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Succinic Semialdehyde Dehydrogenase Deficiency

Synonyms: 4-Hydroxybutyric Aciduria, Gamma-Hydroxybutyric Aciduria, SSADH Deficiency

Phillip L Pearl, MD,[1] Natrujee Wiwattanadittakul, MD,[2] Jean-Baptiste Roullet, PhD,[3] and K Michael Gibson, PhD, FACMG[4]

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Summary

Clinical characteristics

Succinic semialdehyde dehydrogenase (SSADH) deficiency is characterized by infantile-onset hypotonia, developmental delay, cognitive impairment, expressive language deficit, and mild ataxia. Epilepsy is present in about half of affected individuals and is more common in adults. Hyperkinetic behavior, aggression, self-injurious behaviors, hallucinations, and sleep disturbances have been reported in nearly half of all affected individuals, more commonly in those who are older. Basal ganglia signs including choreoathetosis, dystonia, and myoclonus have been reported in a few individuals with earlier-onset, more severe disease. Involvement beyond the central nervous system has not been described.

Individuals with SSADH deficiency typically have 4-hydroxybutyric aciduria present on urine organic acid analysis. Head MRI reveals T_2 hyperintensities in multiple regions, involving the globus pallidi, cerebellar dentate nuclei, subthalamic nuclei, subcortical white matter, and brain stem, as well as cerebral and sometimes cerebellar atrophy. EEG findings include background slowing and spike discharges that are usually generalized.

Diagnosis/testing

The diagnosis of SSADH deficiency is established by the identification of biallelic pathogenic variants in *ALDH5A1*.

Management

Treatment of manifestations: Management is most often symptomatic, directed at the treatment of seizures and neurobehavioral disturbances. A broad spectrum of antiepileptic medication has been used to treat this

Author Affiliations: 1 Professor of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; Email: phillip.pearl@childrens.harvard.edu. 2 Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; Email: natrujee.w@gmail.com. 3 Professor, College of Pharmacology, Washington State University, Spokane, Washington; Email: j.roullet@wsu.edu. 4 Professor and Head, Section of Clinical Pharmacology, College of Pharmacy, Washington State University, Spokane, Washington; Email: mike.gibson@wsu.edu.

condition. While vigabatrin is an irreversible inhibitor of GABA-transaminase and thus inhibits the formation of succinic semialdehyde, it has shown inconsistent results in treatment of seizures associated with SSADH deficiency. Methylphenidate, thioridazine, risperidal, fluoxetine, and benzodiazepines have been used for treatment of increased anxiety, aggressiveness, and inattention. Additional, non-pharmacologic treatments may include physical and occupational therapy, sensory integration, feeding and/or speech therapy.

Surveillance: Regular neurologic and developmental assessments as indicated.

Agents/circumstances to avoid: Valproate may inhibit residual SSADH enzyme activity; however, valproate may be considered in individuals with refractory epilepsy who have failed other treatments.

Genetic counseling

SSADH deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives is possible if the pathogenic variants have been identified in the family. Biochemical testing is not accurate or reliable for carrier determination. Prenatal testing for a pregnancy at increased risk is possible using molecular genetic testing if the pathogenic variants have been identified in the family, or using biochemical testing (either measurement of 4-hydroxybutyric acid in amniotic fluid or assay of SSADH enzyme activity in chorionic villus tissue and cultured amniocytes).

Diagnosis

Suggestive Findings

Succinic semialdehyde dehydrogenase (SSADH) deficiency **should be suspected** in individuals with the following clinical, imaging, EEG, and supportive laboratory findings:

Clinical features. Late-infantile to early-childhood onset, slowly progressive or static encephalopathy characterized by:

- Cognitive deficiency
- Prominent expressive language deficit
- Hypotonia
- Epilepsy
- Hyporeflexia
- Ataxia

Neuroimaging features

- Cranial MRI that demonstrates:
  - A pallidodentatoluysian pattern [Pearl et al 2009c], showing increased T_2-weighted signal involving the globus pallidi bilaterally and symmetrically, in addition to the cerebellar dentate nuclei and subthalamic nuclei
  - T_2-hyperintensities of subcortical white matter and brain stem
  - Cerebral atrophy
  - Cerebellar atrophy
  - Delayed myelination
- Magnetic resonance spectroscopy that demonstrates elevated levels of GABA and related compounds in the Glx peak (e.g., GHB [gammahydroxybutyrate, also known as 4-hydroxybutyric acid], glutamate, and homocarnosine)

EEG findings. Background slowing and spike discharges that are usually generalized. Note: EEG studies are normal in about one third of affected individuals.

