REVIEW

Taurine and epilepsy

Simo S. Oja\textsuperscript{a,b,*}, Pirjo Saransaari\textsuperscript{b}

\textsuperscript{a} Department of Paediatrics, Tampere University Hospital, Finland
\textsuperscript{b} Medical School, University of Tampere, Finland

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Summary Dysfunction of excitatory and inhibitory neurotransmitters or neuromodulators is thought to underlie epileptic symptoms. Taurine, 2-aminoethanesulfonate, is a ubiquitous free amino acid abounding in the brain of humans and most animal species. It hyperpolarizes neurons and inhibits their firing. It may be a participating factor in certain subpopulations of epilepsy patients but its deficiency is not a universal prerequisite for seizures. Here, the participation of taurine in animal seizure models and human epilepsy patients is reviewed.

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Introduction

An imbalance between the actions of excitatory and inhibitory neurotransmitters is believed to be one possible pathomechanism underlying epileptic symptoms. Seizures and epileptogenesis may be due to either overactivation of excitatory or diminished activity of inhibitory mechanisms.
Experimental to partially Autopsy Lombardini, agent acids epilepsy but in primary The pennicillin...inhibtion of firing of neurons (Saransaari and Oja, 2008). The concentrations of the above amino acids may be altered in epilepsy (Wilson et al., 1996; Sejima et al., 1997). An elevation in glutamate and GABA levels immediately after fits of seizures has been found in the rat hippocampus (Lothman et al., 1987; Ueda and Tsuru, 1995). However, the relationship between changes in the local concentration of amino acids in different brain structures and seizures is not well recognized (Szyndler et al., 2008).

Taurine in epileptic brain

Animal studies

A decrement in the concentration of taurine in the brain could increase the overall excitability of neuronal populations and thus contribute to the initiation of seizures. As reviewed earlier by the present authors (Oja and Kontro, 1983a,b), in early studies the total tissue taurine concentration was indeed found to be decreased in the primary epileptic foci in different animal epileptic models (van Gelder, 1972; Koyama, 1972; Craig and Hartman, 1973; Carruthers-Jones and van Gelder, 1978; Emson, 1978) but not consistently (Hansen et al., 1973; Frigyesi and Lombardini, 1979; Iwata et al., 1979; Battistin et al., 1979; van Gelder et al., 1980). In secondary foci the decrease in taurine was less pronounced (Joseph and Emson, 1976). Autopsy or biopsy samples from human epileptic brains have similarly yielded strikingly discrepant data on taurine concentrations (van Gelder et al., 1972; Perry et al., 1975; van Gelder, 1976). The involvement of taurine in the epileptogenesis thus remained unsettled, though taurine was the only amino acid to show a significant decrement in experimental epilepsy induced by topical administration of penicillin or cobalt in the cat cerebral cortex (Mutani et al., 1977). Furthermore, a deficit in taurine also caused prolongation of seizure activity and it was therefore assumed that the ensuing increase in overall excitability could contribute to the initiation of seizures (Oja and Kontro, 1983a). The extracellular taurine levels were increased markedly in the rat piriform cortex, an area highly susceptible to seizure-induced neuropathology, reaching two- and fourfold baseline levels during the second hour of soman- and kainate-induced seizures, respectively (Wade et al., 1987).

In more recent investigations it has emerged that concentration changes in neurotransmitter levels in the epileptic brain are more complex and variable (Oja and Saransaari, 2007). The phenomenon known as kindling, initially introduced by Goddard (1967), induces seizures which are widely accepted as an animal model of temporal lobe epilepsy (Löschler, 1997). In kindling repeated subthreshold brain stimulation (electrical or chemical) leads to tonic and clonic seizures. Pentylenetrazole has frequently been used to evoke seizures in such animal models. Pentylenetrazole kindling in rats has increased taurine levels in the initial phases of seizures in the entorhinal cortex and subsequently in the amygdala, nucleus accumbens and piriform cortex, concomitant with increases in glutamate in the same structures (Maciejak et al., 2010). During the interictal periods in kainate-induced epilepsy in cats the taurine content in the cerebrospinal fluid is not significantly altered (Griffith et al., 1991). In contrast to the assumption that a deficit in brain taurine could predispose animals to epileptic seizures, in genetically epilepsy-prone rats (Lasley, 1991) and in epileptic El mice (Hiramatsu et al., 1990) the brain taurine contents are higher than in control rats and mice. However, K⁺ depolarization evokes less inhibitory taurine and GABA and excitatory glutamate and aspartate release in epilepsy-prone rats than in controls in the substantia nigra, which is thought to be involved in seizure generalization (Doretto et al., 1994). Also in rats in which seizures were induced by pilocarpine the taurine content increased in the cerebral cortices together with excitatory glutamate and aspartate (Radwan et al., 2009). In penicillin-induced seizures in rats, the extracellular level of taurine has increased significantly in the hippocampus (Shen and Lai, 2002). However, the concentrations of taurine measured from brain tissue predominantly reflect intracellular taurine, since in the extracellular spaces the concentrations are 300–600-fold less in different brain structures (Oja and Piha, 1966; Kontro et al., 1980; Molchanova et al., 2004). So far, it is not known whether the intracellular or extracellular concentrations are more influential in the regulation of seizure activity.

