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# Succinic semialdehyde dehydrogenase deficiency: Lessons from mice and men

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## Summary

Succinic semialdehyde dehydrogenase (SSADH) deficiency, a disorder of GABA degradation with subsequent elevations in brain GABA and GHB, is a neurometabolic disorder with intellectual disability, epilepsy, hypotonia, ataxia, sleep disorders, and psychiatric disturbances. Neuroimaging reveals increased T2-weighted MRI signal usually affecting the globus pallidus, cerebellar dentate nucleus, and subthalamic nucleus, and often cerebral and cerebellar atrophy. EEG abnormalities are



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usually generalized spike-wave, consistent with a predilection for generalized epilepsy. The murine phenotype is characterized by failure-to-thrive, progressive ataxia, and a transition from generalized absence to tonic-clonic to ultimately fatal convulsive status epilepticus. Binding and electrophysiological studies demonstrate use-dependent downregulation of GABA(A) and (B) receptors in the mutant mouse. Translational human studies similarly reveal downregulation of GABAergic activity in patients, utilizing flumazenil-PET and transcranial magnetic stimulation for GABA(A) and (B) activity, respectively. Sleep studies reveal decreased stage REM with prolonged REM latencies and diminished percentage of stage REM. An *ad libitum* ketogenic diet was reported as effective in the mouse model, with unclear applicability to the human condition. Acute application of SGS–742, a GABA(B) antagonist, leads to improvement in epileptiform activity on electrocorticography. Promising mouse data using compounds available for clinical use, including taurine and SGS–742, form the framework for human trials.

## Introduction

Given the rarity of the inherited disorders of neurotransmitters, succinic semialdehyde dehydrogenase (SSADH) deficiency (OMIM # 271980) is relatively prevalent, with approximately 400 identified cases worldwide. The diagnosis requires a high degree of clinical suspicion and specific-ion monitoring for gamma-hydroxybutyric aciduria for laboratory screening (Pearl et al 2003). Thus, this autosomal recessively inherited disorder, with legion neuropsychiatric sequelae, is likely underdiagnosed. The gene locus (*Aldh5A1*) and enzymatic deficiency are known, and a transgenic animal model has been fundamental in beginning to understand the pathophysiology. While there is some heterogeneity in the clinical manifestations, all patients are severely affected and any progress in developing therapies would represent a major advance for affected families and serve to potentially heighten our understanding of highly prevalent disorders featuring the problems of intellectual disability, epilepsy, ataxia, sleep disorders, and neuropsychiatric disturbances.

## Metabolism and pathophysiology

SSADH deficiency is a disorder of the γ-amino-butyric acid (GABA) degradation pathway (Fig. 1). GABA is the major inhibitory neurotransmitter of the brain, and derives primarily from glutamate, the major excitatory neurotransmitter. The first step of GABA degradation pathway involves GABA transaminase (GABA-T), which removes an amino group from GABA and adds it to α-ketoglutarate, thus replenishing glutamate and producing succinic semialdehyde, a relatively unstable intermediate compound. This is followed by the reaction catalysed by SSADH, whereby succinic semialdehyde is converted into succinic acid. Succinic acid enters the Krebs cycle, the final common pathway of aerobic oxidation. This process preserves the delicate balance between (glutamatergic) excitation and (GABAergic) inhibition in the brain.

SSADH deficiency prevents the successful conversion of succinic semialdehyde to succinic acid, and leads to diversion to an alternative by-product, γ-hydroxybutyrate (GHB), via succinic semialdehyde reductase (aldo-keto reductase 7A2, e.g. AKR7A2). GHB is known as a drug of abuse and assault, although it has been approved by the FDA as treatment for narcolepsy-cataplexy. GHB rapidly crosses the blood–brain barrier and has effects on multiple neurotransmitter systems, including dopamine, serotonin, acetylcholine and GABA. The biochemical hallmark of SSADH deficiency is accumulation of GHB in physiological fluids. CSF analysis of human patients shows elevated levels of GHB (mean 449 μmol/L, normal level <3 μmol/L), GABA (Total) (mean 29.3 μmol/L, normal level <12.2 μmol/L) and GABA (Free) (mean 0.37 μmol/L, normal level <0.17 μmol/L) and lowered levels of glutamine (mean 337 μmol/L, normal range 357–750 μmol/L) (Gibson et al 2003).

## Clinical phenotype

SSADH deficiency usually has a relatively consistent phenotype characterized by intellectual disability with prominent deficits in expressive language, hypotonia, nonprogressive ataxia, and hyporeflexia. Neuropsychiatric symptoms are prominent and include sleep disorders, inattention, hyperactivity and anxiety (Pearl and Gibson 2004). Unlike other metabolic disorders, this disease is not intermittent or episodic, and has a relatively static course, which renders distinction from static encephalopathies difficult. About 10% of patients have a degenerative course characterized by regression and prominent extrapyramidal manifestations (Pearl et al 2005b). These manifestations include chorea, myoclonus, and dystonia. A video-manuscript report of two adolescent brothers demonstrates exercise-induced paroxysmal dyskinesias, manifested by a prominently lurching gait, which showed some improvement following vigabatrin therapy (Leuzzi et al 2007).

