

# Neuroprotective effects of some newer and potential antiepileptic drugs

Stanisław J. Czuczwar<sup>1,2</sup>, Renata Ferenc<sup>2</sup>, Barbara Błaszczyk<sup>3,4</sup>, Kinga K. Borowicz<sup>2</sup>

<sup>1</sup> Department of Physiopathology, Institute of Agricultural Medicine, Lublin, Poland

<sup>2</sup> Department of Pathophysiology, Skubiszewski Medical University, Poland

<sup>3</sup> Department of Neurological Diseases, Institute of Medical Education, Kielce

<sup>4</sup> Department of Neurology, Neuropsychiatric Hospital, Kielce, Poland

**Abstract:** Experimental models of epilepsy or *status epilepticus* (SE) provide evidence that seizures result in diffuse brain damage. Other neurological conditions are also associated with neurodegeneration, for example, stroke, head injury and chronic neurodegenerative diseases. In this review, the neuroprotective effects of a number of newer or potential antiepileptic drugs (AEDs) are considered in general in models of experimental epilepsy and ischemia. Among newer AEDs, felbamate, gabapentin, tiagabine and topiramate proved to be neuroprotective agents against seizure, or ischemia-generated neuronal death. The same profile of activity was presented by a potential AED, talampanel. Vigabatrin and levetiracetam were effective against ischemia-induced neurodegeneration, while their effects in seizure models were less consistent. It may be assumed that the neuroprotective effects of AEDs in models of epilepsy or SE may prevent continuous progression of epileptogenesis, thus improving the condition of epileptic patients. However, this possible association may not be that clear. There are data indicating that in spite of clear-cut neuroprotection in models of SE, the subsequent occurrence of spontaneous seizure activity was not prevented. There is also no significant correlation between neuroprotection in experimental ischemia and clinical data. Neuroprotection afforded by AEDs is evident. However, it is not still clear whether this can have a clinically relevant potential. The available clinical data on brain ischemia and AEDs are not encouraging. So far, there are no clinical data whether the neuroprotective effects of AEDs in experimental models of epilepsy possess any impact on the severity of epilepsy. It is possible that AEDs will prove effective in some chronic neurodegenerative diseases.

**Key words:** antiepileptic drugs, neuroprotection, neurodegeneration

**Abbreviations:** AMPA –  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate, AEDs – antiepileptic drugs, FBM – felbamate, GBP – gabapentin, MES – maximal electroshock, NMDA – N-methyl-D-aspartate, KA-kainate, LEV – levetiracetam, PGB – pregabalin, PTZ – pentetrazol, SE – status epilepticus, TGB – tiagabine, TLP – talampanel, TPM – topiramate, VGB – vigabatrin

## INTRODUCTION

Despite the development of a number of newer antiepileptic drugs since the 1990s, about 30% of epileptic patients are not sufficiently treated with antiepileptic drugs (AEDs) [1]. However, treatment with AEDs begins following the onset of seizures, and the drugs are known to alleviate this main manifestation of epilepsy. In this context, they cure the symptom but not the cause of epilepsy. An initial brain insult (infection, febrile seizures, inflammation), sometimes even difficult to identify, may trigger a sequence of pathological events which eventually lead to the manifestation of seizures [2]. This long-lasting process, sometimes taking years – called epileptogenesis – remains untreated.

However, a relationship between initial brain insults, or seizures, and neurodegeneration has been sufficiently proved. For instance, Klitgaard et al. [3] have shown that even a short seizure episode, lasting less than 2 minutes, can induce neuronal cell loss. *Status epilepticus* (SE), which may last for

hours, is a devastating condition for neurons – many models of SE in rodents indicate diffuse brain lesions [4].

The degree to which excitotoxic neuronal damage occurs during SE is dependent on the presence and duration of electrographic seizure activity. Therefore, the most effective way to minimize neuronal damage is to stop seizures as soon as possible after their onset. A large proportion of SE-induced neuronal death is necrotic, but a small proportion of cells appears to die by programmed caspase-mediated mechanisms. Activation of ionotropic glutamate receptors, however, has been thought to play an integral role in the pathophysiology of SE-induced neuronal damage. Therefore, as Fisher et al. [5] have shown, it would be expected that glutamate antagonists would be effective in reducing the initiation and propagation of seizure-induced excitotoxicity and its associated neuropathology.

