Biomarkers in a Taurine Trial for Succinic Semialdehyde Dehydrogenase Deficiency

John M. Schreiber • Phillip L. Pearl • Irene Dustin •
Edythe Wiggs • Emily Barrios • Eric M. Wassermann •
K. Michael Gibson • William H. Theodore

Received: 14 August 2015 / Revised: 10 November 2015 / Accepted: 26 November 2015 / Published online: 24 June 2016
© SSIEM and Springer-Verlag Berlin Heidelberg 2015

Abstract *Aim:* We tested the hypothesis that patients with succinic semialdehyde dehydrogenase (SSADH) deficiency on taurine would have decreased cortical excitability as measured by transcranial magnetic stimulation (TMS) and improved cognition, due to taurine's partial GABA(A and B) receptor agonist effects and rescue in the null mouse model from status epilepticus and premature lethality.

Method: Biomarkers including neuropsychological testing, TMS, and CSF metabolites were studied in a cohort of patients on and off three months' taurine treatment.

Results: Seven patients (5M/2F; age range 12–33 years) were enrolled in this open-label crossover study. Baseline average full-scale IQ (FSIQ) was 44.1 (range 34–55). Of six who returned at 6-month follow-up, five completed cognitive testing (3M/2F) on therapy; average FSIQ = 43.4 (range 33–51). CSF biomarkers ($n = 4$ subjects) revealed elevation in taurine levels but no change in free or total GABA. Baseline cortical excitability measured with TMS agreed with previous findings in this population, with a short cortical silent period and lack of long-interval intra-

cortical inhibition. Patients on taurine showed a decrease in cortical silent period and short-interval intracortical inhibition compared to their off taurine study.

Interpretation: TMS demonstrated decreased inhibition in patients on taurine, in contrast to the study hypothesis, but consistent with its failure to produce clinical or cognitive improvement. TMS may be a useful biomarker for therapy in pediatric neurotransmitter disorders.

Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare autosomal recessive defect in the catabolic pathway of GABA (gamma-aminobutyric acid), leading to elevated levels of GABA and gamma-hydroxybutyric acid (GHB) in body fluids and brain parenchyma (Pearl et al. 2003a, b). The typical clinical phenotype has been described as a slowly progressive or static encephalopathy. Most patients present with developmental delay noted in the first 2 years of life, as well as hypotonia, hyporeflexia, ataxia, speech disturbance, and intellectual disability, and at least half have seizures.

Several lines of evidence indicate that SSADH deficiency results in chronic, overuse-dependent down-regulation of GABA(A) and GABA(B) receptors. In the mouse model, decreased binding of the selective GABA(A) receptor antagonist *tert*-butylbicyclophosphorothionate ([³⁵S]TBPS) was observed in the cerebral cortex, hippocampus, and thalamus of the mutant strain compared to wild type, and reduced GABA(A)-mediated inhibitory postsynaptic potentials and enhanced postsynaptic population spikes were recorded from hippocampal slices of the mutant strain (Wu et al. 2006). There was also significantly decreased binding of a specific GABA(B) receptor antagonist in the mutant strain and attenuated GABA(B)-mediated synaptic potentials (Buzzi et al. 2006). We demonstrated

Communicated by: Verena Peters

J.M. Schreiber (✉) • I. Dustin • E. Wiggs • W.H. Theodore
Clinical Epilepsy Section, Bethesda, MD, USA
e-mail: jschreib@childrensnational.org

P.L. Pearl • E. Barrios
Department of Child Neurology, Children's National Medical Center (CNMC), Washington, DC, USA

E.M. Wassermann
Cognitive Neuroscience Section, NINDS, NIH, Bethesda, MD, USA

K.M. Gibson
Experimental and Systems Pharmacology, Washington State University (WSU), Spokane, WA, USA

decreased binding of flumazenil, a GABA(A) receptor agonist, in multiple regions of interest studied using cerebral PET (Pearl et al. 2009). In addition, transcranial magnetic stimulation (TMS) studies showed shortening of the cortical silent period and loss of long-interval intracortical inhibition using single and paired pulse stimulation, consistent with impaired GABA(B) receptor function (Reis et al. 2012).

