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ORIGINAL ARTICLE

Changes in plasma amino acid concentrations with increasing age in patients with propionic acidemia

Sabine Scholl-Bürgi · Jörn Oliver Sass · Peter Heinz-Erian · Edda Amann · Edda Haberlandt · Ursula Albrecht · Claudia Ertl · Sara Baumgartner Sigl · Florian Lagler · Kevin Rostasy · Daniela Karall

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Abstract The objective of the study is to analyze plasma amino acid concentrations in propionic acidemia (PA) for the purpose of elucidating possible correlations between propionyl-CoA carboxylase deficiency and distinct amino acid behavior. Plasma concentrations of 19 amino acids were measured in 240 random samples from 11 patients (6 families) with enzymatically and/or genetically proven propionic acidemia (sampling period, January 2001–December 2007). They were compared with reference values from the literature and correlated with age using the Pearson correlation coefficient test. Decreased plasma concentrations were observed for glutamine, histidine, threonine, valine, isoleucine, leucine, phenylalanine and arginine. Levels of glycine, alanine and aspartate were elevated, while values of serine, asparagine, ornithine and glutamate were normal. For lysine, proline and methionine a clear association was not possible. Significant correlations with age were observed for 13 amino acids (positive correlation: asparagine, glutamine, proline, alanine, histidine, threonine, methionine, arginine; negative correlation: leucine, phenylalanine, ornithine, glutamate and aspartate). This study gives new insight over long-term changes in plasma amino acid concentrations and may provide options for future therapies (e.g., substitution of anaplerotic substances) in PA patients.

Keywords Amino acid concentrations · Propionic acidemia · Anaplerosis

S. Scholl-Bürgi (✉) · E. Haberlandt · U. Albrecht · C. Ertl · S. B. Sigl · K. Rostasy · D. Karall
Division of Neuropediatrics and Inherited Metabolic Disorders, Department of Pediatrics, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria
e-mail: sabine.scholl-buergi@uki.at

J. O. Sass
Labor für Klinische Biochemie und Stoffwechsel, Zentrum für Kinder- und Jugendmedizin, Universitätsklinikum Freiburg, Freiburg, Germany

P. Heinz-Erian
Division of Pediatric Gastroenterology, Department of Pediatrics, Innsbruck Medical University, Innsbruck, Austria

E. Amann
Department of Medical Statistics, Informatics, and Health Economics, Innsbruck Medical University, Innsbruck, Austria

F. Lagler
Division of Biochemical Pharmacology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Innsbruck, Austria

Abbreviations

PA	Propionic acidemia
PCC	Propionyl-CoA carboxylase
MMA	Methyl malonic aciduria
CoA	Coenzyme A
ATP	Adenosine triphosphate

Introduction

Propionic acidemia (PA, McKusick 232000) first described in 1961 by Childs is caused by propionyl-CoA carboxylase (PCC; E.C. 6.4.1.3) deficiency PCC is a mitochondrial enzyme that catalyzes the ATP-dependent carboxylation of propionyl-CoA to D-methylmalonyl-CoA (Childs et al. 1961). Propionyl-CoA is produced by catabolism of isoleucine, methionine, threonine, valine, odd-chain fatty acids, thymine, uracil and cholesterol (Fenton et al. 2001).

Table 1 Phenotypes, genotypes and clinical outcomes of 11 patients with propionic acidemia

