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Inherited Disorders of Lysine Metabolism: A Review

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ABSTRACT

Lysine is an essential amino acid, and inherited diseases of its metabolism therefore represent defects of lysine catabolism. Although some of these enzyme defects are not well described yet, glutaric aciduria type I (GA1) and antiquitin (2-aminoadipic-6-semialdehyde dehydrogenase) deficiency represent the most well-characterized diseases. GA1 is an autosomal recessive disorder due to a deficiency of glutaryl-CoA dehydrogenase. Untreated patients exhibit early onset macrocephaly and may present a neurological deterioration with regression and movement disorder at the time of a presumably "benign" infection most often during the first year of life. This is associated with a characteristic neuroimaging pattern with frontotemporal atrophy and striatal injuries. Diagnosis relies on the identification of glutaric and 3-hydroxyglutaric acid in urine along with plasma glutarylcarnitine. Treatment consists of a low-lysine diet aiming at reducing the putatively neurotoxic glutaric and 3-hydroxyglutaric acids. Additional therapeutic measures include administration of L-carnitine associated with emergency measures at the time of intercurrent illnesses aiming at preventing brain injury. Early treated (ideally through newborn screening) patients exhibit a favorable long-term neurocognitive outcome, whereas late-treated or untreated patients may present severe neurocognitive irreversible disabilities. Antiquitin deficiency is the most common form of pyridoxine-dependent epilepsy. α-Aminoadipic acid semialdehyde (AASA) and Δ-1-piperideine-6-carboxylate (P6C) accumulate proximal to the enzymatic block. P6C forms a complex with pyridoxal phosphate (PLP), a key vitamer of pyridoxine, thereby reducing PLP bioavailability and subsequently causing epilepsy. Urinary AASA is a biomarker of antiquitin deficiency. Despite seizure control, only 25% of the pyridoxine-treated patients show normal neurodevelopment. Low-lysine diet and arginine supplementation are proposed in some patients with decrease of AASA, but the impact on neurodevelopment is unclear. In summary, GA1 and antiquitin deficiency are the 2 main human defects of lysine catabolism. Both include neurological impairment. Lysine dietary restriction is a key therapy for GA1, whereas its benefits in antiquitin deficiency appear less clear. *J Nutr* 2020;150:2556S–2560S.

Keywords: inborn errors of metabolism, lysine, glutaric aciduria type 1, pyridoxine-dependent epilepsy, antiquitin deficiency

Introduction

Lysine is an essential amino acid, and inherited diseases of its metabolism therefore represent defects of lysine catabolism (**Figure 1**). Lysine, hydroxylysine, and tryptophan are supposedly chiefly catabolized in the mitochondrion (**Figure 2**), initially via separate pathways, which converge into a common pathway at the point of α-aminoadipic semialdehyde (hydroxylysine catabolism and pipecolic acid pathway of lysine catabolism) and at the point of α-ketoadipic acid (tryptophan catabolism; Figure 1). The major route of lysine catabolism in most tissues is via the bifunctional enzyme, α-aminoadipic semialdehyde synthase (AASS; Figure 1, enzyme 1). However, a small amount of lysine is catabolized in the peroxisome via pipecolic acid by pipecolic acid oxidase (enzyme 2); although this pathway was classically regarded as the major route of lysine catabolism in the brain, recent studies have challenged this dogma (1, 2). These studies have indeed demonstrated that the major route of lysine catabolism in the brain was indeed through the saccharopine pathway (AASS). α-Aminoadipic semialdehyde is converted into α-aminoadipic acid by α-aminoadipic semialdehyde dehydrogenase (antiquitin; enzyme 4), which is then converted to α-ketoadipic acid by α-aminoadipate aminotransferase (enzyme 5). α-Ketoadipic acid is mostly converted to glutaryl-CoA by the α-ketoglutarate dehydrogenase-like complex (enzyme 6a) because its E1 subunit (DHTKD1) has a higher substrate affinity for α-ketoadipic acid than the α-ketoglutarate dehydrogenase complex in the Krebs cycle (enzyme 6b). α-Ketoadipic acid is dehydrogenated and decarboxylated to crotonyl-CoA by glutaryl-CoA dehydrogenase (enzyme 7). This enzyme transfers electrons to FAD and hence to the mitochondrial respiratory chain via electron transfer protein (ETF)/ETF dehydrogenase. We focus on the 2 most well-characterized human inherited