A clinical database using systematic questionnaires of 60 patients indicates that developmental delay is a universal presentation. Common clinical features include intellectual disability, behaviour problems, and motor dysfunction (Tables 1 and 2). To address the long-term outlook, we reported on 33 patients (52% males) over 10 years of age (Knerr et al 2008a), and have further updated this with our current database (Tables 3, 4 and 5). The mean age of this patient cohort is 17.1 years ±6.4 years (range 10.1–39.6 years). The mean age when symptoms first appeared was 11 months (range 0–44 months) and the mean age at diagnosis was 6.6 years (with a wide range of 0–25 years).

Nearly half of patients have epilepsy, usually with generalized tonic-clonic and atypical absence seizures, and a minority with myoclonic seizures (Pearl et al 2007a). A majority (64%) of patients in our database had abnormal electroencephalograms, characterized by background slowing, epileptiform abnormalities (usually generalized and sometimes multifocal), and rarely photoparoxysmal responses and electrographic status epilepticus of slow-wave sleep.

Sleep disturbances are reported in nearly half of patients (Pearl et al 2007a). The majority of patients manifest excessive daytime somnolence, and approximately 20% have disorders of initiating or maintaining sleep. A study of a single patient having two nights of polysomnography demonstrated prolonged stage REM onset and, on the second consecutive night, excessive EEG background slowing after a generalized seizure during stage 4 sleep (Arnulf et al 2005). We have studied 10 patients with overnight polysomnography and daytime multiple sleep latency testing and have reported prolonged REM latency and reduced stage REM percentage with over 90% sleep efficiency and absence of decreased daytime sleep latency or sleep-onset REM (Pearl et al 2005a). Thus, there appears to be a reduction in REM sleep in SSADH deficiency. Animal models have demonstrated that hyper GABAergic states, e.g. via inhibition of GABA transaminase using L-cycloserine, are associated with reduction of REM sleep and prolongation of the transition phase between sleep stages NREM and REM (Scherschlicht 1985).

Recently the first postmortem examination of SSADH deficiency became available. The diagnosis has been made retrospectively in a 19-year-old deceased woman following the confirmed diagnosis in her living sister. The decedent presented with developmental delay, seizure onset at age 13 years, and SUDEP (sudden unexpected death in epilepsy patients) at age 19 years after having experienced accelerating convulsive seizure activity. A postmortem evaluation was performed with the assigned diagnosis of epilepsy of unknown aetiology. The major neuropathological finding was striking discoloration of the globus pallidi. Her living sister had been followed with a history of developmental delay and borderline cognition (IQ = 70), until presenting with seizures and a subsequent diagnosis of SSADH deficiency. She has an *Aldh5A1* mutation (p.Gly409Asp). Although DNA analysis on the decedent is in

progress, this case report has provided our first glimpse into the neuropathology of the disorder (Knerr et al 2008b).

Neuroimaging has shown abnormalities in two-thirds of patients in our database, most characteristically increased T2-weighted signal in the globus pallidus, subcortical white matter, cerebellar dentate nucleus, and brainstem (Pearl et al 2007a). Other findings include cerebral atrophy, cerebellar atrophy, delayed myelination, and a pattern of dentate-pallidal hyperintensity (Yalçinkaya et al 2000; Ziyeh et al 2002). While the pallidal hyperintensity is usually homogeneous and equally affects the internal and external portions, we have had occasional patients with heterogeneous involvement and persistent asymmetry of the signal abnormality of the globus pallidus. Of 7 patients studied in our recent clinical protocol at NIH, 5 had bilaterally symmetric homogeneous signal abnormalities in the globus pallidus and dentate nuclei, as well as subthalamic nuclei. One patient had asymmetric involvement of the globus pallidus which has proved to be stable over 7 years, with minimal abnormality on the right but marked increased T2-weighted and decreased T1-weighted signal on the left accompanied by expansion of the left globus pallidus and bilateral ventriculomegaly. In the oldest patient studied (age 27 years), the pallidal signal abnormality was subtle, but associated with clear volume loss and commensurate *ex vacuo* dilatation of the third ventricle, without abnormalities of the subthalamic or dentate nuclei. Magnetic resonance spectroscopy that is edited for small molecules has shown elevated levels of GABA and related compounds (including GHB and homocarnosine) in patients but not obligate heterozygotes (Ethofer et al 2004; Pearl and Gropman 2004).

