Ketone Bodies as a Possible Adjuvant to Ketogenic Diet in PDHc Deficiency but Not in GLUT1 Deficiency

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Abstract Objective: Ketogenic diet is the first line therapy for neurological symptoms associated with pyruvate dehydrogenase deficiency (PDHD) and intractable seizures in a number of disorders, including GLUT1 deficiency syndrome (GLUT1-DS). Because high-fat diet raises serious compliance issues, we investigated if oral L,D-3-hydroxybutyrate administration could be as effective as ketogenic diet in PDHD and GLUT1-DS.

Methods: We designed a partial or total progressive substitution of KD with L,D-3-hydroxybutyrate in three GLUT1-DS and two PDHD patients.

Results: In GLUT1-DS patients, we observed clinical deterioration including increased frequency of seizures and myoclonus. In parallel, ketone bodies in CSF decreased after introducing 3-hydroxybutyrate. By contrast, two patients with PDHD showed clinical improvement as dystonic crises and fatigability decreased under basal metabolic conditions. In one of the two PDHD children, 3-hydroxybutyrate has largely replaced the ketogenic diet, with the latter that is mostly resumed only during febrile illness. Positive direct effects on energy metabolism in PDHD patients were suggested by negative correlation between ketonemia and lactatemia ($r^2 = 0.59$). Moreover, in cultured PDHc-deficient fibroblasts, the increase of CO₂ production after ¹⁴C-labeled 3-hydroxybutyrate supplementation was consistent with improved Krebs cycle activity. However, except in one patient, ketonemia tended to be lower with 3-hydroxybutyrate administration compared to ketogenic diet.

Conclusion: 3-hydroxybutyrate may be an adjuvant treatment to ketogenic diet in PDHD but not in GLUT1-DS under basal metabolic conditions. Nevertheless, ketogenic diet is still necessary in PDHD patients during febrile illness.

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Introduction

Pyruvate dehydrogenase complex deficiency (PDHD) and GLUT1 deficiency syndrome (GLUT1-DS) are two energetic diseases, respectively caused by a deficiency of any component of the PDHc (E1 α (OMIM 312170), E1 β (OMIM 614111), E2 (OMIM 245348), E3 (OMIM 246900) or E3BP (OMIM 245349)), or heterozygous mutations/deletions in *SLC2A1* gene (OMIM 606777). Both diseases lead to impairment of glucose metabolism, an essential energetic substrate, by defect in either pyruvate oxidation in mitochondria or glucose transport across the blood–brain barrier (BBB) and astrocytes. Patients have neurological involvement, ranging from severe encephalopathy to later and milder symptoms such as dystonia (Patel et al. 2012; Hully et al. 2015; De Giorgis et al. 2016).

Because ketone bodies (KB), a source of acetyl-CoA, can compensate for energetic defect in PDHD and GLUT1-DS, ketogenic diet (KD), a high-fat, low-carbohydrate and normal protein diet is the first line treatment for both diseases, with a global improvement in neurological condition in PDHD (Barnerias et al. 2010). Seizure control is obtained within a week to a month in most GLUT1-DS patients (Klepper et al. 2005) while improvement in other paroxysmal symptoms is poorly documented (Leen et al. 2010).

A major limit of KD is its unpallability and side effects (digestive symptoms, nephrolithiasis, hyperlipidemia, osteopenia) (Klein et al. 2014). Indeed, the classical KD contains from 70% (1/1KD) to 90% (4/1KD) of fat. Our aim was to substitute partially or totally KD with L,D-3-hydroxybutyrate in three GLUT1-DS patients and two PDHD patients in order to improve patients quality of life and compliance. The results were highly divergent, with an

improvement for PDHD patients in basal conditions, which contrasted with worsening of GLUT1-DS patients.

Patients and Methods

Patients

GLUT1-DS Patients

Hypoglycorrhachia, decreased CSF/blood glucose ratio, and heterozygous mutation/deletion in the *SLC2A1* gene led to GLUT1-DS diagnosis in the three patients (P) (Table 1).

P1 presented with early onset epileptic encephalopathy. GLUT1-DS was diagnosed at age 2 years.

P2 presented early onset myoclonic epilepsy, spastic cerebellar syndrome, and psychomotor delay. Diagnosis was performed at age 11 years.

