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Review article

The lysine degradation pathway: Subcellular compartmentalization and enzyme deficiencies

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ABSTRACT

Lysine degradation via formation of saccharopine is a pathway confined to the mitochondria. The second pathway for lysine degradation, the pipecolic acid pathway, is not yet fully elucidated and known enzymes are localized in the mitochondria, cytosol and peroxisome. The tissue-specific roles of these two pathways are still under investigation. The lysine degradation pathway is clinically relevant due to the occurrence of two severe neurometabolic disorders, pyridoxine-dependent epilepsy (PDE) and glutaric aciduria type 1 (GA1). The existence of three other disorders affecting lysine degradation without apparent clinical consequences opens up the possibility to find alternative therapeutic strategies for PDE and GA1 through pathway modulation. A better understanding of the mechanisms, compartmentalization and interplay between the different enzymes and metabolites involved in lysine degradation is of utmost importance.

1. The mitochondrial localization of enzymes involved in lysine catabolism

L-Lysine is an essential proteogenic amino acid in humans. Lysine degradation is ketogenic yielding two acetyl-CoAs and several reduction equivalents, and may be initiated either by ε-deamination or α-deamination (Fig. 1). The ε-deamination is also known as the saccharopine pathway and is localized to the mitochondria. It is considered to be the major route for lysine degradation and is well-characterized at the molecular and biochemical level. The first two steps are catalyzed by a bifunctional enzyme, the mitochondrial 2-aminoadipic acid semialdehyde synthase (AASS), and lead to the production of 2-aminoadipic acid semialdehyde (AASA). In the first step, lysine and 2-oxoglutaric acid (OG) are converted into saccharopine by the lysine-ketoglutarate reductase domain (LKR; EC 1.5.1.8). Saccharopine is then oxidized to AASA and L-glutamate by the saccharopine dehydrogenase domain (SDH; EC 1.5.1.9) [1–3].

AASA is further converted into 2-aminoadipic acid (AA) by the action of 2-aminoadipic acid semialdehyde dehydrogenase (ALDH7A1, E.C. 1.2.1.31), an aldehyde dehydrogenase (also known as antiquitin or AASDH). Although often depicted as a cytosolic enzyme, ALDH7A1 has a dual cytosolic and mitochondrial localization. Studies performed in different cell lines have demonstrated that the protein can localize to the nucleus, cytosol and mitochondria [4–6]. A mitochondrial localization is further supported by the human and mouse MitoCarta [7]. In the next step, AA is converted into 2-oxoadipic acid (OA) by the action of kynurenine/α-aminoadipic acid aminotransferase (AADAT; E.C. 2.6.1.39), a transaminase [8]. AADAT is one of the four known kynurenine aminotransferases (KATII), but can also accept AA acid as substrate [9]. AADAT is also often depicted has a cytosolic enzyme, but it is most likely a mitochondrially localized protein. AADAT activity has been detected in the mitochondrial fraction of human, cow, and rat liver and kidney extracts [8,10–13] and it has a high score for mitochondrial localization in MitoCarta [7].

In the next step, OA undergoes oxidative decarboxylation to glutaryl-CoA by the relatively recently characterized 2-oxoadipic acid dehydrogenase complex (OADHc; E.C. 1.2.4.2). This complex consists out of DHTKD1 (E1a), DLST (dihydrolipoyl succinyltransferase; E2o

Abbreviations: 3-OH-GA, 3-hydroxyglutaric acid; AASA, L-2-aminoadipic acid 6-semialdehyde; AASS, 2-aminoadipic acid semialdehyde synthase; ALDH7A1, 2-aminoadipic acid semialdehyde dehydrogenase; AMOXAD, 2-aminoadipic and 2-oxoadipic aciduria; DHTKD1, dehydrogenase E1 and transketolase domain containing protein 1; GA, glutaric acid; GA1, glutaric aciduria type 1; GA3, glutaric aciduria type 3; GCDH, glutaryl-CoA dehydrogenase; OADHc, 2-oxoadipic acid dehydrogenase complex; PDE, pyridoxine-dependent epilepsy; PIPOX, pipecolic acid oxidase; OA, 2-oxoadipic acid; OG, 2-oxoglutaric acid; P6C, Δ1-piperideine 6-carboxylate; SUGCT, succinyl-CoA:glutarate-CoA transferase

