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Review

Profile of anticonvulsant activity and neuroprotective effects of novel and potential antiepileptic drugs – an update

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Abstract:
Although neuroprotection is effective only against certain aspects of a complex cascade of pathological events during the development and course of epilepsy, it might be a promising option in the treatment of this disease. Some new data on the pathophysiology of epilepsy raised some hopes that the epileptogenesis process can be prevented. A question arises whether it is possible to make the epilepsy develop in a milder, easier to treat and non-progressive way without cognitive decline and drug-resistance. Moreover, once the epilepsy has already been triggered, there is as yet no conclusive evidence that the harmful effects of seizures on the brain can be reduced. So a great deal of further evaluation of antiepileptic drugs (AEDs) is required. Many similarities exist between cerebral ischemia and epilepsy regarding brain-damaging and autoprotective mechanisms that are activated following the injurious insult. Therefore, drugs that are effective in minimizing seizure-induced brain damage may also be useful in minimizing ischemic injury. Most AEDs have been tested in animal models of focal or global ischemia and some were already tested in humans for a possible neuroprotective effect. The existing data are rather scanty and insufficient but it appears that only drugs that have multiple mechanisms of action have some potential in conferring a degree of neuroprotection that could be clinically applicable to stroke patients. In this review, we focus on evidence of neuroprotective properties of novel and potential AEDs, based on animal experimental models of neurodegeneration. In conclusion, some of the newer AEDs show promise as possible neuroprotectants in epilepsy and acute ischemia but more studies are needed before clinical trials in humans could be undertaken.

Key words:
antiepileptic drugs, neuroprotection, neurodegeneration, animal model of seizures, mode of action, antiepileptic drug.

Abbreviations: AEDs – antiepileptic drugs, BIC – bicuculline, CLO – clonazepam, CBZ – carbamazepine, b.i.t; t.i.d.; q.i.t. – two, three, four times daily, DZP – diazepam, ESM – etosuximide, FBM – felbamate, GBP – gabapentin, ip – intraperitoneal, MES – maximal electroschock, LTG – lamotrigine, LEV – levetiracetam, LSG – losigamone, OGD model – oxygen/glucose deprivation model, OXC – oxcarbazepine, PHT – phenytoin, PTZ – pentetrazole, PTX – picrotoxin, RCM – remacemide, SE – status epilepticus, TGB – tiagabine, TLP – talampanel, TPM – topiramate, VPA – valproate, VGB – vigabatrin, ZNS – zonisamide.

Introduction

Resistance to currently used pharmacological treatment of epilepsy is evident in about 30% of patients [20]. Consequently, it is necessary to find alternative strategies and possibilities to interfere with the basic processes determining the development of epilepsies or to promote compensatory processes that repair these dysfunctions.

The increasing knowledge about the basic neuronal changes underlying epilepsy facilitates the analysis of the potential role of neuroprotective agents in epileptogenesis. In epilepsy, the most frequent combination is the concomitant presence of damage and overexcitation. Halasz et al. [35] have shown that after primary damage, an increase in excitability may develop in post-traumatic epilepsy. Alternatively, the outburst of epileptic excitability may cause neuronal damage as in the case of cell loss after status epilepticus (SE) or cytotoxic damage from extensive glutamatergic stimulation.

According to Pitkanen et al. [74] in the case of benign and easy-to-treat epilepsy without cognitive decline, disease modification may be clinically beneficial, which may result in, for example, less severe memory impairment.

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. However, activation of ionotropic glutamate receptors has been thought to play an integral role in the pathophysiology of SE-induced neuronal damage. Therefore, as Fisher et al. [27] have shown, glutamate antagonists would be expected to be effective in reducing the initiation and propagation of seizure-induced excitotoxity and its associated neuropathology.

Neuronal death can be due to the initial epileptogenic brain-damaging trauma, progression of pathological processes or recurrent seizures. Such damage can cause both neurotic and apoptotic cell death. Klitgaard et al. [47] have indicated that convulsions, typically lasting less than two minutes, can induce apoptosis. Neurons are susceptible to death under circumstances associated with seizures.