**Mechanisms leading to neurodegeneration.** Neurons may die through 2 independent processes: necrosis and apoptosis [6]. Necrosis is mainly dependent upon the excitotoxicity mediated by the major excitatory neurotransmitter – glutamate, which acts through 2 populations of receptors: ionotropic and metabotropic receptors [for review, see 7]. N-methyl-D-aspartate (NMDA) ionotropic receptors mediate the

Corresponding author: Prof. Stanisław J. Czuczwar, MD, PhD, Department of Pathophysiology, Skubiszewski Medical University, Jaczewskiego 8, 20-090 Lublin, Poland. E-mail: czuczwarj@yahoo.com

Received: 28 May 2007; accepted: 30 June 2007

influx of calcium and sodium ions into the neurons. Sodium currents are also mediated via the remaining 2 types of glutamate ionotropic receptors – for  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) and kainate (KA). Sodium ions are the first to enter the neurons, following glutamate-induced overexcitation, triggered by seizure activity [8]. An excess of intraneuronal sodium content results in water influx, eventually leading to neuronal swelling. This is an initial phase of neurodegeneration. In the second phase, increased calcium influx is associated with the activation of a number of catabolic enzymes (calpains and phospholipases) which destroy the neuronal cytoskeleton and produce microtubular dysfunction [9]. It seems that calcium ions play the most important role in the process of neurodegeneration via a necrotic route; the hippocampal granulae cells are relatively resistant to the glutamate-induced neurodegeneration [10]. This is evidently due to the high concentration of calbindin (a calcium binding protein) in these cells [10]. Glutamate-induced overexcitation evidently activates neuronal nitric oxide synthase, which leads to overproduction of nitric oxide, and consequently increased concentration of free radicals [11] which may further enhance neurodegeneration.

#### FELBAMATE (FBM)

FBM is an antiepileptic drug possessing a very broad anticonvulsant spectrum. Due to the possibility of induction of fatal adverse effects (bone marrow suppression), its current use has been drastically reduced [7]. FBM has been documented to block voltage-dependent sodium and calcium channels, as well as enhance GABA-ergic inhibition. This antiepileptic can also decrease glutamate-induced excitation via a glycine-sensitive site on the NMDA glutamate receptor [12].

**Neuroprotective activity.** There is broad evidence for the neuroprotective properties of FBM. FBM proved to be neuroprotective against CA1 traumatic neuronal injury at FBM serum concentrations similar to those reported in FBM monotherapy for seizures [7]. FBM administered after a hypoxic-ischemic insult, caused by bilateral carotid ligations in rat pups, has been proved effective in reducing cerebral infarction, and extremely effective in preventing delayed neuronal necrosis [13]. In a gerbil model of global ischemia, FBM administered *post hoc* is remarkably effective in preventing delayed apoptosis secondary to global ischemia, but in doses higher than those used for anticonvulsant treatment [13]. Also, FBM significantly protects cells in hippocampal slice cultures from death induced by oxygen/glucose deprivation [7].

#### GABAPENTIN (GBP)

Although GBP, as a cyclic, GABA analogue designed to enter the brain easily, was intended to yield GABA following its passage throughout the blood-brain barrier; however, this is rather not the case. So far, the drug has been proved to moderately increase brain GABA concentration, and its crucial mechanism of action related to blocking the alpha-2-delta subunit of voltage sensitive calcium channels [12].

The existing evidence points to GBP as an effective adjunctive drug against refractory partial seizures in adults and children [14].

**Neuroprotective activity.** There is one negative study indicating the ineffectiveness of the drug (up to 300 mM *in vitro*) to protect neurons against deprivation of oxygen or

glucose in the medium which, to a certain degree, imitates ischemia [15]. On the other hand, existing evidence points to clear-cut neuroprotective effects of GBP in a KA model of SE in rats: administration of GBP was started 24 h after termination of SE and continued for one month [16].

#### LEVETIRACETAM (LEV)

LEV is unique in that it does not interfere with practically any receptors for brain neurotransmitters, apart from the beta-carboline site of the benzodiazepine receptor [12]. There are data pointing to the blockade by LEV of the N calcium channel [12]. The main target of this drug is probably SV2A, the synaptic vesicle protein involved in exocytosis [17]. The exact nature of this interaction is far from being completely understood, but it is likely that LEV may affect the release of neurotransmitters via this mechanism. It is remarkable that a correlation exists between the potency of binding shared by LEV or its derivatives and their ability to control the tonic component of audiogenic seizures in mice [18]. This AED is effective against idiopathic generalized as well as against drug-resistant partial epilepsies [19, 20].