The homozygous deficient mouse model is characterized by onset of absence seizures, typically at day P17, with evolution to ultimately fatal convulsive status epilepticus by three weeks of age. This process occurs coincident with weaning of suckling mice, and the observation that taurine is the major constituent of murine breast milk led to an experimental trial and survival benefit (Gupta et al. 2002). Taurine (2-aminoethanesulfonic acid) is an abundant free amino acid in various tissues and has important roles in neuromodulation and osmoregulation (Bidri and Choay 2003). Taurine may be an important modulator of GABA transmission. Taurine increases GABA function by acting as a low-affinity agonist for GABA(A) receptors (Junyent et al. 2009) and also activates metabotropic GABA(B) receptors to a lesser extent (Belluzzi et al. 2004). The rationale for our hypothesis that taurine may be effective for this condition was thus based on the aforementioned evidence for overuse-dependent downregulation of GABA (A) and GABA(B) receptor activity and perhaps interference with the neuronal hyperexcitability of the syndrome manifested by the transition from absence to convulsive seizures in the murine model.

Early reports of uncontrolled trials suggested a potential benefit of taurine intervention in patients (Saronwala et al. 2008), although we were unable to document significant changes using an adaptive behavior scale in an open-label study (Pearl et al. 2014). Here, we report the effects of taurine on TMS measures of cortical excitability and inhibition, CSF biomarkers, and cognitive testing in a group of these patients participating in the open-label taurine trial. We hypothesized that orally administered taurine would result in increased cortical inhibition, improvement in cognition, and an elevation in CSF taurine.

Method

Participants over age 12 years, with SSADH deficiency, who were already enrolled in the open-label taurine trial, were offered enrollment in this biomarker study. All studies were performed at the National Institutes of Health from June 2012 through March 2013. Subjects were eligible based on a diagnosis of SSADH deficiency by 4-OH-butyric aciduria and enzymatic or genotypic identification. Participants used GNC™ brand taurine supplements in

tablet form and were titrated weekly from 50 mg/kg/day to a target dose of 200 mg/kg/day oral maximum of 10 g/day. Subjects were studied on and off taurine, with cognitive testing, CSF taurine and GABA measurements, and transcranial magnetic stimulation (TMS). The protocol provided for a 3-month treatment period and 3-month washout before repeat testing.

Cognitive Testing

Neuropsychological tests included the Wechsler Nonverbal Scale of Ability or the Wechsler Adult Intelligence Scale-III selected subtests and the *Neuropsychological Assessment Battery: Language Module*. Areas assessed with the Wechsler scales included nonverbal reasoning using pattern completion, a digit-symbol substitution for processing speed, and spatial span administered as a nonverbal test of attention, similar to digit repetition. Both forward and backward spans were assessed. A test of sequential reasoning was also included; using “story pictures” the subject was asked to arrange the pictures in logical order. Verbal abilities were further assessed with parts of the *Neuropsychological Assessment Battery: Language Module* through confrontation naming using large photographs.

CSF

Lumbar puncture was attempted during both visits for measurement of routine studies (cell count and differential, protein, glucose) in addition to taurine and GABA levels. Lumbar puncture was performed with local anesthetic only. The fluid designated for special metabolites was placed immediately in dry ice and then stored in a freezer. Samples were deep-frozen at minus 80 centigrade until analysis. GABA was then quantified by the method of Kok et al. (1993) using electron-capture negative-ion mass fragmentography and isotopically labeled GABA (13C/N15).

TMS

TMS was delivered through a round coil (90 mm diameter) connected to two Magstim 200² magnetic stimulators via a Bistim module (Magstim, Dyfed, UK). The coil was placed over the contralateral motor cortex at the site, and in the orientation, that consistently produced the maximum motor-evoked potential (MEP) amplitude from the right first dorsal interosseous (FDI) muscle.

