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Current concepts in organic acidurias: understanding intra- and extracerebral disease manifestation

Stefan Kölker · Peter Burgard · Sven W. Sauer · Jürgen G. Okun

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Abstract This review focuses on the pathophysiology of organic acidurias (OADs), in particular, OADs caused by deficient amino acid metabolism. OADs are termed classical if patients present with acute metabolic decompensation and multiorgan dysfunction or cerebral if patients predominantly present with neurological symptoms but without metabolic crises. In both groups, however, the brain is the major target. The high energy demand of the brain, the gate-keeping function of the blood–brain barrier, a high lipid content, vulnerable neuronal subpopulations, and glutamatergic neurotransmission all make the brain particularly vulnerable against mitochondrial dysfunction, oxidative stress, and excitotoxicity. In fact, toxic metabolites in OADs are thought to cause secondary impairment of energy metabolism; some of these toxic metabolites are trapped in the brain. In contrast to cerebral OADs, patients with classical OADs have an increased risk of multiorgan dysfunction. The lack of the anaplerotic propionate pathway, synergistic inhibition of energy metabolism by toxic metabolites, and multiple oxidative phosphorylation (OXPHOS) deficiency may best explain the involvement of organs with a high energy demand. Intriguingly, late-onset organ dysfunction may manifest even under metabolically stable conditions. This might be explained by chronic mitochondrial DNA depletion, increased production of reactive oxygen species, and altered gene expression due to histone modification. In conclusion, pathomechanisms underlying the acute disease manifestation in OADs, with a particular focus on the brain, are partially understood. More work is required to predict the risk and to elucidate the mechanism of late-onset organ dysfunction, extracerebral disease manifestation, and tumorigenesis.

Abbreviations

BBB	Blood–brain barrier
mtDNA	Mitochondrial DNA
OAD(s)	organic aciduria(s)
ROS	Reactive oxygen species
TCA	Tricarboxylic acid cycle

Introduction

Definitive breakdown of many amino acids occurs mostly intramitochondrially through degradation of coenzyme A (CoA)-activated carbonic acids, the so-called acyl-CoA compounds. Inherited enzymatic deficiencies in these catabolic pathways result in the accumulation of mono-, di-, or tricarboxylic acids if enzymatic defects are located in distal steps. These metabolites have been termed organic acids, and accordingly, inherited disorders with accumulation of these metabolites are called organic acidurias (OADs). These non-amino-organic acids are not detectable by amino acid analysis and, as a consequence, OADs were discovered after the introduction of gas-chromatography techniques. Thus, the current terminology regarding OADs is not based on pathophysiological differences but simply reflects the analytical approach. OADs therefore comprise a heterogeneous group of inherited deficiencies (Hoffmann and Kölker 2010; Hoffmann and Kölker 2011). This review mostly focuses on OADs caused by inherited disorders of amino acid metabolism.

Clinical presentation

Based on recent knowledge, it seems impossible to correctly address the time point when the clinical presentation of

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S. Kölker (✉) · P. Burgard · S. W. Sauer · J. G. Okun
Department of General Pediatrics, Division of Inherited Metabolic Diseases, Centre for Child and Adolescent Medicine, Clinic I, University Hospital Heidelberg, Im Neuenheimer Feld 430, 69120 Heidelberg, Germany
e-mail: stefan.koelker@med.uni-heidelberg.de

patients with OADs starts. Although most studies have focused on the postnatal clinical phenotype, evidence is increasing that substantial metabolic perturbations may already occur in utero. These perturbations may affect fetal intrauterine development and result in frontal bossing, widened nasal bridge, epicanthal folds, a long philtrum, and inverted nipples of newborns with propionic and methylmalonic aciduria (Nyhan et al. 2005a; Nyhan et al. 2005b). Furthermore, temporal hypoplasia, immature gyral pattern, and delayed myelination are thought to reflect (reversible) intrauterine developmental delay in patients with glutaric aciduria type I (Harting et al. 2009). Much more work is required to understand the underlying mechanisms and long-term consequences of these abnormalities.