**Neuroprotective activity.** LEV has been documented to exert neuroprotective effects in a model of SE (self-sustaining SE) in rats [21]. However, the AED remained ineffective against pilocarpine-induced hippocampal damage [16]. There are reports that LEV may be neuroprotective in models of focal (but not global) ischemia [22].

#### PREGABALIN (PGB)

PGB, similar to GBP, potently binds to the alpha-2-delta subunit of voltage sensitive calcium channels, which leads to a considerable reduction of calcium influx into the neurons [12]. Interestingly, this AED is completely ineffective for all types of GABA receptors and does not interfere with either GABA release, uptake or metabolism [12]. In animal models of epilepsy, PGB inhibits MES-, PTZ-, sound-induced seizures, as well as amygdala-induced convulsions [23]. This AED is effective against partial seizures with (or without) secondary generalization [12].

**Neuroprotective activity.** In the lithium/pilocarpine model, chronic PGB significantly reduced neurodegeneration of the basal cortex, and retarded the development of subsequent spontaneous seizures [23].

#### TALAMPANEL (TLP)

This AED, undergoing intensive clinical trials, is actually a selective antagonist of AMPA/KA receptors [13]. To date, the data indicate that it is effective against refractory partial seizures [24].

**Neuroprotective activity.** The existing evidence points to its protection of rat neonatal striatal neurons against AMPA neurotoxicity [25]. TLP is also effective against experimental perinatal hypoxia/ischemia [26].

#### TIAGABINE (TGB)

TGB inhibits intraneuronal and intragial GABA uptake, thus increasing the concentration of this inhibitory neurotransmitter in the synaptic cleft [12]. This AED is especially recommended as an add-on therapy for drug-resistant partial epilepsies [14].

**Neuroprotective activity.** Perforant pathway stimulation model of *status SE* in unprotected animals evokes evident lesions to the CA1 and CA3 hippocampal pyramidal cells, and subsequent spatial memory deficits [7]. TGB has effectively alleviated the above-mentioned abnormalities, including behavioural memory deficit [7].

#### TOPIRAMATE (TPM)

TPM is an AED sharing a couple of important mechanisms of action. The drug reduces glutamate-mediated excitation by blocking AMPA/KA receptors and enhancing GABA<sub>A</sub>-mediated chloride currents. Apart from its receptor activities, TPM blocks voltage-dependent sodium and calcium channels. Finally, TPM increases potassium currents and may be regarded as a weak inhibitor of some carbonic anhydrase isosymes [12].

This AED possesses a very broad spectrum of activity against diverse seizure models, including MES, amygdala-kindling, audiogenic convulsions, and genetically determined spontaneous convulsions in rats [7]. However, it is considerably less active against chemically-induced seizures [7].

According to French *et al.* [14], TPM is clinically effective against generalized tonic-clonic convulsions, as well as partial epilepsies, including refractory convulsions. Interestingly, this AED may also be used in the form of monotherapy [12].

**Neuroprotective activity.** TPM has been found to effectively protect hippocampal neurons *in vivo* against death produced by SE obtained by prolonged electrical hippocampal stimulation in rats. The conventional AED, phenytoin, was completely ineffective in this respect [27]. Rigolout *et al.* [28] have studied brain neurodegeneration and subsequent epileptogenesis in rats exposed to lithium/pilocarpine-induced SE. TPM apparently provided a clear-cut neuroprotection in the hippocampus and in the ventral cortex when compared to animals not pretreated with this AED. Strikingly, the subsequent occurrence of spontaneous seizure activity was evident in both vehicle and the TPM-pretreated group.

Interesting data exists on the neuroprotection provided by TPM in conditions not associated with seizure activity. For instance, Follett *et al.* [29] have proved that TPM efficiently protected against hypoxic-ischemic injury to the white matter, evidently sparing oligodendrocytes. This has been positively correlated with an improved neurological outcome in that subsequent motor deficits in rats were significantly reduced [29].

#### VIGABATRIN (VGB)

VGB, similar to TGB, has one major mechanism of action related to the GABA-ergic system in that the AED produces an irreversible inhibition of GABA transaminase, thus leading to elevated GABA concentration in the synaptic cleft [12]. There are also suggestions that VGB may reduce the brain concentration of excitatory amino acids and increase the level of glycine in the brain [12].