Subjects were seated in a comfortable chair with their hands resting on a pillow. Electrodes were applied to the skin over the right FDI in a belly-tendon montage with the reference electrode placed at least 4 cm distal to the active electrode and a ground electrode positioned over the dorsum of the hand. The electromyogram (EMG) signal

was amplified (Coulbourn Isolated Bioamplifier, model V75-04), band-pass filtered (90 Hz to 1 kHz), digitized (analog/digital rate 40 kHz), and recorded (Signal version 4.05, Cambridge Electronics, UK) for offline analysis. The EMG was monitored continuously for relaxation by visual inspection. The resting motor threshold (MT) was determined by increasing stimulus intensity in increments of 5 % of maximum output until a MEP was recorded and then adjusting by 1% increments to the lowest stimulator output required to produce MEPs of at least 50 μ V on five out of ten consecutive trials.

MEP recruitment curve (RC), cortical silent period (CSP), short- and long-interval intracortical inhibition (SICI and LICI), and intracortical facilitation (ICF) were measured. Subjects were instructed to rest during the RC and paired pulse paradigms and to sustain a contraction of the FDI by pinching the thumb and first finger during CSP determination. Individual trials were repeated or later excluded if muscle activity was apparent in the 100 ms before stimulation in the RC and paired pulse paradigms or if EMG amplitude dropped below baseline, determined visually, in the 100 ms prior to stimulation for CSP. For RC determination, five MEPs were recorded at each of eight percentages of the MT in the following order: 90, 130, 100, 140, 110, 150, 120, and 160%. The CSP was measured visually from the end of stimulus artifact to the first return of sustained EMG activity for ten trials at 110, 120, 130, and 140 % MT. For SICI and ICF measurements, we set the conditioning stimulus at 70 % and the test stimulus at 120 %, of MT. Interstimulus intervals were 2 and 10 ms. For LICI, we used 120 % of MT for both stimuli with an interstimulus interval of 100 ms. We used the mean MEP to the conditioning stimulus in the LICI experiment as the control MEP. ICI and ICF were determined by the ratio of the mean conditioned MEP to this control. We delivered and averaged ten trials for each measurement.

Statistical analysis was performed with SPSS 22 (IBM), using paired *t*-tests or repeated measures ANOVA for normally distributed continuous variables or nonparametric

tests (related samples Wilcoxon signed-rank test or Spearman's correlation). A *p* value of <0.05 was considered significant.

Both the NINDS and CNMC institutional review boards approved this protocol. Written informed consent was obtained from all parents or guardians of subjects participating in the study.

Results

Results: Seven subjects were consented and enrolled in the NIH. Mean age was 20 years at enrollment (range 12–33) and 2/7 (29 %) were female. One subject was already taking taurine and completed the “on” assessment first. All subjects were titrated to 10 g daily, the maximum dose based on hypersomnolence noted on higher doses as reported in the open-label trial (Pearl et al. 2014). No adverse events were reported during TMS. One study patient had a new-onset seizure associated with stress, sleep deprivation, and diphenhydramine administration. Six subjects successfully completed TMS. One patient had been treated chronically with carbamazepine for epilepsy but had no seizures for several years prior to enrollment. We excluded one subject from the TMS analysis because we were unable to produce MEPs at the baseline assessment.

The TMS results are shown in Table 1. Treatment-related decreases in the CSP at 140 % MT and SICI both reached significance ($p < 0.05$) (Figs. 1 and 2). Baseline EMG activity was no different on or off taurine for each of the paired pulse stimuli ($p = 0.249, 0.211$, and 0.469 for SICI, ICF, and LICI, respectively). There was no significant main effect of taurine on RC, $F(1, 4) = 3.34$, $p = 0.142$, or CSP, $F(1, 5) = 1.361$, $p = 0.296$.

