Neuroprotection possibilities in epileptic children

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Abstract

Purpose: The aim of this paper was to summarize of current knowledge about neuronal injuries during epileptogenesis process and possibilities of neuroprotection.

Results: Many of agents from a wide range of classes have been proposed to possess neuroprotective potential, but especially in experimental and preclinical conditions. Among the antiepileptic drugs topiramate (TPM) and levetiracetam (LEV) possess neuroprotective effects in experimental models of brain damage. Promising protection against cell loss display antioxidants and neurotrophins.

Conclusions: Important and difficult problem of neuroprotective therapy in childhood epilepsy require further experimental and clinical investigations.

Key words: neuroprotection, seizures, epilepsy, epileptogenesis.

Introduction

Epilepsy is one of the most common neurologic disorder, affecting approximately 0.8% of the population, especially it is frequent in children [1]. The immature brain differs from the adult brain in its susceptibility to seizures, seizures characteristics and responses to antiepileptic drugs [2]. Clinical experiences suggest the existence of relationship between brain maturation and susceptibility to seizures and epilepsy [3]. There are evidences of later-life epilepsy in cases of symptomatic seizures in the neonate period or complex and recurrent febrile seizures in childhood [4]. Patients with temporal lobe epilepsy (TLE) associated with mesial temporal sclerosis (MTS) have a reported increased incidence of previous neonatal or childhood febrile seizures [5,6]. There are hypotheses raise the possibility that childhood seizures that occur during a critical maturational period could alter brain development to increase the susceptibility to MTS and TLE [3].

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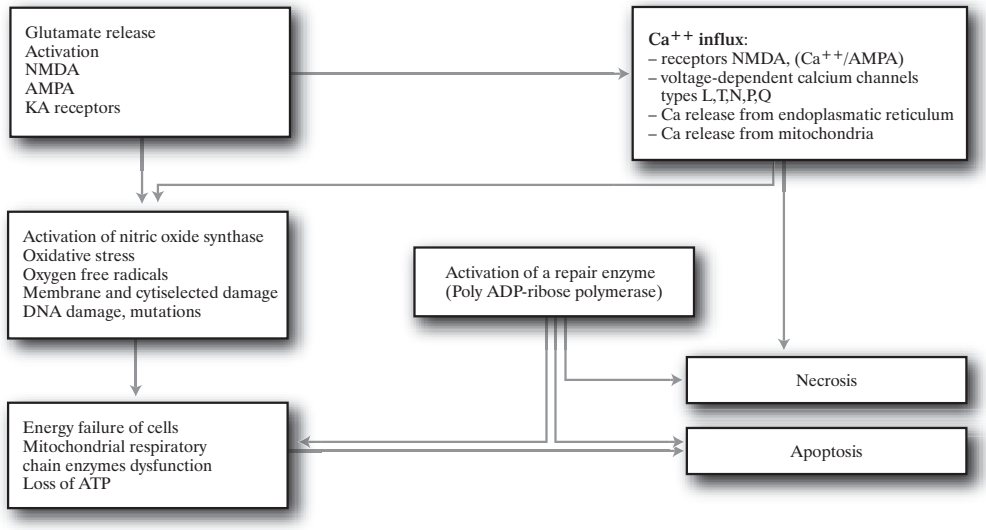
Seizure as way to epileptogenesis

In general, effective symptomatic treatment of seizures leads to stop seizures and reduce the morbidity and mortality associated with epilepsy. Gowers' concept that "seizures beget seizures" may have an element of truth because there are evidences that severe seizures are associated with neuronal injury and refractory epilepsy.

The clinical examples of potential epileptogenic events are: chronic epilepsy secondary to status epilepticus, temporal lobe partial seizures secondary to complex febrile seizures, and encephalopathic epilepsy secondary to neonatal hypoxia-ischaemia [7].