Pentylenetrazole kindling has significantly and sustainably increased the extracellular concentration of glutamate in the rat frontal cortex, and the convulsive dose of pentylenetrazole has reduced the taurine concentration, whereas no significant changes have occurred in taurine in the kindled rats (Li et al., 2000). In contrast to the abovementioned studies, Wilson et al. (1996) reported that bilateral injections of kainate into the rat hippocampus induced no significant changes in extracellular glutamate and taurine, but in the hippocampus of epilepsy patients the concentrations of both increased during seizures. In mice exposed to hyperbaric oxygen, the taurine levels were increased in the cerebral cortex and brain stem in animals which did not convulse, while in those which convulsed no changes were seen (Mialon et al., 1995). On the other hand, pentylenetrazole administration has been found to increase taurine concentrations in the rat hippocampus and parietotemporal cortex (Bikjdaouene et al., 2003). When quinolinic acid was unilaterally injected into the hippocampus, taurine was elevated prior to the onset of electrographic seizures but this did not occur in the contralateral uninjected side of the hippocampus, where seizure activity was equally severe (Vezzani et al., 1985). The authors interpreted this finding to indicate that the increase in extracellular taurine may reflect a selective tissue response to the neurotoxic rather than the convulsant effect of quinolinic acid.

Effects of antiepileptic drugs

The effects of antiepileptic drugs on the taurine levels in experimental animals have been markedly divergent. For instance, chronic lamotrigine treatment increases the cerebral taurine levels in rats (Hassel et al., 2001),

(Dichter and Ayala, 1987). Glutamate, GABA, and glycine thus apparently play essential roles, but aspartate and taurine are also likely to be involved (Meldrum et al., 1999; Morimoto et al., 2005; Baran, 2006). Taurine is an inhibitory agent in the brain, causing hyperpolarization and inhibition of firing of neurons (Saransaari and Oja, 2008). The concentrations of the above amino acids may be altered in epilepsy (Wilson et al., 1996; Sejima et al., 1997). An elevation in glutamate and GABA levels immediately after fits of seizures has been found in the rat hippocampus (Lothman et al., 1987; Ueda and Tsuru, 1995). However, the relationship between changes in the local concentration of amino acids in different brain structures and seizures is not well recognized (Szyndler et al., 2008).
while the antiepileptic drug levetiracetam significantly reduces extracellular taurine in the rat hippocampus and frontal cortex (Tong and Patsalos, 2001). In acute experiments lamotrigine did not influence the basal or K+-enhanced extracellular levels of taurine in freely moving rats, whereas the veratridine-evoked release was markedly reduced. In contrast, chronic, constant administration of lamotrigine increased the taurine content in the hippocampus (Ahmad et al., 2004). The effects of lamotrigine, carbamazepine and phenytoin on the extracellular levels of taurine were markedly different, as also on the levels of other neuroactive amino acids (Ahmad et al., 2005a,b).

Epilepsy patients

In human patients with intractable epilepsy alterations in extracellular taurine in epileptic foci have been relatively minor during interictal periods (Ronne-Engström et al., 1992) and during seizures (Carlson et al., 1992). In the human epileptogenic cortex the concentrations of taurine, glutamate and aspartate show a significant covariance (Hamberger et al., 1993). In patients with severe temporal lobe epilepsy the decrement in taurine content has been assumed to result from an abnormally high neuronal efflux of glutamate (Lleu et al., 1994). In keeping with this assumption glutamate and glutamate agonists have been shown to evoke taurine release in the mouse brain (Saransaari and Oja, 1991, 1994; Saransaari and Oja, 1997, 1999a, 2000). In newly diagnosed, untreated human patients with epilepsy, the cerebrospinal fluid taurine is reduced after tonic–clonic seizures (Rainesalo et al., 2004). Autopsy or biopsy samples from human epileptic brains have thus yielded strikingly discrepant data on taurine concentrations (van Gelder et al., 1972; Perry et al., 1975; van Gelder, 1976). The analyses on taurine concentrations in epileptic foci and in microdialysis effluents have likewise yielded inconclusive data.