We have utilized positron emission tomography (PET) with two ligands, [$^{18}$F] fluorodeoxyglucose ([$^{18}$F]FDG PET) and [$^{11}$C]flumazenil (FMZ), a benzodiazepine receptor antagonist. Decreased cerebellar glucose metabolism has been demonstrated in patients with cerebellar atrophy demonstrated on structural MRI (Al-Essa et al 2000; Pearl et al 2003). Flumazenil PET was obtained with co-registration to MRI in 7 SSADH deficiency patients, 10 unaffected parents (obligate heterozygotes), and 8 healthy adult controls. Significant reductions in flumazenil binding were noted in all regions of interest (basal ganglia, amygdala, hippocampus, and cerebellar vermis, frontal, parietal, and occipital cortices) in patients ($p < 0.001$), with no significant differences between controls and parents (Pearl et al 2007b). There was no sex effect. Given that previous flumazenil PET studies have shown that binding is higher in healthy children than in adults, these results support the presence of decreased GABA (A)-benzodiazepine binding site availability in SSADH deficiency, consistent with use-dependent downregulation of GABA receptors as demonstrated in the animal model (see below).

In order to study neurophysiological parameters noninvasively and allow for a quantitative approach to measurement of excitatory versus inhibitory factors, transcranial magnetic stimulation (TMS) was utilized with both single- and paired-pulse stimuli. Eight families (parents and affected probands) were studied with determination of standard TMS parameters: resting motor threshold, motor evoked potential recruitment, short and long interval intracortical inhibition, cortical silent period, and intracortical facilitation (Reis et al 2007). There was a loss of long interval intracortical inhibition in patients compared with heterozygous and control groups ($p < 0.0001$), and the cortical silent period was significantly shorter in SSADH-deficient patients compared with parents and volunteers ($p < 0.01$). These indicators of decreased inhibitory factors are consistent with impaired GABA(B) receptor cortical activity. This supports use-dependent downregulation of GABA(B) receptors in the human condition, consistent with analogous activity in the animal model (see below).

The treatment for SSADH deficiency remains problematic and no consistently successful therapy has emerged (Gropman 2003). Treatment is generally symptomatic and targeted.

Options include anxiolytic agents or SSRIs and related medications for obsessive-compulsive disorder. Appropriate antiepileptics are chosen for generalized epilepsy, although valproate is avoided due to its ability to inhibit any residual SSADH enzymatic activity (Shinka et al 2003). Vigabatrin, an irreversible inhibitor of GABA-transaminase, is a logical choice because it will inhibit the conversion of GABA to GHB, a putative pathogen in this condition. Vigabatrin, however, has not been a consistently helpful therapeutic for these patients, and there have been many reports of lack of effect or, worse, worsening of symptoms ranging from seizure control to alertness. Further, there have been concerns regarding vigabatrin, resulting thus far in absence of US Food and Drug Administration approval, initially because of intramyelinic oedema and white-matter vacuolation in rats and dogs (Butler et al 1987; Peyster et al 1995; Qiao et al 2000). In clinical trials, 30% of patients treated with vigabatrin for epilepsy report visual field defects following one year of treatment (Krauss et al 1998; Spence and Sankar 2001; Vanhatalo et al 2002). As this deficit begins with peripheral visual field constriction, it would be particularly difficult for patients with a neurodevelopmental disorder such as SSADH deficiency to be alert to the early signs of visual toxicity. We have recently identified MRI signal changes, particularly prominent in the thalamus and basal ganglia, in infants treated with relatively high doses of vigabatrin (Pearl et al 2008).

While vigabatrin will lead to at least transient decreases in CSF GHB levels (Ergezinger et al 2003), there may be a deleterious effect related to attendant increases in CSF (and brain) GABA levels (Pearl and Gropman 2004).

## Mouse model

A murine model was developed with gene-targeting methodology, utilizing deletion of exon 7 leading to complete absence of enzyme activity in neural and peripheral tissues (Hogema et al 2001). Clinical features of the murine model include progressive ataxia, seizures and failure to thrive. At approximately day 16, mutants manifest a transition from absence seizures to tonic-clonic seizures and into status epilepticus. The semiology of the motor seizures in the Aldh5a1 null mouse has been described as wild running clonus with jumping and bouncing behaviours having a circadian pattern, with peak incidence after dark onset (Stewart et al 2008).