P3 presented with neonatal hypotonia, strabismus, and abnormal head movements. He worsened with fasting and had “absences” in the morning. At age 5 years, psychomotor delay, pharmacoresistant epilepsy, abnormal movements, and dystonia led to the diagnosis.

PDHD Patients

P4, a girl, started fever-induced episodes of fatigue at age 8 months. At age 3 years, right leg dystonic crises appeared, whose frequency increased progressively: they occurred daily, were exercise-induced, and involved the right half of the body and the left foot. Psychomotor development was normal. She developed a peripheral neuropathy. At age 7 years, cerebral MRI showed dentate nucleus and globi pallidi hypersignals and corpus callosum

Table 1 Genetic and biochemical findings in three GLUT1-DS and two PDHc-deficient patients

	Genetic findings	Biochemical findings
Patient 1 (current age 11 years)	De novo complete <i>SLC2A1</i> deletion	Glycorrachia: 1.9 mmol/L Glycemia: 4.2 mmol/L CSF/Blood glucose: 0.45
Patient 2 (current age 22 years)	<i>SLC2A1</i> Exon 4 c.436G>A p.Glu146Lys	Glycorrachia: 1.7 mmol/L Glycemia: 6.8 mmol/L CSF/Blood glucose: 0.25
Patient 3 (current age 12 years)	<i>SLC2A1</i> Exon 1 c.32_33delGC p.Arg11fProfs ^a 77	Glycorrachia: 1.4 mmol/L Glycemia: 4.7 mmol/L CSF/Blood glucose: 0.3
Patient 4 (current age 15 years)	<i>PDHA1</i> Exon 8 c.787C>G p.Arg263Gly	PDH activity ^a : 2,069 pmol/min/mg of protein
Patient 5 (current age 12 years)	<i>PDHA1</i> Exon 7 c.650C>G p.Pro217Arg	PDH activity ^a : 785 pmol/min/mg of protein

^a PDH activity was measured in lymphocytes. Normal range: 1,570–3,430 pmol/min/mg of proteins

abnormalities suggesting the diagnosis of PDHD. A previously described mutation in *PDHA1* was identified (Table 1) (Imbard et al. 2011). PDHc activity measured in lymphocytes was within normal range (Table 1), due to the X-chromosome inactivation bias in tissues (Matthews et al. 1994).

P5, a boy, presented with peripheral neuropathy, cerebellar syndrome, and episodes of fatigability. A de novo mutation in *PDHA1* was found at age 3 years, and PDHc activity was decreased in lymphocytes (Table 1).

Methods

Treatments

Clinical presentation and initial treatments were variable among patients, whose number was limited. Patients were chosen for their symptoms easy to parameterize and because of parents' will to test an alternative to KD. L,D-3-hydroxybutyrate sodium salt (INRESA, Bartenheim, France) was mixed with water and given three times daily. Treatment's clinical effectiveness was evaluated by occurrence and frequency of seizures for P1, P2, and P3, and by dystonia crises or fatigability episodes frequency (pallor, very hypotonic, sleeping) for P4 and P5, respectively, thanks to notes taken daily by parents and educators.

Ketone Bodies, Lactate, and PDHc Activity Measurement

Blood/CSF KB concentrations and lactatemia were measured on a Konelab 30 analyzer (Vassault et al. 1991). Urinary 3-hydroxybutyrate was assayed by gas chromatography-mass spectrometry with standard clinical laboratory methods. PDHc activity was carried out as described (Imbard et al. 2011).

In Vitro Oxidation Rate Measurement

Oxidation rates of 3-hydroxybutyrate and glucose were measured after incubation with 10 mM $1\text{-}^{14}\text{C}$ labeled substrates in cultured fibroblasts from a control and an unrelated PDHD patient presenting with an intermittent strabismus and an axial hypotonia related to a de novo mutation in *PDHA1* (p.Arg378His) (Imbard et al. 2011). Fibroblasts from GLUT1-DS patients were not available.

Results

Clinical Follow-Up

In GLUT1-DS P1 to P3, treatments consisted first in 3/1 or 4/1KD alone then 4/1 to 2/1KD associated with increasing

doses of L,D 3-hydroxybutyrate (from 400 to 1,200 mg/kg/day). Under 3/1 or 4/1KD, the number of generalized seizures dramatically decreased. However, the partial substitution of KD with L,D-3-hydroxybutyrate led to clinical deterioration (Fig. 1).