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component) and DLD (dihydrolipoyl dehydrogenase, E3 component). As all other 2-oxo acid dehydrogenase complexes, OADHc is mitochondrial sharing its E3 (and E2) component. Glutaryl-CoA dehydrogenase (GCDH, E.C. 1.3.8.6) is a member of the acyl-CoA dehydrogenase family of mitochondrial flavoproteins, and catalyzes the oxidative decarboxylation of glutaryl-CoA in crotonyl-CoA [14,15]. Its product, crotonyl-CoA, is also an intermediate in the final cycle of mitochondrial fatty acid β-oxidation, which starts with butyryl-CoA. Therefore it seems logical to assume that the last three steps of lysine and fatty acid metabolism are shared. ECHS1, also known as crotonase, is a mitochondrial short-chain enoyl-CoA hydratase (E.C. 4.2.1.150) that catalyzes the conversion of crotonyl-CoA into (*S*)-3-hydroxybutyryl-CoA. ECHS1 also catalyzes the hydration of other enoyl-CoAs in valine and isoleucine degradation [16–19]. HADH is a mitochondrial

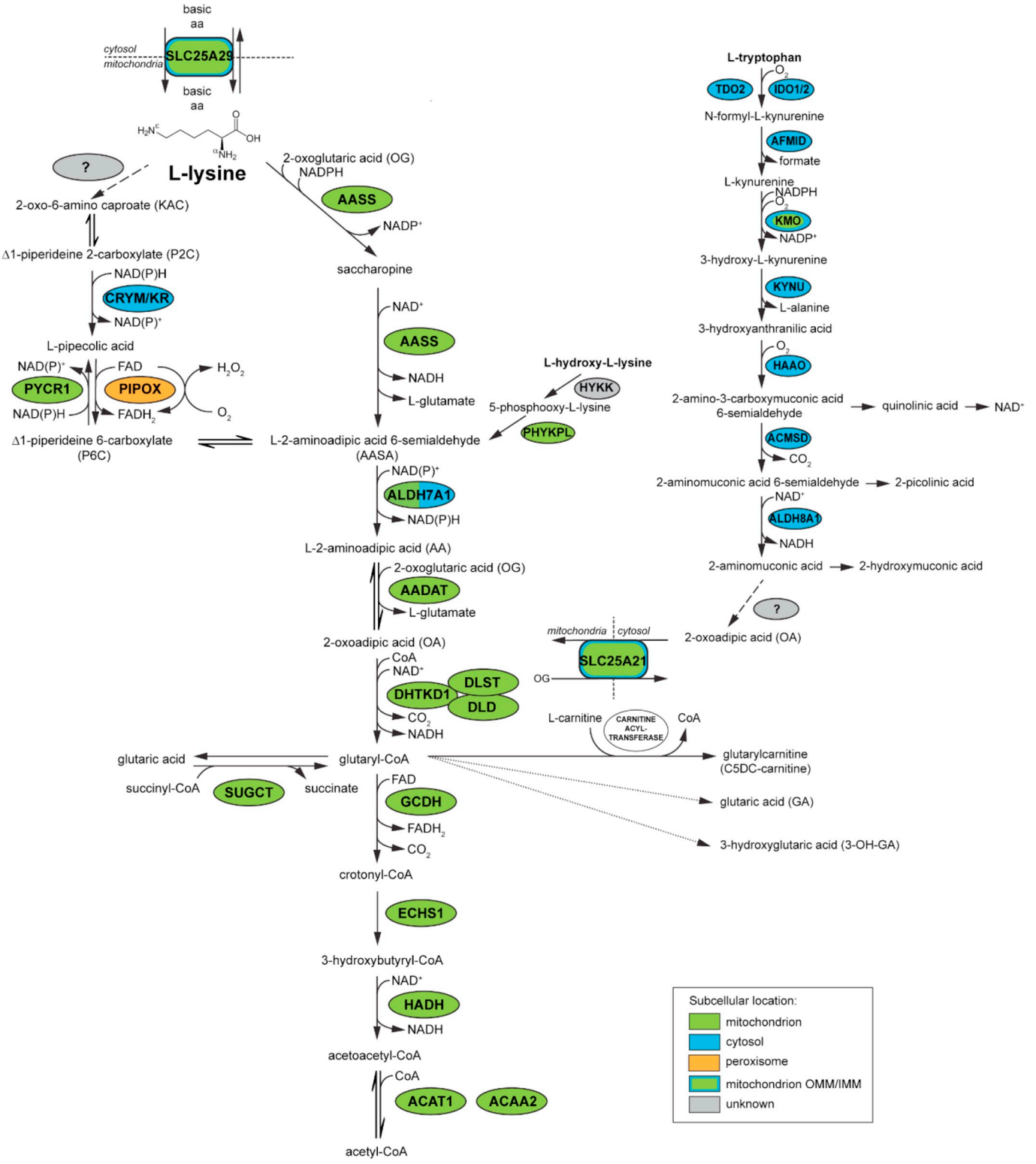

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Fig. 1. The lysine degradation pathways. The degradation of L-lysine may occur via the mitochondrial saccharopine pathway with ε-deamination of lysine or the pipecolic acid pathway with α-transamination or α-deamination of lysine. The saccharopine pathway is considered the major pathway and consists of nine different enzymatic steps that ultimately yield two acetyl-CoA units and several reducing equivalents. The pipecolic acid pathway is not fully elucidated and known enzymes are localized in three subcellular compartments. Degradation of L-hydroxy-L-lysine leads to L-2-aminoadipic acid 6-semialdehyde (AASA) and cytosolic degradation of tryptophan with kynurenine as intermediate leads to the production of 2-oxoadipic acid (OA). Lysine and OA are transported into the mitochondria by a uniport/counter exchange SLC25A29 mediated mechanism and a 2-oxoglutaric acid (OG) dependent counter exchange SLC25A21 mediated transport, respectively. 2-aminoadipic acid semialdehyde synthase (AASS) deficiency leads to hyperlysinemia. 