Baseline mean full-scale IQ, on the appropriate Wechsler scale for age, was 44.1 (range 34–55) and 3.6 SD below the population mean. There was no significant relationship between baseline IQ and MT, SICI, ICF, LICI, RC slope, or CSP at 140% MT. Of six individuals who returned at

Table 1 TMS results on and off taurine with corresponding *p* values

	“Off” mean $\pm$ SD	“On” mean $\pm$ SD	<i>P</i> value
RC slope	0.028 $\pm$ 0.015	0.022 $\pm$ 0.006	0.40
SICI	69 % $\pm$ 26	159 % $\pm$ 93	< 0.05
ICF	129 % $\pm$ 27	141 % $\pm$ 72 %	0.917
LICI	96 % $\pm$ 107	93 % $\pm$ 98	0.753
CSP at 140 % MT (ms)	128 $\pm$ 50	96 $\pm$ 48	< 0.05
MT (motor threshold)	53.67 % $\pm$ 11	55.17 % $\pm$ 12	0.586

SICI, ICF, and LICI values are expressed as a percent of the baseline conditioning MEP determined at the same stimulus intensity, 120% MT

Fig. 1 Box plot (with 25–75 % quartiles, range, and outliers) of individual cortical silent period (CSP) measures (expressed in seconds) at different stimulus intensities off and on taurine; data

combined from all subjects. Taurine treatment was associated with decreased cortical silent period values at the 140% MT ($p < 0.05$)

Fig. 2 Mean SICI (short-interval intracortical inhibition), expressed as percent of baseline MEP (motor-evoked potential), off and on taurine for each subject, showing a treatment-related decrease in inhibition ($p < 0.05$)

6-month follow-up, five completed testing (3M/2F) on therapy; average FSIQ = 43.4 (range 33–51; nonsignificant). Similarly, there was no change in confrontation naming, which was completed in four subjects; the average confrontation naming score off taurine was 22 (range

19–32) and on taurine was 20 (range 19–24). Results of CSF biomarkers ($n = 4$ subjects) are displayed in Table 2, demonstrating no change in CSF free or total GABA levels but a significant increase in CSF taurine, indicating that it does cross the blood–brain barrier.

Table 2 CSF taurine, free GABA, and total GABA levels on and off taurine, with corresponding *p* values

Measure (and ref range)	“Off” mean $\pm$ SEM	“On” mean $\pm$ SEM	<i>P</i> value (on vs. off)
Taurine (not established)	9 $\pm$ 1 μ M	26 $\pm$ 6 μ M	<0.05
Free GABA (32–170 nM)	394 $\pm$ 88 nM	403 $\pm$ 62	NS
Total GABA (3.3–12.1 mM)	14.3 $\pm$ 1 mM	14.9 $\pm$ 2.4	NS

Discussion

This study reports results of a clinical trial of taurine supplementation in SSADH deficiency along with biomarker data utilizing transcranial magnetic stimulation, CSF metabolites, and neuropsychological data. This is the first published report of formal IQ testing in this disorder. Our baseline (off taurine) measures agree with prior data in patients with SSADH deficiency (Reis et al. 2012), demonstrating a low recruitment curve slope, shortened cortical silent period, and markedly reduced long-interval intracortical inhibition with relatively preserved short-interval intracortical inhibition and intracortical facilitation. Furthermore, we found a shift from inhibition to facilitation in the short-interval paired pulse paradigm and a reduction in the CSP with taurine, implying a shift in the balance of cortical regulation toward greater excitability. Taurine was tolerated at high doses (10 g/day). Oral administration results in significant elevations in CSF taurine without significant changes in free or total GABA concentrations.

Taurine is an aminosulfonic acid, sold as a dietary supplement, and has neuromodulatory, osmoregulatory, and tropic roles. It may also serve a neuroprotective function, preventing glutamate-induced neuronal excitotoxicity (Chen et al. 2001). Taurine has shown benefit in the SSADH-deficient mouse model (Gupta et al. 2002).