In P1, at diagnosis, a 3/1 then 4/1KD was established and 250 mg/day valproic acid was introduced, which allowed to control seizures except in context of poor compliance. Under KD, only a motor improvement was noticed. Under 2/1KD and 800 mg/kg/day L,D-3-hydroxybutyrate, myoclonus/seizure reoccurred on a monthly basis. A 1/1KD and 1,200 mg/kg/day L,D-3-hydroxybutyrate combination led to equilibrium disorders and seizures crises. As a precursor of succinyl-CoA and as such an anaplerotic compound, valine supplementation was transiently attempted but was inefficient.

In P2, 4/1KD was started at age 12 years and controlled myoclonus. Combinations of 3/1KD and various doses of L,D-3-hydroxybutyrate led to increased myoclonus (up to once a day under 3/1KD and 1,080 mg/kg/day L,D-3-hydroxybutyrate) and seizure (up to 1–2 crises per month under 3/1KD and 700 mg/kg/day L,D-3-hydroxybutyrate) frequency. An acute worsening happened with the combination of 2/1KD and 900 mg/kg/day L,D-3-hydroxybutyrate, leading us to switch to 3/1KD and 900 mg/kg/day L,D-3-hydroxybutyrate. As precursors of succinyl-CoA and oxaloacetate, respectively, valine and aspartate were given but without effect.

In P3, absences disappeared under 3/1KD, soon established after diagnosis. After 1-day interruption in KD, he experienced increased fatigability without any abnormal movement, whereas after several days movement disorders reoccurred. Of note, absences and seizures were still under control. Combinations of 3/1KD and from 500 to 1,140 mg/kg/day L,D-3-hydroxybutyrate were well-tolerated, without any change in his condition. When a 2/1KD with 900–1,200 mg/kg/day L,D-3-hydroxybutyrate was established, his condition worsened with the reappearance of seizures and 3–4 absences every morning.

All patients stopped L,D-3-hydroxybutyrate administration and were moved back to their initial KD treatment, respectively, 4/1KD for P1 and P2 and 3/1KD for P3. They recovered their initial condition.

The two PDHD patients showed a dramatically positive response. We designed either a total (in P4) or partial (in P5) substitution of KD with L,D-3-hydroxybutyrate. In basal conditions, this suppressed the dystonic crisis in P4, and strongly reduced fatigability in P5 (Fig. 2).

In P4, 1/1KD and 100 mg/day thiamine decreased the dystonic crises frequency from 3 per day to 1–2 per week depending on physical activities. A 1/1KD associated with 500 mg/kg/day L,D-3-hydroxybutyrate was well-tolerated and as efficient as 1/1KD alone. The increase of L,D-3-

Fig. 1 Biological investigations, treatments, and clinical evolution in GLUT1-DS patients. **(a, b, c)** Ketonemia, treatments and clinical evolution in 3 GLUT1-DS patients (**a**: patient 1; **b**: patient 2; **c**: patient 3). *Boxplots* show median, minimum, maximum, first and third quartiles of ketonemia. **(d)** CSF ketone bodies and clinical evolution

hydroxybutyrate up to 900 mg/kg/day improved her condition, with only one dystonic crisis a month. Then a “less than 1/1KD” was started with up to 1,200 mg/kg/day L,D-3-hydroxybutyrate: one to two dystonic crises occurred monthly, favored by walking. Finally, KD was stopped: 1,000–1,200 mg/kg/day L,D-3-hydroxybutyrate controlled dystonia crises under basal conditions.

Under 2/1 or 3/1KD during illness and 100 mg/day thiamine, P5 had several fatigability episodes per week. First, a combination of 3/1KD and 500 mg/kg/day L,D-3-hydroxybutyrate was established and well-tolerated during few days, with improved condition. Then a degradation event occurred outside any febrile episode: he was very tired, his legs were painful, he dribbled and could not drink, with an unchanged appetite. Finally he recovered soon. Under 2/1KD and 500 mg/kg/day L,D-3-hydroxybutyrate, fatigability episodes occurred daily, but were less intense than before. Then 1/1KD and doses of L,D-3-hydroxybutyrate ranging from 700 to 900 mg/kg/day improved his condition. No overt fatigability episodes were recorded. Recently, he developed episodes of right leg dystonia in a context of poor compliance. During fever, a 3/1 to 4/1KD was transiently administered whereas oral KB administration was ineffective on clinical symptoms.