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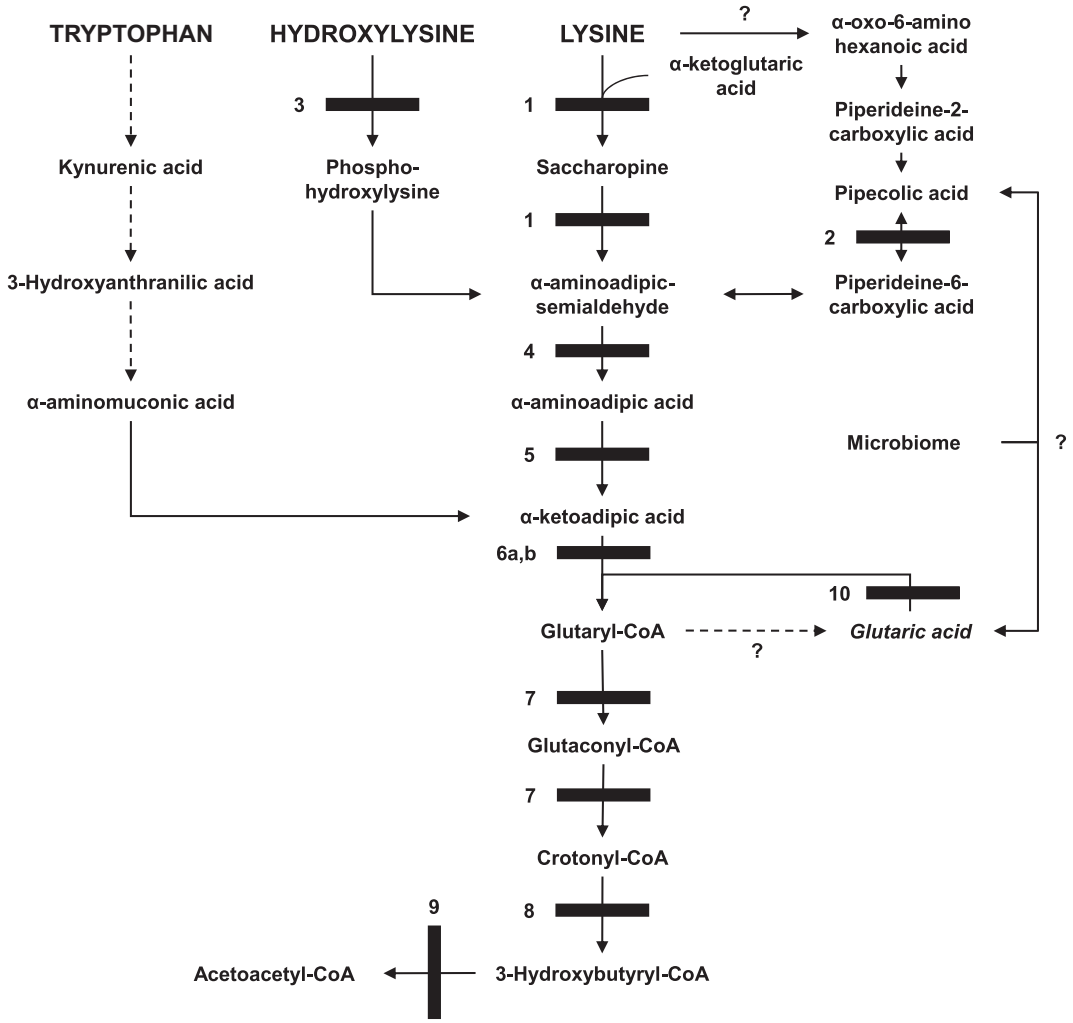