Especially status epilepticus can produce irreversible neuronal injury. Retrospective study Hesdorffer et al. found that epilepsy developed in 41% of individuals who had an episode of SE and in 13% of those with acute symptomatic seizure thereby suggesting a relationship between the prolonged seizure, SE and subsequent epileptogenesis [8]. The Barnard's study of children with status epilepticus but no history of seizures found that 36% developed epilepsy and 25% resistant epilepsy [9]. There are not evidence that prolonged seizures or complex febrile seizures progress to TLE, but in retrospective studies French et al. [10] reported that 78% of adults with TLE had febrile seizures in childhood and nearly 50% had prolonged febrile seizures. Recurrent seizures may cause structural and functional changes in the hippocampus, as demonstrated by findings that duration

Figure 1. **Mechanisms of neuronal injury**



of epilepsy correlated with hippocampal volume loss and progressive neuronal loss and dysfunction [11]. Seizure that develop during the first few hours of life in hypoxic-ischaemic neonates are clinical markers of later encephalopathy with high risk of epilepsy, cerebral palsy, cognitive impairment [12].

Neuronal loss is the major neurobiologic abnormality in epileptogenic and epileptic brain. It is important that neuronal loss occurs together with other alterations, including gliosis, axonal and dendritic plasticity, neurogenesis and molecular reorganisation of cell membranes and extracellular matrix [13].

Mechanisms of brain injury in epilepsy

At least two mechanisms are implicated in neuronal death: activation of the excitotoxic cascade (elevated calcium levels, activation of nitric oxide synthase and production of oxygen free radicals) and induction of apoptosis [14]. Mechanisms of neuronal damage and death are presented on *Fig. 1*. Once began the excitotoxic cascade can propagate. Release of intracellular glutamate from dying cells can raise the concentration of glutamate around neighbouring neuron to toxic concentration [15]. Thus, intervention in glutamate excitotoxic cascade is important possibility of disease modification.

The latent period of epileptogenesis and epilepsy development is the time that may be window of therapeutic intervention that might prevent the occurrence of unprovocated seizures. The interrupt of epileptogenesis will need to target critical processes and events during initial period of changes. Agents with multiple mechanisms of action may be capable to act at different points in the cascade of biochemical and structural changes. Intervention in epileptogenic cascade may provide: neuroprotection (preventing neuronal injury and death), neurostabilisation (restoring of neuronal function) and regeneration.

Neuroprotection

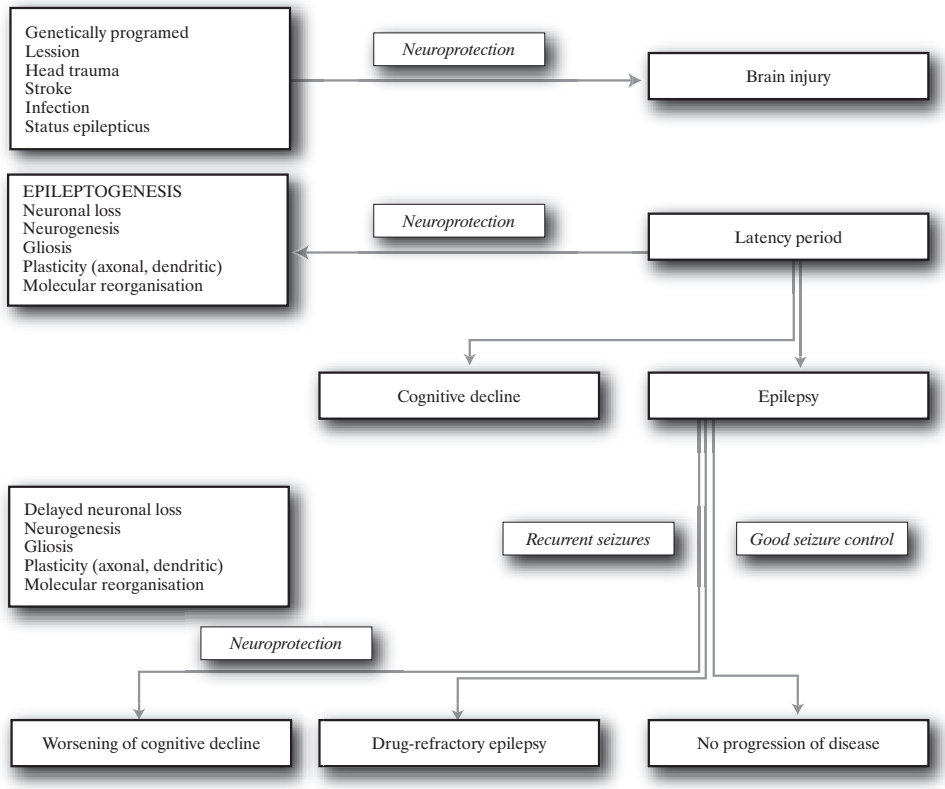
The term "neuroprotection" means the ability to prevent injury or loss of neurons. Pharmacological neuroprotection against the consequences of seizures can be considered as primary and secondary [16]. The primary neuroprotection is provided by antiepileptic drugs and compounds acting on voltage-sensitive Na^+ and Ca^{++} channels or on glutamate receptors. Secondary neuroprotection may be a result of acting on the cascade leading to necrosis or apoptosis [16]. Other possibilities may diminish the long-term morfological and functional consequences of seizures. According to Meldrum [16] neuroprotective treatment includes two areas: the prevention of cell death and the prevention of all the delayed functional consequences of seizures. The *Fig. 2* presents neuroprotection as a treatment target during epileptic process according to Pitkanen [17].