2-aminoadipic acid semialdehyde dehydrogenase (ALDH7A1) is deficient in children with pyridoxine-dependent epilepsy. The E1 subunit of the 2-oxoadipic acid dehydrogenase complex is encoded by *DHTKD1* and is deficient in 2-aminoadipic and 2-oxoadipic aciduria. Glutaryl-CoA dehydrogenase (GCDH) is deficient in glutaric aciduria type 1 leading to the accumulation of glutaryl-CoA metabolites: glutarylcarnitine (C5DC-carnitine), glutaric acid (GA) and 3-hydroxyglutaric acid (3-OH-GA). SUGCT catalyzes the succinyl-CoA-dependent conversion of glutaric acid into glutaryl-CoA and is deficient in glutaric aciduria type 3. Dashed arrows represent not fully characterized enzymatic steps. Color code indicates subcellular localization: mitochondrion (green), cytosol (blue), orange (peroxisome) and gray (unknown). Mitochondrial carriers (blue/green) are localized in the inner mitochondrial membrane (IMM) and KMO (blue/green) is localized in the outer mitochondrial membrane (OMM).
AADAT, kynurenine/α-aminoadipic acid aminotransferase; ACAA2, 3-ketoacyl-CoA thiolase; ACAT1, acetoacetyl-CoA thiolase; ACMSD, 2-amino-3-carboxymuconate-6-semialdehyde decarboxylase; AFMID, kynurenine formamidase; ALDH8A1, 2-aminomuconic semialdehyde dehydrogenase; CRYM/KR, μ-crystallin/ketimine reductase; DHTKD1, dehydrogenase E1 and transketolase domain containing protein 1; DLD, dihydrolipoyl dehydrogenase; DLST, dihydrolipoyl succinyltransferase; ECHS1, enoyl-CoA hydratase; HAAO, 3-hydroxyanthranilate 3,4-dioxygenase; HADH, 3-hydroxyacyl-CoA dehydrogenase; HYKK, hydroxylysine kinase; IDO1/2, indoleamine 2,3-dioxygenase 1/2; KMO, kynurenine 3-monooxygenase; KYNU, kynureninase; PHYKPL, 5-phosphohydroxy-L-lysine phospho-lyase; PIPOX, peroxisomal sarcosine oxidase, also known as pipecolic acid oxidase; PYCR1, pyrroline-5-carboxylate reductase 1; SLC25A21, mitochondrial oxodicarboxylate carrier; SLC25A29, mitochondrial basic amino acid transporter; TDO2, tryptophan 2,3-dioxygenase.(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

short-chain (*S*)-3-hydroxyacyl-CoA dehydrogenase (E.C. 1.1.1.35) that converts 3-hydroxybutyryl-CoA into acetoacetyl-CoA. HADH not only plays an important role in fatty acid β-oxidation [20], but also in the regulation of insulin secretion via interaction with glutamate dehydrogenase in pancreatic β cells [21]. In the final step of the pathway, the mitochondrial acetyl-CoA acyltransferase (ACAA2, E.C. 2.3.1.9) cleaves acetoacetyl-CoA into two acetyl-CoA molecules that can feed into the TCA cycle [22]. Alternatively, a second 3-ketoacyl-CoA thiolase (ACAT1, E.C. 2.3.1.9, also known as T2), which is involved in ketone body and isoleucine metabolism, may catalyze this reaction [23–25].

