Neurochemistry International 99 (2016) 72–84

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

Invited review

Succinic semialdehyde dehydrogenase deficiency (SSADHD): Pathophysiological complexity and multifactorial trait associations in a rare monogenic disorder of GABA metabolism

P. Malaspina [a], J.-B. Roullet [b], P.L. Pearl [c], G.R. Ainslie [b], K.R. Vogel [b], K.M. Gibson [b, *]

[a] Department of Biology, University "Tor Vergata", Rome, Italy
[b] Division of Experimental and Systems Pharmacology, College of Pharmacy, Washington State University, Spokane, WA, USA
[c] Department of Neurology, Boston Children's Hospital, Boston, MA, USA

ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form
9 June 2016
Accepted 10 June 2016
Available online 14 June 2016

Keywords:
GABA (4-aminobutyric acid)
GHB (4-hydroxybutyric acid)
Knockout mouse model
Neurological disease
Pathophysiology
Oxidative damage
Crystal structure
Autophagy
Mitophagy
Succinic semialdehyde dehydrogenase deficiency (SSADHD)
Pathogenic mutations
Polymorphisms
SNP (single nucleotide polymorphism)
Multifactorial traits
GWAS
Genome wide association study
GABAergic neurotransmission
Pathophysiology

ABSTRACT

Discovered some 35 years ago, succinic semialdehyde dehydrogenase deficiency (SSADHD) represents a rare, autosomal recessively-inherited defect in the second step of the GABA degradative pathway. Some 200 patients have been reported, with broad phenotypic and genotypic heterogeneity. SSADHD represents an unusual neurometabolic disorder in which two neuromodulatory agents, GABA (and the GABA analogue, 4-hydroxybutyrate), accumulate to supraphysiological levels. The unexpected occurrence of epilepsy in several patients is counterintuitive in view of the hyperGABAergic state, in which sedation might be expected. However, the epileptic status of some patients is most likely represented by broader imbalances of GABAergic and glutamatergic neurotransmission. Cumulative research encompassing decades of basic and clinical study of SSADHD reveal a monogenic disease with broad pathophysiological and clinical phenotypes. Numerous metabolic perturbations unmasked in SSADHD include alterations in oxidative stress parameters, dysregulation of autophagy and mitophagy, dysregulation of both inhibitory and excitatory neurotransmitters and gene expression, and unique subsets of SNP alterations of the SSADH gene (so-called ALDH5A1, or aldehyde dehydrogenase 5A1 gene) on the 6p22 chromosomal arm. While seemingly difficult to collate and interpret, these anomalies have continued to open novel pathways for pharmacotherapeutic considerations. Here, we present an update on selected aspects of SSADHD, the ALDH5A1 gene, and future avenues for research on this rare disorder of GABA metabolism.

Contents

1. Introduction 73
2. Succinic semialdehyde dehydrogenase deficiency (SSADHD) 73
3. Patient registries and associations 73
4. The primary defect in SSADHD and metabolic perturbations in patients and knockout mice 73
5. Pathophysiological mechanisms in SSADHD 75
   5.1. Imbalances in GABAergic/glutamatergic neurotransmission 75

* Corresponding author. Section of Experimental and Systems Pharmacology, College of Pharmacy, Washington State University, 412 E. Spokane Falls Blvd, Pharmaceutical and Biomedical Sciences Building, Room 347, Spokane, WA 99214. USA.
E-mail address: mike.gibson@wsu.edu (K.M. Gibson).

http://dx.doi.org/10.1016/j.neuint.2016.06.009
0197-0186/

5.2. Oxidative stress and damage 76
5.3. Autophagy dysregulation 77
6. Treatment of SSADHD 77
7. Molecular genetics of the ALDH5A1 gene encoding SSADH 78
8. Multifactorial traits and ALDH5A1 gene structure 79
9. Concluding remarks 80
Acknowledgements 81
References 81

1. Introduction

It is widely accepted that monogenic disorders represent extreme examples of metabolic variations, the latter present to a much lower degree of severity in the majority of the population. Succinic semialdehyde dehydrogenase deficiency (SSADHD), a rare disease caused by mutations of the ALDH5A1 gene, pointedly reminds us of this issue. Compound heterozygous or homozygous pathogenic mutations associate with a debilitating disease, whereas functional single nucleotide polymorphisms (SNPs) associated with more common or milder neurological impairments which can also be identified in various populations. The focus of this review is to summarize selected aspects of our current knowledge of the role of the SSADH enzyme and its genetic counterpart, the ALDH5A1 gene, in human diseases, with an emphasis on the diverse pathophysiology of the disease linked to gene polymorphism and susceptibility to multifactorial traits.