The affected mice accumulate GABA and GHB in the CNS and have receptor dysfunction involving GABA(A), GABA(B), and GHB receptors. The mouse exhibits elevated GABA and decreased glutamine levels in brain (Gupta et al 2004), analogous to CSF findings in humans (Gibson et al 2003). This suggests uncoupling of the glutamine/glutamate shuttle that exists between glial synthesis of glutamine, then transport to neurons with synthesis of glutamate and then GABA. The mouse model also demonstrates use-dependent downregulation of both GABA(A) and GABA(B) transmission. A combination of binding studies and electrophysiological procedures demonstrated impaired expression and function of these receptors. A progressive decrease in binding of a selective GABA(A) receptor antagonist [$^{35}$S]TBPS (*tert*-butylbicyclophosphorothionate) was observed in the mutant strain cerebral cortex, hippocampus, and thalamus from postnatal day 7 until its nadir at 3 weeks, coincident with the emergence of generalized convulsive seizures (Wu et al 2006). There were also reduced GABA(A)-mediated inhibitory postsynaptic potentials and enhanced postsynaptic population spikes recorded from hippocampal slices. Further work demonstrated a significant decrease in binding of a specific GABA(B) receptor antagonist in SSADH null mice compared with wild-type control animals, and decreased GABA(B)-mediated synaptic potentials (Buzzi et al 2006). Thus, the mutant mouse is characterized by evidence of downregulation of both GABA(A) and (B) receptors, for which we demonstrated comparable findings in the clinical condition utilizing PET and TMS technology.

Neuroimaging studies of Aldh5a1$^{-/-}$ mice showed smaller cerebral, cerebellar and total brain volumes versus controls (Acosta et al 2005). MR spectroscopy in the SSADH null mice, consistent with the human data, is characterized by higher cortical extract levels of GABA, GHB, aspartate and alanine, and lower levels of glutamate, glutamine and taurine than in controls (Chowdhury et al 2007).

The murine model has been exploited for rescue studies, with prolonged animal survival following administration of vigabatrin, NCS 382 (GHB receptor antagonist), CGP 35348 (GABA(B) receptor antagonist), and taurine (Gupta et al 2002). The latter amino acid is a prominent constituent in murine breast milk, and was utilized because of the observation that the seizure onset corresponds to the time of weaning of suckling animals.

A recent animal study suggested efficacy of the ketogenic diet, with decreased frequency and delayed onset of seizures, decreased epileptiform activity on electrocorticography, delayed onset of ataxia, improved weight gain, and prolonged longevity (Nylen et al 2008). The rationale for the ketogenic diet in SSADH deficiency is unclear. The ketogenic diet is indicated in metabolic conditions when it can fulfil the role of providing an alternative brain fuel and entry point into the Krebs cycle, e.g. glucose transporter 1 deficiency and pyruvate dehydrogenase complex deficiency. While Aldh5a1 null mice show evidence of respiratory chain defects, specifically decreased hippocampal glutathione and complexes I–IV, Krebs cycle activities are normal (Sauer et al 2007). The ketogenic diet study investigators presented evidence of restitution of GABAergic neurotransmission, with restoration of hippocampal miniature inhibitory postsynaptic currents and [$^{35}$S]TBPS binding to the GABA(A) receptor chloride channel, in the diet-fed mutant mouse. The applicability of the diet to the human condition, however, has been questioned (Knerr and Pearl 2008). The ketogenic diet-fed mutant mice had more weight gain than the mutant mice fed the regular chow diet. The ketogenic diet-fed mice also had higher glucose levels, and no differences in free fatty acid concentrations compared with mutant and wild-type mice fed the regular diet. The ketogenic diet-fed mice essentially fed *ad libitum* and could have benefited simply from treatment of their malnourished, failure-to-thrive condition. There may be an unintended consequence of the ketogenic diet in that β-hydroxybutyrate, a key by-product, could be converted to its isomer, γ-hydroxybutyrate. Thus, the role of the ketogenic diet in affected patients, having a phenotype that is not that closely reminiscent of the animal, is at best unclear.

## Current status of therapeutic trials

The human and animal investigations have pointed to several specific therapeutic trials.

Taurine, an aminosulfonic acid sold as a dietary supplement, has osmoregulatory, neuromodulatory, and tropic roles but its exact mechanism of action is unknown. The SSADH mutant mouse study showed a survival rate of 55.6% at day 20 following intraperitoneal injection of 250 mg/kg (Gupta et al 2002). Oral taurine at a 5000 mg/kg dosage improved survival to 46.0% ($p < 0.01$). Taurine is associated with an observed safe level in humans at 3 g/day, and higher dosages have been tested without significant adverse effects (Shao and Hathcock 2008). In a single case report, taurine was reported to improve gait, coordination and energy of a 2 1/2-year-old boy with SSADH deficiency (Saronwala et al 2008). The patient was given 4 g/day (~200 mg/kg) over one year. Higher doses were associated with insomnia. At 9 months, teachers reported improved behaviour, peer interactions, increased level of activity and coordination. At 12 months, the boy's MRI was interpreted as improved. No correlation was found between improved behaviour and urine GHB levels. The case was neither controlled or blinded, but has led to planning of further clinical trials.