SUGCT is a succinyl-CoA:glutarate-CoA transferase that also appears to play a role in the lysine degradation pathway. Formation of glutaric acid from glutaryl-CoA, may occur non-enzymatically or be mediated by a thioesterase [26,27]. SUGCT was identified using genetic mapping in patients with glutaric aciduria type 3 (GA3) [28]. Metabolite accumulation in GA3 patients and a *Sugct* KO mouse model suggests that SUGCT mainly catalyzes the succinyl-CoA-dependent conversion of glutaric acid into glutaryl-CoA [29,30]. Initially GA3 was thought be caused by a presumed peroxisomal glutaryl-CoA oxidase [31,32], but SUGCT has been firmly established as a mitochondrial enzyme by several studies: identification of a dicarboxyl-CoA: dicarboxylic acid CoA transferase in the mitochondria, the presence of a mitochondrial targeting sequence and no peroxisomal targeting signal in the SUGCT protein and the localization of SUGCT-GFP fusion protein in the mitochondria [28,29,33,34].

2. The pipecolic acid pathway

The alternative route for lysine degradation, the α-deamination pathway or pipecolic acid pathway, is initiated by α-transamination or α-deamination of lysine (Fig. 1). When compared to the saccharopine pathway, the pipecolic acid pathway is relatively poorly characterized at the molecular level. Early studies on rat and more recent ones on mouse brain suggested that in the brain the initial steps in lysine degradation proceed via α-deamination with formation of pipecolic acid rather than via ε-deamination and formation of saccharopine, with the latter pathway being more active in peripheral tissues [35–39]. However, in contrast to the AASS-mediated pathway, the gene encoding the first enzyme involved in the α-deamination is unknown. Subsequent steps include the spontaneous conversion of 2-oxo-6-aminocaproic acid into Δ1-piperideine-2-carboxylate (P2C). Conversion of P2C to pipecolic acid may be mediated by the cytosolic CRYM/ketamine reductase [37]. Pipecolic acid is further converted into Δ1-piperideine 6-carboxylate (P6C) by pipecolic acid oxidase (PIPOX), a peroxisomal enzyme. The pipecolic acid and saccharopine pathways then converge at the level of AASA. Importantly, the enzymes involved in lysine degradation via the pipecolic acid pathway are localized in the mitochondria, cytosol and peroxisome. This implies a complex metabolite transport mechanism that has not been characterized yet.

Our understanding of the lysine degradation was recently challenged by two remarkable observations. The first observation was that AASA may undergo spontaneous conversion into P6C and the latter can be converted into L-pipecolic acid by PYCR1 (E.C. 1.5.1.2), also a mitochondrial enzyme [38,40]. Humans have three PYCR isozymes, two mitochondrial (PYCR1 and PYCR2) and one cytosolic (PYCR3, also known as PYCRL), and therefore it is possible that this reaction can also be catalyzed by PYCR2 and PYCR3. Thus, pipecolic acid is not only a peroxisomal metabolite, but can also be formed within mitochondria from saccharopine after ε-deamination of lysine. Recent studies also challenged the major contribution of the pipecolic acid pathway to lysine catabolism in the brain. It was demonstrated that in mouse brain, human astrocytes and a human neural progenitor cell line, the AASS-mediated pathway via saccharopine is the main route for lysine degradation [41–44]. In stark contrast, α-deamination of lysine led to the production of pipecolic acid, but did not significantly contribute to formation of the downstream metabolite AA [41,42,44].

Pipecolic acid is also a diagnostic marker for peroxisome biogenesis disorders. Patients with peroxisome biogenesis disorders accumulate pipecolic acid alongside very long-chain fatty acids, phytanic- and pristanic acid and C27-bile acids in plasma and have decreased levels of plasmalogens in erythrocytes signifying a generalized peroxisomal dysfunction [45].