Taurine induces chloride influx through GABA(A) receptors (Belluzzi et al. 2004), specific taurine receptors (Okamoto et al. 1983), and glycine receptors (Han et al. 2001) and may also activate metabotropic GABA(B) receptors to a lesser extent (Belluzzi et al. 2004). Furthermore, it directly attenuates NMDA receptors through multiple mechanisms, specifically by reducing affinity for glycine and reducing peak current without changing steady-state current through the NMDA receptor (Chan et al. 2014). SICI is thought to be mediated by GABA(A) receptors (Ilic et al. 2002), while GABA(B) receptor activity produces LICI (McDonnell et al. 2006). Therefore, we hypothesized that taurine would increase both short- and long-interval intracortical inhibitions. Our results indicate that taurine may have opposite effects on these phenomena.

The unexpected loss of SICI may be partially understood through taurine's action as a weak agonist at GABA(A) receptors. Taurine, at high doses, would interfere with

synaptically released GABA, resulting in disinhibition of GABAergic transmission. Alternatively, chronic administration of taurine may further downregulate GABA receptors, as shown previously. In addition to reflecting reduced inhibition, the shift to facilitation exhibited by most of our subjects could also result from potentiation of excitatory mechanisms. Facilitation may occur at short interstimulus intervals when the intensity of the conditioning stimulus is increased (Ilic et al. 2002), and SICI probably represents the net effect of facilitatory and inhibitory influences. In general, while TMS is a noninvasive means of providing information about neurotransmission, there is surely some overlap in what networks and neurotransmitters contribute to a given measure.

Taurine administration was associated with a reduction in the CSP at only the highest stimulus intensity tested (140% MT), possibly indicating disproportionate antagonism of GABA(B) (relative to GABA(A)) receptors by taurine. CSP duration increases with intensity (Inghilleri et al. 1993), and while it is believed to reflect largely GABA(B) receptor function, GABA(A) receptor activation may contribute at lower stimulus intensities. Evidence from invasive experiments in animals (Mody et al. 1994) shows that GABA(A)-mediated inhibition can be evoked at lower stimulation thresholds than that produced by GABA(B) receptor activation. Moreover, lorazepam, which enhances the activity of GABA(A) receptors, has varying effects on the CSP at different stimulus intensities. It is therefore important to test a range of stimulus intensities when evaluating an intervention's effects on the CSP. Lorazepam, which potentiates GABA(A) receptor function, actually decreases CSP at higher stimulus intensities, perhaps due to selective inhibition of inhibitory interneurons in the motor cortex (Kimiskidis et al. 2006).

Other TMS measures did not reveal any significant changes with taurine administration. However, low patient recruitment rendered this study insufficiently powered to detect a significant change. MT, RC, and ICF are measures of excitability, reflecting chiefly the excitability of cortical interneurons, which is, in turn, a function of their excitatory input. LICI, like CSP, is thought to be determined mainly by GABA(B) receptor function (McDonnell et al. 2006). The lack of change in LICI would appear to contradict a decrease in CSP at the highest stimulus intensity, given that

both indicate GABA(B) receptor function. However, taurine's effects on the CSP were only seen at the highest stimulus intensity, 20% higher than the conditioning stimulus delivered during LICI.

We previously reported a lack of significant change in adaptive behavior in a group of 25 patients with SSADH deficiency using taurine in an open-label trial. The current study recruited a subset of the original cohort to study biomarkers selected to provide information about effects of GABAergic activity related to taurine intervention and is also the first systematic analysis of this patient population with neuropsychological testing. The mean score on the Wechsler scales is 100 ± 15 ; our average nonverbal IQ score of 43.5 (range 33–55) is in the extremely low range and indicative of moderate intellectual impairment. Verbal tests yielded similar findings. Confrontation naming is a normed test with a mean of 50 ± 10 . Our average naming score of 22 is in the impaired range and is indicative of limited recognition naming capacity. Following directions was also assessed by asking subjects to identify colors and simple shapes and then follow one-, two-, and three-step directions using those figures. All scores were below the first percentile. These results are consistent with the results of the Wechsler tests of ability and indicate that both nonverbal and verbal abilities are in the moderately impaired range. There was no significant change on or off taurine therapy.