Pat#	Current age	Gender	Gene	Mutation	Number of invest.	Age at onset of symptoms	Age at diagnosis	Outcome	Observation period (6 years)	Therapy at end of observation period	Antiepileptic drugs
1	22.5	Female	*PCC B*	V205D[a]	41	1 month	2 months	2	Seizures, prolonged QT-interval	Prot, carn, vit	LEV, CLOB, (VPA)
2	9.9	Male	*PCC B*	V205D[a]	15	5 days	5 days	1	Prolonged QT-interval	Prot, carn, aa, vit	–
3	7.4	Male	*PCC B*	V205D[a]	25	Asymptomatic	2 days	3	Severe metabolic decompensation with 9 months, prolonged QT-interval	Prot, carn, aa, vit	–
4	5.2	Male	*PCC B*	V205D[a]	12	Asymptomatic	Prenatally	2	Normal	Prot, carn, vit	–
5	16.3	Male	*PCC B*	V205D[a]	7	Asymptomatic	2 days	1	Seizures, prolonged QT-interval	Prot, carn, vit	–
6	15.5	Female	*PCC B*	V205D[a]	2	12 months	12 months	1	Died in traffic accident, prolonged QT-interval		
7	6.7	Male	*PCC B*	IVS11-2A > G[b]	36	Asymptomatic	1 day	3	Died because of meningitis		
8	10.2	Female	*PCC B*	IVS11-2A > G[b]	33	3 days	5 days	3	Seizures, prolonged QT-interval	Prot, carn, aa, vit	LEV
9	18.0	Male	*PCC A*	M373 K[c]	21	1 week	2 weeks	2	Seizures, prolonged QT-interval	Prot, carn, aa, vit	VPA, atenolol
10	21.6	Female	*PCC A*	M373 K[c]	26	1 month	4 months	2	Seizures, prolonged QT-interval	Prot, carn, aa, vit	VPA, TOP
11	1.1	Male	*PCC A*	M373 K[c]	22	Asymptomatic	10 days (newborn screening)	1	Normal	Prot, carn, aa, vit	–

All patients originate from the alpine region of Tyrol at the Austrian-Italian border. Patients 2 and 3; 4, 5 and 6; 7 and 8; 9 and 10 are siblings and patients 2, 3 and 4, 5, 6 are cousins

aa Amino acid mixture, *vit* supplementation with vitamins, *prot* protein-defined nutrition, *carn* supplementation of carnitine, *LEV* levetiracetame, *CLOB* clobazame, *VPA* valproic acid, *TOP* topiramate

Mutations of PCC described in [a] (Muro et al. 1999), [b] (Pérez et al. 2003), [c] (Ugarte et al. 1999, renamed by Campeau et al. 2001)

Clinical outcome: *1* mild, patient with near-normal development; *2* moderate, patient with moderate psychomotor delay; *3* severe, patient severely impaired

Table 2 Time table for elution with 5 lithium citrate buffer solutions, a change of column temperature is indicated with "−1"

Step	Run time (h:min:s)	P21 (pH 2.98)	P12 (pH 3.28)	P13 (pH 3.46)	P14 (pH 2.83)	P15 (pH 3.65)	Temperature (°C)
1	00:00	100	0	0	0	0	34
2	05:40	100	0	0	0	0	
3	14:20	−1	−1	0	0	0	43
4	18:20	0	100	0	0	0	
5	32:50:00	0	−1	0	0	0	72
6	33:20:00	0	100	0	0	0	
7	37:20:00	0	70	30	0	0	
8	43:00:00	0	70	30	0	0	
9	43:01:00	0	0	100	0	0	
10	54:40:00	0	0	100	0	0	
11	54:41:00	0	0	0	100	0	
12	55:00:00	0	0	0	−1	0	60
13	01:03:00	0	0	0	100	0	
14	01:03:01	0	0	0	0	100	
15	01:25:00	0	0	0	0	100	

Stable isotope studies lead to the estimation that despite wide individual variations in patients with PA and methylmalonic aciduria (MMA) approximately 50% of propionate production is due to amino acid metabolism, 25% to odd-chain fatty acid metabolism, and 25% to bacterial activity in the gut (Leonard 1997).

PCC is a heteropolymer, composed of six α- and β-subunits, with the α-subunit containing the biotin binding site. The α-subunit is encoded by the *PCCA* gene (chromosome 13q32), the β-subunit is encoded by the *PCCB* gene (chromosome 3q32). Propionic acidemia follows an autosomal recessive trait of inheritance (Wolf et al. 1981; Ugarte et al. 1999; Fenton et al. 2001).