Differences have been obtained between results from animal experiments and human epileptic patients. Animal models may not adequately reflect the pathophysiology of human epilepsy. Epilepsy patients may have suffered from seizures for years, whereas experiments with animal epilepsy models last only few weeks or days. In human epilepsy patients synaptic reorganization of the excitatory and inhibitory neural networks has occurred and also in many cases hippocampal sclerosis. Nor is it known whether the changes observed result from seizure activity itself or whether they are possibly the underlying reason for seizures. Taurine-deficiency models of epilepsy may thus apply only to certain types of seizure-generating conditions. The inference of Fariello et al. (1985) that taurine deficiency is neither a necessary, nor a sufficient or universal prerequisite for seizures in animals and epilepsy patients is still true. However, taurine may be a participating factor underlying epileptic symptoms in certain subpopulations of patients.

Effects of taurine on seizures

Animal experiments

The assumption that an imbalance of the excitatory and inhibitory mechanisms in the brain could be one of the reasons for epileptic syndromes has prompted tests on the effects of taurine on seizures in animal models and treatment of some epilepsy patients with taurine. In 1970s about 20 reports were published of taurine having alleviated seizures in various animal models (e.g. Frigyesi and Lombardini, 1979; Barbeau, 1973; Barbeau et al., 1975; Izumi et al., 1975; Durelli et al., 1976, 1977; van Gelder et al., 1977). However, in a number of studies no effects were recorded (Joseph and Emson, 1976; Wada et al., 1975; Burnham et al., 1978; Ramabadran et al., 1980). In taurine-deficient and taurine-supplemented kittens results from cerebral cortical microdialysis did not either corroborate the conception of a role for endogenous taurine in the control of epileptiform discharge initiation and/or spread (Lehman, 1987). Reduction in brain taurine content by the transport inhibitor guanidinoethanesulfonate in mice has likewise not affected the convulsions evoked by maximal electroshocks (Izumi et al., 1985). However, the seizure threshold to excitatory 4-aminopyridine is lowered in taurine-deficient rats (Pasantes-Morales et al., 1987).

In more recent studies intravenous 0.95 μmol taurine has inhibited wet-dog shakes and hippocampal seizures induced by opioid peptides in rats (Izumi et al., 1987). The same treatment has also prevented wet-dog shakes produced by [D-Ala², Met⁵]enkephalinamide (Yoshida et al., 1986), intra-amygadaloid 500 nmol taurine seizures in amygadaloid-kindled rats (Uemura et al., 1991), and intracerebroventricular taurine 80–100 μg/mouse convulsions induced by hypoxia (Malcangio et al., 1989). Reduction in the brain concentration of taurine by the transport inhibitor guanidinoethanesulfonate has been reported to cause the loss of anticonvulsive potency of phenobarbital and phenytoin in mice (Goddard, 1967). However, supplementation of 1.5% taurine in drinking water for four weeks has failed to reduce the number or latency of partial or clonic seizures or wet dog shakes in a kainate model of epilepsy in rats (Eppler et al., 1999). In contrast, a taurine-deficient diet even decreased tonic–clonic and partial seizures. On the other hand, the epileptiform activity induced by removal of Mg²⁺ in combined rat entorhinal cortex-hippocampal slices has been markedly suppressed in media supplemented with taurine, being totally blocked at the 2-mM concentration (Kirchner et al., 2003). Taurine (43 mg/kg) has also been shown to exert a significant antiepileptic effect in kainate-induced seizures in mice when injected subcutaneously, whereas supplementation of 0.05% taurine in drinking water increased the susceptibility to them (El Idrissi et al., 2003). In a similar model intraperitoneal injections of 150 mg/kg of taurine preceding kainate administration have likewise reduced or even prevented the seizure activity (Junyent et al., 2009). In studies by a Chinese group taurine has been able to exert an antiepileptic effect in both penicillin- and kainate-induced seizures in rats. These taurine actions were accentuated by electroacupuncture, which was thought to enhance taurine release by upregulating the taurine transporter (Li et al., 2005; Jin et al., 2005; Yang et al., 2006).