Pharmacological possibilities of neuroprotection

Many of agents from a wide range of classes have been proposed to possess neuroprotective potential, especially in experimental and preclinical conditions. Meldrum [16] presents two groups of agents with neuroprotective effects. To first group (primary neuroprotective agents) belong: Sodium channel inactivators, Voltage-sensitive Ca^{++} channel blockers, NMDA antagonists, AMPA antagonists, Group I glutamate metabotropic receptor antagonists, GABA A receptor potentiators.

Other ways of neuroprotection (secondary neuroprotection) include: blocking the cascade to necrosis, free radical scavengers: antioxidants, vitamin E, NO synthase inhibitors, COX-2 inhibitors, blocking the cascade to apoptosis: blocking

Figure 2. **Neuroprotection as a treatment target during epileptic process**



the inflammatory response, complex secondary effects: PAF antagonists, group II metabotropic agonists, neurotrophins and growth factors.

Clinical experience with traditional antiepileptic drugs suggest that these drugs prevent the symptomatic manifestation of seizures but they are less effective in influence on other important consequences of epilepsy such as neuronal loss, gliosis, and molecular reorganisation of cell membranes and extracellular matrix.

Date from experimental studies show that majority of antiepileptic drugs protect against fully kindled seizures in rats but kindling acquisition is not influenced by traditional sodium channel blocking agents and only those antiepileptic drugs with a GABA-ergic component to their mechanism of action [17]. Of these topiramate (TPM) and levetiracetam (LEV) have particular efficacy [18,19]. LEV protect against the development of kindled seizures for up to one week after discontinuation of the drug [19]. It seems that GABA-ergic mechanism of action is most important to neuroprotective effect of drugs.

Antiepileptic drugs as neuroprotectants in experimental studies

Many studies have been conducted to evaluate disease-modifying activity of antiepileptic drugs following initiating event.

In kindling models, repetitive subconvulsive stimulation creates a hyperexcitable state in which spontaneous seizures can develop without any stimulus. The fully kindled state has been viewed as a model of chronic epilepsy (complex partial seizures with secondary generalisation). Inhibition of this process with antiepileptic drugs has been interpreted as potential antiepileptogenic prophylactic effect. In animal kindling models valproate (VPA), phenobarbital (PB) and benzodiazepines (BZD) exert prophylactic effect – inhibit acquisition of the kindled state [20]. Of the new antiepileptic drugs both TPM and tiagabine (TGB) delayed seizure acquisition in kindling models and inhibited kindled seizures [18,21]. Kindling acquisition is inhibited by LEV and this effect persisted after acute treatment was discontinued [19]. However, a follow-up study found a loss of anticonvulsant activity during chronic treatment with LEV in kindled rats [22]. Unfortunately, the kindling model may not adequately replicate the human condition. In acquired epilepsies spontaneous seizures follow a latent period in which there is no repeated stimulation. Thus, effect in kindling model may not emulate clinical condition.

In experimental animal models of SE, recurrent spontaneous seizures often develop weeks to months after an episode of status epilepticus [23]. Subsequent studies indicate that alterations in GABA receptors precede or coincide with the development of epileptic seizures suggesting that these changes may be epileptogenic [24]. Treatment of status epilepticus with an intravenous BZD, phenytoin (PTH) or phenobarbital (PB) terminate SE without preventing development of late seizures. In experimental model of SE topiramate administered after

status epilepticus prevent neuronal loss in hippocampal regions CA1, CA3 and dentate hilus [25].

