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Thirty Years Beyond Discovery—Clinical Trials in Succinic Semialdehyde Dehydrogenase Deficiency, a Disorder of GABA Metabolism

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Summary

This review summarizes a presentation made at the retirement Symposium of Prof. dr. Cornelis Jakobs in November of 2011, highlighting the progress toward clinical trials in succinic semialdehyde dehydrogenase (SSADH) deficiency, a disorder first recognized in 1981. Active and potential clinical interventions, including vigabatrin, L-cycloserine, the GHB receptor antagonist NCS-382, and the ketogenic diet, are discussed. Several biomarkers to gauge clinical efficacy have been identified, including cerebrospinal fluid metabolites, neuropsychiatric testing, MRI, EEG, and measures of GABAergic function including (11C)flumazenil positron emission tomography (PET) and transcranial magnetic stimulation (TMS). Thirty years after its discovery, encompassing extensive studies in both patients and the corresponding murine model, we are now running an open-label trial of taurine intervention, and are poised to undertake a phase II trial of the GABA_B receptor antagonist SGS742.

Introduction

The treatment of inborn errors of metabolism presents a host of challenges for the clinician, some of which include compartmentalization of the primary defect, alternative pathways for metabolism, interlinked metabolic pathways (e.g., oxidative phosphorylation with fat oxidation), the confounds of first-pass drug metabolism in the liver, the blood brain barrier,

and many others. When considering neurometabolic disorders, these challenges magnify as we must entertain the largely anabolic and inaccessible brain. Does the primary metabolic lesion affect mainly the putamen, the amygdala, the striata or cortex, or cerebellum? Is the defect global or localized, and are there effective treatments that will cross the blood brain barrier? Are metabolites that form in the brain able to enter the peripheral metabolism, or are they intracellularly trapped? Adding to the complexity are neuronal-glial interactions, brain remodeling, and a number of other physiological parameters associated with brain metabolism such that it becomes a remarkable achievement that we can *ever* effectively treat a neurometabolic disorder.

SSADH deficiency mirrors all of these treatment challenges, and has posed additional considerations when entertaining effective treatment strategies. A defect of GABA metabolism, SSADH deficiency features accumulation of two neuromodulators, GABA and GHB, and paradoxically represents a hyperGABAergic seizure disorder (Fig. 1) (Wong et al 2004; Maitre 1997; Pearl et al 2011). One pathophysiological mechanism includes GABA_A receptor downregulation, shown on positron emission tomography with ¹¹C-flumazenil (Pearl et al 2009a). Clinical reports on dozens of patients reveal a neurological disorder that may often be misdiagnosed as autism or autism spectrum, oppositional defiance, ADHD or other behavioral disorders (Pearl et al 2003). Most therapies have been symptomatic, targeting occasional seizures, behavioral dysfunction, or other clinical manifestations, but few interventions target the primary lesion in this disease. Further complicating the situation is the fact that some GABA receptors in neural tissue are excitatory during development (as opposed to inhibitory, the common role for GABA in brain) (Rheims et al 2008; Herlenius and Lagercrantz 2001), the observation that GHB produced in the periphery (liver has about 70% of the SSADH activity of brain; Chambliss et al 1995) can freely traverse the blood brain barrier (BBB), and the probable main neurotoxin, GABA, can only be removed by enhanced metabolism or conjugation.

In this review, a synopsis of interventional strategies for SSADH deficiency is presented, highlighting what has been attempted, and what appears to be on the horizon (Knerr et al 2007). Most of the therapies that are planned, or studies in progress with patients, have springboarded from preclinical findings in the murine model of SSADH deficiency, *aldh5a1*^{-/-} mice (Gibson et al 2002). Brief reference will be made to important findings in the mouse model that have revealed novel treatment concepts.