Supportive laboratory findings

- Absence of metabolic acidosis
- Urine organic acid analysis
  - 4-hydroxybutyric acid concentration of 100-1200 mmol/mol creatinine (normal: >0-7 mmol/mol creatinine)
  - Note: (1) Specific ion monitoring may be required for the detection of this metabolite, as its presence is sometimes obscured by a large normal urea peak on routine organic acid qualitative studies [Pearl et al 2003]; (2) falsely elevated urinary concentrations of 4-hydroxybutyric acid (GHB) have been reported in individuals in whom the urine sample was obtained using Coloplast SpeediCath catheters, which have been found to have GHB concentrations as high as 11 mmol/L [Wamelink et al 2011].
  - Small amounts of 4,5-dihydroxyhexanoic acid and 3-hydroxyproprionic acid and significant amounts of dicarboxylic acids may be detected. Urine organic acids can be confusing with the presence of elevated levels of d-2-hydroxyglutaric acid, but in the routine organic acid analysis this will only be reported as 2-hydroxyglutaric acid.
  - Increased glycine concentration
- Plasma amino/organic acid analysis
  - 4-hydroxybutyric acid concentration of 35-600 µmol/L (normal: 0-3 µmol/L)
  - Increased glycine concentration
- Cerebrospinal fluid (CSF) analysis
  - 4-hydroxybutyric acid concentration of 100-850 µmol/L (normal: 0-2 µmol/L)
  - A transient increase in CSF glycine concentration
  - Elevated free and total GABA and homocarnosine concentrations coupled to lowered glutamine

Note: Newborn screening is not routinely done for this disorder at this time.

Establishing the Diagnosis

The diagnosis of SSADH deficiency **is established** in a proband by the identification of biallelic pathogenic variants in *ALDH5A1* on molecular genetic testing (see Table 1).

Molecular testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ALDH5A1* is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *ALDH5A1* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Succinic Semialdehyde Dehydrogenase Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
ALDH5A1	Sequence analysis [3]	97% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Sixty-two families [Liu et al 2016]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Kwok et al [2012] reported a novel 34-bp insertion in exon 10 that resulted in a pathogenic frameshift variant leading to a truncated SSADH protein lacking 50 amino acids in the C-terminus.

Clinical Characteristics

Clinical Description

SSADH deficiency is characterized by a relatively non-progressive encephalopathy presenting with hypotonia and delayed acquisition of motor and language developmental milestones in the first two years of life. Common clinical features include intellectual disability, behavior problems, and motor dysfunction.

Symptoms are first reported at a mean age of 11 months (range 0-44 months) and the mean age at diagnosis is 6.6 years (range 0-25 years) [Pearl et al 2009a]. One study reported an adult man who was diagnosed in the sixth decade of life [Lapalme-Remis et al 2015]. Psychiatric symptoms may be the most disabling; they include sometimes prominent ADHD and even aggression in early childhood, and anxiety and obsessive-compulsive disorder in adolescence and adulthood [Pearl & Gibson 2004, Knerr et al 2008].

Affected individuals do not usually have episodic decompensation following metabolic stressors as is typical of other organic acidemias and metabolic encephalopathies, although some have been diagnosed after having unanticipated difficulty recovering from otherwise ordinary childhood illnesses. Clinical presentation with acute onset of generalized hypotonia and choreiform movement following upper-respiratory tract infection has been reported [Wang et al 2016].

Approximately 10% of affected individuals have a more severe phenotype including early-onset prominent extrapyramidal manifestations and a regressive course [Pearl et al 2005b].

Seizures. Half of affected individuals have epilepsy, usually with generalized tonic-clonic or atypical absence seizures [Pearl et al 2003]. Epilepsy is more common in adults, and may be progressive [Lapalme-Remis et al 2015]. In one family two heterozygotes for SSADH deficiency (one parent and a sib of a proband with the disorder) had generalized spike-wave discharges, photosensitivity, and absence and myoclonic seizures [Dervent et al 2004].