Clinical signs of PA are heterogeneous, reaching from episodic vomiting to lethargy, developmental retardation, and intolerance to protein. Most patients present in the newborn period with severe metabolic acidosis manifesting as feeding difficulties, episodic vomiting, lethargy and muscular hypotonia. Seizures, dehydration and hepatomegaly occur less frequently (Wolf et al. 1981; Sass et al. 2004).

Biochemical disturbances of PA include ketoacidosis and hyperglycinemia. Besides, hyperammonemia, leucopenia, thrombopenia and hypoproteinemia can occur. The most valuable diagnostic metabolites found in urine are 2-methyl-3-oxovaleric acid, methylcitric acid and 3-hydroxypropionic acid (Lehnert et al. 1994) and in blood propionylcarnitine (Chace et al. 2001).

As glycine elevations and ketosis in PA are frequently observed, the disease was initially called ketotic hyperglycinemia (Childs et al. 1961) in contrast to nonketotic hyperglycinemia (Applegarth and Toone 2001). Mild hyperlysinemia is also common in PA (Lehnert et al. 1994; Parvy et al. 1988).

Concentrations of other amino acids have been reported in combination with ammonia levels or in case reports, but to our knowledge so far long-term changes in amino acid concentrations have not been reported in the literature. This led us to investigate plasma amino acid concentrations in PA and their changes with age.

Materials and methods

Subjects

A total of 11 patients from 6 families with PA were included. Treatment consisted of a protein-defined diet (with or without substitution of precursor-free amino acids), carnitine and vitamin substitution and therapy of complications like convulsions (Haberlandt et al. 2004) and long QT-syndrome (Baumgartner et al. 2007). Details are summarized in Table 1.

Laboratory measurements

All plasma amino acid measurements assessed during routine visits or hospital admissions from January 2001 to December 2007 were evaluated retrospectively. Blood samples were obtained mainly during daytime hours independent of nutritional status and were processed within 1–2 h; 19 plasma amino acids were quantified by ion exchange chromatography with post-column ninhydrin detection as described previously (Scholl-Bürgi et al. 2008a,