Treatment Strategies for SSADH Deficiency

Vigabatrin

Perhaps the most widely employed intervention for SSADH deficiency, at least in Europe, has been vigabatrin (VGB; gamma-vinylGABA; Sabril[®]; Lundbeck Corp.). VGB, an irreversible inhibitor of GABA-transaminase (Fig. 1), acts pharmacologically to increase brain GABA. VGB is employed for infantile spasms (IS) (especially in tuberous sclerosis patients), as well as refractory complex partial seizures. In the case of SSADH deficiency, the use of VGB is predicted to lead to decreased production of succinic semialdehyde (Fig. 1), the probable precursor of GHB (Gropman 2003). High-dose VGB in the *aldh5a1*^{-/-} model led to significant extension of lifespan, although metabolic measurements (brain

GHB/GABA) were not performed (Hogema et al 2001). Along these lines, the results of clinical intervention support decreased production of GHB, but a concern with VGB is the potential to further increase GABA in an already hyperGABAergic disorder (Pearl and Gropman 2004; Tables I & II).

Despite a clear rationale for VGB in SSADH deficiency, surprisingly few literature reports have been presented, and no blinded, controlled trial has been published. The case reports of clinical improvements with VGB (Table 1) have been tempered by other reports of worsening of symptoms, including seizure control (Matern et al 1996). Although approved in Europe since the 1980s for intervention in IS, VGB was not approved until 2009 by the US FDA for treatment of IS in pediatric patients and uncontrolled complex partial seizures in adults. The delays in FDA approval related to early studies in animals, including rats and dogs, which suggested edema in myelin tracts and vacuolation of white matter (Butler et al 1987; Qiao et al 2000; Peyster et al 1995). VGB may have particular utility for IS in patients under 2 years of age, since these seizures are particularly challenging, and a common intervention for IS, ACTH (adrenocorticotrophic hormone), may be difficult to obtain. Moreover, VGB showed adverse effects on visual fields in approximately 1/3 of patients receiving it for epilepsy (Krauss et al 1998; Spence and Sankar 2001; Vanhatalo et al 2002). The mechanism of retinal toxicity remains undefined, although reduced ornithine aminotransferase (OAT) activity observed with VGB consumption may elevate retinal ornithine and induce a form of gyrate atrophy (De Biase et al 1991; Sorri et al 2010). Moreover, GABA is a feedback regulator of OAT (Daune and Seiler 1988). These observations suggest that monitoring ornithine levels during VGB intervention would be prudent. In addition, 8 of 23 patients taking VGB had new-onset, reversible MRI T(2)-weighted hyperintensities and restricted diffusion in thalami, globus pallidus, dentate nuclei, brainstem, or corpus callosum (Pearl et al 2009b). Because of significant concerns, the FDA permits the use of VGB only for clinical instances in which the potential benefit against seizure outweighs the risk of visual loss. As well, VGB has a number of “black-box” warnings, and the FDA requires routine ocular exams/visual field testing.

Receptor studies in *aldh5a1*^{-/-} mice have shown significant alterations of GABA_B and GABA_A receptors (GABA_BR and GABA_AR), yet no alterations in GHB receptor (GHBR) binding or number (Cortez et al 2004; Buzzi et al 2006; Wu et al 2006; Mehta et al 2006). These data suggest that GHB is not necessarily the primary neurotoxin in SSADH deficiency, a role more likely fulfilled by GABA. The absence of GHBR alterations may associate with the capacity of GHB to freely traverse the blood-brain barrier, which GABA cannot. The cumulative data suggests that elevating brain GABA levels via VGB intervention in SSADH deficiency might not be prudent. Additionally, GABA-T exists in the periphery, including liver, kidney and even blood (Tillakaratne et al 1995), and the kinetic characteristics of the neural enzyme are different from those of GABA-T in the periphery. Thus, incomplete inactivation of peripheral GABA-T's by VGB may still result in elevated intracerebral GHB. This hypothesis is supported by metabolic findings in patients receiving VGB (Table 2; Gibson et al 1995). Four patients treated with VGB (40–100 mg/kg/d) for 1–12 months underwent lumbar puncture for CSF collection. During treatment, there were variable improvements in cerebellar signs, concentration,

hyperactivity, agility and cognitive function. As predicted, CSF total GABA increased and GHB decreased, although the absolute decrease in GHB was never as great as the GABA increase. Single body fluid measures such as these (Table 2) are limited by an absence of parallel measurements in other fluids, including plasma and urine. The fact that GHB levels did not decrease to the extent seen for total GABA increase (Table 2) is consistent with the hypothesis of peripheral resupply of GHB due to incomplete inactivation of peripheral GABA-T's by VGB.