Apart from mechanisms of action of antiepileptic drugs (AEDs), the main themes of this review include animal models used for studying seizure protection by AEDs, proven or potential neuroprotective activity and multicenter trials on epileptic patients. Despite differences between mechanisms of action of AEDs and seizure types, AEDs seem to be promising in terms of neuroprotection. Although animal data cannot be always extrapolated to humans, there is a hope that AEDs are potential neuroprotectants not only in seizures, but also in other neurodegenerative conditions.

Felbamate

Mechanisms of action

Felbamate (FBM) is a novel antiepileptic drug with a broad anticonvulsant profile [for review see: 88]. Several mechanisms of its antiseizure effect have been identified. FBM inhibits voltage-sensitive sodium channels (by prolonging their inactivation) and blocks voltage-sensitive calcium channels (by reduction of calcium influx). FBM potentiates GABA-mediated events and acts on NMDA glutamate receptor, reducing glutamate-mediated excitation. FBM is a weak inducer of the cytochrome P450 (CYP) isoenzyme 3A4, whereas it inhibits CYP2C19 [89]. Also, FBM enhances GABA-mediated events through a barbiturate-like modulatory effect on the $GABA_A$ receptor [18].

Activity profile in seizure models

In animal models, FBM presents wide spectrum of anticonvulsant activity. It has been proven that FBM is effective against maximal electroshock-induced seizures (MES) in mice [11] and against seizures induced by glutamate agonists, NMDA and quisqualic acid [88]. Trojnar et al. [88] have indicated that FBM is also active against amygdala-kindled seizures in rats and a recent study conducted on the same epilepsy model showed that the combination of FBM and carbamazepine (CBZ) resulted in a decrease in seizure severity [10]. Synergistic interactions at some drug ratios have been shown for the combinations of all major conventional AEDs with FBM [20]. At or below therapeutic concentrations FBM has no effect on glycine site-mediated currents, while at suprathera-peutic concentrations it produces moderate reversible inhibition [44].

Neuroprotective activity

There is a broad evidence of neuroprotective properties of FBM, which were observed in several ischemic models both in immature and mature brain [51, 73]. It was shown [51] to reduce cell mortality in both *in vitro* and *in vivo* models of global ischemia. Trojnar et al. [88] have stated that FBM provided neuroprotection against hypoxia in the rat hippocampal slices and from hypoxia induced by an interaction with glycine

[76]. Moreover, the drug has been proven to provide neuroprotection against CA1 traumatic neuronal injury at FMB serum concentrations similar to those reported in FBM monotherapy for seizures [28]. FBM given after a hypoxic-ischemic insult involving bilateral carotid ligations in rat pups, has been found to be effective in reducing cerebral infarction and to be extremely effective in preventing delayed neuronal necrosis [7, 73]. In a gerbil model of global ischemia, FBM given *post hoc* was remarkably effective in preventing delayed apoptosis secondary to global ischemia but at doses higher than those used for anticonvulsant treatment [52]. Also, FBM significantly protected cells in hippocampal slice cultures from death induced by oxygen/glucose deprivation (OGD) [68].

Human studies

Trojnar et al. [88] have shown that the spectrum of FBM activity has been confirmed clinically. There are some reports of psychosis and other behavioral disturbances after FBM and the serious adverse effects like hepatotoxity and aplastic anemia [5]. Despite this fact, FBM is recommended by FDA [10]. Although some experimental data have shown the efficacy of combined therapy, recent clinical publications suggest that using the newer antiepileptic agents, also FBM, in monotherapy, even as an initial therapy would appear to be an appropriate clinical decision [34].

Gabapentin

Mechanisms of action

Gabapentin (GBP) is structurally related to GABA. GBP has been shown to increase GABA content in neuronal tissues and to bind to the alpha$_2\delta$ subunit of calcium channels [7].