3. Hydroxylysine and tryptophan degradation

The hydroxylysine and tryptophan degradation pathways also feed into the lysine degradation pathway by formation of AASA and OA, respectively (Fig. 1). Hydroxylysine originates from degradation of proteins that have undergone post-translational modification of lysine to 5-hydroxylysine by lysyl hydroxylases (e.g. collagen) [46,47]. Free hydroxylysine is then phosphorylated by HYKK (hydroxylysine kinase, also known as AGPHD1) and further converted into AASA, ammonia, inorganic phosphate by the action of PHYKPL (5-phosphohydroxy-L-lysine phospho-lyase, also known as AGXT2L2) [48]. Tryptophan degradation occurs via eight enzymatic steps, essentially in the cytosol, but the identity of the last enzyme remains unknown [49–51]. KMO (kynurenine monooxygenase) seems to be localized on the outer mitochondrial membrane. Tryptophan degradation leads to the production of OA that enters the mitochondria via the mitochondrial oxodicarboxylate carrier (see below).

4. Metabolite transport

The role of the mitochondrial carriers, specifically the basic amino acid carrier SLC25A29 and the mitochondrial oxodicarboxylate carrier SLC25A21 (Fig. 1), in the lysine degradation pathway is sometimes neglected. SLC25A29 transports arginine, lysine, homoarginine, methylarginine and to a lesser extent ornithine and histidine into the mitochondria [52]. To date no disorder has been associated with inactivating mutations in *SLC25A29*. SLC25A21 transports OA from the cytosol (derived from the tryptophan pathway) into the mitochondrial matrix by a counter exchange mechanism with OG [53]. A patient carrying a deleterious p.Lys232Arg homozygous missense mutation in *SLC25A21* presented with a spinal muscular atrophy and mitochondrial myopathy with an increase in urinary excretion of OA, pipecolic and quinolinic acid [54].

5. Inborn errors of lysine metabolism

Lysine degradation is a clinically relevant biochemical pathway, because defects in five enzymes cause inborn errors of metabolism. Hyperlysinemia (MIM #238700), pyridoxine-dependent epilepsy (PDE; MIM #266100), 2-aminoadipic and 2-oxoadipic aciduria (AMOXAD, MIM #204750), glutaric aciduria type 1 (GA1; MIM #231670) and glutaric aciduria type 3 (GA3; MIM #231690) are caused by mutations in *AASS*, *ALDH7A1*, *DHTKD1*, *GCDH* and *SUGCT*, respectively (Table 1). Hyperlysinemia, AMOXAD and GA3 are considered biochemical phenotypes of questionable clinical significance [55], whereas PDE and GA1 cause severe neurometabolic disorders. Below, we will briefly review these 5 inborn errors of lysine metabolism.

5.1. AASS and hyperlysinemia type I and type II

2-Aminoadipic acid semialdehyde synthase (AASS) is a mitochondrial enzyme that performs the first and most likely rate-limiting step in lysine degradation. AASS is a bifunctional enzyme with two domains: lysine-ketoglutarate reductase (LKR) and saccharopine dehydrogenase (SDH) [2]. Mutations in *AASS* lead to hyperlysinemia type I, if the defect affects the activity of the LKR domain or the expression of the full-length protein leading to the accumulation of lysine; or to hyperlysinemia type II, also known as saccharopinuria, if the defect only affects the SDH domain and therefore leads to the accumulation of lysine and saccharopine. Most hyperlysinemia patients have hyperlysinemia type I due a combined LKR and SDH deficiency. Only very few patients have hyperlysinemia with saccharopinuria due to an isolated SDH defect. Interestingly, hyperlysinemia can also be caused by changes in the levels of the (co-)substrates OG and NADPH. Decreased availability of mitochondrial OG is known to cause hyperlysinemia [56]. A deficiency in the mitochondrial NAD kinase 2 (NADK2; E.C. 2.7.1.23, MIM 615787) is characterized by impaired metabolism of polyunsaturated fatty acids and lysine causing a dienoyl-CoA reductase (DECR) deficiency (MIM 222745) with hyperlysinemia and other hallmarks of a mitochondrial disorder. NADK2 is a key enzyme in the biosynthesis of NADPH, which is the cosubstrate of both DECR and AASS [57].

Hyperlysinemia type I is considered a biochemical phenotype without clinical significance [55,58]. The disease was associated with clinical symptoms such as intellectual disability and seizures, but the existence of clinically normal family members with the same biochemical defect, the existence of apparently healthy cases identified in population screening approaches and no beneficial outcome of dietary restriction of lysine has led to a consensus that hyperlysinemia type I is a non-disease [59–62]. In some cases, alternative genetic causes were identified that may better explain the phenotype including a novel contiguous gene deletion syndrome [58]. The clinical consequences of hyperlysinemia type II, remains a challenging clinical question, especially due to scarcity of cases diagnosed. Nevertheless, a recent study using *Caenorhabditis elegans* and mice suggest that saccharopinuria due to an isolated SDH defect damages mitochondria, whereas hyperlysinemia due to an LKR defect was without obvious consequences [63]. Therefore, the LKR domain of AASS is currently the preferred target for future inhibition studies of substrate reduction therapies in the lysine degradation pathway [64].