L-cycloserine

It is rational to attempt inhibition of GABA-T in patients with SSADH deficiency, as described above for VGB. However, if the primary source of pathology in this disease is elevated GABA, the expected decrease in GHB formation may be thwarted by further GABA elevations. L-Cycloserine (LCS) provides another potential inhibitor of GABA-T that warrants examination.

Cycloserine exists as two enantiomers: 1) the D-isomer (also known as Seromycin), used to treat tuberculosis and selected neurological disorders (associated with its potent NMDA receptor agonist activity (Lowther et al 2010)); and 2) the synthetic L-isomer. The latter, LCS, has been characterized in a number of model systems, yet the literature presents somewhat contradictory and conflicting findings. Early data highlighted the capacity of LCS to inactivate GABA-transaminase (see Fig. 1) as well as alanine aminotransferase (ALA-T; Beuster et al 2011). Linked to its capacity to raise intracerebral GABA levels (Fig. 1), LCS has been piloted in several seizure models, including petit-mal seizures in the rat (Marescaux et al 1985) and audiogenic seizures in mice (Polc et al 1986). Nonetheless, clinical development of LCS has been hampered because it also inhibits the first enzyme of sphingolipid formation, 3-ketodihydrosphingosine synthase (serine palmitoyltransferase; Cho 2007). The capacity of LCS to elevated intracerebral GABA is dose-dependent, with smaller doses (10–30 mg/kg p.o. or i.p. in rodents) reducing hyperexcitability, while higher doses (30–100 mg/kg) evoke central depressant actions (Polc et al 1986). As well, the literature indicates that inhibition of sphingomyelin formation may be dose-dependent, and may not be substantial at low pharmacologic doses of LCS.

Despite several rodent studies, there has been no report of LCS intervention in higher mammals or humans, which would make interventional studies in SSADH-deficient patients a very distant goal. Nonetheless, LCS may provide inhibition of GABA-T without the associated ocular side effects found with VGB, and preclinical studies in *aldh5a1*^{-/-} mice would be of interest.

SGS742

SGS-742 (originally CGP-36742) is one of a long line of phosphinic-acid analogues of GABA that are antagonists of the GABA_BR (Farlow 2009). These antagonists were originally developed by Ciba-Geigy Corporation (Froestl et al 2004), and eventually the proprietary rights moved to other corporations. As mentioned above, studies in *aldh5a1*^{-/-} mice have provided compelling evidence for use-dependent alterations of both GABA_AR and GABA_BR (Gupta et al 2002; Cortez et al 2004; Wu et al 2006; Buzzi et al 2006).

Accordingly, antagonists may prove beneficial as a treatment strategy in SSADH deficiency through blockade of supraphysiological agonist (GABA) levels. In preliminary studies in *aldh5a1*^{-/-} mice, high-dose CGP 35348 (an early phosphinic acid progenitor of SGS742) provided significant extension of lifespan for mice that succumbed to early status epilepticus (Hogema et al 2001; Gupta et al 2002). The phosphinic acid analogue SGS742 was subsequently introduced by Saegis Pharmaceuticals and Novartis Corporation, and proposed for clinical trials in patients with mild cognitive impairment (MCI; Bowery 2006; Bullock 2005; Froestl et al 2004). The rationale for SGS742 in MCI patients centers on the known inhibition of learning and memory associated with functional activation of the GABA_BR by its ligand, GABA. SGS742 has undergone phase I/II safety and tolerability evaluation in humans, and has shown efficacy in MCI patients (Froestl 2004), yet extended trials have not been reported. Currently, the proprietary rights to SGS-742 have been obtained by the National Institutes of Health of the United States.