Preliminary animal work in the SSADH mutant model has suggested benefit from treatment with SGS–742, a GABA(B) receptor antagonist. Early reports showed cognitive enhancement such as improved attention, reaction time, visual information processing and working memory in mice, rats and monkeys. We present here the results of application of SGS–742 to SSADH-deficient ($Aldh5a1^{-/-}$) mice. The study design compared the effects of either SGS–742 or topiramate treatment on electrocorticography (ECoG). Topiramate is a polymechanistic antiepileptic, with properties including enhancement of GABAergic effects, attenuation of voltage-gated $Na^+$ currents, and inhibitory actions on kainate and AMPA receptors (Landmark 2007). ECoG recordings ($n = 4$) were taken from frontal and parietal cortex bilaterally following electrode implantation at day-of-life 18 (P18). The drugs were administered intraperitoneally under continuous ECoG monitoring at P19 with topiramate (3, 4.5, and 6 mg/kg) and SGS–742 (30, 100 mg/kg). Figure 2 reveals that SGS–742 showed a dramatic dose-dependent improvement in the ECoG tracings, while topiramate was ineffective. As the ECoG is state dependent, the doses of SGS–742 and topiramate utilized were chosen by experimentally determining the dose below the threshold for sleep.

The minimum level of SGS-742 found to be effective in the ECoG studies was then used for assessment of spike-wave discharges and survival. The cumulative spike-wave duration effects of SGS–742 at different concentrations are characterized in Fig. 3. As shown at baseline (no drug administered), $Aldh5a1^{-/-}$ mice displayed significantly higher spike-wave discharge duration as compared to their wild-type ($Aldh5a1^{+/+}$) littermates ($p < 0.05$). SGS–742 significantly improved the spike-wave duration in dose-dependent fashion and controlled absence seizures. These data support earlier data using CGP 35348 (Cortez et al 2004) and verify a prominent GABA(B) component associated with the absence seizures in $Aldh5a1^{-/-}$ mice. SGS–742 significantly reduced spike-wave duration in animals of both mutant SSADH-deficient mice and wild-type mice who received γ-butyrolactone, a precursor of GHB. We can improve the survival of $Aldh5a1^{-/-}$ mice with the ketogenic diet (Nylen et al 2008), and are currently exploring developmental treatment experiments with SGS–742 and topiramate in $Aldh5a1^{-/-}$ mice to further test the connection between seizures and the poor survival phenotype and determine the utility of additional pharmacological treatments for SSADH deficiency.

In a Phase II double-blind, placebo-controlled study in 110 patients with mild cognitive impairment, oral administration of 1800 mg divided into three daily dosages for 8 weeks significantly improved attention, reaction time, visual information processing, and working memory (Froestl et al 2004; Tomlinson et al 2004). Future plans are to administer this compound to patients with SSADH deficiency and utilize accompanying TMS measurements as a biomarker of GABA(B)-mediated neurotransmission.

## Conclusions

A convergence of mouse and human data has promoted improved understanding of the pathophysiology of inherited 4-hydroxybutyric aciduria, an organic acidopathy having protean neurological features attributable to autosomal recessive deficiency of succinic semialdehyde dehydrogenase. An intercontrovertible exchange from bench to bedside and back remains an active strategy in the development of therapy. Both the human and murine condition have analogous biochemical changes including elevations of GABA and GHB and, to some degree, decreased glutamine. The human condition presents with developmental delay and diagnosis typically made at a median age of 2 years, but with a wide range and oftentimes much later diagnosis. The phenotype subsequently reveals intellectual deficiency, prominent expressive language deficits, hypotonia, ataxia and decreased fine motor praxis, sleep disturbances, epilepsy, and sometimes extrapyramidal movement disorders. The murine phenotype is

characterized by failure to thrive, progressive ataxia, and an epileptic transition of absence to generalized tonic-clonic seizures to ultimately fatal status epilepticus.

GABA receptor function and expression is consistent with use-dependent downregulation of both GABA(A) and (B) receptors in the mutant mouse. Flumazenil-PET and transcranial magnetic stimulation have demonstrated similar downregulation in the human condition. MR spectroscopy has demonstrated increased GABA and related compounds (GHB, homocarnosine) in the brain parenchyma of null mice and affected humans. Alternatively, structural imaging has shown decreased cerebral and cerebellar volume in the affected mouse, versus more specific and localizing signal abnormalities in the human predominantly affecting the globus pallidus, dentate nucleus, and subthalamic nucleus.