Two groups of OADs, classical and cerebral, have been delineated based on postnatal clinical presentation. Patients with classical OADs, such as propionic and methylmalonic aciduria, often present in the newborn period or in infancy after a short symptom-free interval of days or weeks, with acute sepsis-like metabolic decompensation, including metabolic acidosis, keto- and lactic acidosis, and hyperammonemia (Hörster et al. 2007; Hörster et al. 2009; Pena et al. 2011). Such metabolic crises can occur at any age and are usually precipitated by catabolism and inappropriately high protein intake; the risk of developing metabolic crises decreases with age. During metabolic decompensations, patients with classical OADs are at risk of developing irreversible, life-threatening organ damage. The most vulnerable organ is the brain. Brain edema and acute injury of basal ganglia (so-called metabolic stroke) are frequent manifestations and result in motor and mental retardation, movement disorders, and epilepsy. However, multiorgan failure with acute hepatic failure, (dilatative) cardiomyopathy and dysrhythmias, acute renal failure, and pancreatitis may accompany acute brain injury and may result in long-term organ dysfunction (Hoffmann and Kölker 2010; Hörster et al. 2007; O'Shea et al. 2012; Pena et al. 2011). Growing evidence, however, points to chronic deterioration of organ function (De Keyzer et al. 2009; Komatsuzaki et al. 2012; Marquard et al. 2011; Prada et al. 2011; Romano et al. 2010; Traber et al. 2011). These complications may occur even in patients who are apparently metabolically stable.

In contrast to classical OADs, patients with cerebral OADs present with predominant neurological symptoms, which usually develop in the absence of severe metabolic decompensation (Heringer et al. 2010; Kölker et al. 2006a, b; Kranendijk et al. 2012a, b Pearl et al. 2003; Steenweg et al. 2010). Neurological symptoms may manifest acutely, such as in glutaric aciduria type I (Harting et al. 2009; Kölker et al. 2006a, b), or may slowly progress after a variable symptom-free period, for example, in L-2-hydroxyglutaric aciduria (Steenweg et al. 2010; Topcu et al. 2005) or late-onset glutaric aciduria type I (Külkens et al. 2005). Neurological symptoms are overlapping in individual cerebral OADs and may range from retarded motor, mental, and speech development; movement disorders (e.g. dystonia, chorea, ataxia, spasticity); optic nerve atrophy; and muscular hypo- or hypertonia to epilepsy (Harting et al. 2009; Kranendijk et al. 2012a, b; Kyllerman et al. 2004; Pearl et al. 2003; Steenweg et al. 2010; Topcu et al. 2005). Macrocephaly is frequently found in glutaric aciduria type I, D-2-hydroxyglutaric aciduria, and is most pronounced in Canavan disease. Magnetic resonance imaging (MRI) studies may detect characteristic patterns, such as progressive loss of arcuate fibers combined with progressive cerebellar atrophy and signal changes in globus pallidus and dentate nuclei in L-2-hydroxyglutaric aciduria (Steenweg et al. 2009); temporal atrophy; dilated Sylvian fissures and external cerebrospinal fluid (CSF) spaces in combination with T2 hyperintensities; and later on, atrophy in putamen, caudate, and globus pallidus, as well as age-dependent T2 hyperintensity in (periventricular) white matter in glutaric aciduria type I (Harting et al. 2009; Neumaier-Probst et al. 2004).

To better understand the natural history and long-term outcome in OAD patients and other intoxication-type metabolic diseases, we began the E-IMD (European Registry and Network for Intoxication-type Metabolic Disease; URL: www.e-imd.org), a European Union (EU)-funded project, in 2011. One of the major tasks of this project is the establishment of a web-based patient registry (URL: https://www.eimd-registry.org). At present, more than 520 patients have been registered.

The brain as the major target

Despite the etiological and clinical heterogeneity of OADs, the brain is the major target. What can we learn from the selective vulnerability of the brain with regard to underlying pathomechanisms?

There are several aspects of brain metabolism that include a specific risk for injury:

1. The brain requires about 20 % of the total daily glucose and oxygen demand (in adults) (Sokoloff 1960). In infants, and in particular during the brain growth spurt, the cerebral energy demand is even higher.
2. Neurons and astrocytes form a metabolic unit in which three distinct pathways have been delineated (Fig. 1): (a) the glutamate/glutamine cycle (Bak et al. 2006), (b) the lactate shuttle (Pellerin and Magistretti 2012), and (c) the dicarboxylic acid shuttle (Schousboe et al. 1997). Disruption of these pathways