It is known that perinatal hypoxia induces acute seizures and subsequent seizure susceptibility with seizure-induced neuronal injury. Jensen et al. have been observed that an AMPA antagonist, but not a NMDA antagonist, was able to prevent acute and late epileptogenic effects of perinatal hypoxia in immature rats [26]. On this base it has been evaluated the antiepileptogenic effect of TPM – drug with the action at the AMPA receptor – in model of perinatal hypoxia. TPM administered to immature animals before global hypoxia suppressed hypoxia-induced acute seizures and reduced later-life susceptibility to seizures [27].

Neuroprotective effects of antioxidants

Cells contain natural defense system composed of enzymes that detoxify free radicals such as superoxide dismutase (SOD), catalase and peroxidase and, on the other hand, antioxidants such as vitamins C, E, glutathione, ferritin and uric acid. These system help the cell to maintain its homeostasis by neutralizing the oxidative effects of oxygen and its reactive metabolites [28]. Antioxidants therapies as neuroprotection involve either the administration of antioxidants which may react with free radicals or the strengthening of the endogenous antioxidant defences by enhancing the activity of superoxide dismutase, catalase and glutathione peroxidase [28,29]. Antioxidants can give protection against excitotoxic cell death in various in vitro systems, including selective neuronal loss induced by burst discharges which can be ameliorated by vitamin E [30]. Vitamin E and glutathione prevent the increase of lipid peroxides and neuronal death in hippocampus and reduce the seizure-induced neurodegeneration in cultured hippocampal cells CA3 [31,32].

Poor penetration of the blood-brain barrier is a problem with the antioxidants therapy. This may to be a reason for the relatively poor clinical response in most trials in neurological disorders [16,29]. A double blind trial with vitamin E as add-on therapy in children with epilepsy did, however, report a reduction in seizure frequency [33].

Neurotrophins as neuroprotective agents

Very interesting problem is the role of neurotrophins in long-term modification in neuronal excitability and synaptic function and their probably involvement in mechanisms of epileptogenesis and neuroprotection [34,35]. Brain-derived neurotrophic factor (BDNF) may be protecting the developing hippocampus against cell loss [36], nerve growth factor (NGF) and BDNF both promote the expression of antioxidative enzymes and thus can protect against cell death due to calcium overload mitochondria [16]. BDNF is more important in epileptogenesis and related processes but NGF and transforming growth factor β (TGF-β) in neuroprotection. In therapy delivery neurotrophins to the brain is problematic, but theoretically many indirect approaches are possible – factors modulating the release stimulating the synthesis of neurotrophins [37].

Our experience in neuroprotective therapy

In our studies, we have evaluated the mechanisms of neuronal damage in experimental models of seizures and possibilities of neuroprotection in experimental and clinical conditions [38]. We have been shown an increase of lipid peroxidation in almost all structures of the rat brain, particularly in cortex, hippocampus and cerebellum, after electroshock-induced seizures and beneficial effects of antioxidant – vitamin E on these processes [39,40]. Sobaniec [41] observed beneficial effect of combined therapy with VPA and vitamin E in epileptic children. We have been shown that oxidants-antioxidants balance in epileptic children is disturbed and antiepileptic therapy influence on these processes [42]. We have studied also the protective role of calcium antagonists in epilepsy including status epilepticus [43-45].

Conclusions

Neuroprotective therapy in epileptic children is very important but difficult problem. The antiepileptic drugs display their neuroprotective effects predominantly in experimental models or preclinical conditions. These data, however, promising, are unfulfilled. Experimental models are often not sufficiently representative of the clinical use and may sometimes offer false encourage. It is increasingly apparent that neuronal damage associated with epileptogenesis or other chronic neurological disorders involves multiple pathological processes which can interact and result in synergistic deleterious effects. To provide effective neuroprotection in epileptic children, the use of broad-spectrum therapy is necessary. Safety under chronic treatment conditions and with recognised penetration of blood-brain barrier drugs have to be used.