Crossover between the animal and human models vis-à vis treatment represents a new hurdle. The efficacy of the ketogenic diet when fed *ad libitum* to the mutant mouse, which then gains more weight than the mutant mouse fed regular chow, may be more related to treatment of undernutrition than of the primary GABA metabolic disorder. Evidence for improved survival and seizure control in the mouse treated with taurine or the GABA(B) receptor antagonist SGS 742 is paving the way to clinical trials in patients. Baseline work using biomarkers to assess the functionality of the GABA(A) and (B) systems in humans provides an important backdrop to test hypotheses related to treatment efficacy. Whether clinical efficacy is determined will be the ultimate challenge of the symbiosis between mice and men.

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## Abbreviations

ECoG, electrocorticography; FMZ, flumazenil; GABA, γ-amino-butyric acid; GHB, γ-hydroxybutyrate; PET, positron emission tomography; SSADH, succinic semialdehyde dehydrogenase; TMS, transcranial magnetic stimulation.

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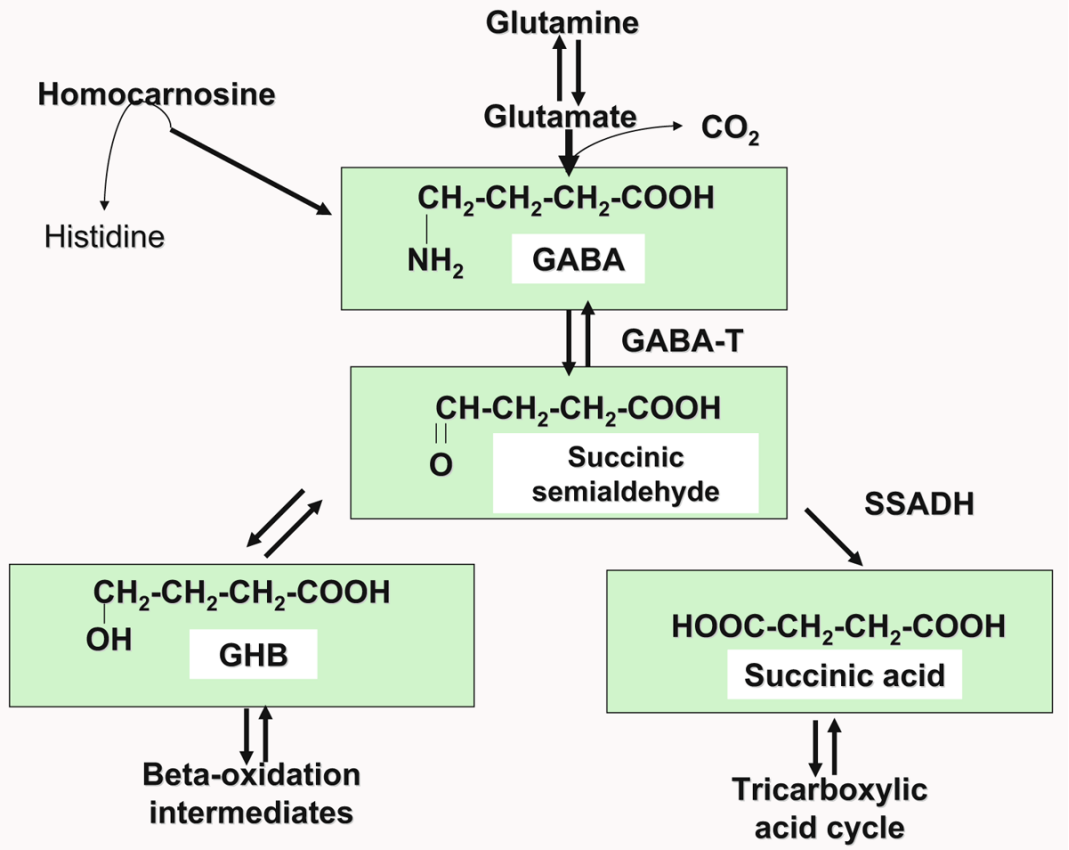