Pilot trials of SGS742 in *aldh5a1*^{-/-} mice have shown promising results. Moderate levels (30–100 mg/kg/d, i.p. administration) reduced spike-wave discharge, and led to near normalization of the electrocorticograph (Pearl et al 2009c). These data formed the foundation of a planned clinical intervention with SGS742 in SSADH-deficient patients. Two important hurdles must be cleared prior to undertaking this trial, however: 1) all safety and tolerability studies of SGS742 were performed in adults, and there are many adolescent patients with SSADH deficiency which could be enrolled in a blinded clinical trial; and 2) an application to the US Food and Drug Administration (FDA) for an IND (Investigational New Drug). Despite these challenges, we envision undertaking a blinded, placebo-controlled trial of SGS742 in SSADH-deficient patients shortly.

Ketogenic diet

Nylen and colleagues (2008; 2009; Stewart et al 2008) posited that early lethality in *aldh5a1*^{-/-} mice occurred proximal to the weaning period. These investigators proposed that the high-fat content of dam's milk was protective to the pups, and hypothesized that the use of the ketogenic diet (KD), a broadly employed dietary intervention for refractory epilepsy (Cusmai et al 2012; McNally and Hartman 2012), would lead to beneficial outcomes in the murine model (Nylen et al 2008, 2009; Stewart et al 2008). Implementation of a 4:1 (fat:carbohydrate) KD in *aldh5a1*^{-/-} mice led to a significant improvement in seizure profiles, body weights and energy production, as well as extended lifespan. These findings have led a number of clinicians to consider using the KD in SSADH-deficient patients for whom control of convulsions has proven challenging. Nonetheless, no clinical report on its use has been presented. The other major drawback to use of the KD is the fact that most convulsions in SSADH-deficient patients can be controlled with standard antiepileptics (AEDs), such as lamotrigine, levetiracetam, or topiramate, and the KD is both challenging to implement and maintain. Thus, conventional seizure control has predominantly employed standard AEDs (Pearl et al 2011).

NCS-382

As noted above, one of the paradoxical findings in *aldh5a1*^{-/-} mice is the absence of GHBR alterations despite high levels of GHB (Wu et al 2006; Mehta et al 2006). Nonetheless, in

early studies on *aldh5a1*^{-/-} mice, the drug most effective in rescuing these animals from early lethality was NCS-382 (6,7,8,9-tetrahydro-5-hydroxy-5H-benzocyclohept-6-ylidene acetic acid), a pure GHBR antagonist (Hogema et al 2001; Gupta et al 2002). These data suggest some role for GHB (and its receptor) in the process of early lethality, yet this remains paradoxical in the face of normal GHBR pharmacology observed *in vivo* (Mehta et al 2006). Despite positive outcomes with NCS-382 in *aldh5a1*^{-/-} mice, no detailed studies on its use have been performed in these mice, and NCS-382 is not an FDA-approved drug. Considerable data on the safety and tolerability of NCS-382 would be required, not only in higher mammals (dog, primate, etc), but minimally phase I/II safety and tolerability data in humans, before any consideration of this compound could be undertaken in SSADH-deficient individuals.

Taurine

The high content of taurine in dam's milk prompted Hogema and colleagues (2001) to examine this non-physiological amino acid as an intervention in *aldh5a1*^{-/-} mice, and these investigators observed significant extension of truncated lifespan. Efficacy of taurine intervention in *aldh5a1*^{-/-} mice prompted Saronwala and colleagues (2008) to perform a pilot investigation in an SSADH-deficient patient. The patient, a 2-year old male, was treated with 200 mg/kg/day taurine over a 12 month period, and tolerated it well. Plasma taurine levels ranged from 2–8 fold normal, and there was no correlation between taurine level and GHB excretion. By 9 months of treatment, marked behavioral improvements were noted, as well as improved peer interactions, level of activity and coordination. Repeat MRI obtained at 12 months of treatment was interpreted as resolution of prior restricted diffusion abnormality of the globus pallidus, with a very small residual T2 signal MRI abnormality.