in patient 1. For each patient, the total duration of partial KD substitution with L,D-3-hydroxybutyrate was about 2 years. Clinical evolution was evaluated based on frequency of myoclonus or seizures. Clinical condition worsening was represented by *darker rectangles*

Biological Follow-Up

In GLUT1-DS patients, the different treatments allowed to maintain a sustained ketosis. Mean ketonemia was 3.53 (Standard Deviation (SD): 1.49) in P1, 2.08 (SD: 1.03) in P2, and 3.17 (SD: 1.22) in P3 (Fig. 1a–c), all concentrations in mmol/L. However, the highest ketonemias were measured under 4/1KD. CSF ketone bodies concentrations, in mmol/L, ranged in P1 between 0.39 and 0.96 under 3/1 or 4/1KD alone, respectively, (mean: 0.76; SD: 0.32), and reached 0.7 under 3/1KD with 400 mg/kg/day L,D-3-hydroxybutyrate (Fig. 1d). The highest CSF ketone bodies concentration was measured under 4/1KD (Fig. 1d).

In PDHD patients, mean ketonemia, in mmol/L, was milder: 0.32 (SD: 0.22) in P4, and 1.82 (SD: 0.95) in patient 5 (Fig. 2a, b). Of note, lactatemia correlates negatively with ketonemia ($r^2 = 0.39$ in patient 4; $r^2 = 0.59$ in patient 5; Fig. 2c, d). Under L,D-3-hydroxybutyrate and KD association, ketonemias tended to be lower than under KD alone. Ketonuria was highly variable under the different treatments in GLUT1-DS and PDHD patients (data not shown). Mean blood free fatty acids levels were, in mmol/L, 0.82 (SD: 0.34) in GLUT1-DS patients, and 0.62 (SD: 0.47) in PDHD patients.

Fig. 2 Biological investigations, treatments, and clinical evolution in PDHc-deficient patients, and in vitro study of 3-hydroxybutyrate and glucose oxidation ability in PDHD fibroblasts. (**a**, **b**) Ketonemia, treatment and clinical evolution in two PDHc-deficient patients (**a**: patient 4; **b**: patient 5). *Boxplots* show median, minimum, maximum, first and third quartiles of ketonemia. Clinical evolution

was evaluated based on frequency of dystonic crises or fatigability. Clinical condition worsening was represented by *darker rectangles*. (**c**, **d**) Correlation between lactatemia and ketonemia in two PDHc-deficient patients (**c**: patient 4; **d**: patient 5). (**e**) CO₂ production in control and PDHc-deficient fibroblasts using glucose and/or 3-hydroxybutyrate as substrates

In Vitro Study of 3-Hydroxybutyrate and Glucose Oxidation Ability in PDHD Fibroblasts

In PDHD fibroblasts, CO₂ production from glucose was decreased by half, consistent with impaired glucose oxidation (Fig. 2e). PDHD cells were able to oxidize 3-hydroxybutyrate as efficiently as in control, either alone or in combination with glucose, consistent with increased Krebs cycle activity because of PDHc-independent production of acetyl-CoA from 3-hydroxybutyrate.

Discussion

This study was designed as a proof of concept test for any added value of KB in PDHD and GLUT1-DS treatment. To improve quality of life and compliance, we tried to replace KD partially or totally with L,D-3-hydroxybutyrate in three

GLUT1-DS and two PDHD patients. The clinical evolution of GLUT1-DS and PDHD patients was strikingly different. In all GLUT1-DS patients, a partial replacement of KD with L,D-3-hydroxybutyrate led to clinical degradation. Conversely, a positive effect of KB administration was obvious in two PDHD patients although KD was still necessary when energetic needs increase, for example, during febrile illness periods.

Interestingly, in our GLUT1-DS patients, oral 3-hydroxybutyrate administration was unable to raise blood and CSF KB concentrations as high as 4/1 or 3/1KD (see Fig. 1c). CSF 3-hydroxybutyrate concentrations were comparable to those described by Klepper et al. in 5 GLUT1-DS under 3/1KD (Klepper et al. 2004).