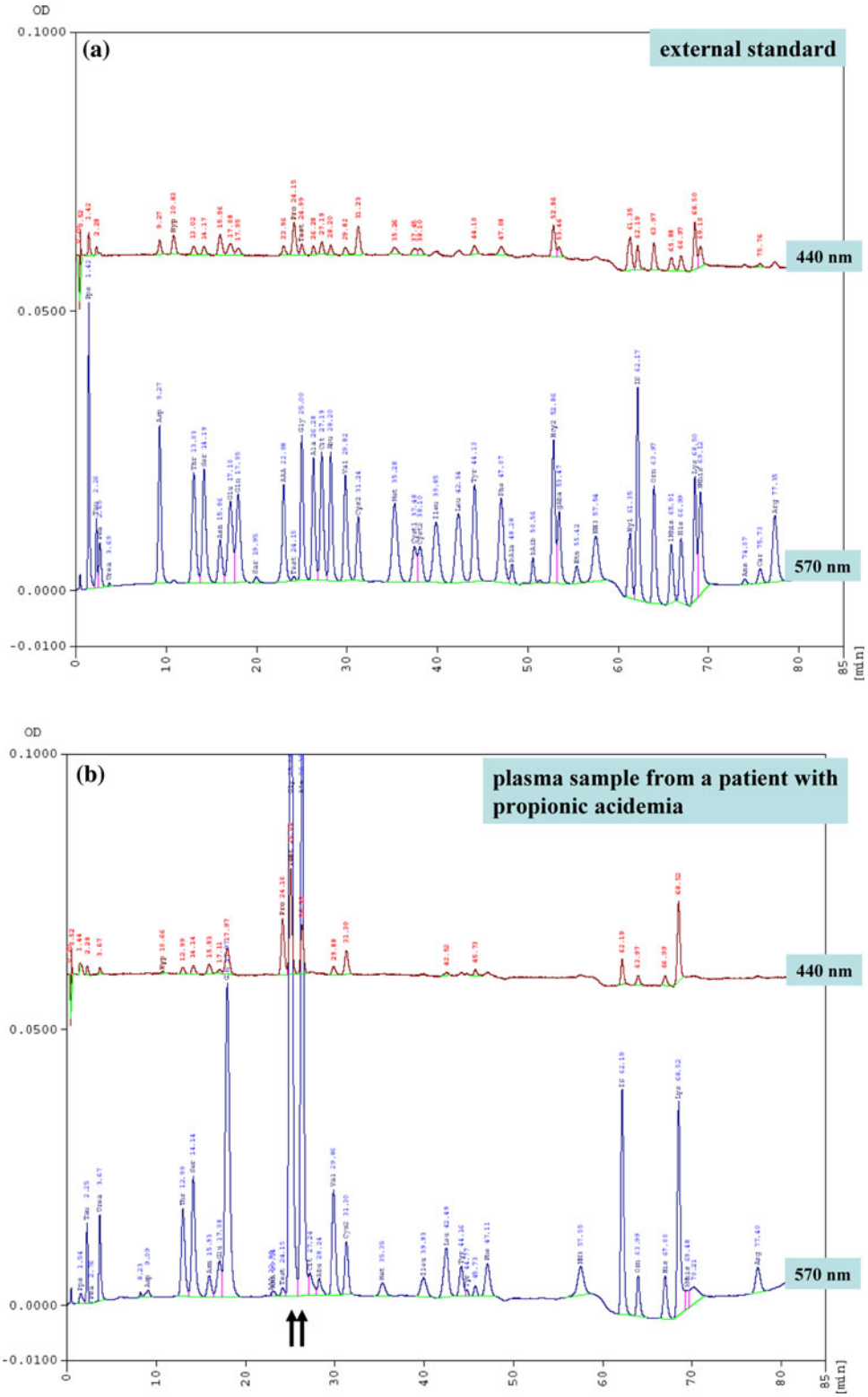

Fig. 1 Chromatograms of external standard (**a**) and a plasma sample from a patient with propionic acidemia (**b**), *arrows* indicate elevated amino acid concentrations (*IS* internal standard)

b). The elution was conducted using 5 lithium citrate buffer solutions (pH 2.83 to 3.65, Jeol, England) successively with a flow rate of 0.52 mL per minute (for details see Table 2). Detection was performed at 2 wavelengths (570 nm for detection of primary amino acids and 440 nm for detection of secondary amino acids like hydroxyproline and proline). Details for assay performance are presented by Scholl-Bürgi et al. 2008a, b. A chromatogram of an external standard

Table 3 Comparison of amino acid concentrations of plasma samples from PA patients measured in our laboratory with reference values published by Lepage et al. 1997

	Amino acid concentrations		
	Decreased	Decreased	Elevated
Serine	14	161	65
Asparagine	99	129	12
Glutamine	139	96	5
Proline	5	118	117
Glycine	0	3	237
Alanine	14	79	147
Histidine	166	64	10
Threonine	161	74	5
Valine	223	16	1
Methionine	118	114	8
Isoleucine	197	35	8
Leucine	182	46	12
Tyrosine	50	159	31
Phenylalanine	147	81	12
Ornithine	60	129	51
Lysine	78	103	59
Arginine	178	61	1
Glutamate	3	161	76
Aspartate	4	54	182

Numbers given denote the number of amino acid determinations

[amino acid concentrations 50 or 100 µmol/L (Sigma, Germany)] and of a patient's plasma sample is shown in Fig. 1.

Statistical methods

The data were tabulated in an Excel datasheet (Microsoft Office Excel, Version 2003). The measured amino acid concentrations were compared with previously published reference values (Lepage et al. 1997). The quantiles (10th, 50th and 90th) for the amino acid concentrations were used in our study. If more than 50% of the concentrations were below the 10th quantile, the changes were labeled as decreased; if more than 50% of the measured concentrations were above the 90th quantile they were considered elevated. For patients older than 16 years the values for the 16 years old were used. In contrast to our investigation where random samples were obtained, amino acid concentrations for establishing reference values were determined after 12 h of fasting.