Sleep disorders are common and manifest either as excessive daytime somnolence or as disorders of initiating or maintaining sleep [Philippe et al 2004, Arnulf et al 2005]. Ten affected individuals studied with overnight polysomnography and daytime multiple sleep latency testing (MLST) had prolonged REM latency (mean 272±89 min) and reduced stage REM percentage (mean 8.9%, range 0.3%-13.8%) [Pearl et al 2009b]. Half of

these individuals showed a decrease in daytime mean sleep latency on MSLT, indicating excessive daytime somnolence. Overall, REM sleep appears to be reduced.

Neuropathology from one individual with a confirmed diagnosis revealed discoloration of the globus pallidus and leptomeningeal congestion on gross pathology. On microscopic examination, hyperemia and granular perivascular calcification of the globus pallidus and superior colliculus were identified, and interpreted as consistent with chronic excitotoxic injury. There was not significant neuronal loss or gliosis of CA1 of the hippocampus, the area that would have been considered most vulnerable to epileptic or hypoxic injury in this individual, who died with a clinical diagnosis of SUDEP (sudden unexpected death in epilepsy patients) after having had escalating seizures [Knerr et al 2010]. The authors are aware of two additional affected individuals who had SUDEP [Authors, unpublished data].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed.

Prevalence

Approximately 450 individuals have been diagnosed with SSADH deficiency [Gibson & Jakobs 2001; Gibson & Jakobs, personal communication], but it has been estimated to occur in 1:1,000,000 individuals [KM Gibson, unpublished data].

Because of the nonspecific nature of SSADH deficiency and the related difficulty in diagnosing affected individuals, the disorder may be significantly underdiagnosed. Thus, the true prevalence is unknown [Pearl et al 2003].

Parental consanguinity has been reported in approximately 40% of all published cases [Gibson et al 1997a, Gibson et al 1997b, Al-Essa et al 2000, Yalçinkaya et al 2000].

Genetically Related (Allelic) Disorders

No phenotypes other than those described in this *GeneReview* are known to be associated with pathogenic variants in *ALDH5A1*.

One family (3 affected individuals) with developmental delay and a small chromosome duplication involving *ALDH5A1* has been described [Siggberg et al 2011]. Elevated SSADH enzymatic activity in the affected individuals was confirmed in cultured white blood cells and may have a negative impact on GABA metabolism, possibly leading or contributing to the phenotype (see Molecular Genetics).

Differential Diagnosis

Other disorders of GABA metabolism:

- **4-aminobutyrate aminotransferase (GABA-transaminase, GABA-T) deficiency** (OMIM 613163). GABA transaminase deficiency was first reported in an index sibship and an additional unrelated proband [Medina-Kauwe et al 1999], and then in an infant identified using MR spectroscopy [Tsuji et al 2010]. The phenotype is characterized by psychomotor retardation, hypotonia, hyperreflexia, lethargy, refractory seizures of neonatal or infantile onset, agenesis of the corpus callosum, and cerebellar hypoplasia. Additional cases are being recognized especially with increased use of next-generation sequencing [Besse et al 2015]. Free and total GABA concentration levels are elevated in the CSF, without elevation in GHB. Biallelic pathogenic variants in *ABAT* are causative. Inheritance is autosomal recessive.

- **Homocarnosinosis** (OMIM 236130). Homocarnosine is a dipeptide of histidine and GABA. A single case of primary homocarnosinosis has been reported; the enzyme defect has not been conclusively proven [Gibson & Jakobs 2001].

SSADH deficiency cannot easily be differentiated clinically from other disorders that cause intellectual disability. Screening by urine organic acid analysis is necessary to detect SSADH deficiency.

Elevated glycine can be seen in glycine encephalopthy (nonketotic hyperglycinemia), which is distinguished from SSADH based on the absence of GHB in individuals with glycine encephalopathy.

Abnormal signal bilaterally in the globus pallidus can be seen in other organic acidurias, particularly methylmalonic aciduria (see Methylmalonic Acidemia), mitochondrial disorders (see Mitochondrial Disorders Overview), pantothenate kinase-associated neurodegeneration (PKAN), and neuroferritinopathy [Curtis et al 2001].

Unlike other metabolic encephalopathies and some other organic acidurias, SSADH deficiency does not usually present with metabolic stroke, megalencephaly, episodic hypoglycemia, hyperammonemia, acidosis, or intermittent decompensation [Pearl et al 2003].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with succinic semialdehyde dehydrogenase (SSADH) deficiency, the following evaluations are recommended:

- Neuroimaging (MRI)
- EEG
- Developmental evaluation
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

The management of SSADH deficiency is most often symptomatic, directed at the treatment of seizures and neurobehavioral disturbances.