Taurine is an abundant free amino acid in various tissues, and has important roles in neuromodulation and osmoregulation (Olive 2002). Taurine is known to interact with both GABA_ARs and GABA_BRs, and increases chloride conductance in excitable tissues. The neuroprotective action of taurine against beta-amyloid and glutamate receptor agonists in chick retinal neurons is blocked by the GABA_AR antagonist picrotoxin (Louzada et al 2004). There is evidence that the taurine transporter is able to utilize GABA as a substrate, and that GABA competitively inhibits this transporter (Tomi et al 2008). There appears to be a reciprocal relationship between GABA and taurine, as taurine transporter null mice show increased GABA_AR densities in the hippocampal dentate gyrus and in the cerebellum (Oermann et al 2005). Thus, since taurine appears to modulate GABA transmission, there may be beneficial competitive effects with respect to GABA in SSADH-deficient patients.

We extended the single-patient evaluation of taurine described above by enrolling patients into an open label trial in order to collect baseline data while preparing for a controlled trial with biomarkers used to evaluate this population without pharmacologic intervention. Subjects with confirmed SSADH deficiency were eligible for recruitment. Following informed consent, subjects were titrated weekly from 50mg/kg/day until reaching a target dose of 200 mg/kg/day to a maximum dosage of 16 grams/day. The Adaptive Behavior Assessment Scale-II (ABAS-II) was administered at baseline and requested at six and twelve months of therapy. The ABAS II measures adaptive skills from conceptual, social,

and practical domains in study participants. This scale has normative data and is offered for the age ranges 0–5, 5–21, and 16–89 years. Patients initiated at age 16 years and older were administered the adult version. We used linear longitudinal modeling to compare ABAS scores during the period pre- to the time-averaged scores in the period during taurine use. The model adjusted variance estimates, analogous to a paired *t*-test, were used to account for the correlation of scores within the same participant.

Sixteen patients were recruited and provided baseline data: 6M/10F, age range at enrollment 2–28 yrs (mean 12 yrs). One patient had a serious adverse event on 16 grams/day (200 mg/kg): hospitalization for hypersomnia. This led to a dose lowering paradigm with a new maximum daily dose of 10 grams. The taurine has been otherwise well-tolerated. Six subjects have completed the trial; 3 withdrew early due to perceived lack of efficacy. For patients who provided follow-up data during active therapy, there were no significant changes between pre- and Rx-composite scores in general adaptive, conceptual, practical, or social skills. However, a borderline lower score was observed on the conceptual ($p=0.1$) index during taurine use. Our open-label pilot trial of taurine in patients with SSADH deficiency did not reveal demonstrable improvement in adaptive neurobehavioral functioning (Pearl et al 2012). Nonetheless, additional biomarker studies during taurine intervention are in progress.

Other potential interventions in SSADH deficiency

As mentioned above, interventions targeting reduced GHB production through inhibition of GABA-T may be complicated by concomitant GABA elevations. One approach to mitigating this side-effect may be co-application of 3-mercaptopropionate, an inhibitor of glutamic acid decarboxylase (Netopilova et al 1997; Roberts et al 1978). Such studies could be piloted in *aldh5a1*^{-/-} mice, but the intracerebral levels of both glutamate and GABA would require cautious evaluation. A further mechanism to mitigate GABA elevation in SSADH deficiency, in the presence or absence of drug intervention, might be supplementation with L-histidine with the objective of enhancing homocarnosine (the GABA:L-histidine dipeptide). Homocarnosine is a major component of excitable tissues, with roles in neuromodulation, osmoregulation, and neuroprotection (Bauer et al 2005). Increasing intracerebral homocarnosine in SSADH deficiency may have additional therapeutic benefit, in relation to its capacity to quench 4-hydroxy-2-nonenal (4-HNE), a major lipid peroxidation product and cytotoxic carbonyl agent (Aldini et al 2005). Since SSADH is the major aldehyde dehydrogenase responsible for degradation of 4-HNE in mammals (Murphy et al 2003), the quenching role of homocarnosine might have therapeutic relevance. Quantitation of 4-HNE levels in neural tissue of *aldh5a1*^{-/-} mice, or fluids/tissues derived from SSADH-deficient patients, however, has not been reported.

