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Minireview

Adenylosuccinate lyase deficiency

Erin K. Spiegel [a,b,*], Roberta F. Colman [c], David Patterson [a,b]

[a] *Eleanor Roosevelt Institute at University of Denver, Denver, CO, USA*
[b] *Human Medical Genetics Program, University of Colorado Health Sciences Center, Denver, CO, USA*
[c] *Department of Chemistry and Biochemistry, University of Delaware, Newark, DE, USA*

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Abstract

Adenylosuccinate lyase deficiency is a disease of purine metabolism which affects patients both biochemically and behaviorally. The symptoms are variable and include psychomotor retardation, autistic features, hypotonia, and seizures. Patients also accumulate the substrates of ADSL in body fluids. Both the presence of normal levels of ADSL enzyme activities in some patient tissues and the absence of a clear correlation between mutations, biochemistry, and behavior show that the system has unexplored biochemical and/or genetic complexity. It is unclear whether the pathological mechanisms of this disease result from a deficiency of purines, a toxicity of intermediates, or perturbation of another pathway or system. A patient with autistic features and mild psychomotor delay carries two novel mutations in this gene, E80D and D87E. The creation of a mouse model of this disease will be an important step in elucidating the *in vivo* mechanisms of the disease. Mice carrying mutations that cause ADSL deficiency in humans will be informative as to the effects of these mutations both during embryogenesis and on the brain, possibly leading to therapies for this disease in the future.

Keywords: Autism; Psychomotor retardation; Purine biosynthesis; Enzyme; Succinylpurines

Introduction

Adenylosuccinate lyase (ADSL, EC 4.3.2.2) deficiency is a defect of purine metabolism causing serious neurological and physiological symptoms. It was first described in 1984 by Jaeken and Van den Berghe [1], who found succinylpurines in the cerebrospinal fluid (CSF), plasma, and urine of three patients with severe psychomotor delay and autistic features. These succinylpurines, succinyladenosine (S-Ado) and succinylaminoimidazolecarboxamide riboside (SAICAr) are the dephosphorylated derivatives of ADSL substrates. This accumulation in their patients' CSF suggested a deficiency in ADSL activity, and indeed, the investigators reported significantly reduced ADSL enzyme activity in these patients. ADSL catalyzes two steps in the *de novo* purine biosynthetic pathway, which consists of 13 metabolic steps in the conversion of ribose-5-phosphate into AMP or GMP (Fig. 1). These two steps are: the conversion of succinylaminoimidazolecarboxamide ribonucleotide (SAICAR) into aminoimidazolecarboxamide ribonucleotide (AICAR), and the conversion of succinyladenosine monophosphate (AMPS) to adenosine monophosphate (AMP).

Regulation of the *de novo* purine biosynthetic pathway is highly controlled and occurs at multiple steps. Disruption of this regulation is known to cause other syndromes with neurodevelopmental abnormalities. For example, levels of PRPP, a substrate for the second step of *de novo* purine synthesis, are very important in the regulation of the pathway (Fig. 1). Mutations in PRPP synthetase leading to elevated activity of this enzyme cause elevated de novo purine synthesis and, in some families, neurodevelopmental impairment [2].

Lesch–Nyhan syndrome is caused by a deficiency of HPRT, an enzyme in the purine salvage pathway [3,4]. Since PRPP is a substrate in the reaction of HPRT, a deficiency of HPRT causes levels of free PRPP to rise and therefore stimulate flux through the *de novo* purine

* Corresponding author. Fax: +1 303 333 8423.
E-mail address: erin.spiegel@uchsc.edu (E.K. Spiegel).

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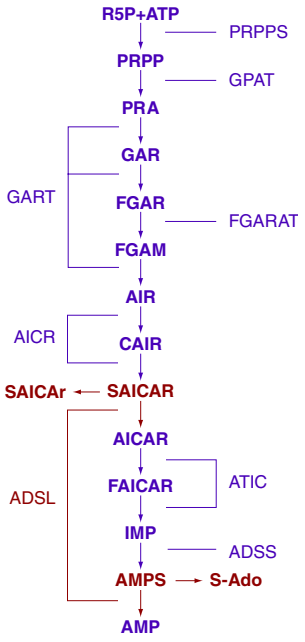