Epilepsy patients

The early partial success of the attenuation of seizures in animal epilepsy models gave an impetus to clinical trials.
of human epilepsy treatment with taurine (Barbeau and Donaldson, 1973, 1974; Bergamini et al., 1974; Pennetta et al., 1977; Takahashi and Nakane, 1978; Mongioli, 1978; Mantovani and De Vivo, 1979; Airaksinen et al., 1980). In epilepsy patients the success has likewise been partial. For example, of nine patients with intractable epilepsy the seizures disappeared in five patients when they received orally 1.5–7.5 g taurine daily for two weeks (König et al., 1977). An effect was also reported in a 21-year-old girl with progressive myoclonus epilepsy (Rumpl et al., 1977). Abnormalities in the brain electrical activity have generally disappeared more slowly and less completely than the clinical symptoms (König et al., 1977; Rumpl et al., 1977). On the other hand, in only one study daily oral 375–8000 mg taurine failed to bring forth any improvement in six patients (Mongioli, 1978). Of ten patients with drug-resistant progressive myoclonus epilepsy, grand mal or secondary generalized epilepsy, only three showed marked improvement when given 300 mg/day of taurine for seven weeks in addition to the continued conventional antiepileptic medication (Airaksinen et al., 1980). Only in this study a group of 29 persons without epilepsy was used as control. The responses in the trials cited above have varied greatly from patients to patients; not all showed significant improvement despite comparable taurine dosage, which varied from trial to trial from 200 mg to 21 g/day. On average, about one third of patients (16–90%) have shown significant alleviation of seizures.

However, all above clinical trials are characterized by small numbers of patients, representing unselectively different types of epilepsies, almost always missing adequate control groups, variations in taurine doses and the continued other anticonvulsant medication. All these pitfalls hamper definite inferences as to the efficacy of taurine in human epilepsy. One cannot therefore conclude whether any specific type of epilepsy is more amenable to taurine treatment than others. Furthermore, the effects of taurine tend gradually to vanish if the treatment is continued for a few weeks.

Mechanisms of taurine action

It remains open by what mechanism(s) taurine could alleviate seizure susceptibility and why it is effective only in some cases. Taurine attenuates the release of γ-aminobutyric acid, the analog of L-glutamate, in mouse corticostriatal slices (Molchanova et al., 2006). Taurine can probably protect neurons from glutamate-induced neuronal excitotoxicity by lowering the intracellular level of free Ca2+ (El Idrissi and Trenkner, 1999; Chen et al., 2001). It has been suggested that taurine protects neurons against glutamate excitotoxicity by preventing glutamate-induced membrane depolarization, probably through its effect on opening of chloride channels (Oja et al., 1990) and, therefore, preventing the glutamate-induced increase in calcium influx and other downstream events (Wu et al., 2005). This is, however, only one plausible explanation and gives no indication why taurine is in some cases effective, in some cases ineffective or even worsens the seizures.

Taurine may have a role in establishing equilibrium between the excitatory and inhibitory processes in the brain (Maciejak et al., 2009). As a structural analog of the main inhibitory transmitter GABA, it preferentially interacts with GABA_A receptors in the brain (Malminen and Kontro, 1986), activating them but less effectively than GABA itself (del Olmo et al., 2000; Frosini et al., 2003). Of different GABA_A receptors, taurine has reported to act as strongest agonist at those which contain the β2 subunit enriched in the mammalian dentate gyrus, substantia nigra, cerebellar molecular layer, medial thalamic nuclei and hippocampal CA3 field (Bureau and Olsen, 1991). Taurine also binds to GABA_A and glycine receptors, though their affinities for taurine are generally not very pronounced in the adult brain (Saransaari and Oja, 2008). However, in the brain of newborn rats taurine is a potent agonist at glycine receptors (Flint et al., 1887). During development taurine’s receptor target undergoes a shift from glycine receptors to GABA_A receptors (Tang et al., 2008). The release of taurine from neurons may also reduce cell swelling and thus aid neurons to osmoregulate under excitotoxic conditions (Eppler et al., 1999).

The failure of taurine to protect against convulsions in some cases may result from its poor penetration into the brain (Oja et al., 1976). However, high taurine doses administered may also distort the amino acid balances in brain tissues and thus be adverse in respect of seizure prevention. Taurine is also excreted readily in urine, but there are subpopulations of people in which the excretion rates are different. This may signify that the transport of taurine, rather than the absolute taurine concentrations, may explain the efficacy of taurine administration in some epileptics but not in others (Goodman et al., 1980). It is a general belief that taurine is not harmful even at high doses. The body adapts itself to different amounts of taurine available. When the supply is abundant, the excretion in urine increases. This may undermine the vanishing efficacy of taurine upon prolonged medication. However, Iyadurai and Chung (2007) have suggested the possibility that excessive consumption of popular energy drinks fortified with taurine could cause seizures in some susceptible young individuals. In this context, we may also pay attention to findings that high doses of taurine in combination with ethanol are lethal in mice (Taranukhin et al., 2011). This is a clear warning sign to young people not to mix alcohol with taurine-containing energy drinks.