Outcome Measures for Clinical Trials

A challenge for any effective clinical trial is the identification of surrogate biomarker outcomes that can be quantified to gauge efficacy. Along these lines, numerous studies in *aldh5a1*^{-/-} mice, and SSADH-deficient patients, have highlighted potential biomarkers, some of which have already been clinically validated. Along these lines, GABAergic anomalies (both GABA_BR and GABA_AR) in *aldh5a1*^{-/-} mice have led to corollary studies

of GABA receptor function in patients (Pearl et al 2009a; Reis et al, in press). For example, (11C)flumazenil (FMZ) binding (a marker for GABA_AR function) is decreased throughout all brain regions in patients with SSADH deficiency. Similar anomalies have been documented for GABA_BR function in patients employing transcranial magnetic stimulation (TMS), a technique in which depolarization or hyperpolarization of the neurons is induced using weak electric currents from a magnetic field (de Vries et al 2012). Both (11C)FMZ binding and TMS will be considered as outcome measures in clinical trials of SSADH-deficient patients.

Additional standard clinical measures that can be employed for clinical trials include neurobehavioral evaluation (as described for taurine intervention), as well as EEG and MRI. Several reports of EEG in SSADH-deficient patients have revealed slowing in both hemispheres and spike-wave discharges (Vanadia et al, in press), an observation consistent with the effect of GHB on EEG (Snead 1978; 2000; Snead and Gibson 2005). As well, a consistent finding in patients has been hyperintensity on the T1-weighted MRI images in the globus pallidi bilaterally (Pearl et al 2009a; Yalcinkaya et al 2000; Ziyeh et al 2002). This finding is non-specific, and most likely represents localized cytotoxicity associated with metabolite accumulation and/or downstream metabolic disruptions. Nonetheless, brain MRI remains a valid clinical biomarker to test therapeutic efficacy, and was employed as an outcome marker in the index patient treated with taurine (Saronwala et al 2008). Optimally, a phase II trial (targeting tolerability, dosing, safety, and other features without assessing efficacy) could be employed to identify which of the biomarkers outlined above is the most responsive and reproducible for interventional evaluation in SSADH-deficient patients.

Pathophysiological considerations in SSADH deficiency

Most data from the *aldh5a1*^{-/-} mouse model points to GABA as the primary mediator of neuropathology in SSADH deficiency (Pearl et al 2009c). Insights into discrete metabolic effects (GABA, GHB) might be gleaned, therefore, by contrasting the phenotypes of SSADH and GABA-T deficiencies. The index siblings with GABA-T deficiency presented with severe psychomotor retardation, hypotonia, hyperreflexia and growth acceleration (Jaeken et al 1984), while a recently described third patient (Tsuji et al 2010) presented with intractable seizures. SSADH deficiency features intellectual disability with disproportionate deficit in expressive language, hypotonia, ataxia, infrequent seizures, and a component of neuropsychiatric morbidity in adolescence and adulthood. The severity of GABA-T deficiency supports a prominent neuropathological role for increased GABA in both diseases, although both disorders feature other metabolic disturbances, such as elevated β-alanine and homocarnosine in GABA-T deficiency, and increased 4,5-dihydroxyhexanoic acid, D-2-hydroxyglutaric acid, homocarnosine and succinic semialdehyde in SSADH deficiency.