The AED is effective against amygdala-kindled seizures in rats [30], sound- and KA-induced convulsions [12]. Clinically, it is especially recommended in West syndrome [31]. It is also effective against drug-resistant complex partial seizures. However, its clinical use has been complicated by reports on visual field constriction observed in patients receiving VGB therapy [12,18].

**Neuroprotective activity.** In the perforant path stimulation model of SE in rats, VGB has been documented to reduce the subsequent brain damage [9]. The AED has also been shown to exert a clear-cut neuroprotection in the hippocampus, following lithium/pilocarpine-induced SE [7]. VGB has been also found effective as a neuroprotectant in the pilocarpine model of SE, but failed to provide neuroprotection when electrostimulation of hippocampus was applied [16].

It is remarkable that VGB given chronically to rodents, evoked reduced myelin staining in the external capsule, as well as vacuolization of myelin and degeneration of glial cells in the white matter. However, these apparently negative effects have never been observed in primates [7].

The neuroprotective effects of AEDs are summarized in Table 1.

**Table 1** Neuroprotective properties of newer and potential antiepileptic drugs (AEDs)

AEDs	Neuroprotection in ischemia	Neuroprotection in experimental epilepsy
Felbamate	+	+
Gabapentin	NT*	+
Levetiracetam	+/-	+/-
Pregabalin	NT	+
Tiagabine	+	+
Topiramate	+	+
Vigabatrin	+	+/-
Talampanel (a potential AED)	+	+

+ consistent positive data; +/- inconsistent data; NT – not tested;

\* Not tested *in vivo*

Although, a number of AEDs have been proved to exert evident neuroprotective effects in models of experimental ischemia, there is no clinical support for this [32]. This may indicate that AEDs may not improve the therapy of ischemic patients.

Considering that even a single seizure has been shown to precipitate neuronal loss [3], the neuroprotective effects of AEDs in models of experimental epilepsy provide hope that this particular effect may have a clinically relevant potential. As reviewed above, some AEDs exert potent neuroprotective activity in models of severe SE, producing diffuse brain damage in untreated animals. It is noteworthy to underline that in mice with lesioned by intracerebroventricular KA hippocampi, the anticonvulsant activity of benzodiazepines and barbiturates is significantly reduced, both against electroconvulsions and PTZ-induced seizures [33, 34]. Therefore it is not unreasonable to assume that neurodegeneration may, in fact, reduce the protective potential of some AEDs. In this context, neuroprotection would be a valuable factor preventing the loss of therapeutic efficacy of at least some AEDs. If hippocampal lesion is associated with an impaired activity of benzodiazepines and barbiturates, lesions to other brain structures may negatively affect the protection offered by other AEDs. However, this intriguing possibility needs verification through experiments.

Another expectation with neuroprotection would be slowing down the process of epileptogenesis. However, a study by Brandt *et al.* [35] indicates that there may be no association between neuroprotection and epileptogenesis. They have documented that prevention by dizocilpine the hippocampal neurodegeneration caused by KA-induced SE in rats, had no

impact on the development of spontaneous seizure activity. In fact, the percentage of animals displaying spontaneous convulsions was not significantly different in the control (lesioned) and dizocilpine-treated (unlesioned) groups. Some data, however, indicate that neuroprotection may be positively correlated with cognitive performance [7].

One of the newer AEDs, zonisamide, improved motor functions in patients with Parkinson's disease when co-administered with levodopa [36]. Although this beneficial effect may be not directly associated with neuroprotection, the horizons for therapeutic targets of AEDs may be broadened. TLP has been evaluated, anyway, in a primate model of Parkinson's disease with very encouraging effects [37]. Another example is LEV, documented as improving the quality of the lives of patients with Huntington's chorea [38].

An additional important problem deserves special attention. Specifically, a number of AEDs (clonazepam, diazepam, phenobarbital, phenytoin, valproate, and VGB) have been proved to induce massive apoptosis when administered in anticonvulsant doses in young rodents [39]. Also, TPM has been tested as an apoptotic potential and it became evident that this AED induced apoptosis at doses several times higher, in the neurotoxic range [40]. This may indicate particular hazards when some AEDs are administered to children. To date, some newer AEDs have not been verified in this respect.