Taurine appears effective in the mouse model of SSADH deficiency when administered from birth (Gupta et al. 2002). Early therapy may be the key – a “critical period” during which taurine or other interventions might be beneficial. The brain changes rapidly during early development; GABA receptor function shifts from depolarizing to hyperpolarizing shortly after birth (Cherubini et al. 1991). Affinity of taurine for glycine receptors drops after the neonatal period in the rat (Tang et al. 2008). The use-dependent downregulation of GABA(A) and GABA(B) receptors occurs in the first few weeks of life in the SSADH-deficient mouse (Buzzi et al. 2006; Wu et al. 2006), and metabolites are already elevated in newborn mice (Jansen et al. 2008). Perhaps earlier intervention would yield significant changes in cognition and behavior.

Oral taurine, administered chronically in patients with SSADH deficiency, produces decreased cortical inhibition as measured by TMS. This finding parallels the lack of apparent cognitive or clinical improvement.

Take-Home Message

Taurine therapy in succinic semialdehyde dehydrogenase deficiency, a disorder known to impair GABAergic neurotransmission, yields no improvement in cognitive outcomes

and decreases cortical inhibition as measured by transcranial magnetic stimulation.

Compliance with Ethics Guidelines

The trial was funded by The National Institute of Neurological Disorders and Stroke Division of Intramural Research and NIH R01 HD58553.

Dr. Schreiber, Wiggs, Wassermann, and Theodore and Mrs. Dustin performed this research as part of their employment with the National Institutes of Health.

Otherwise, John M. Schreiber, Phillip L. Pearl, Irene Dustin, Edythe Wiggs, Emily Barrios, Eric M. Wassermann, K. Michael Gibson, and William H. Theodore declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from all parents or guardians of subjects participating in the study. Proof that informed consent was obtained is available upon request.

John Schreiber, M.D., contributed to study design, data collection, statistical analysis, and manuscript preparation.

Phillip L. Pearl, M.D., contributed to study design and manuscript preparation.

Irene Dustin contributed to study design and manuscript review.

Edythe Wiggs, Ph.D., contributed to study design, data collection, and manuscript review.

Emily Barrios contributed to statistical analysis and manuscript review.

Eric M. Wassermann, M.D., contributed to study design and manuscript review.

K. Michael Gibson, Ph.D., contributed to study design, CSF analysis, and manuscript review.

William H. Theodore, M.D., contributed to study design and manuscript review.

References

- Belluzzi O, Puopolo M, Benedusi M, Kratskin I (2004) Selective neuroinhibitory effects of taurine in slices of rat main olfactory bulb. *Neuroscience* 124:929–944
- Bidri M, Choay P (2003) Taurine: a particular aminoacid with multiple functions. *Ann Pharm Fr* 61:385–391
- Buzzi A, Wu Y, Frantseva MV et al (2006) Succinic semialdehyde dehydrogenase deficiency: GABAB receptor-mediated function. *Brain Res* 1090:15–22
- Chan CY, Sun HS, Shah SM, Agovic MS, Friedman E, Banerjee SP (2014) Modes of direct modulation by taurine of the glutamate NMDA receptor in rat cortex. *Eur J Pharmacol* 728:167–175