Seizures. Antiseizure medications employed for the treatment of SSADH deficiency tend to be broad spectrum, although valproate is avoided when possible because of inhibition of potential residual enzymatic activity [Shinka et al 2003]. Vigabatrin, an irreversible inhibitor of GABA-transaminase, inhibits the formation of succinic semialdehyde [Matern et al 1996]. However, vigabatrin has shown inconsistent results [Howells et al 1992, Gropman 2003], suggesting that it is not effective at inhibiting peripheral GABA-transaminase, leading to a peripheral supply of 4-hydroxybutyric acid to the brain and thus decreasing its own efficacy. Brain MRI signal changes, particularly prominent in the thalamus and basal ganglia, have been seen in infants treated with relatively high doses of vigabatrin [Pearl et al 2009c].

However, reports of uncontrolled, nonblinded trials of vigabatrin in two affected children described a decrease in plasma GHB concentrations and clinical improvement (specifically in verbal communication) in one child age eight years [Casarano et al 2012] and slow clinical improvement (although not unexpected based on natural history) in a child age 2.5 years [Escalera et al 2010].

Neurobehavioral symptoms. Methylphenidate, thioridazine, risperidal, fluoxetine, and benzodiazepines have been used for the treatment of increased anxiety, aggressiveness, and inattention [Gibson et al 2003].

Beneficial non-pharmacologic treatments include physical therapy directed at developing strength, endurance, and balance; occupational therapy for improvement of fine motor skills, feeding, and sensory integration; and speech therapy [Gropman 2003].

Surveillance

Regular neurologic and developmental assessments are indicated.

Agents/Circumstances to Avoid

Valproate is generally contraindicated as it may inhibit residual SSADH enzyme activity [Shinka et al 2003]. However, Vanadia et al [2013] reported an individual with SSADH deficiency who had refractory epilepsy after possible limbic encephalitis. The refractory epilepsy was finally controlled with magnesium valproate. One year after initiation of magnesium valproate therapy, the affected individual remained seizure free and had marked behavioral improvements, including decreases in aggression, coprolalia, and non-recognition of danger. In addition, the EEG demonstrated improved background organization.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Biomarkers have been studied with plans for utilization in clinical trials. Positron emission tomography (PET) with [11C]flumazenil (FMZ), a benzodiazepine receptor antagonist, showed reduced binding in cortical, basal ganglia, and cerebellar regions of interest versus controls consistent with downregulation of GABA receptors [Pearl et al 2007]. Transcranial magnetic stimulation similarly showed downregulation of GABAergic activity in affected individuals versus controls [Pearl et al 2009a]. A single case of improvement in gait, coordination, and energy was reported as an abstract in a 30-month-old male administered 200 mg/kg/day of taurine [Saronwala et al 2008]. However, an open-label study of eighteen individuals with SSADH deficiency treated with taurine did not show significant improvement in adaptive behavior scores. This study was assigned a class IV level of evidence because it did not involve a control group [Pearl et al 2014].

SGS-742, a GABA-B receptor antagonist, demonstrated in the murine model a significant effect on electrocorticography when compared with topiramate [Pearl et al 2009a]. Liver-mediated gene therapy in the mouse model did lead to reductions in GHB levels in liver, kidney, serum, and brain extracts [Gupta et al 2004]. A clinical trial of SGS-742 is currently enrolling (ClinicalTrials.gov).

Recent data demonstrated that administration of rapamycin to an SSADH-deficient mouse model reduced mTOR activity, reduced the elevated numbers of mitochondria in the liver and brain (due to improved mitophagy), and normalized aberrant antioxidant levels; mTOR inhibitors such as rapamycin may lead to the treatment of many diseases, including SSADH [Lakhani et al 2014].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

Animal experiments utilizing the murine model have demonstrated partial efficacy involving the amino acid taurine, vigabatrin, and $GABA_B$ and GHB receptor inhibitors [Gupta et al 2004].

A murine trial has demonstrated some efficacy of the ketogenic diet [Nylen et al 2008], although the mechanism of the observed changes (and thus the potential for success in a human trial) is unknown [Knerr & Pearl 2008].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Succinic semialdehyde dehydrogenase (SSADH) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ALDH5A1* pathogenic variant).
- Heterozygotes (carriers) are typically asymptomatic. One report suggests that absence epilepsy with myoclonus and photosensitivity may be related to the heterozygous state [Dervent et al 2004].