## CONCLUSIONS

Finally, although there are still more questions than actual answers in the field of neuroprotection provided by AEDs, this area of research may yield new efficient treatment strategies, also in conditions other than epilepsy, such as Alzheimer's disease, Parkinson's disease, or other neurodegenerative conditions as Huntington's chorea.

## REFERENCES

- Czuczwar SJ, Patsalos P: The new generation of GABA-enhancers. Potential in the treatment of epilepsy. *CNS Drugs* 2001, **15**, 339-350.
- Pitkanen A: New pharmacotherapy for epilepsy. *Drugs* 2004, **7**, 471-477.
- Klitgaard H, Pitkanen A: Antiepileptogenesis, neuroprotection, and disease modification in the treatment of epilepsy: focus on levetiracetam. *Epileptic Disord* 2003, **5**, 9-16.
- Turski WA, Czuczwar SJ, Kleinrok Z, Turski L: Cholinomimetics produce seizures and brain damage in rats. *Experientia* 1983, **39**, 1408-1411.
- Fisher A, Wang X, Cock HR, Thom M, Patsalos PN, Walker MC: Synergism between topiramate and budipine in refractory status epilepticus in the rat. *Epilepsia* 2004, **45**, 1300-1307.
- Vajda FJE: Neuroprotection and neurodegenerative disease. *J Clin Neurosci* 2002, **9**, 4-8.
- Trojnar MK, Malek R, Chrościńska M, Nowak S, Błaszczuk B, Czuczwar SJ: Neuroprotective effects of antiepileptic drugs. *Pol J Pharmacol* 2002, **54**, 557-566.
- Urbańska E, Czuczwar SJ, Kleinrok Z, Turski WA: Excitatory amino acids in epilepsy. *Restor Neurol Neurosci* 1998, **13**, 25-39.
- Pitkanen A: Treatment with antiepileptic drugs: possible neuroprotective effects. *Neurology* 1996, **47**, 12-16.
- Sloviter RS: Calcium-binding protein (calbindin-D28k) and parvalbumin immunocytochemistry: localization in the rat hippocampus with specific reference to the selective vulnerability of hippocampal neurons to seizure activity. *J Comp Neurol* 1989, **280**, 183-196.
- Bittigau P, Ikonomidou C: Glutamate in neurologic diseases. *J Child Neurol* 1997, **12**, 471-485.
- Czapiński P, Błaszczuk B, Czuczwar SJ: Mechanisms of action of antiepileptic drugs. *Curr Top Med Chem* 2005, **5**, 3-14.
- Bialer M, Johannessen JC, Kupferberg HJ, Levy RH, Loiseau P, Perucca E: Progress report on new antiepileptic drugs: a summary of the 6th Eilat Conference (EILAT VI). *Epilepsy Res* 2002, **51**, 31-71.
- French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Theodore WH, Bazil C, Stern J, Schachter SC, Bergen D, Hirtz D, Montouris GD, Nespeca M, Gidal B, Marks WJ Jr, Turk WR, Fischer JH, Bourgeois B, Wilner A, Faught RE Jr, Sachdeo RC, Beydoun A, Glauser TA: Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2004, **62**, 1261-1273.
- Rekling JC: Neuroprotective effects of anticonvulsants in rat hippocampal slice cultures exposed to oxygen/glucose deprivation. *Neurosci Lett* 2003, **335**, 167-170.
- Pitkanen A: Efficacy of current antiepileptics to prevent neurodegeneration in epilepsy models. *Epilepsy Res* 2002, **50**, 141-160.
- Lynch B, Lambeng N, Nocka K, Kensel-Hammes P, Bajjellieh SM, Matagne A, Fuks B: The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci* 2004, **101**, 9861-9866.
- Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Perucca E, Tomson T: Progress report on new antiepileptic drugs: a summary of the 7th Eilat Conference (EILAT VII). *Epilepsy Res* 2004, **61**, 1-48.
- Lagae L, Buyse G, Deconinck A, Ceulemans B: Effect of levetiracetam in refractory childhood epilepsy syndromes. *Eur J Pediatr Neurol* 2003, **7**, 123-128.
- Patsalos PN: Properties of antiepileptic drugs in the treatment of idiopathic generalized epilepsies. *Epilepsia* 2005, **46** (Suppl. 9), 140-148.