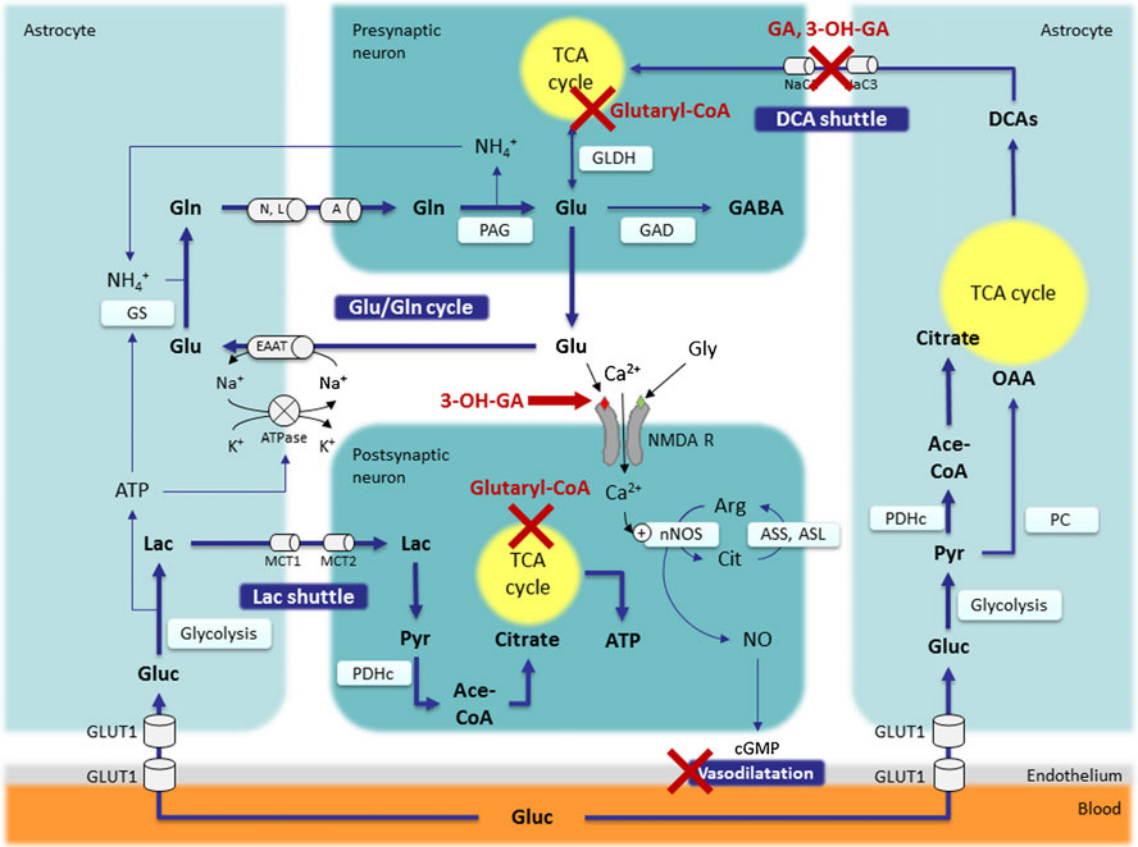

Fig 1 Proposed pathomechanism of glutaric aciduria type I. Three distinct pathways have been delineated that form the basis of bioenergetical coupling between astrocytes and neurons and between excitatory glutamatergic signalling, glucose homeostasis, and autoregulation of cerebral perfusion, i.e. the glutamate (Glu)/glutamine (Gln) cycle, the lactate (Lac) shuttle, and the dicarboxylic acid (DCA) shuttle. In glutaric aciduria type I, entrapment of dicarboxylic metabolites—glutaryl-coenzyme A (CoA), glutaric acid (GA), and 3-hydroxyglutaric acid (3-OH-GA)—in the brain compartment are though to occur as a consequence of strongly limited efflux transport of these metabolites across the blood–brain (BBB). Glutaryl-CoA inhibits the 2-oxoglutarate dehydrogenase of the tricarboxylic acid (TCA) cycle in neurons, whereas GA and—less pronounced—3-OH-GA inhibit the anaplerotic dicarboxylic acid (DCA) shuttle between astrocytes and neurons. Bioenergetic impairment may be further aggravated by hemodynamic alterations and during catabolism. Activation of energy-demanding glutamatergic signalling by 3-hydroxyglutarate might result in overexcitation of bioenergetically impaired postsynaptic neurons. Inhibitory actions are visualized as a *red cross*. *Ace-CoA* acetyl coenzyme A, *Arg* L-arginine, *ASL* argininosuccinate lyase, *ASS* argininosuccinate synthetase, *cGMP* cyclic guanosine monophosphate, *Cit* L-citrulline, *EAAT* excitatory amino acids transporters 1-3, *GABA* gamma-aminobutyric acid, *GAD* glutamate decarboxylase, *GLDH* glutamate dehydrogenase, *Gluc* glucose, *GLUT1* glucose transporter 1, *Gly* L-glycine, *MCT* monocarboxylate transporter, *GS* glutamine synthetase, *NaC* sodium-dependent dicarboxylic acid transporter, *NMDA-R* N-methyl-D-aspartate receptor, *nNOS* neuronal nitric oxide synthase, *PAG* phosphate-activated glutaminase, *PC* pyruvate carboxylase, *PDHc* pyruvate dehydrogenase complex, *Pyr* pyruvate, *TCA* tricarboxylic acid, *OAA* oxaloacetate