Additionally, plasma amino acid concentrations were correlated with age (Pearson correlation coefficients). Statistical analysis was performed using SPSS version 15.0 for Windows. The level of significance was set to $P < 0.05$.

Results

During the observation period (January 2001–December 2007) 240 plasma amino acid analyses were performed. Decreased plasma amino acid concentrations (>50% lower than 10th quantile) were observed for glutamine, histidine, threonine, valine, isoleucine, leucine, phenylalanine and arginine (Table 3; in Fig. 2a the changes of isoleucine concentrations with increasing age are shown as an example for these amino acids) and elevated concentrations (>50% higher than 90th quantile) for glycine, alanine and aspartate (Table 3; in Fig. 2b glycine concentrations are shown). The concentrations for serine, asparagine, tyrosine, ornithine and glutamate were normal (>50% within the 10th–90th quantile). For methionine, proline and lysine a clear association was not possible. The concentrations of lysine were increased in patients younger than 10 years, but decreased thereafter (Table 3; in Fig. 2c lysine concentrations are shown).

Correlation coefficients for age and amino acid concentrations are shown in Table 4. Significant changes with increasing age were observed for 13 amino acids (positive correlation: asparagine, glutamine, proline, alanine, histidine, threonine, methionine, arginine; negative correlation: leucine, phenylalanine, ornithine, glutamate and aspartate).

Discussion

Propionic acidemia is an inborn disorder of intermediary metabolism leading to elevated propionyl-CoA concentrations. Much attention has been paid to the urinary excretion of organic acids, but only a few reports on changes in plasma amino acid concentrations exist. To our knowledge, the long-term changes in plasma amino acid concentrations in PA patients under treatment have not been reported previously. The results of our retrospective study are summarized in Fig. 3 and discussed below with regard to several amino acid disturbances in relation to PA.

Glycine

Hyperglycinemia and hyperlysinemia have frequently been observed in PA. Hyperglycinemia in PA acidemia is linked to inhibition of the glycine cleavage system in liver, but not in brain (Hayasaka and Tada 1983; Scholl-Bürgi et al. 2008a). Hyperglycinemia was observed in all patients.

Lysine

Hyperlysinemia may result from inhibition of saccharopine dehydrogenase by propionyl-CoA and/or its metabolites.