- Mazarati AM, Baldwin R, Klitgaard H, Matagne A, Wasterlain CG: Anticonvulsant effects of levetiracetam and levetiracetam-diazepam combinations in experimental status epilepticus. *Epilepsy Res* 2004, **58**, 167-174.
- Leker RR, Neufeld MY: Anti-epileptic drugs as possible neuroprotectants in cerebral ischemia. *Brain Res* 2003, **42**, 187-203.
- Ben-Menachem E: Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia* 2004, **45** (Suppl. 6), 13-18.
- Chappell AS, Sander JW, Brodie MJ, Chadwick D, Lledo A, Zhang D, Bjerke J, Kiesler GM, Arroyo S: A crossover, add-on trial of talampanel in patients with refractory partial seizures. *Neurology* 2002, **58**, 1680-1682.
- Vilagi I, Takacs J, Gulyas-Kovacs A, Banczerowski-Pelyhe I, Tarnawa I: Protective effect of the antiepileptic drug candidate talampanel against AMPA-induced striatal neurotoxicity in neonatal rats. *Brain Res Bull* 2002, **59**, 35-40.
- Lodge D, Bond A, O'Neill M, Hicks CA, Jones MG: Stereoselective effects of 2,3 benzodiazepines *in vivo*: Electrophysiology and neuroprotection studies. *Neuropharmacology* 1996, **35**, 1681-1688.
- Niebauer M, Gruenthal M: Topiramate reduces neuronal injury after experimental status epilepticus. *Brain Res* 1999, **837**, 263-269.
- Rigoulot MA, Koning E, Ferrandon A, Nehlig A: Neuroprotective properties of topiramate in the lithium-pilocarpine model of epilepsy. *J Pharmacol Exp Ther* 2004, **308**, 787-795.
- Follett PL, Deng W, Dai W, Talos D M, Massillon L J, Rosenberg PA, Volpe JJ, Jensen FE: Glutamate receptor-mediated oligodendrocyte toxicity in periventricular leukomalacia: A protective role for topiramate. *J Neurosci* 2004, **24**, 4412-4420.
- Schwabe K, Ebert E, Loscher W: Bilateral microinjections of vigabatrin in the central piriform cortex retard amygdala kindling in rats. *Neuroscience* 2004, **129**, 425-429.
- Mitchell WG, Shah NS: Vigabatrin for infantile spasms. *Pediatr Neurol* 2002, **27**, 161-164.
- Weinberger JM: Evolving therapeutic approaches to treating acute ischemic stroke. *J Neurol Sci* 2006, **249**, 101-109.
- Czuczwar SJ, Turski L, Kleinrok Z: Effects of some antiepileptic drugs in pentetrazol-induced convulsions in mice lesioned with kainic acid. *Epilepsia* 1981, **22**, 407-414.
- Czuczwar SJ, Turski L, Turski W, Kleinrok Z: Anticonvulsant action of phenobarbital, diazepam, carbamazepine, and diphenylhydantoin in the electroshock test in mice after lesion of hippocampal pyramidal cells with intracerebroventricular kainic acid. *Epilepsia* 1982, **23**, 377-382.
- Brandt C, Potschka H, Loscher W, Ebert U: N-methyl-D-aspartate receptor blockade after status epilepticus protects against limbic brain damage but not against epilepsy in the kainate model of temporal lobe epilepsy. *Neuroscience* 2003, **118**, 727-740.

36. Murata M, Haneqawa K, Kanazawa I: The Japan Zonisamide on PD study group: Zonisamide improves motor function in Parkinson disease: a randomized, double-blind study. *Neurology* 2007, **68**, 45-50.
37. Wu SS, Frucht SJ: Treatment of Parkinson's disease; what's on the horizon? *CNS Drugs* 2005, **19**, 723-743.
38. de Tommaso M, Di Fruscolo O, Sciruicchio V, Specchio N, Cormio C, De Caro MF, Livrea P: Efficacy of levetiracetam in Huntington's disease. *Clin Neuropharmacol* 2005, **28**, 280-284.
39. Bittigau T, Sifringer M, Ikonomidou C: Antiepileptic drugs and apoptosis in the developing brain. *Ann NY Acad Sci* 2003, **993**, 103-114.
40. Glier C, Dzierko M, Bittigau P, Jarosz B, Korobowicz E, Ikonomidou C: Therapeutic doses of topiramate are not toxic to the developing rat brain. *Exp Neurol* 2004, **187**, 403-409.