may lead to astrocytic dysfunction and neuronal cell death.

3. The blood–brain barrier (BBB) strongly limits the paracellular transport of hydrophilic compounds, which can only pass this barrier if specific transporters are expressed (Ohtsuki 2004; Pardridge 1998). Transport of glucose, amino acids, and monocarboxylic acids is highly effective, whereas transport of other hydrophilic compounds such as creatine or dicarboxylic acids is strongly limited (Braissant 2012; Sauer et al. 2010a, b).
4. Glutamate is the major excitatory neurotransmitter of the human brain, and glutamatergic neurons are major consumers of brain energy. Increased glutamate concentrations in the synaptic cleft, however, facilitate overactivation of postsynaptic neurons, which in turn activates a neurodegenerative process called excitotoxicity (Rothman and Olney 1995). Some neuronal cell populations, such as striatal medium spiny neurons, are highly susceptible to excitotoxicity (Mitchell et al. 1999).
5. The brain has a high fat content and active lipid metabolism, which is particularly required for synthesis and maintenance of myelin. This lipid-rich environment and oligodendrocytes are highly susceptible to damage caused by reactive oxygen species (ROS) (Dewar et al. 2003).

From neurotoxic metabolites to disease manifestation

Pathologic metabolites that accumulate in patients with OADs are proposed to act as neurotoxins in that they:

1. Inhibit specific enzymes of brain-energy metabolism (Morath et al. 2008; Sauer et al. 2005; Schwab et al. 2006)
2. Impair metabolic coupling between astrocytes and neurons (Lamp et al. 2011; Yodoya 2006)
3. Stimulate excitotoxic pathways (Kölker et al. 2002; Kölker et al. 2004)
4. Interfere with autoregulation of cerebral blood flow (Strauss et al. 2010)
5. Stimulate ROS production (Kölker et al. 2004; Wajner and Goodmann 2011).

These actions are mostly based on structural similarities between accumulating pathologic metabolites and natural substrates. For example, glutaryl-CoA inhibits 2-oxoglutarate dehydrogenase complex in analogy to succinyl-CoA (Sauer et al. 2005), propionyl-CoA inhibits pyruvate dehydrogenase complex in analogy to acetyl-CoA (Schwab et al. 2006), and glutarate and 3-hydroxyglutarate compete with dicarboxylic TCA cycle intermediates such as succinate for transport across sodium-dependent dicarboxylic acid transporters (Lamp et al. 2011; Yodoya 2006). Figure 1 summarizes the proposed pathomechanism of glutaric aciduria type I.

Although pathologic metabolites have a lower affinity to these target enzymes and transporters than their natural substrates, negative effects will become prominent at high metabolite concentrations, particularly during catabolism or following high protein intake. These observations led to the formulation of the so-called toxic metabolite hypothesis and coenzyme A sequestration, toxicity, and redistribution (CASTOR) hypothesis (Mitchell et al. 2008). The latter hypothesis is a restatement of findings and ideas from previous studies dating back to the late 1960s (Oberholzer et al. 1967). Intramitochondrial accumulation of toxic acyl-CoA esters is facilitated by the fact that acyl-CoA esters do not cross biological membranes. Therefore, the main action of acyl-CoA esters is primarily intramitochondrial. Intramitochondrial concentrations of these toxic metabolites cannot be precisely predicted based on the quantification of corresponding organic acids in blood and urine. This is a significant limitation for biochemical therapy monitoring. Furthermore, intracerebral accumulation of dicarboxylic metabolites is facilitated by the naturally occurring lack of effective efflux transport across the BBB for dicarboxylic compounds (Hassel et al. 2002; Sauer et al. 2006; Sauer et al. 2010a, b). Therefore, it has been hypothesized (trapping hypothesis) that the physiologic function of the BBB relevantly contributes to the manifestation of neurological phenotype in these OADs that produce putatively toxic dicarboxylic acids (Kölker et al. 2006a, b). Again, plasma, urine, and CSF analysis for these metabolites do not predict the intracellular concentration in the brain. In summary, evidence is increasing that transport of putatively toxic compounds across biological membranes and thus compartmentation is important for understanding neuropathology and that determination of metabolite concentrations in body fluids is not reliable to predict the long-term neurological outcome.