FIGURE 1 Schematic overview of the lysine, tryptophan, and hydroxylysine catabolism pathway. 1, α-aminoadipic semialdehyde synthase; 2, pipecolic acid oxidase; 3, hydroxylysine kinase; 4, α-aminoadipic semialdehyde dehydrogenase (antiquitin); 5, α-aminoadipate aminotransferase; 6a, α-ketoglutarate dehydrogenase-like complex using DHTKD1 as E1 subunit; 6b, alternatively, α-ketoglutarate dehydrogenase complex also has substrate affinity for α-ketoadipic acid; 7, glutaryl-CoA dehydrogenase; 8, short-chain enoyl-CoA hydratase 1 (crotonase); 9, 3-hydroxyacyl-CoA dehydrogenase; 10, succinate hydroxymethylglutarate-CoA transferase. Enzyme deficiencies are indicated by solid bars.

disorders of lysine catabolism—that is, glutaric aciduria type I (GA1) caused by deficient glutaryl-CoA dehydrogenase (enzyme 7) and α-aminoadipic semialdehyde (AASA) dehydrogenase (antiquitin; enzyme 4) deficiency causing pyridoxine-dependent epilepsy (PDE).

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Abbreviations used: AASA, α-aminoadipic acid semialdehyde; AASS, α-aminoadipic semialdehyde synthase; CNS, central nervous system; DECR, dienoyl-CoA reductase; ETF, electron transfer protein; GA1, glutaric aciduria type I; NBS, newborn screening; OMIM, Online Mendelian Inheritance in Man; PDE, pyridoxine-dependent epilepsy; PLP, pyridoxal phosphate; P6C, Δ-1-piperideine-6-carboxylate; 3-OH-GA, 3-hydroxyglutaric acid.

GA1

GA1 [Online Mendelian Inheritance in Man (OMIM) 231670] is a rare inherited disorder of lysine, hydroxylysine, and tryptophan catabolism due to deficiency of glutaryl-CoA dehydrogenase resulting in accumulation of glutaryl-CoA and its dicarboxylic derivatives glutaric acid (GA), 3-hydroxyglutaric acid(3-OH-GA), glutaconic acid, and glutarylcarnitine in body fluids and tissues, especially the central nervous system (CNS). The estimated incidence of GA1 relies on data from Germany (1 in 112,700 newborns) (3). Between the ages of 3 and 36 mo, most untreated patients develop a complex movement disorder with predominant dystonia due to bilateral striatal injury associated with high morbidity and mortality (4–7). This may occur acutely following an acute encephalopathic crisis usually triggered by a presumably benign infectious disease or insidiously (7). Conversely, some individuals may remain free from symptoms lifelong. Such wide phenotypic heterogeneity is not well understood and not related to specific genotypes or level of excretion of toxic metabolites. Likewise, low-excreter and high-excreter patients have been described according to the amount of urinary GA, both seemingly sharing the same risk of developing movement disorder if untreated. Approximately

half of affected infants exhibit macrocephaly that can be present from birth (nonfamilial) or progress with time. Brain MRI is a key diagnostic tool and shows abnormalities even in asymptomatic individuals—that is frontotemporal atrophy and white matter lesions without striatal involvement. Striatal injury (8) with white matter lesions is observed in patients with movement disorder (acute or insidious) (9). Because glutarylcarnitine can be detected by tandem mass spectrometry and early treatment has demonstrated its preventative beneficial effect, GA1 has been increasingly included in national newborn screening (NBS) programs. A recent study on patients diagnosed by NBS showed that deviations from metabolic maintenance treatment, particularly deviations from low-lysine diet, are the major risk factor for dystonia of insidious onset (3). GA1 therapy aiming at reducing CNS accumulation of neurotoxic dicarboxylic metabolites relies on a low-lysine and tryptophan diet using an amino acid mixture without lysine and tryptophan, along with L-carnitine supplementation for maintenance treatment and emergency treatment during fever episodes (6). If treated before the onset of irreversible neurological symptoms, the encephalopathic crises can be prevented in the majority of children (3, 4). Studies in the glutaryl-CoA dehydrogenase (*Gcdh*$^{-/-}$) mouse have confirmed that lysine is neurotoxic and that lysine dietary restriction is neuroprotective in GA1 (10). In addition to the direct toxic effects of accumulated dicarboxylic acids in the CNS (mainly GA and 3-OH-GA), pathophysiology may include dicarboxylic metabolites intracerebral trapping and secondary brain energy mitochondrial defects (11).