5.2. ALDH7A1 and pyridoxine-dependent epilepsy

Pyridoxine-dependent epilepsy (PDE) is caused by mutations in 2-aminoadipic acid semialdehyde dehydrogenase *(ALDH7A1)*. The hallmark of the disease is accumulation of the ALDH7A1 substrate AASA and its cyclic form P6C. The latter leads to inactivation by condensation of pyridoxal 5′-phosphate (PLP) [65], the active form of vitamin B6 and an essential coenzyme for several enzymes [66]. Patients have recurrent and sometimes intractable neonatal or infantile seizures that are alleviated by high doses of pyridoxine or PLP [67–69]. Early diagnosis and treatment are valuable, but AASA and P6C are relatively unstable metabolites making their use as biomarker complex [65,70]. A recent study has identified 6-oxopipecolic acid as a biomarker for PDE. 6-oxopipecolic acid results from the oxidation of 6-hydroxy-pipecolic acid (an intermediate in the equilibrium between AASA and P6C) by a still unknown enzyme or by direct oxidation of pipecolic acid [71]. However, irrespective of seizure control with pyridoxine supplementation, around 75% of PDE patients still suffer from developmental delay and intellectual disability, most likely due to the highly reactive nature of AASA and its neurotoxic properties [72–75]. Triple treatment with pyridoxine supplementation, arginine supplementation and dietary lysine restriction has shown promising results and validates an approach that limits flux through the lysine degradation pathway [72]. Therefore, inhibition of the upstream AASS enzyme has been proposed as substrate reduction therapy for the treatment of PDE [41,42,76]. A zebrafish model of ALDH7A1 deficiency was developed that recapitulate essential hallmarks of human PDE [77] and could help in future studies to shed light on the pathophysiology of PDE and the effectiveness of AASS inhibition as a therapeutic strategy.

5.3. DHTKD1 and 2-aminoadipic and 2-oxoadipic aciduria

The identification of mutations in *DHTKD1* in individuals with 2-aminoadipic and 2-oxoadipic aciduria (AMOXAD) demonstrated that DHTKD1 is the E1 component of a novel 2-oxoadipic acid dehydrogenase complex (OADHc) [78–82]. DHTKD1 is a close protein homolog of OGDH, the E1 component of the 2-oxoglutaric acid dehydrogenase complex (OGDHc) that acts in the TCA cycle. In general, 2-oxo acid dehydrogenase complexes (OGDHc, pyruvate dehydrogenase complex and branched-chain 2-oxo acid dehydrogenase complex) have unique E1 and E2 components, but share the same E3 component. DHTKD1 and OGDH are an exception, because they share both the E2 (DLST) and E3 (DLD) components. Indeed, recombinant DHTKD1, DLST and DLD can assemble into an active OADHc in vitro [83,84]. We recently demonstrated that DHTKD1 interacts with OGDH as well as DLST and DLD to form a new hybrid 2-oxoglutaric and 2-oxoadipic acid dehydrogenase complex [85].

AMOXAD is considered a biochemical phenotype with questionable clinical significance [55,79,80]. Some studies have associated the defect with clinical symptoms such as intellectual disability and seizures, but a causal relationship has not been established [86]. Similar to hyperlysinemia, there are healthy cases in family members with the same biochemical defect. In addition, cases identified by neonatal screening were followed over time and remained asymptomatic and dietary restriction of lysine was considered not beneficial [80,81,86–89]. In some individuals alternative genetic causes were identified that may contribute to the observed phenotype including 22q11.2 deletion syndrome, Kearns-Sayre syndrome and Niemann-Pick disease type C [80,90].

Table 1
The inborn errors of lysine metabolism.