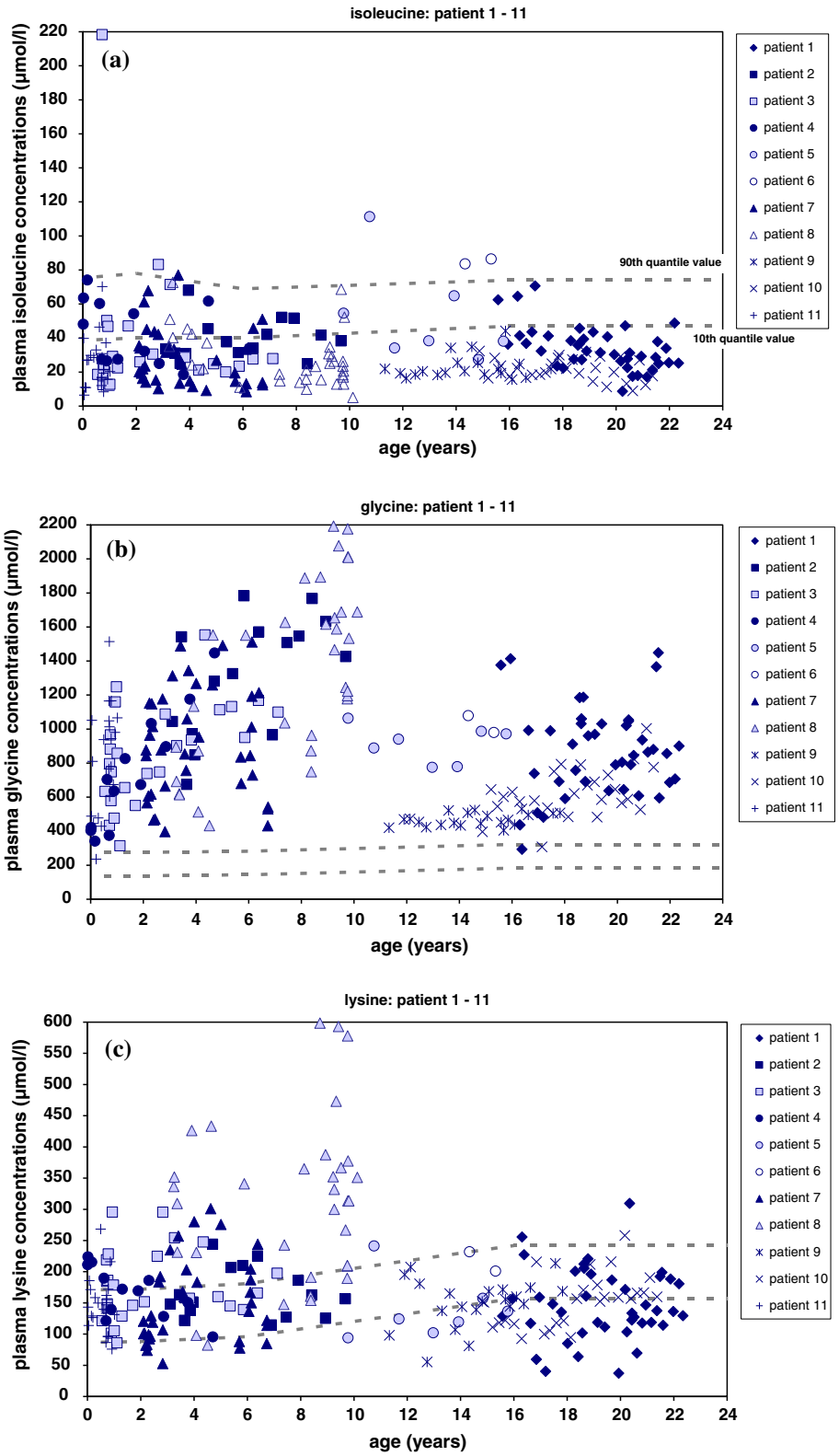

Fig. 2 **a–c** Plots of concentrations of amino acids in PA patients compared with reference values (reference values from Lepage et al. 1997 are shown in *grey lines*). **a** Isoleucine concentrations as an example for decreased amino acids. **b** Glycine concentrations as an example for increased amino acids. **c** Lysine concentrations as an example for amino acids without clear association

This enzyme catalyzes the first step of lysine degradation (Lehnert et al. 1994) where α-ketoglutarate is bound to lysine. In our patients, lysine was higher in younger subjects (up to 10 years) and then tended to decrease with age (Fig. 2c). Decreased levels of α-ketoglutarate may limit the catabolism of lysine and hence result in hyperlysinemia. The

Table 4 Correlation coefficients (Pearson) between age and plasma amino acid concentrations

	Correlations between age and amino acid concentrations	
	r	*P*
Serine	−0.080	0.218
Asparagine	**0.323**	**<0.001**
Glutamine	**0.234**	**<0.001**
Proline	**0.214**	**0.001**
Glycine	−0.111	0.085
Alanine	**0.551**	**<0.001**
Histidine	**0.411**	**<0.001**
Threonine	**0.298**	**<0.001**
Valine	−0.072	0.266
Methionine	**0.375**	**<0.001**
Isoleucine	−0.090	0.163
Leucine	**−0.375**	**<0.001**
Tyrosine	−0.109	0.091
Phenylalanine	**−0.190**	**0.003**
Ornithine	**−0.143**	**0.027**
Lysine	−0.079	0.221
Arginine	**0.142**	**0.027**
Glutamate	**−0.479**	**<0.001**
Aspartate	**−0.389**	**<0.001**