Fig. 1. A schematic representation of the pathway of *de novo* purine biosynthesis leading to the creation of AMP. Steps shown in red are catalyzed by ADSL. Abbreviations are as follows: ATP, adenosine triphosphate; R5P, ribose 5 phosphate; PRPP, phosphoribosylpyrophosphate; PRA, phosphoribosylamine; GAR, phosphoribosylglycineamide; FGAR, phosphoribosylformylglycineamide; FGAM, phosphoribosylformylglycineamidine; AIR, phosphoribosylaminoimidazole; CAIR, phosphoribosylcarboxyaminoimidazole; SAICAR, phosphoribosylsuccinylaminoimidazolecarboxamide; SAICAr, succinylaminoimidazolecarboxamide riboside; AICAR, phosphoribosylaminoimidazolecarboxamide; FAICAR, phosphoribosylformylaminoimidazolecarboxamide; IMP, inosine monophosphate; AMPS, succinyladenosine monophosphate; S-Ado, succinyladenosine; AMP, adenine monophosphate; PRPPS, PRPP Synthase; GPAT, phosphoribosylamidotransferase; GART, GAR synthase, GAR transformylase, AIR synthase (trifunctional protein); FGARAT, FGAR amidotransferase; AICR, AIR carboxylase, SAICAR synthetase (bifunctional protein); ADSL, adenylosuccinate lyase (bifunctional protein); ATIC, AICAR formyltransferase, IMP synthase (bifunctional protein). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this paper.)

pathway [3,4]. The hallmark of this disorder is compulsive self-mutilation, although other characteristics include hyperuricemia, choreoathetosis, spasticity, aggression, and sometimes, mental retardation [3,4].

Another syndrome of purine synthesis is AICA-Riboziduria, caused by a deficiency of the bifunctional enzyme AICAR transformylase/IMP cyclohydrase (ATIC) [5]. This enzyme acts in the two *de novo* pathway steps following the first ADSL step (Fig. 1). A deficiency of this enzyme causes psychomotor retardation, epilepsy, congenital blindness, and dysmorphic features [5]. Like patients with ADSL deficiency, this patient accumulates SAICAr and S-Ado, as well as AICA-riboside (AICAr), the nucleoside derivative of AICAR, one substrate of ATIC [5].

Clearly, perturbations in the *de novo* purine pathway have profound effects on many neurological functions, though the mechanisms are not understood.

Diagnosis and clinical features of ADSL deficiency

In general, patients with ADSL deficiency are discovered during screens of children with unexplained developmental delay using the Bratton–Marshall assay for diazotizable amines [6]. This assay reveals accumulation of SAICAr in body fluids, which is the main diagnosis criterion for this disease. However, since the Bratton–Marshall assay can cause false positive results if patients are taking certain medications, a diagnosis of ADSL deficiency is generally then made using HPLC analysis showing accumulation of both SAICAr and S-Ado.

There is wide variation in the clinical presentation observed in patients with ADSL deficiency. In most documented cases, the disorder leads to profound psychomotor retardation (PMR), though there are some notable cases with only mild delay. This may reflect an ascertainment bias: as ADSL deficiency was thought to cause profound developmental delay, generally only patients with such delay were being tested for ADSL deficiency. Due to the heterogeneous nature of this disease, however, many clinical investigators are now calling for screening of patients with a wider range of PMR and behavioral phenotypes.

Other, variable features of ADSL deficiency include severe hypotonia, abnormal brain glucose utilization, muscular wasting, and failure of muscle energy metabolism [7–10]. Epilepsy and autistic features are also frequently seen [11–13]. The autistic features seen in patients with ADSL deficiency include failure to make eye contact, repetitive behaviors, agitation, temper tantrums, and autoaggressivity [14]. In most cases autistic behavior persists, except for occasional improvement of eye contact [14].

The genetics of ADSL deficiency

The human ADSL gene has been mapped to chromosome 22q13.1-13.2 [15–17]. The gene is 23 kb in length, consists of 13 exons, and encodes a protein of 484 amino acids [18]. In 1992, Stone et al. [13] reported the first sequence of a mutation in the ADSL gene leading to this syndrome. To date, 38 different mutations have been reported in the ADSL gene that lead to ADSL deficiency (Table 1). Each mutation is a single base pair change that produces an altered ADSL protein. All are missense mutations with two exceptions: one exceptional mutation creates a new splice site and results in a 39 base pair deletion [19,20] and the other is a mutation in an NRF2 binding site in the promoter region of ADSL [21]. Most ADSL deficiency patients are compound heterozygotes and in cases in which the parents have been genotyped, each parent carries one mutant and one normal allele and is asymptomatic. No individuals with ADSL deficiency are completely lacking in enzyme activity [22,23]; complete lack of ADSL activity in humans is probably incompatible with life. Almost 50 cases of ADSL deficiency have been described to date, but attempts to correlate ADSL mutations or ADSL activity with the severity of the phenotype have uncovered no obvious patterns (Table 1).