Inborn error	Gene	Full name	MIM	Incidence	Biochemical alterations	Symptoms	Therapy and outcome	References
Hyperlysinemia	*AASS*	2-aminoadipic acid semialdehyde synthase	238700 268700	unknown	↑ lysine (type I) ↑ lysine, saccharopine (type II, saccharopinuria)	clinical significance unclear (non-disease)	no therapy (no beneficial dietary restriction of lysine)	[2,55,58]
	NADK2	NAD kinase 2	615787	unknown	↑ lysine ↑ C10:2-carnitine ↓ $NADPH_{mitochondrial}$	hallmarks of mitochondrial disorders	no therapy	[57,130,131]
Pyridoxine-dependent epilepsy (PDE)	*ALDH7A1*	2-aminoadipic acid semialdehyde dehydrogenase	266100	1:60,000	↑ AASA, P6C, 6-oxo pipecolic acid, pipecolic acid	intractable neonatal or infantile seizures developmental delay and intellectual disability	high doses of pyridoxine or PLP (75% of PDE patients still suffer from developmental delay and intellectual disability) triple therapy: pyridoxine, arginine supplementation and dietary lysine restriction (better outcome than single therapy) *Proposed*: Inhibition of AASS (LKR domain)	[41,42,67,69,71,72]
2-Aminoadipic and 2-oxoadipic aciduria (AMOXAD)	*DHTKD1*	dehydrogenase E1 and transketolase domain-containing protein 1	204750	unknown	↑ AA, OA	clinical significance unclear (non-disease)	no therapy (no beneficial dietary restriction of lysine)	[79–81,85,91,99,100]
Glutaric aciduria type 1 (GA1)	*GCDH*	glutaryl-CoA dehydrogenase	231670	1:100,000 (up to 1:200 in high risk populations)	↑ C5DC-carnitine, GA, 3OH-GA ↑ glutaryl-CoA ↓ carnitine	macrocephaly may develop a complex movement disorder due to striatal injury extrastriatal changes in late-onset GA1 patients reduced glomerular filtration rate with age	dietary restriction of lysine intake, carnitine supplementation and emergency care (reduced the frequency of acute encephalopathic crises and movement disorders (now 10–20% from 80 to 90%) arginine fortification can be implemented to limit cerebral lysine influx *Proposed*: Inhibition of AASS (LKR domain)	[102,103,108,109,125,128]
Glutaric aciduria type 3 (GA3)	*SUGCT*	succinyl-CoA:glutarate-CoA transferase	231690	unknown	↑ GA	clinical significance unclear (non-disease)	no therapy	[28,29,32,129]

The function of OADHc is one step upstream of glutaryl-CoA dehydrogenase, the enzyme defective in glutaric aciduria type 1. The limited clinical consequences of AMOXAD led to the hypothesis that inhibition of DHTKD1 is a potentially safe therapeutic strategy to treat GA1 [79,85,91]. Unexpectedly, two independent studies, one of a *Gcdh/Dhtkd1* double KO mouse model [91] and another on a *Gcdh* KO mouse model with a spontaneous variant in *Dhtkd1* [85], failed to demonstrate mitigation of the clinical and biochemical phenotype of the *Gcdh* KO mouse model. These results firmly establish that DHTKD1 is not the only source of glutaryl-CoA. Indeed, in vitro and cell studies have shown substantial substrate overlap between OADHc and OGDHc, thus precluding a significant reduction in the accumulation of toxic substrates in GA1 upon reduction of DHTKD1 activity [39,83,85,92–95].

In addition to biallelic *DHTKD1* variants causing AMOXAD, genetic studies have also implicated autosomal dominant *DHTKD1* variants in the pathogenesis of Charcot-Marie-Tooth disease type 2Q (CMT2Q; MIM 615025) and eosinophilic esophagitis (EoE) [96–98]. Currently no satisfactory pathophysiological mechanism exists that explains the observed pleiotropy of *DHTKD1* variants. Recently, the first crystal structures of DHTKD1 bound to the cofactor ThDP were reported [99,100], which could shed light on the biochemical consequences of the different variants. Some variants do not affect the stability or activity of DHTKD1, but seem to interfere with the assembly and function of the OADHc. The p.G729R DHTKD1 variant affects DHTKD1 (E1)-DLST (E2) assembly leading to impaired channeling of OADHc intermediates [101]. The identification of small molecule inhibitors of DHTKD1 [100] may yield valuable tools to dissect the function of DHTKD1 in the different associated diseases.