**Fig. 1.**
GABA metabolic pathway

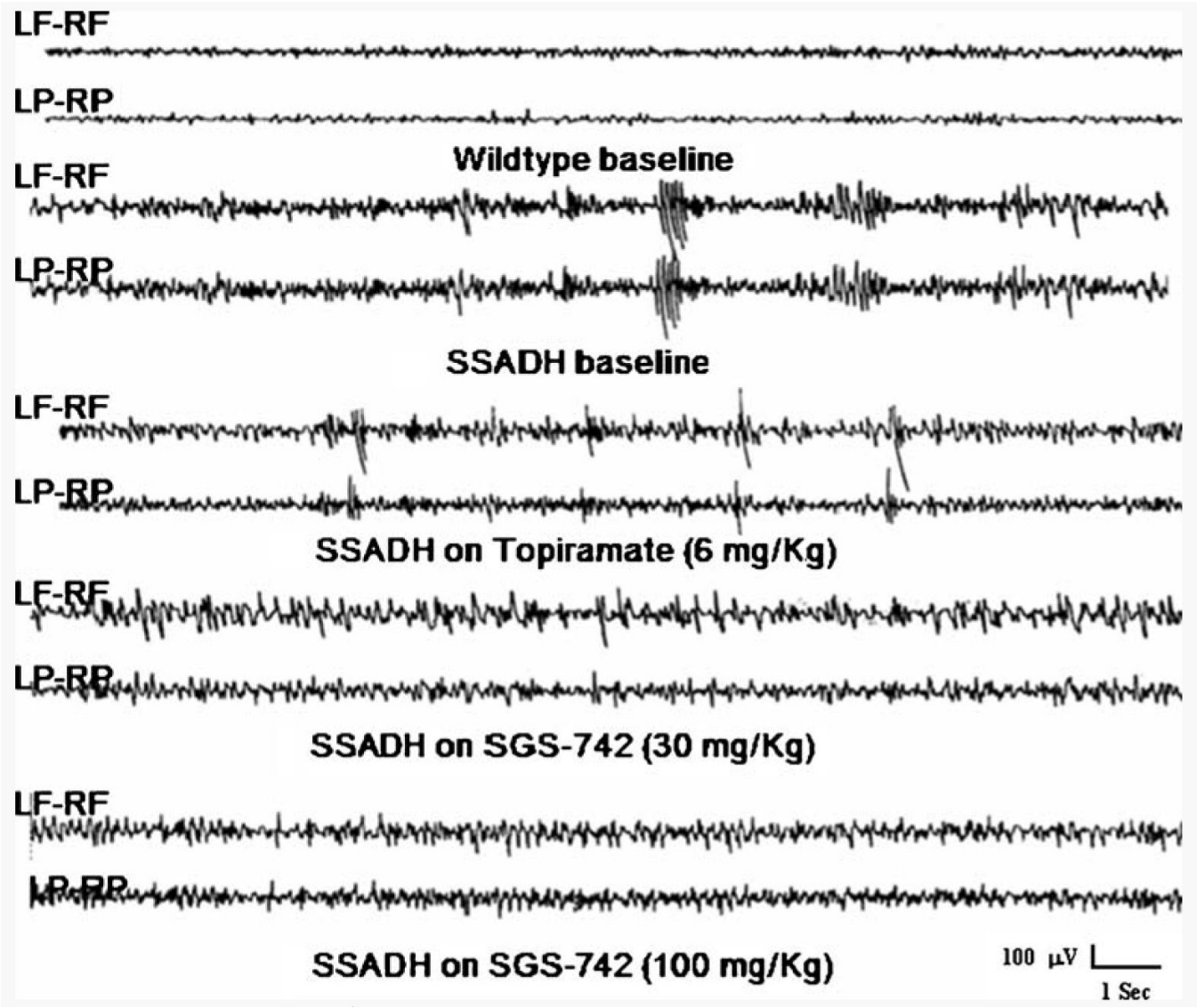


**Fig. 2.**

ECoG tracings for wild-type (*Aldh5a1*$^{+/+}$ mice) and mutant (SSADH = *Aldh5a1*$^{-/-}$ mice) following no acute drug administration (baseline) or acute i.p. administration of topiramate or SGS–742. Multiple animals ($n$ = 4) of both genotypes showed similar results. Time/voltage scale = 100 μV/s. Abbreviations: ECoG, electrocorticogram; LF, left frontal; RF, right frontal; LP, left parietal; RP, right parietal electrode derivations