Therapeutic concepts based on pathophysiologic considerations

Current therapeutic concepts for OADs primarily aim to lower the intracellular concentration of toxic metabolites and prevent sequestration of free CoA and secondary depletion of carnitine (Kölker et al. 2011; Sutton et al. 2012). This is thought to be achieved by limiting the dietary intake of the amino acid precursor, carnitine supplementation, and cofactor application (in cofactor-responsible patients and diseases) for metabolic maintenance treatment as well as transient cessation of protein intake, high-energy intake using carbohydrates, rehydration, forced diuresis, urine alkalization, and extracorporeal detoxification (in severely decompensated patients with classical OADs) for metabolic emergency treatment (Kölker et al. 2011; Sutton et al. 2012). However, the biochemical proof of these concepts for most OADs was usually based on the analysis of toxic metabolites in body fluids instead on intracellular studies. This significantly hampers our recent understanding, and more animal and postmortem studies are required. At present, the therapeutic concepts described above have been most profoundly studied for glutaric aciduria type I using Gcdh-deficient mice, an animal model with complete loss of glutaryl-CoA dehydrogenase activity (Koeller et al. 2002). Intracerebral concentrations of glutaric and 3-hydroxyglutaric acid were 100–1,000 fold higher than those found in plasma (Sauer et al. 2006) due to intracerebral production and the lack of effective transport of these dicarboxylic acids across the BBB (Sauer et al. 2010a, b). The concentration of glutaric and—less pronounced—3-hydroxyglutaric acid in the brain compartment was directly influenced by the amount of dietary intake of L-lysine, the major amino acid precursor of these metabolites (Sauer et al. 2011; Zinnanti et al. 2007). In analogy to low lysine diet, high energy intake using glucose reduced the intracerebral concentration of glutaric acid, whereas carnitine increased the production of nontoxic glutarylcarnitine but had no significant effect on cerebral glutaric acid concentration (Sauer et al. 2011; Zinnanti et al. 2007). In addition to this, new concepts exploiting the physiological function of the BBB have been tested. Application of arginine and homoarginine—which both compete with lysine for transport across biological barriers, such as at cationic amino acid 1 transporter at the BBB—was

shown to reduce cerebral glutaric acid concentration and to amplify the therapeutic effect of low lysine diet in mice (Sauer et al. 2011; Zinnanti et al. 2007). Complementary dietary treatment using arginine-fortified, lysine-free amino acid supplements for patients with glutaric aciduria type I is currently under investigation, with promising first results (Heringer et al. 2010; Kölker et al. 2012; Strauss et al. 2011). Alternative therapeutic strategies, such as fibrate-induced modification of the pipecolate pathway of lysine degradation; or pharmacological inhibition of enzymes, such as the DHTKD1-containing 2-oxoglutarate dehydrogenase-like complex located proximal to glutaryl-CoA dehydrogenase within the lysine degradation pathway, are of theoretical interest but require further experimental confirmation (Danhauser et al. 2012; Sauer et al. 2011). The development of anaplerotic therapeutic strategies for the brain is significantly hampered by the lack of influx transport for dicarboxylic TCA cycle intermediates across the BBB (Hassel et al. 2002), whereas glucose and monocarboxylic energy substrates can easily pass this barrier (Kossoff et al. 2009; Segel et al. 2011). Long-term correction of the (intracerebral) biochemical phenotype for patients with OADs is an important future research goal and might be achieved by gene therapy (Chandler and Venditti 2012), stem cell therapy, intrathecal enzyme replacement, and chaperone treatment. However, much more work is required to understand the safety and efficacy of such concepts.

Extracerebral disease manifestation in organic acidurias affecting propionate metabolism

Extracerebral organ manifestation is a rare finding in cerebral OADs, such as cardiomyopathy in D-2-hydroxyglutaric aciduria type 2 (Kranendijk et al. 2012a, b). In contrast, patients with propionic and methylmalonic aciduria have an increased risk of multiorgan involvement (Hörster et al. 2007; Pena et al. 2012). This may manifest acutely during metabolic decompensation or chronically—even in metabolically stable patients. The clinical spectrum of organ dysfunction is variable, including chronic renal failure, (dilatative) cardiomyopathy, arrhythmia, pancreatitis, pancytopenia (or anemia, neutropenia, and thrombocytopenia), and premature ovarian failure (De Keyzer et al. 2009; Komatsuzaki et al. 2012; Marquard et al. 2011; Pena et al. 2012; Romano et al. 2010). The following disease-causing mechanisms have been proposed for classical OADs (Fig. 2).