- Chen WQ, Jin H, Nguyen M et al (2001) Role of taurine in regulation of intracellular calcium level and neuroprotective function in cultured neurons. *J Neurosci Res* 66:612–619
- Cherubini E, Gaiarsa JL, Ben-Ari Y (1991) GABA: an excitatory transmitter in early postnatal life. *Trends Neurosci* 14:515–519
- Gupta M, Greven R, Jansen EE et al (2002) Therapeutic intervention in mice deficient for succinate semialdehyde dehydrogenase (gamma-hydroxybutyric aciduria). *J Pharmacol Exp Ther* 302: 180–187
- Han NL, Haddrill JL, Lynch JW (2001) Characterization of a glycine receptor domain that controls the binding and gating mechanisms of the beta-amino acid agonist, taurine. *J Neurochem* 79:636–647
- Ilic TV, Meintzschel F, Cleff U, Ruge D, Kessler KR, Ziemann U (2002) Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. *J Physiol* 545:153–167
- Inghilleri M, Berardelli A, Cruccu G, Manfredi M (1993) Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. *J Physiol* 466:521–534
- Jansen EE, Struys E, Jakobs C, Hager E, Snead OC, Gibson KM (2008) Neurotransmitter alterations in embryonic succinate semialdehyde dehydrogenase (SSADH) deficiency suggest a heightened excitatory state during development. *BMC Dev Biol* 8:112
- Junyent F, Utrera J, Romero R et al (2009) Prevention of epilepsy by taurine treatments in mice experimental model. *J Neurosci Res* 87:1500–1508
- Kimiskidis VK, Papagiannopoulos S, Kazis DA et al (2006) Lorazepam-induced effects on silent period and corticomotor excitability. *Exp Brain Res* 173:603–611
- Kok RM, Howells DW, van den Heuvel CC, Guerand WS, Thompson GN, Jakobs C (1993) Stable isotope dilution analysis of GABA in CSF using simple solvent extraction and electron-capture negative-ion mass fragmentography. *J Inher Metab Dis* 16: 508–512
- McDonnell MN, Orekhov Y, Ziemann U (2006) The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. *Exp Brain Res* 173:86–93
- Mody I, De Koninck Y, Otis TS, Soltesz I (1994) Bridging the cleft at GABA synapses in the brain. *Trends Neurosci* 17:517–525
- Okamoto K, Kimura H, Sakai Y (1983) Evidence for taurine as an inhibitory neurotransmitter in cerebellar stellate interneurons: selective antagonism by TAG (6-aminomethyl-3-methyl-4H,1,2,4-benzothiadiazine-1,1-dioxide). *Brain Res* 265:163–168
- Pearl PL, Gibson KM, Acosta MT et al (2003a) Clinical spectrum of succinic semialdehyde dehydrogenase deficiency. *Neurology* 60: 1413–1417
- Pearl PL, Novotny EJ, Acosta MT, Jakobs C, Gibson KM (2003b) Succinic semialdehyde dehydrogenase deficiency in children and adults. *Ann Neurol* 54(Suppl 6):S73–S80
- Pearl PL, Gibson KM, Quezado Z et al (2009) Decreased GABA-A binding on FMZ-PET in succinic semialdehyde dehydrogenase deficiency. *Neurology* 73:423–429
- Pearl PL, Schreiber J, Theodore WH et al (2014) Taurine trial in succinic semialdehyde dehydrogenase deficiency and elevated CNS GABA. *Neurology* 82:940–944
- Reis J, Cohen LG, Pearl PL et al (2012) GABAB-ergic motor cortex dysfunction in SSADH deficiency. *Neurology* 79:47–54
- Saronwala A, Tournay A, Gargus J (2008) Taurine treatment of succinate semialdehyde dehydrogenase (SSADH) deficiency reverses MRI-documented globus lesions and clinical syndrome. Conference Taurine treatment of succinate semialdehyde dehydrogenase (SSADH) deficiency reverses MRI-documented globus lesions and clinical syndrome., Phoenix AZ, 2008, 103.
- Tang ZQ, Lu YG, Chen L (2008) Developmental stability of taurine's activation on glycine receptors in cultured neurons of rat auditory cortex. *Neurosci Lett* 430:54–59
- Wu Y, Buzzi A, Frantseva M et al (2006) Status epilepticus in mice deficient for succinate semialdehyde dehydrogenase: GABAA receptor-mediated mechanisms. *Ann Neurol* 59:42–52