Bold *P* values are considered significant ($P < 0.05$)

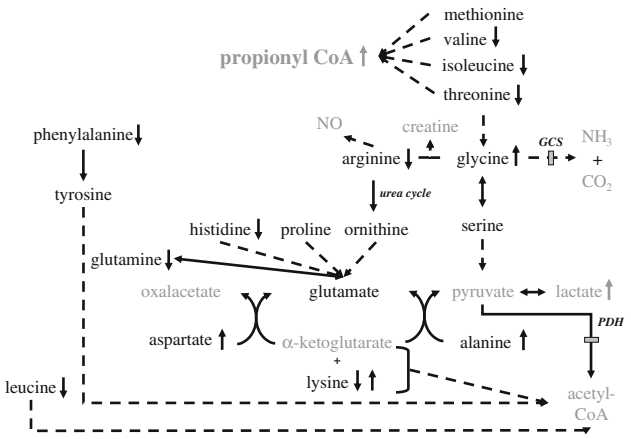

Fig. 3 Changes in plasma amino acid metabolism observed in this retrospective study. The *arrows* indicate the changes in the amino acid concentrations observed, *grey arrows* show changes observed for the substances reported in the literature but not determined in our study

lower concentrations of lysine in older patients may result from insufficient nutritional protein supply as has been shown in our patients (Scholl-Bürgi et al. 2004).

Glutamine and glutamate

Hyperammonemia, frequently observed in patients with PA, is caused by secondary inhibition of the urea cycle enzymes (Fenton et al. 2001). Coude et al. (1979) showed that propionyl-CoA is a competitive substrate (forming *N*-propionylglutamate) of *N*-acetylglutamate synthetase. *N*-Propionylglutamate was found to be only a weak activator of carbamylphosphate synthetase compared with *N*-acetylglutamate. This is underlined by the fact that *N*-carbamylglutamate, the precursor of *N*-acetylglutamate, can decrease concentrations of ammonia in PA patients (Gebhardt et al. 2005). In addition, Ierardi-Curto et al. (2000) showed that in a patient with PA and hyperammonemia plasma glutamine concentrations were decreased, whereas CSF glutamine was elevated. They concluded that decreased glutamine concentrations were caused by an inhibition of glutamine synthetase in liver, but not in brain, and called the phenomenon the "glutamine paradox". Al-Hassnan et al. (2003) investigated five PA patients and showed that there was no significant correlation between plasma glutamine and ammonia concentrations. Filipowicz et al. (2006) showed that hyperammonemia correlated significantly with a decrease of glutamine/glutamate concentrations in three PA patients. They speculated that this decrease indicates that the mechanism producing hyperammonemia in PA patients differs from that in urea cycle disorders. In our patients glutamine concentrations were decreased compared with the reference values in Lepage et al. (1997), whereas glutamate concentrations were normal. The concentrations of the urea cycle metabolite ornithine were normal, whereas arginine concentrations were decreased. Besides its function as a urea cycle metabolite, arginine can react with glycine to form creatine and thus may lead to creatine deficiency especially in brain.

Alanine

Hyperalaninemia was observed especially in our older PA patients. Alanine can be transaminated (with α-ketoglutarate as N-acceptor), which results in production of pyruvate and lactate. Lactic acidosis is common in PA patients (Lehnert et al. 1994) and is due to inhibition of pyruvate dehydrogenase by propionyl-CoA (Gregersen 1979). Elevated alanine concentrations are thought to be a consequence of elevated lactate concentrations (Smeitink et al. 2003). To prove this speculation, correlation of lactate and alanine concentrations should be calculated; however, in this study this was not feasible, as we did not determine lactate concentrations routinely.