Lack of anaplerotic propionate pathway

The primary enzymatic defect in patients with propionic and methylmalonic aciduria is located in the final steps of propionate metabolism. Via this anaplerotic pathway, succinyl-CoA is fuelled into the TCA cycle, and it is assumed that up to 7–8 % of total adenosine triphosphatase (ATP) can be produced by this (Brunengraber and Roe 2006). The heart is thought to particulary rely on propionate as an anaplerotic metabolite. A protective effect of propionylcarnitine on energy-linked processes in ischemic hearts has been shown (Di Lisa et al. 1994; Sumegi et al. 1995).

Synergistic effects of toxic metabolites

The biological effect of the inherited deficiency of the anaplerotic propionate metabolism is aggravated by synergistic secondary effects of accumulating toxic metabolites on energy metabolism (Morath et al. 2008). The TCA cycle flux is impaired by 2-methylcitrate-induced inhibition of citrate synthase, aconitase and isocitrate dehydrogenase (Cheema-Dhadli et al. 1975), propionyl-CoA-induced inhibition of succinate-CoA ligase (Brock and Buckel 2004), and methylmalonate-induced inhibition of mitochondrial succinate uptake (Mirandola et al. 2008; Okun et al. 2002; Kölker et al. 2003). Propionyl-CoA also inhibits pyruvate dehydrogenase complex (Brock and Buckel 2004; Schwab et al. 2006), ureagenesis via N-acetyl-CoA synthase (Coude et al. 1979), and the bc_1 complex (Sauer et al. 2008). This may very well explain the acute and severe clinical presentation of patients with propionic and methylmalonic aciduria during metabolic decompensation and their recovery if anabolism is achieved and the concentration of toxic metabolites is reduced.

Sustained mitochondrial dysfunction and multiple OXPHOS deficiency

The concept of synergistic inhibition does not adequately explain the intriguing observation of late-onset multiple organ dysfunction in propionic and methylmalonic aciduria. This points to mechanisms that are more sustained than acute inhibition of enzymes and transporters. This notion is supported by the finding of multiple OXPHOS deficiencies, in particular, deficiency of bc_1 complex and cytochrome *c* oxidase in liver, skeletal muscle, heart muscle, and kidney of patients with propionic and methylmalonic aciduria (Chandler et al. 2009; De Keyzer et al. 2009; Hayasaka et al. 1982; Schwab et al. 2006). Similar findings, with most pronounced deficiency of cytochrome *c*, were demonstrated in $Mut^{-/-}$ mice (Chandler et al. 2009) and in a hydroxycobalamin[c-lactam]-induced rat model of methylmalonic aciduria (Krähenbühl et al. 1991). One possible explanation for this is mitochondrial DNA (mtDNA) depletion, which was shown in two studies (De Keyzer et al. 2009; Schwab et al. 2006) but was not confirmed by another (Chandler et al. 2009). Chronic mtDNA depletion would