Conclusions

One of many challenges with SSADH deficiency that will remain to be negotiated includes the fact that both GHB and GABA accumulate, and likely each plays a role in the pathophysiology of the disorder. Along these lines, combinatorial therapy (e.g., VGB/SGS742, or NCS-382/SGS742, etc) may be optimal, if regulatory hurdles can be cleared.

Peripheral therapy (whether cell-based or gene therapeutic, targeting the liver) could have value, and preclinical studies in *aldh5a1*^{-/-} mice using adenoviral hepatic gene therapy have shown efficacy (Gupta et al 2004a; 2004b). Intracerebral cell or gene therapy also represents an attractive objective in SSADH deficiency, especially since the phenotype is primarily neurological. Finally, some consideration must be given to *in utero* therapy, since studies in the murine model have revealed that GABA and GHB accumulate in early *aldh5a1*^{-/-} embryos, and the fact that the GABA_AR is excitatory during early development (Jansen et al 2008; Waagepetersen et al 1999; Herlenius and Lagercrantz 2001). Thus, consideration may need to be given to the earliest possible intervention that can mitigate long-term neurological complications.

Looking back on the progress made in SSADH deficiency, it has clearly not been fast enough for the benefit of the patients. Nonetheless, once we traverse into the realms of both animal and human research, multiple regulatory considerations come into play. Today, however, we have a validated animal model, an IRB-approved patient registry, and multiple websites that have enabled patients and parents to interact and exchange information (www.pndassoc.org; www.waveofhope-ssadh.org; www.liamslinks.org). The Pediatric Neurotransmitter Disease Association, a parent support group focused solely on disorders of neurotransmitter metabolism, is supporting research through a competitive grant program. Our goal remains to continue working as a team, focused on identifying better, long-term therapies for patients and families with SSADH deficiency, so that all can enjoy an enhanced quality of life.

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Abbreviations employed

ABAS-II	adaptive behavior assessment scale II
ACTH	adrenocorticotrophic hormone
ADHD	attention deficit hyperactivity disorder
AED	antiepileptic drug
BBB	blood brain barrier
CSF	cerebrospinal fluid
DA	dopamine
EEG	electroencephalography
FDA	Food and Drug Administration (of the USA)
FMZ	flumazenil (GABA _A R ligand, benzodiazepine binding site)
GABA	4-aminobutyric acid

GABA_AR	GABA _A receptor
GABA_BR	GABA _B receptor
GABA-T	GABA-transaminase
GAD	glutamic acid decarboxylase
GHB	4-hydroxybutyric acid
GHBR	GHB receptor
IND	investigational new drug
IQ	intelligence quotient
IS	infantile spasms
KD	ketogenic diet
LCS	L-cycloserine
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
NCS-382	(6,7,8,9-tetrahydro-5-hydroxy-5H-benzocyclohept-6-ylidene)acetic acid
SGS742	phosphinic acid, (3-aminopropyl)butyl-
SSADH	succinic semialdehyde dehydrogenase (or ALDH5A1, aldehyde dehydrogenase 5a1)
TMS	transcranial magnetic stimulation
TCA	tricarboxylic acid
VGB	vigabatrin (gamma-vinyl GABA; Sabril [®] (Lundbeck Corporation))

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Concise 1 sentence take-home message

An overview of current and potential treatment interventions in heritable succinic semialdehyde dehydrogenase deficiency is presented, with a highlight on preclinical studies obtained from the corresponding murine model.

