal tissue can play only a minor role in glucose homeostasis in patients with defective hepatic and/or renal glucose production.

In conclusion, we provide in vivo evidence for both GNG and GGL contributing to EGP in GSD-1a. This, in combination with substantial residual GNG in FBPase deficiency, demonstrates an important role of extrahepatic and extrarenal tissue in glucose homeostasis. Our study strongly suggests a role of muscle in glucose homeostasis via both GGL and GNG.

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