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are typically asymptomatic.

Offspring of a proband. The offspring of an individual with SSADH are obligate heterozygotes (carriers) for a pathogenic variant in *ALDH5A1*.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ALDH5A1* pathogenic variant.

Carrier (Heterozygote) Detection

Molecular genetic testing. Carrier testing for at-risk relatives requires prior identification of the *ALDH5A1* pathogenic variants in the family.

Biochemical testing. Carrier testing using biochemical testing is not accurate or reliable for carrier determination.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *ALDH5A1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for SSADH deficiency are possible.

Biochemical testing. 4-hydroxybutyric acid can be measured accurately in amniotic fluid by means of a sensitive stable-isotope dilution gas chromatography-mass spectrometry assay method using deuterium-labeled 4-hydroxybutyric acid as the internal standard [Gibson & Jakobs 2001].

SSADH enzyme activity can be measured in biopsied chorionic villus tissue and cultured amniocytes.

Molecular genetic and biochemical testing. A combination of a metabolite analysis assay of enzyme activity with molecular genetic testing increases the accuracy of prenatal testing [Hogema et al 2001].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Succinic Semialdehyde Dehydrogenase Deficiency (SSADH) Association**
  498 Lillian Court
  PO Box 180622
  Delafield WI 53018
  Phone: 262-646-5133
  Email: ssadh@ssadh.net
  www.ssadh.net
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Succinic Semialdehyde Dehydrogenase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ALDH5A1	6p22.3	Succinate-semialdehyde dehydrogenase, mitochondrial	ALDH5A1 @ LOVD	ALDH5A1	ALDH5A1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Succinic Semialdehyde Dehydrogenase Deficiency (View All in OMIM)

271980	SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY; SSADHD
610045	ALDEHYDE DEHYDROGENASE 5 FAMILY, MEMBER A1; ALDH5A1

Molecular Pathogenesis

Animal studies have shown loss of locomotor function following γ-hydroxybutyrate (GHB) administration, reversible with inhibition of the mixed amino oxidase (MAO) system, consistent with a dopaminergic effect [Pearl et al 2005a]. Whether the cognitive, epileptic, neurobehavioral, and gait deficits in SSADH deficiency (as well as the extrapyramidal findings in ~10% of affected individuals) are related to chronically elevated endogenous GHB levels is uncertain.

Figure 1 outlines the normal SSADH GABA degradative pathway. A murine model demonstrates downregulation and decreased function of the $GABA_A$ receptor, postulating an important role for GABA (gamma-aminobutyric acid) in the pathophysiology of at least the epileptic manifestations of SSADH deficiency [Wu et al 2006]. More specifically, Errington et al [2011] found that $GABA_A$ receptor-mediated inhibitory gain of abnormal function may be a common feature in murine models of typical absence seizures.

A murine model demonstrated significant cerebral and cerebellar volume loss in homozygous SSADH-deficient mutated mice while no differences in total brain volume were observed in heterozygous mice or wild type controls [Acosta et al 2010].

One case report described an individual who had early-onset SSADH with low-level glutathione (GSH), thus supporting the hypothesis of oxidative stress and mitochondrial dysfunction in SSADH deficiency that was previously described in in vitro studies [Niemi et al 2014].

Gene structure. The *ALDH5A1* transcript NM_000090.3 comprises ten exons distributed over 38 kb of genomic DNA. A longer transcript variant has been described. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Of 27 novel variants identified in 48 unrelated families, six did not strongly affect enzymatic activity and were considered benign variants [Akaboshi et al 2003].

Pathogenic variants. A total of 44 pathogenic variants including missense, nonsense, and splicing errors have been identified. No hotspots were detected [Akaboshi et al 2003, Liu et al 2016]. Bekri et al [2004] reported a 7-bp deletion in exon 10 in a family with an affected child having very low enzymatic activity and reported as having a mild but typical phenotype. Kwok et al [2012] reported a novel 34-bp insertion in exon 10 that predicted a truncated SSADH protein lacking 50 amino acids in the C-terminus. Exon deletions have also been reported [Akaboshi et al 2003].

Normal gene product. GABA is metabolized to succinic acid by the sequential action of GABA-transaminase, in which GABA is converted to succinic semialdehyde, which then, by means of the enzyme succinic semialdehyde dehydrogenase, is oxidized to succinic acid.