Antiepileptic taurine derivatives

The strong polar and lipophobic nature of the taurine molecule, which efficiently prevents its access from the blood into the brain, has been thought to underlie the partial failures encountered in epilepsy treatment. Substances which are less ionized and more lipophilic than taurine and nevertheless retain taurine-like inhibitory actions have been thought to be possibly valuable in the prevention of epileptic symptoms in man. In collaboration with the Finnish pharmacological industry we developed a series of lipophilic 2-acylaminoethanesulfonamides (Andersen et al., 1984). Of them, piperidino, benzamido, phthalimidio and phenylsucinylimido derivatives were active as anticonvulsants, whereas succinylimido, saccharinylimido and norbornendicarboxyimido compounds were not. The phthalimidooethanesulfonamides were subjected to extensive animal tests. Of them 2-phthalimidoethanesulfonamide and
its N-alkylated derivatives, methylamide, dimethylamide, ethylamide and isopropylamide were almost equipotent in pentyleneetetrazol seizure threshold and maximal electroshock tests in mice (Kontro et al., 1983; Lindén et al., 1983; Oja et al., 1983). The effective doses in the seizure prevention were 100–200 mg/kg in mice. The protective indexes for them, and the ratios of the effective anticonvulsant doses to those which interfered with motor coordination in the rotarod test, were in average 3–5 times more favorable than for valproate, diazepam and phenytoin.

2-Phthalimidoethanesulfonamide (MY-103) and 2-phthalimidoethanesulfon-N-isopropylamide (MY-117, taltrimide) were also found to be effective in similar tests on genetically seizure-susceptible rats and in guanidineethanesulfonate (taurine transport inhibitor)-induced convulsions in rats and mice, taltrimide being more potent in these tests (Huxtable and Nakagawa, 1985; Nakagawa and Huxtable, 1983). Both of these compounds interfere with the ligand binding to cerebral membranes and enhance taurine and GABA release from mouse cerebral cortical (Kontro and Oja, 1987) and hippocampal slices (Saransaari and Oja, 1999b). Taltrimide was also subjected to the phase I clinical trials for four weeks at doses up to 4 g/day in 27 epilepsy patients resistant to conventional drugs. It failed to have a positive effect. On the contrary, taltrimide exhibited a tendency to increase seizures, possibly because of the interference with the catabolism of phenytoin, the use of which was continued as the main anticonvulsant drug (Koivisto et al., 1986; Airaksinen et al., 1987).

The activities of 2-phthalimido derivatives of taurine are comparable to the respective glycine derivatives in the maximal electroshock seizure test in mice (Usifoh et al., 2001). Valproyltaurinamide, N-methylvalproyltaurinamide, N, N-dimethylvalproyltaurinamide and N-isopropylvalproyltaurinamide are likewise anticonvulsants in Frings audiogenic seizure susceptible mice (Isoherranen et al., 2003). Of them, N-methylvalproyltaurinamide has the highest anticonvulsant potential, equal to that of valproylglycinamide. Some other taurine derivatives have also been tested for their possible anticonvulsive effects, as reviewed by Gupta (2006). Of them, homotauryl derivatives and γ-aminobutytaurine have evinced some anticonvulsant activity in animal experiments.

Conclusions and future aspects

Changes in the levels of taurine may be a participating factor underlying epileptic symptoms in certain animal seizure models and subpopulations of epileptic patients. Taurine administration has alleviated seizures in a number of animal experiments but failed to do so in some other cases. On average, about one third of human patients have shown significant alleviation of seizures by taurine medication. Its efficacy tends to vanish with time, however, possibly because taurine does not readily penetrate into the brain and the body adapts to the increased taurine supply by enhancing taurine excretion into urine. Taurine derivatives have been tested as antiepileptic drugs, but so far none of them has been added to the arsenal of antiepileptic drugs in human patients. They may have some potential and the derivatives which penetrate more easily into the brain should be systematically studied in future. The potential source of them is not at all exhausted and waits for further exploration. There is no specific taurine antagonist available at present and this is a main reason why we do not know exactly how taurine works in the brain. This also hampers the development of novel taurinergic antiepileptic drugs.

References