References

1. Hauser WA. Incidence and prevalence. In: Engel J, Pedley TA, editors. Epilepsy. A Comprehensive Textbook. Philadelphia, Lippincott-Raven Publishers, 1997; 47-57.
2. Holmes GL. Epilepsy in the developing brain: lessons from the laboratory and clinic. Epilepsia, 1997; 38: 12-30.
3. Sanchez RM, Jenses FE. Maturational aspects of epilepsy mechanisms and consequences for the immature brain. Epilepsia, 2001; 42: 577-85.
4. Bergamasco B, Penna P, Ferrero P. Neonatal hypoxia and epileptic risk: a clinical prospective study. Epilepsia, 1984, 25; 131-46.
5. Cendes F. Early childhood prolonged febric convulsions, atrophy and sclerosis of mesial structures, and temporal lobe epilepsy: an MRI volumetric study. Neurology, 1993; 43: 1083-7.
6. Camfield P, Camfield C, Gordon K. What types of epilepsy are preceded by febrile seizures? A population-based study of children. Dev Med Child Neurol, 1994; 36: 887-92.
7. Koh S, Storey TW, Santos TC. Early-life seizures in rats increase susceptibility to seizure-induced brain injury in adulthood. Neurology, 1999; 53: 915-21.
8. Hesdorfer DC, Logroscino G, Cascino G. Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. Ann Neurol, 1998; 44: 908-12.
9. Barnard C, Wirrell E. Does status epilepticus in children cause developmental deterioration and exacerbation of epilepsy? J Child Neurol, 1999; 14: 787-94.
10. French JA, Williamson PD, Thadani VM. Characteristics of

medial temporal lobe epilepsy. Results of history and physical examination. Ann Neurol, 1993; 34: 774-80.

11. Tasch E, Cendes F, Li LM. Neuroimaging evidence of progressive neuronal loss and dysfunction in temporal lobe epilepsy. Ann Neurol, 1999; 45: 568-76.

12. Hill A, Volpe JJ. Hypoxic-ischaemic cerebral injury in the newborn. In: Swaiman KF, Ashwal S editors. Ped Neurol Princ&Prac, 3rd Ed, St Louis, Mosby, 1999; 191-204.

13. Jutila L, Immonen A, Partanen K, Partanen J, Mervaala E, Ylinen A, Alafuzoff I, Paljarvi L, Karkola K, Vapalahti M, Pitkanen A. Neurobiology of epileptogenesis in the temporal lobe. Adv Tech Stand Neurosurg, 2002; 27: 3-22.

14. Arzimanoglou A, Hirsch E, Nehlig A, Castelnau P, Gressens P, Vasconcelos AP. Epilepsy and neuroprotection: an illustrated review. Epileptic Disord, 2002; 3: 173-82.

15. Lipton S.A., Roseberg PA. Excitatory amino acids as a final common pathway for neurological disorders. N Engl J Med, 1994; 330: 613-22.

16. Meldrum BS. Implications for neuroprotective treatments. In: Sutula T, Pitkanten A, editors. Progress in Brain Research, Elsevier Science, 2002; 35: 488-95.

17. Pitkanen A. Efficacy of current antiepileptics to prevent neurodegeneration in epilepsy models. Epilepsy Res, 2002; 50: 141-60.

18. Amano K, Hamada K, Yagi K, Seino M. Antiepileptic effects of topiramate on amygdaloid kindling in rats. Epilepsy Res, 1998; 31: 123-8.

19. Loscher W, Honack D, Rundfeldt C. Antiepileptogenic effects of the novel anticonvulsant levetiracetam (ucb Lo59) in the kindlind model of temporal lobe epilepsy. J Pharmacol Exp Ther, 1998, 284: 474-9.

20. Silver JM, Shin C, McNamara JO. Antiepileptogenic effects of conventional anticonvulsants in the kindling model of epilepsy. Ann Neurol, 1991; 29: 356-63.

21. Morimoto K, Sato H, Yamamoto Y. Antiepileptic effects of tiagabine, a selective GABA uptake inhibitor, in the rat kindling model of temporal lobe epilepsy. Epilepsia, 1997; 38: 966-74.

22. Loscher W, Honack D. Development of tolerance during chronic treatment of kindled rats with the novel antiepileptic drug levetiracetam. Epilepsia, 2000; 41: 1499-506.

23. Mello LEAM, Cavalheiro EA, Tan AM. Circuit mechanisms of seizures in the pilocarpine model of chronic epilepsy: Cell loss and mossy fiber sprouting. Epilepsia, 1993; 34: 985-95.

24. Coulter DA. Chronic epileptogenic cellular alterations in the limbic system after status epilepticus. Epilepsia, 1999; 40: supl. S23-S33.