2. Succinic semialdehyde dehydrogenase deficiency (SSADHD)

Succinic semialdehyde dehydrogenase deficiency (SSADHD; OMIM #271980) is an autosomal-recessively inherited disorder of GABA degradation caused by mutations in the ALDH5A1 gene on chromosome 6p22.3. The clinical features include global developmental delay, hypotonia, epilepsy, extrapyramidal manifestations, and hyporeflexia (Pearl et al., 2003, 2011, 2005, 2009; Novotny et al., 2003; Knerr et al., 2007, 2008, 2010; Kim et al., 2011; Vogel et al., 2013). Diagnosis of autism spectrum disorder occurs disproportionately (Gibson et al., 2003). Abnormalities in MRI signal involving the globus pallidus, subthalamic nucleus, and cerebellar dentate nuclei are frequently encountered, and all patients have elevated urine excretion of γ-hydroxybutyric acid (GHB), the biochemical hallmark of the disorder. The incidence is unknown, but has recently been estimated at $1:10^6$ (unpublished). While the median age of diagnosis is less than 5 years, 10% of cases are diagnosed in adolescence or adulthood. Late and undiagnosed cases are suspected, although increased detection of SSADHD is anticipated with the increasing utility of next generation gene sequencing. The challenges inherent to late diagnosis is noteworthy. Not only do families undergo a diagnostic odyssey of clinician evaluation and metabolic testing (most likely associated with the non-specific neurological phenotype), but possible therapeutics accompanied by potentially beneficial physical/occupational/speech therapies remain uninitiated. Key landmarks in clinical and basic research of SSADHD are highlighted (Table 1).

3. Patient registries and associations

The SSADHD patient registry began with the goal of leveraging interdisciplinary scientific discussion on SSADHD, undertaking grassroot efforts to raise awareness, and raising much needed research funding for new studies. The patient registry has been maintained since 2003 with continuous IRB approval, and is currently located through the Boston Children's Hospital. All enrolled patients have completed a detailed questionnaire which contains clinical history, developmental status, results of diagnostic testing, contact information for the family and primary care physician, and willingness to be recruited into additional studies. The information is password protected and has been instrumental in providing information on clinical trials thus far. There are currently 120 enrolled patients. The SSADH association (www.ssadh.net) also maintains a patient registry with 92 patients. The two registries are currently in the process of being merged. Since its first description in 1981, the literature reveals 176 patients presenting from 38 distinct countries, underscoring the panethnic nature of SSADHD (Fig. 1).

4. The primary defect in SSADHD and metabolic perturbations in patients and knockout mice

Jakobs and coworkers (Jakobs et al., 1981) first reported increased excretion of GHB in humans. They examined the urine of three developmentally delayed pediatric patients with minimal language development using combined gas chromatography–mass spectrometry methodology. The mass spectrometric data aligned with library data indicating a fragmentation pattern consistent with GHB (gamma-hydroxybutyrate, a derivative of the inhibitory neurotransmitter GABA). The hypothesis developed to explain the presence of GHB was a block at the level of succinic semialdehyde dehydrogenase (SSADH; Fig. 2). In 1983, Gibson and coworkers presented enzymatic data that confirmed Jakob's hypothesis, highlighting the first report of an inborn error of gamma-aminobutyric acid (GABA) metabolism (Gibson et al., 1983). Autosomal-recessive inheritance was suspected since the original three patients were born to related parents, which was subsequently confirmed when the human gene was identified in 1998 (Chambliss et al., 1998) and homozygously inherited mutations were identified. Obligate heterozygotes (parents) each carried the pathogenic allele on one copy of chromosome 6, confirming the inheritance pattern.

Although SSADHD is considered a "neurometabolic" disorder, emerging data indicates a number of systemic disturbances (Fig. 2). A summary of metabolic data available in the literature from SSADHD patients (Table 2) and the corresponding murine knockout mouse model (Hogema et al., 2001) highlights the extent of metabolic abnormalities. In addition to accumulation of GABA and GHB, we and others have found accumulation of a number of likely GABA-associated metabolites in tissues and body fluids derived from both patients and the knockout mouse model. These include D-2-hydroxyglutaric acid (D-2-HG), 4,5-dihydroxyhexanoic acid (DHHA), as well as accumulation of homocarnosine (a precursor dipeptide of GABA composed of L-histidine and GABA), guanidinobutyrate (derived from the substitution of GABA for glycine in the arginine-glycine amidinotransferase reaction involved in