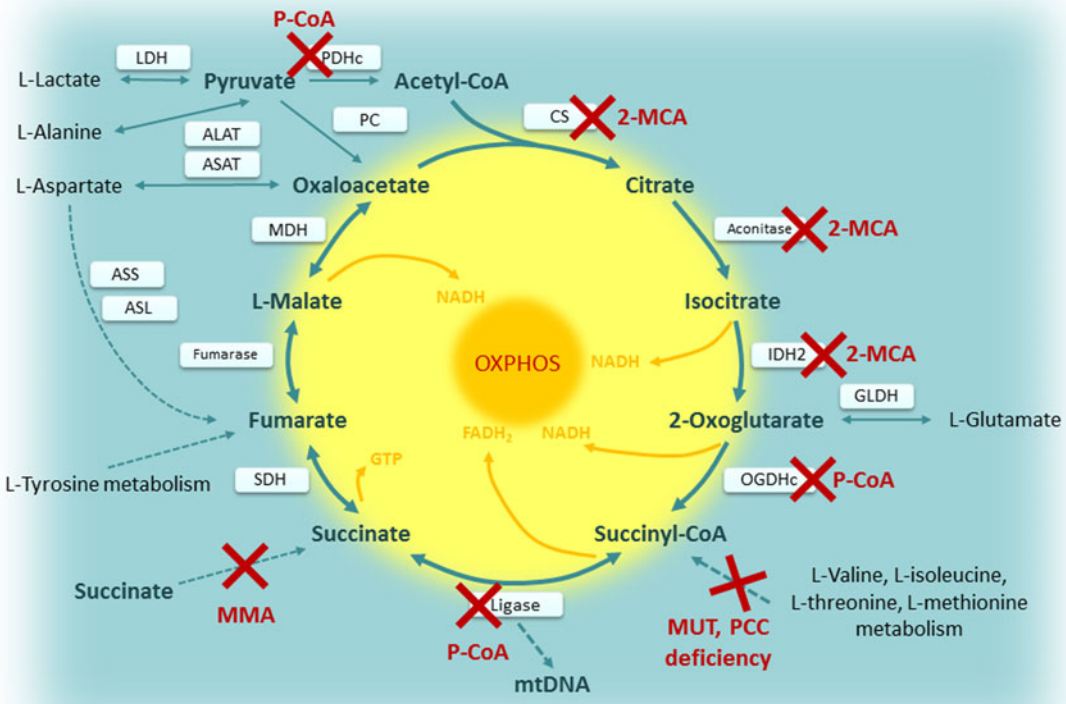

Fig. 2 Proposed pathomechanism of propionic and methylmalonic aciduria—it is all around the tricarboxylic acid (TCA) cycle. Primary deficiency in the anaplerotic propionate pathway due to inherited propionyl-coenzyme A (CoA) carboxylase (PCC) or methylmalonyl-CoA mutase (MUT), as well as secondary deficiency of pyruvate dehydrogenase complex (PDHc), citrate synthase (CS), aconitase, 2-oxoglutarate dehydrogenase complex (OGDHc), succinate-CoA ligase (ligase), and the mitochondrial succinate transport due to inhibition by accumulating propionyl-CoA (P-CoA), 2-methylcitrate (2-MCA), and—in methylmalonic aciduria—methylmalonate (MMA) result in a synergistic impairment of energy metabolism with a particular focus on the TCA cycle. Chronic toxic effects, inhibition of succinate-CoA ligase, and increased reactive oxygen species (ROS) production may also underlie mitochondrial DNA (mtDNA) depletion, multiple oxidative phosphorylation (OXPHOS) deficiency, and the formation of megamitochondria, which were found in some patients with propionic and methylmalonic aciduria. In addition, propionyl-CoA causes hyperammonemia via inhibition of N-acetylglutamate synthase (not shown). Inhibitory actions are visualized as a *red cross*. *Dashed lines* indicate multiple enzymatic steps. *ALAT* alanine aminotransferase, *ASAT*, aspartate aminotransferase; *ASS*, argininosuccinate synthetase; *ASL*, argininosuccinate lyase; *LDH*, lactate dehydrogenase; *MDH*, malate dehydrogenase; *PC*, pyruvate carboxylase; *SDH*, succinate dehydrogenase

result in reduced expression of mitochondrial nicotinamide adenine dinucleotide (reduced) NADH oxidoreductase, bc_1 complex, and cytochrome *c* oxidase. Notably, propionyl-CoA inhibits succinate-CoA ligase (Brock and Buckel 2004). Inherited deficiency of this enzyme due to *SUCLA2* and *SUCLG1* gene mutations causes mtDNA depletion (Elpeleg et al. 2005; Ostergaard et al. 2007). Whether propionyl-induced inhibition of succinate-CoA ligase has the same effect on mtDNA as the mutated enzyme is not yet known.

Mitochondrial dysfunction was also associated with the formation of megamitochondria in liver extracts of $Mut^{-/-}$ mice and mut^0 patients. Such megamitochondria properly arise by a combination of fusion and growth of mitochondria, and their formation can be induced by pharmacological, dietary, and toxicological means (Hoppel et al. 2009). In $Mut^{-/-}$ mice, the formation of megamitochondria and mitochondrial dysfunction occurred in a tissue-specific and age-dependent fashion in liver, pancreas, and proximal tubules (Chandler et al. 2009). Along with the development of megamitochondria, other dysmorphic changes, such as dysmorphic cristae, intramitochondrial lamellar inclusion bodies, and a less electron-dense mitochondrial matrix, appeared. These changes are similar to those found in skeletal muscle of patients with propionic aciduria (Schwab et al. 2006). What drives this process is still unclear. Increased ROS production, decreased antioxidative defence due to glutathione depletion, and epigenetic modifications due to propionyl-CoA-induced histone acetylation and thus chronic alteration of gene expression are likely candidate mechanisms (Chandler et al. 2009; Mirandola et al. 2008; Nguyen et al. 2007; Sauer et al. 2010a, b).