25. Niebauer M, Gruenthal M. Topiramate reduces neuronal injury after experimental status epilepticus. Brain Res, 1999; 837: 263-9.

26. Jensen FE, Blume H, Alvarado S. NBQX blocks acute and late epileptogenic effects of perinatal hypoxia. Epilepsia, 1995; 36: 966-72.

27. Koh S, Jensen FE. Topiramate blocks acute and chronic epileptogenesis in a rat model of perinatal hypoxic encephalopathy. Epilepsia, 1999; 40 (Suppl 7): 5-6.

28. Choi BH. Oxygen, antioxidants and brain function. Yonsei Med J, 1993; 34: 1-10.

29. Delanty N, Dichter MA. Oxidative injury in the nervous system. Acta Neurol Scand, 1998; 98: 145-53.

30. Heinemann U, Buchheim K, Gabriel S, Kann O, Kovacs R, Schuchmann S. Cell death and metabolic activity during epileptoform discharges and status epilepticus in the hippocampus. In: Sutula T, Pitkanen A editors. Do seizures damage the brain. Progress in brain research, Elsevier, Amsterdam, 2002; 135: 197-210.

31. Frantseva MV, Valazquez JL, Hwang PA, Carlen PL. Free radicals production correlates with cell death in an in vitro model of epilepsy. Eur J Neurosci, 2000; 12; 1413-9.

32. Frantseva MV, Valazquez JL, Tsoraklidis G, Mendonca AJ, Adamchik Y, Mills LR, Carlen PL, Burnham MV. Oxidative stress in involved in seizure-induced neurodegeneration in the kindling model of epilepsy. Neurosci, 2000, 97; 431-5.

33. Ogunmekan AO, Hwang PA. A randomised double-blind, placebo-controlled, clinical trial of alfa-tocopheryl acetate (Vitamin E) as add-on therapy, for epilepsy in children. Epilepsia, 1989; 30: 84-9.

34. Binder DK, Croll SD, Gall CM, Scharfman HE. BDNF and epilepsy: too much of a good thing? Neurosci, 2001, 24: 47-53.

35. Jankowsky JL, Patterson PH. The role of cytokines and growth factors in seizures and their sequelae. Prog Neurobiol, 2001; 63: 125-49.

36. Tandon P, Yang Y, Das K, Holmes GL, Stafstrom C. Neuroprotective effects of brain-derived neurotrophic factor in seizures during development. Neurosci, 1999; 92: 293-303.

37. Young D, Lawlor PA, Leone P, Dragunow M, During MJ. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. Nat Med, 1999; 5: 448-53.

38. Sobaniec W, Kułak W, Boćkowski L, Śmigielska-Kuzia J, Sobaniec-Łotowska M, Sołowiej E, Sobaniec H, Artemowicz B. Badania procesów uszkodzenia układu nerwowego i możliwości neuroprotekcji. Przegl Lek, 2001, 58 (Supl. 1); 41-7.

39. Kułak W, Sobaniec W, Sobaniec-Łotowska M, Drozdowski W. The inhibition of lipid peroxidation in rat brain by nifedipine and vitamin E after electroshock. Ann Med Univ Bial, 1992; 37: 67-72.

40. Sobaniec W, Kułak W, Sobaniec H, Farbiszewski R, Drozdowski W. Effects of clobazam and vitamin E on the lipid peroxidation in rat brain after electroconvulsive shock. Ann Med Univ Bial, 1999; 44: 134-40.

41. Sobaniec W. Lipid peroxidation in experimental and clinical epilepsy and the effects of sodium valproate and vitamin E on these processes. Neurosciences, 1992; 18: 1231-40.

42. Artemowicz B, Sołowiej E, Sobaniec W. The disturbance of the oxidants-antioxidants balance in epileptic children. IJNN, 2004; 1: 27-31.

43. Kułak W, Sobaniec W, Wojtal K, Czuczwar SJ. Calcium modulation in epilepsy. Pol J Pharmacol, 2004; 56: 29-41.

44. Kułak W, Sobaniec W. Zastosowanie nimodypiny w leczeniu napadów gromadnych u dzieci. Streszcz VI Dni Neurol Dziec, Poznań, 11-12.10.2001: 78.

45. Sills G. Antiepileptic drugs as neuroprotective agents. IJNN, 2004; 1: 13-20.