Prelude

It is doubtful that any reader of the Journal would question the concept that the care and treatment of patients with inborn errors of metabolism functions optimally through a “team” approach. The team is generally defined as the clinician, supported by clinical chemists, dietitians, physical and/or occupational therapists, clinical psychologists, nurse practitioners, and other colleagues. This “team” approach represents the foundation of the current article, when a young analytical chemist named Cornelis Jakobs came to the University of California, San Diego, to pursue his Doctoral studies in stable-isotope dilution mass spectrometry with Dr. Lawrence Sweetman and Dr. William Nyhan. Jakobs had identified three patients who excreted gamma-hydroxybutyric acid in urine, and he hypothesized that the defect in these patients was in succinic semialdehyde dehydrogenase (SSADH, or ALDH5A1 (aldehyde dehydrogenase 5a1) (Jakobs et al 1981). What he needed was an enzymologist to test this hypothesis, and the senior author was fortunate enough to have been that individual (Gibson et al 1983). The path to the current paper highlights the team approach, with clinicians, molecular biologists, mammalian geneticists, neurophysiologists, and so many other scientists that it is challenging to identify (much less remember) them all. The good news is that we now possess sufficient knowledge of the pathophysiology of this disorder to institute clinical trials! Where these trials take us remains to be seen, but we can say with certainty that without Cornelis, we would never have started. The senior author will miss the daily interactions by e mail, but a 30-year friendship is not easily lost or forgotten.

Fig. 1.

The GABA metabolic pathway. The block in SSADH deficiency is indicated by the crosshatched box. Upward arrows indicate metabolite elevations in patients and *aldh5a1*^{-/-} mice. High levels of GHB will inhibit presynaptic DA (dopamine) release and enhance turnover. The site of VGB acting on GABA-transaminase (GABA-T) is indicated. Additional abbreviations: GAD, glutamic acid decarboxylase; TCA, tricarboxylic acid.

Fig. 2.
Chemical structures of the compounds discussed in the text, including the species accumulating to pathological levels in SSADH deficiency, GHB and GABA (bottom).

Table 1Outcomes of VGB intervention in SSADH Deficiency^a

<u>Age (yrs)</u>	<u>Sex</u>	<u>VGB (Months)</u>	<u>Clinical Improvement</u>	<u>Reference</u>
3	F	20–100 mg/kg (4 mo)	none	Gibson et al (1989)
2	F	75 mg/kg/d (16 mo)	ataxia, EEG (swd) ^b	Jaeken et al(1989)
12	F	500–3500 mg/d (9 mo)	ataxia, IQ	Jakobs et al (1992)
1	F	1500 mg/d	hypotonia	Uziel et al (1993)
12	M	25–75 mg/kg/d	cognition, behavior (low dose)	Matern et al (1996)
5	M	1500 mg/d (6 mo)	hypotonia, myoclonus	Al-Essa et al (2000)
10	F	22–34 mg/kg/d (57 mo)	hyperactivity, agitation behavior	Ergezinger et al (2003)
2.5	F	20 mg/kg/d (12 mo)	hypotonia	Escalera et al (2010)
8	F	25 mg/kg/d (9 mo)	communication	Casarano et al (2011)

^aWhen reported, CSF GHB decreased 14–72% and CSF GABA increased 2.3 to 6-fold during VGB intervention (Ergezinger et al 2003);

^bElectroencephalogram, spike wave discharge. Two additional reports indicated clinical improvement in ~ 1/3 of patients treated with VGB, without clinical details (Rahbeeni et al 1994; Gibson et al 1997).

Table 2

Cerebrospinal fluid (CSF) metabolites during VGB intervention in 4 SSADH-deficient patients

<u>Metabolites</u>	<u>Patient</u>	<u>Pre-treatment</u>	<u>Post-treatment</u>	<u>% Change</u>
GHB: Total GABA	1	116: 13.6	62: 31.2	-47: +229
	2	1110: 22.4	708: 32.1	-36: +143
	3	615: 18.3	457: 38.8	-26: +212
	4	525: 22.1	384: 33.6	-27: +152

All metabolites in units of $\mu\text{mol/L}$. CSF control ranges: GHB, 0–2.6 $\mu\text{mol/L}$ (n=10); total GABA, 4.7–11.8 $\mu\text{mol/L}$ (n=10). Total GABA refers to free and “bound” GABA (e.g., homocarnosine, and other GABA compounds) (reprinted from Gibson et al 1995).