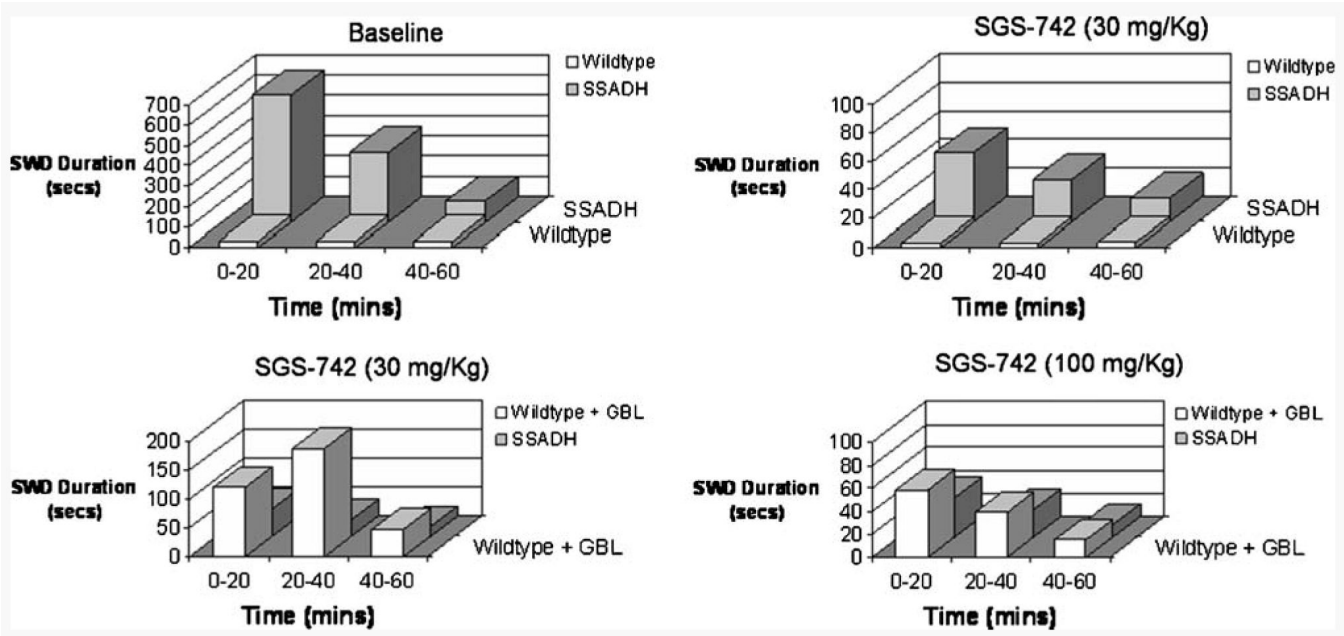


**Fig. 3.**

Effects of SGS–742 on spike-wave discharge (SWD) duration in SSADH (Aldh5a1$^{-/-}$) and wild-type (Aldh5a1$^{+/+}$) mice. Baseline is in the *upper left* (no drug intervention). SGS–742 (30 mg/kg (*upper right*)) significantly reduced SWD duration in Aldh5a1$^{-/-}$ mice, Student *t*-test ($p < 0.05$). SWD duration again after 30 mg/kg dose of SGS–742 (*bottom left*); Aldh5a1$^{+/+}$ mice received a single dose of γ-butyrolactone (GBL, a GHB precursor) 100 mg/kg for comparison (no SGS–742). SGS–742 again reduced SWD duration in Aldh5a1$^{-/-}$ mice, Student *t*-test ($p < 0.05$). SWD duration following 100 mg/kg SGS–742 (*bottom right*). For comparison, Aldh5a1$^{+/+}$ mice received GBL 100 mg/kg. SGS–742 significantly reduced SWD duration in Aldh5a1$^{-/-}$ and Aldh5a1$^{+/+}$ mice who had received GBL; Student *t*-test ($p < 0.05$), versus baseline. SWD was measured in 20 min epochs over a 1 h period ($n = 4$ each genotype and graph)

**Table 1**

Clinical findings in SSADH patients (*N*= 60)

| | ***n*** | **%** |
|---|---|---|
| Developmental delay | 60 | 100% |
| Mental retardation (intellectual disability) | 60 | 100% |
| Hypotonia | 49 | 82% |
| Seizures | 27 | 45% |
| Ataxia | 46 | 77% |

**Table 2**

Neuropsychiatric problems (*N*= 60)

| | *n* | % |
|---|---|---|
| Aggression | 8 | 13% |
| Anxiety | 16 | 27% |
| Hallucinations | 5 | 8% |
| Hyperactivity | 22 | 37% |
| Inattention | 27 | 45% |
| OCD | 15 | 25% |
| Sleep disturbances | 27 | 45% |
| Autistic features[a] | 15 | 25% |

[a] Autistic features: withdrawn affect, poor eye contact, poor pretend play, stereotypies, inability to transition and strong preference for routine.

**Table 3**

Clinical phenotype in adolescent and adult patients (*N*= 35)

| | *n* | % |
|---|---|---|
| Intellectual disability | 35 | 100% |
| Ataxia | 26 | 74% |
| Seizures | 20 | 57% |
| Hypotonia | 31 | 89% |
| Sleep disturbances | 19 | 54% |

**Table 4**

Behaviour problems in adolescent and adult patients (*N*= 35)

| | ***n*** | **%** |
|---|---|---|
| Attention deficit | 21 | 60% |
| Hyperactivity | 17 | 49% |
| Anxiety | 12 | 34% |
| Obsessive-compulsive | 13 | 37% |
| Aggressive behaviour | 6 | 17% |
| Hallucination-like | 5 | 14% |
| Autistic features | 10 | 29% |

**Table 5**

Ataxia/motor problems in adolescent and adult patients (*N*= 35)

| | *n* | % |
|---|---|---|
| Decreased balance | 18 | 51% |
| Uncoordinated movements | 11 | 31% |
| Wide based gait | 11 | 31% |
| Uncoordinated walking | 10 | 29% |
| Hand tremors | 7 | 20% |
| Excessive movements | 6 | 17% |