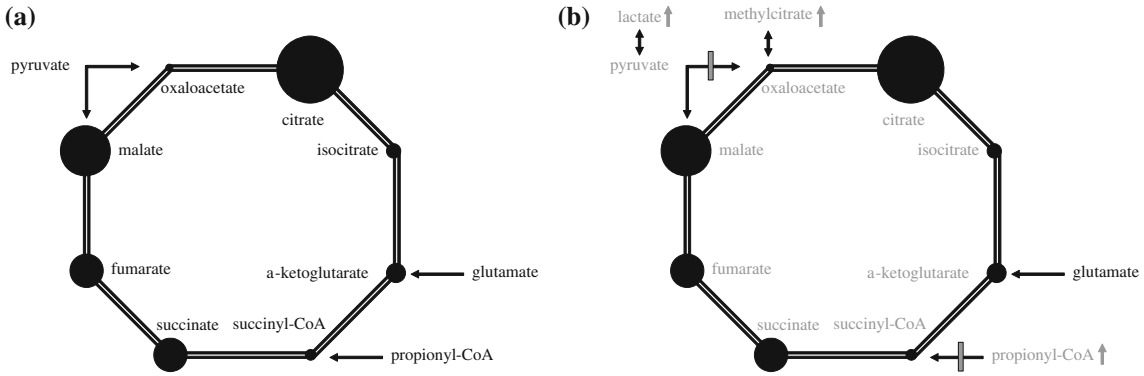

Fig. 4 **a** Anaplerotic reactions feeding the Krebs cycle (adapted from Brunengraber and Roe 2006). **b** Disturbance of anaplerosis in PA (*grey arrows* show changes observed for the not measured substances reported in the literature)

Branched-chain amino acids

In our patients, concentrations of the branched-chain amino acids leucine, isoleucine and valine were decreased, but only leucine concentrations showed a significantly negative correlation with age. Filipowicz et al. (2006) demonstrated that in PA patients hyperammonemia correlated positively with an increase in leucine and isoleucine, whereas low isoleucine concentrations were associated with an acrodermatitis enteropathica-like syndrome (Bosch et al. 1998). In our patients, only nonspecific skin lesions during episodes of metabolic decompensation were observed. According to their age-related protein requirement, they received a protein-defined diet (with or without substitution of an amino acid mixture free of isoleucine, methionine, threonine and valine). We observed that especially older patients self-restricted protein intake in their diet, thus possibly decreasing branched-chain amino acid concentrations in their plasma (Scholl-Bürgi et al. 2004).

We have shown that propionyl-CoA carboxylase deficiency leads to extensive disturbances in amino acid metabolism during long-term treatment. Some of the changes may be linked directly or indirectly to low concentrations of α-ketoglutarate (Fig. 3), which was not measured in our study. α-Ketoglutarate and succinyl-CoA, its product of oxidative decarboxylation, are metabolites of the Krebs cycle, which are refilled by anaplerosis (Brunengraber and Roe 2006). As in PA, the formation of succinyl-CoA from propionyl-CoA is disturbed. This may result in the depletion of Krebs cycle metabolites and an enhancement of ketogenesis from fatty acids, as shown by Rosario and Medina (1982) in isolated rat hepatocytes. Additionally, pyruvate oxidation is inhibited by propionic acid (Gregersen 1979), leading to a situation where two major anaplerotic pathways are disturbed in PA (Fig. 4). The therapeutic options in patients with PA, a protein-defined diet and substitution of carnitine, reduce the synthesis of propionyl-CoA and enhance the excretion of propionylcarnitine (Di Donato et al. 1984). Additional substitution of α-ketoglutarate in form of glutamate, which has not been attempted yet as an anaplerotic substrate would theoretically supply the Krebs cycle. Further studies with focus on a different therapeutic strategy (i.e., greater supply of protein or amino acids with additional substitution of anaplerotic substances) may be helpful.

In our retrospective study only the influence of age on amino acid concentrations in PA patients was investigated. Additionally, other factors like genotype, nutrition, nutritional and hormonal status, medication (notably valproic acid) and circadian rhythm may also influence plasma amino acid concentrations to a variable degree. Despite these limitations, the results of our retrospective study should give insight over long-term changes in plasma amino acid concentrations and provide ideas for additional options for therapy of PA patients.

Conflict of interest statement None.

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