Abnormal gene product. In the absence of succinic semialdehyde dehydrogenase, the transamination of GABA to succinic semialdehyde is quite likely followed by its reduction to GHB (gamma-hydroxybutyrate, a short monocarboxylic fatty acid whose role is unclear [Gupta et al 2003]. GHB, which accumulates in the urine, serum, and CSF of individuals with SSADH deficiency, has historically been considered the neurotoxic agent most responsible for the clinical manifestations of the disease [Pearl et al 2005a]. However, receptor studies in SSADH-deficient mice have shown alterations of $GABA_A$ and $GABA_B$ receptors but no alterations in GHB receptor binding or number, suggesting that the role of primary neurotoxin may be fulfilled by GABA [Vogel et al 2013].

Siggberg et al [2011] reported a family with developmental delay segregating a duplication of 6p22.2 that included *ALDH5A1*. SSADH enzyme studies in cultured white cells revealed elevated SSADH activity, consistent with duplication as well as increased urinary SSA associated with oxidative stress. Hyperactive levels of SSADH activity may also have negative consequences for GABA metabolism and other metabolic sequences.

The main function of GHB in the central nervous system is the inhibition of presynaptic dopamine release. It is currently used to induce a model of absence in rodents and to control cateplexy and alcohol withdrawal syndromes; GHB is also a recreationally abused drug.

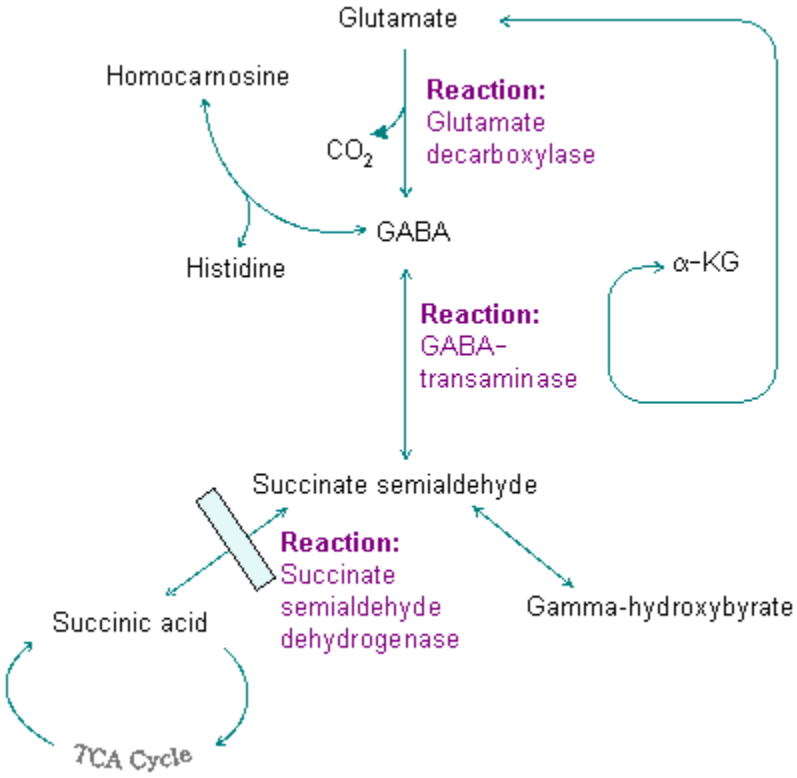

Figure 1. In the absence of SSADH, transamination of γ-aminobutyric acid (GABA) to succinic semialdehyde is followed by reduction to 4-hydroxybutyric acid (γ-hydroxybutyrate [GHB]). SSADH deficiency leads to significant accumulation of GHB and GABA.

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Author History

Emily S Barrios; Children's National Medical Center (2013-2016)
Jessica L Cabalza; George Washington University (2006-2010)
Philip K Capp; George Washington University (2004-2006)
Adrianne M Dorsey; Children's National Medical Center (2013-2016)
Ian Drillings; Children's National Medical Center (2010-2013)
Maciej Gasior, MD, PhD; National Institutes of Health (2004-2006)
K Michael Gibson, PhD, FACMG (2004-present)
Thomas R Hartka, MS; George Washington University (2006-2010)
Phillip L Pearl, MD (2004-present)
Tom Reehal; Sheffield University (2010-2013)
Jean-Baptiste Roullet, PhD (2016-present)
Emily Robbins; George Washington University (2004-2006)
Natrujee Wiwattanadittakul, MD (2016-present)

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