5.4. GCDH and glutaric aciduria type 1

Glutaric aciduria type 1 (GA1) is an autosomal recessive disease caused by a defect of glutaryl-CoA dehydrogenase (GCDH) due to mutations in *GCDH* [102–104]. GCDH catalyzes the oxidative decarboxylation of glutaryl-CoA into crotonyl-CoA and its deficiency leads to the accumulation of glutaryl-CoA, glutaric acid and 3-hydroxyglutaric acid, which are thought to be neurotoxic. GA1 is considered a cerebral organic aciduria. The disease mechanism was derived from data showing markedly increased levels of glutaric acid and 3-hydroxyglutaric acid in different brain regions of patients [105,106]. This is most likely caused by cerebral accumulation and entrapment of the dicarboxylic acids due to the low capacity of the brain to export these metabolites across the blood-brain barrier [107–109]. The exact pathophysiological mechanisms by which the accumulation of these metabolites causes striatal damage remain unclear. Several mechanisms have been proposed including excitotoxicity due to stimulation of *N*-methyl-D-aspartate and/or glutamate receptors, increased production of reactive oxygen species, perturbation of specific mitochondrial functions and increased protein glutarylation due to accumulation of glutaryl-CoA [110–120].

GA1 patients can present with macrocephaly and may develop a complex movement disorder due to striatal injury with acute or insidious onset [103,104,121,122]. Some late-onset GA1 patients have been reported with extrastriatal changes [123]. In addition, a reduced glomerular filtration rate with age highlighted an increased risk of developing chronic kidney disease later in life [124]. GA1 is currently treated by restricting lysine intake, carnitine supplementation and emergency care [125,126]. In addition, arginine fortification can be implemented to limit cerebral lysine influx [127]. A substrate reduction therapy that limits the accumulation of GCDH substrates may ultimately substitute all current treatment modalities. DHTKD1 inhibition does not permit this reduction due to the overlap substrate specificity of DHTKD1 with OGDH. We have recently demonstrated that loss of AASS function in GCDH-deficient HEK-293 cells leads to a ~ 5-fold reduction in the established GA1 clinical biomarker glutarylcarnitine [128]. More importantly, we have shown that in the GA1 mouse model, deletion of *Aass* leads to a 4.3-, 3.8- and 3.2-fold decrease in the glutaric acid levels in urine, brain and liver, respectively. Parallel decreases were observed in urine and brain 3-hydroxyglutaric acid levels, and plasma, urine and brain glutarylcarnitine levels [128]. These data support the notion that saccharopine pathway is the main source of glutaric acid production in the brain and periphery of a mouse model for GA1, and that pharmacological inhibition of AASS limits the accumulation of GCDH substrates. Currently inhibition of AASS, in particular the LKR domain, is the most promising novel avenue to treat GA1 as well as PDE.

5.5. SUGCT and glutaric aciduria type 3

Glutaric aciduria type 3 (GA3) results from mutations in *SUGCT*, which encodes succinyl-CoA:glutarate-CoA transferase. SUGCT catalyzes the succinyl-CoA-dependent conversion of glutaric acid into glutaryl-CoA [29]. GA3 patients who have defective SUGCT have increased plasma and urine levels of glutaric acid, but in contrast to GA1 patients they do not have elevated glutarylcarnitine and 3-hydroxyglutaric acid. Currently GA3 is considered a biochemical phenotype of questionable clinical significance [28,55]. Despite the existence of reports of intellectual disability in some patients, the existence of asymptomatic patients discovered through newborn screening programs has questioned the causal relationship between SUGCT and GA3 clinical phenotype [28,31,32,129]. In some cases the symptoms were explained by the presence of other factors as monosomy 6q26-qter, β-thalassemia and autoimmune hyperthyroidism [31,32].

Urinary glutaric acid excretion further increases in GA3 patients after lysine loading clearly establishing an important role in endogenous lysine metabolism [32]. Although SUGCT is not part of the canonical lysine degradation pathway, these observations suggest that a significant fraction of glutaryl-CoA undergoes spontaneous [26] or enzyme-mediated hydrolysis by a thioesterase [27] to glutaric acid before further metabolism by GCDH can take place (Fig. 1). Therefore, the role of SUGCT in lysine degradation in normal and disease states warrants further evaluation as a possible modulator of the pathway.

6. Conclusion

A future pharmacological treatment for the two severe inborn errors of lysine catabolism, PDE and GA1, holds promise by the fact that three other deficiencies in the same pathway, hyperlysinemia, AMOXAD and GA3 seem to have no clinical consequences. These observations open up the possibility of modulating the pathway to prevent the accumulation of toxic metabolites. A full knowledge of the pathway, the subcellular compartmentalization of the different enzymatic steps and the exact action of the toxic metabolites will benefit the quest for an effective cure for diseases affecting mitochondrial lysine degradation.

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