PDE (Antiquitin Deficiency)

PDE (OMIM 266100) was initially described as a potential disorder of the lysine catabolism pathway due to the presence of elevated pipecolic acid. Subsequently, the defect in this pathway was identified as a deficiency of antiquitin (likely mitochondrial enzyme, α-AASA dehydrogenase encoded by *ALDH7A1*) (12), leading to the accumulation of α-AASA and Δ-1-piperideine-6-carboxylate (P6C) (Figure 2). Accumulated P6C complexes with pyridoxal phosphate (PLP) and decreases PLP function by drastically limiting its bioavailability. PLP is the vitamin B6 (pyridoxine) vitamer acting as a cofactor for numerous enzymes, especially CNS-functioning ones. Therefore, inactivation of PLP causes epilepsy that is treatable by pharmacological doses of pyridoxine. Elevated urinary AASA is a more reliable biomarker for PDE than elevated blood pipecolic acid; importantly, urinary AASA remains elevated after initiation of pyridoxine treatment (13).

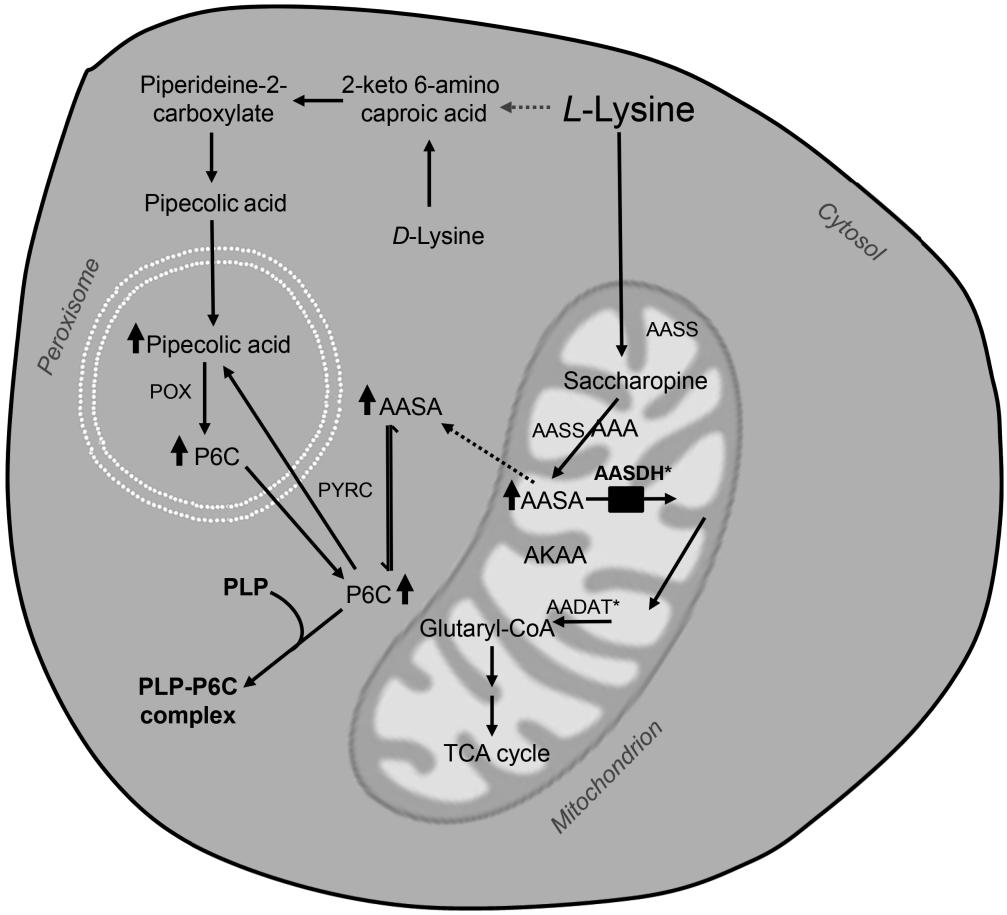

FIGURE 2 *ALDH7A1* deficiency or antiquitin deficiency or PDE: a defect of the lysine catabolism pathway. PDE is caused by a defect of AASDH (solid bar) with subsequent upstream accumulation of AASA and P6C. The latter forms a complex with PLP, thereby drastically limiting PLP bioavailability with further impacts on PLP-dependent enzymes. The asterisks indicate that antiquitin (AASDH, *ALDH7A1*) and AADAT are classically shown as cytosolic enzymes. However, there is evidence that both enzymes also have a mitochondrial localization [most likely dual cytosol and mitochondrial localization (14, 15)]. AAA, α-aminoadipate; AADAT, α-aminoadipate aminotransferase; AASDH, α-aminoadipate semialdehyde dehydrogenase; AASS, α-aminoadipate semialdehyde; AKAA, α-ketoadipate; PDE, pyridoxine-dependent epilepsy; PLP, pyridoxal phosphate; POX, L-pipecolate oxidase; PYRC, pyrroline-5-carboxylate reductase; P6C, Δ-1-piperideine-6-carboxylate; TCA, tricarboxylic acid.

Since the identification of its molecular basis, the clinical spectrum of antiquitin deficiency has widened from abnormal fetal movements and a multisystem neonatal disorder to onset of seizures and autistic features after the first year of life (16, 17). The most typical clinical picture is that of a neonatal seizure disorder refractory to conventional antiepileptic drugs and responsive to pyridoxine. However, clinical response to pyridoxine may remain partial and delayed. Seizures of patients with *ALDH7A1* deficiency are usually controlled on pyridoxine monotherapy in ~90% of cases; however, ≥75% of children have intellectual disability and developmental (speech) delay despite, and independent of, prompt pyridoxine therapy initiated in the neonatal period (18). Two additional therapeutic options have been trialed in relatively small numbers of patients. The first approach is a lysine-restricted diet to lower potentially toxic AASA concentrations (19). The second is the use of arginine, which competes with lysine in the process of transport, thereby reducing its intestinal absorption and transport into the brain at the blood–brain barrier (20). "Triple therapy" (pyridoxine and arginine supplementation, lysine restriction) is probably a suitable option because it clearly appears that these treatments allow a decrease in the putatively toxic metabolites and biomarkers in body fluids including CNS along with most often short-term neurodevelopmental improvements (21, 22). Optimum results were reported for patients for whom treatment was started early; however, larger cohorts and longer term data with extensive neurocognitive testing are mandatory.

The key role of the saccharopine pathway in whole-body [especially the brain (2)] lysine catabolism opens new therapeutic avenues for PDE. In particular, inhibition of this pathway upstream of AASA/P6C synthesis may prevent AASA accumulation, thus benefiting PDE patients.

Future Directions

Hyperlysinemia caused by mutations in *AASS* encoding for the bifunctional AASS (Figure 1, enzyme 1), the first enzyme in the lysine degradation pathway (23), is generally considered as a benign metabolic variant and a nondisease without overt clinical consequences (24). More recently, NADK2 deficiency (mitochondrial NAD kinase deficiency; OMIM 615787) was identified by whole-exome sequencing in patients exhibiting a mild to severe neurodevelopmental phenotype with hyperlysinemia with or without accumulation of C10:2-carnitine (25–27). It was shown that NADK2 produces NADPH, which acts as a molecular chaperone activating and stabilizing AASS and dienoyl-CoA reductase (DECR). Although the clinical spectrum and pathophysiology of NADK2 deficiency remain to be further defined, the severe neurometabolic NADK2 phenotype does not seem to be related to hyperlysinemia nor DECR deficiency but, rather, to the dysfunction of mitochondrial NADPH-dependent pathways.

Conclusions

Lysine-related inborn errors of metabolism comprise 2 main entities, GA1 and PDE, which are both amenable to efficacious therapy: lysine/tryptophan-restricted diet along with L-carnitine supplementation in GA1 and pyridoxine in PDE. In both disorders, lysine plasma concentration is not elevated. The role for lysine-restricted diet and arginine therapy in PDE remains to be further studied in larger cohorts of patients, but preliminary data provide promising insights on its beneficial clinical impact.

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