According to Morris, the major determinants of brain KB metabolism are blood KB concentration and availability of suitable monocarboxylate transporters (MCT) (Morris 2005). However, in our patients, there was no obvious

correlation between clinical condition and ketonemia, as previously reported (Freeman et al. 2006). Oral administration of KB might inhibit ketogenic synthesis (Balasse and Neef 1975). KB is produced in liver and exported into blood through MCT1 and 2, transported across the BBB via MCT1, and taken up by neurons and astrocytes via MCT1 or MCT2 (Halestrap and Wilson 2012). MCT1 and GLUT1 expression increased in brain of rats fed with high-fat diet for 6 weeks (Leino et al. 2001). MCT2 mRNA was reported to increase after a 48 h food deprivation (Matsuyama et al. 2009). Pan et al. highlighted the importance of 3-hydroxybutyrate transport induction: after 3-hydroxybutyrate infusion, brain 3-hydroxybutyrate concentrations were lower than those measured in fasted adults (Pan et al. 2001). By reducing KD, perhaps a less important induction of MCT1 and GLUT1 was achieved, leading to decreased energetic substrates availability in brain. Our three GLUT1-DS patients might have been more sensitive to such a regulatory process than our two PDHD patients.

Our findings illustrate the dual function of glucose as supplier of acetyl-CoA and Krebs cycle intermediates. Both these functions are presumably impaired in GLUT1-DS whereas only acetyl-CoA production is reduced in PDHD. Under KD, glycolysis and glucose oxidative metabolism decrease. In PDHD patients, when KD was less restrictive or suppressed, glycolysis might re-increase. Glucose-derived pyruvate may enter the Krebs cycle via pyruvate carboxylase (PC), thus ensuring 3-hydroxybutyrate-derived acetyl-CoA combustion. Of note, KD and 3-hydroxybutyrate have been shown to stimulate pyruvate carboxylation and thus Krebs cycle anaplerosis (Melo et al. 2006), as they supply cells with acetyl-CoA, a well-known activator of PC. In PDHD-patients, combination of a less restrictive KD with L,D-3-hydroxybutyrate might have led not only to increased “fuel” (acetyl-CoA) oxidation but also to increased anaplerosis through PC in astrocytes, a process probably impaired in GLUT1-DS due to glucose transport impairment across the BBB and astrocyte membrane.

This point might be particularly important since seizures are thought to cause a deficiency in Krebs cycle intermediates, especially oxalo-acetate and alpha-ketoglutarate (Melo et al. 2005). Our study suggests that an anaplerotic mechanism may be involved because in PDHD patients, lactatemia correlates negatively with ketonemia (Fig. 2).

If anaplerosis is indeed defective in GLUT1-DS, the use of triheptanoin, a heptanoate triglyceride which can provide acetyl-CoA and propionyl-CoA, might be interesting as recently described (Pascual et al. 2014; Mochel et al. 2016). Combinations of 3-hydroxybutyrate with other anaplerotic compounds (such as multiple amino acids) may also be considered.

In conclusion, the clinical condition improved in two PDHD patients when we attempted to replace KD with L,D-3-hydroxybutyrate, arguing for a direct beneficial effect of KB in this energetic disease. However, KD was still necessary during febrile illness episodes and more patients would be necessary to confirm our finding before any recommendation. By contrast, GLUT1-DS patients worsened with increased seizures or myoclonus frequency, suggesting that additional metabolic processes, possibly Krebs cycle anaplerosis and mechanisms unrelated to energy metabolism, may be affected.

Take-Home Message

3-Hydroxybutyrate may be used as an adjuvant to ketogenic diet in PDHD, not in GLUT1-DS, and only under basal metabolic conditions.

Contribution of Individual Authors

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Competing Interest Statement

F. Habarou, N. Bahi-Buisson, E. Lebigot, C. Pontoizeau, M.T. Abi-Warde, A. Brassier, K.H. Le Quan Sang, C. Broissand, S. Vuillaumier-Barrot, A. Roubertie, A. Boutron, C. Ottolenghi, and P. de Lonlay declare that they have no conflict of interest.

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Ethics Approval and Patient Consent

This work was approved by our institutional ethical committee after declaration to the *Département de la Recherche Clinique et du Développement*, and informed consent was obtained from the parents.

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