Long-term organ failure and tumorigenesis: at a crossroads of epigenetics

Evidence is increasing that adult patients with propionic and methylmalonic aciduria may develop late-onset organ manifestation even if they have been considered as metabolically stable for years. Late-onset organ manifestation includes optic nerve atrophy, long QT syndrome, dilatative cardiomyopathy, pancreatitis, chronic renal failure, and premature ovarian failure, among others (Baumgartner et al. 2007; Komatsuzaki et al. 2012; Marquard et al. 2011; Pena et al. 2011; Prada et al. 2011; Romano et al. 2010; Williams et al. 2009). The concept of metabolical stability is misleading, as relevant pathological changes are not reliably predictable based on biochemical therapy monitoring in blood and urine. Furthermore, these clinical observations emphasize the need for establishing new therapeutic concepts and for reevaluating available strategies, such as early liver transplantation, to protect against these long-term complications (Chapman et al. 2012; Davison et al. 2011; Kasahara et al. 2012; Meyburg and Hoffmann 2005).

Besides long-term organ dysfunction, the development of malignant tumors might also occur on the way to adulthood. Patients with L-2-hydroxyglutaric aciduria have an increased risk of developing malignant (glial) brain tumors (Moroni et al. 2004). Furthermore, D-2-hydroxyglutaric aciduria due to somatic mutations in *IDH1* and *IDH2* genes encoding for cytosolic/peroxisomal and mitochondrial nicotinamide adenine dinucleotide phosphate ($NADP^+$)-dependent isocitrate dehydrogenases 1 and 2 have been associated with the formation malignant gliomas and acute myeloid leukemia (Dang et al. 2009, Reitman and Yan 2010). In contrast, malignant brain tumors have rarely been reported in other OADs (Burlina et al. 2012), if at all. Finally, massive liver hepatoblastoma has thus far been described in one patient with methylmalonic aciduria 7 years following renal transplantation and immunosuppressive therapy (Cosson et al. 2008).

Although—except for patients with L-2-hydroxyglutaric aciduria and somatic gain-of-function mutations in *IDH1* and *IDH2* genes—the association between OADs and tumorigenesis is still vague, basic mechanisms have been elucidated that strongly support the notion of facilitated tumorigenesis in OADs in general. Specifically, there is a known link between altered TCA cycle flux and tumorigenesis. Isocitrate dehydrogenases 1 and 2 function at an important crossroads of cellular metabolism. They regulate the intracellular production of NADPH and 2-oxoglutarate and thus the reduction of glutathione, cholesterol synthesis, glucose-stimulated insulin secretion, oxygen-sensing signal transduction, and histone modification (Reitman and Yan 2010; Xu et al. 2011). Prolyl hydroxylases, which inactivate hypoxia-inducible factor 1α, require 2-oxoglutarate as a substrate and are inhibited by succinate, fumarate, and other dicarboxylic acids, such as D-2-hydroxyglutarate (Kranendijk et al. 2012a, b; Xu et al. 2011). If intracellular 2-oxoglutarate concentrations decrease or the concentrations of inhibitory dicarboxylic acids increase, hypoxia-inducible factor 1α is stabilized. This results in increased glucose transport, aerobic glycosis (Warburg effect), and angiogenesis, which all are known risk factors for tumorigenesis (Bayley and Devilee 2010; Baysal et al. 2000; Kaelin 2009). In addition, accumulating metabolites in OADs may alter gene expression by modifying histone acetylation (e.g., propionyl-CoA) and methylation (e.g., D-2-hydroxyglutarate) (Nguyen et al. 2007; Chowdbury et al. 2012; Xu et al. 2011).

In conclusion, current pathophysiologic concepts for OADs have identified some mechanisms underlying intra- and extracerebral disease manifestation. Impairment of energy metabolism due to mitochondrial dysfunction and concomitantly increased ROS production caused by various putative toxins is thought to play a key role. There is also increasing evidence for chronic organelle and organ dysfunction, which is not yet fully understood. Furthermore, the risk of developing malignant tumors might be increased in some OADs. Much more work is required to understand late-onset organ dysfunction and to protect patients against them.

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Conflict of interest None.

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