Activity profile in seizure models

According to Trojnar et al. [88], GBP is moderately effective in antagonizing tonic convulsions induced by pantetrazole (PTZ) and sound-induced seizures in DBA/2 mice. GBP reduced the generalized seizures in amygdala-kindled rats and attenuated afterdischarge duration of amygdala-kindled seizures. The isobolographic analysis has revealed that combinations of GBP with other AEDs generally result in synergistic (supraadditive) interactions [12].

Neuroprotective activity

Pitkanen [73] has indicated that GBP reduced hippocampal damage after kainate-induced SE when treatment was started approximately 24 h after induction of SE and continued for approximately 1 month.

In one of the previous experimental works, valproate (VPA) or GBP, at the highest concentrations used (10 mM and 300 μM, respectively), did not rescue cells from death induced by OGD in the slice cultures. The anticonvulsant action of these drugs has been ascribed to their effects on GABAergic inhibition, Na^+ and Ca^{2+} channels, and the absence of an effect in the OGD model was, therefore, a surprise [76]. According to Trojnar et al. [88], GBP was proven to be effective in an *in vitro* ischemia test.

Human studies

GBP was found to be appropriate for adjunctive treatment of refractory partial seizures in adults [30], effective for the treatment of mixed seizure disorders and for the treatment of refractory partial seizures in children [31]. Evidence for the effectiveness of GBP in newly-diagnosed patients with other generalized epilepsy syndromes is lacking [30]. GBP monotherapy was as effective as lamotrigine (LTG) in terms of seizure control and tolerability. Overall, 69.6% of patients in the GBP group and 66.2% of patients in the LTG group completed the study, and 76% of patients in both groups were seizure-free within 12 weeks of treatment [7].

Levetiracetam

Mechanism of action

A recent preclinical discovery has revealed that the 90 kDa binding site to which levetiracetam (LEV) binds might represent a new target for therapeutic intervention in epilepsy [56]. However, it remains unknown how LEV modulates SV2A [8], which is an integral membrane protein [41].

Activity profile in seizure models

Experimentally, LEV has been associated with numerous pharmacodynamic interactions with other AEDs. In particular, it appears that the anticonvulsant efficacy of LEV in animal models of seizures, for example audiogenic seizure-prone mice and amygdala-kindled rats, is substantially and synergistically enhanced by GABAergic drugs. Furthermore, the combination of LEV and DZP in a rat model of experimental SE is also associated with anticonvulsant synergy [71]. Interestingly, LEV is ineffective in acute models of experimental epilepsy, including MES-induced convulsions or clonic phase of seizures provoked by picrotoxin (PTX) or other chemical convulsants. In contrast, it is highly effective against amygdala-kindling in rats and in a number of genetic models of epilepsy [18].

Neuroprotective activity

Mazarati et al. [62] have shown that apart from high efficacy against SSSE (self-sustaining status epilepticus), good solubility, low acute toxicity and a potent interaction with DZP, LEV possesses also neuroprotective activity. Pitkanen [73] has underlined that LEV administered at the dose of 54 mg/kg per day for 21 days, did not reduce hippocampal damage caused by pilocarpine-induced SE when assessed 3 weeks later. In that study, the drug treatment was initiated 30 min after the beginning of pilocarpine-induced SE in rats. However, Hanon et al. [36] have proven that LEV induces significant neuroprotection in a rat model of focal cerebral ischemia. Leker at al. [51] have recently underlined that LEV is effective in focal ischemia, but not in global one [51].

Human studies

LEV treatment, that started with 10 mg/kg/day and the dose was increased every 4 days to a maximum dose of 60 mg/kg/day [48], was effective in the pediatric population across different seizure types. So far, the drug is recommended as an adjuvant for treatment of partial drug-resistant epilepsy [72]. It is remarkable that monotherapy with LEV, following the add-on phase, also proved to be very effective in refractory patients, and the adverse effects were only minimal [72, 92]. Contrary to many AEDs, LEV did not impair cognitive functions in experimental animals or epileptic patients [92].

Losigamone

Mechanisms of action

The mechanism of losigamone's (LSG) action has not been fully clarified, but the drug shows calcium antagonistic effects and activates GABA-dependent chloride channels without directly binding to GABA, benzodiazepine, or PTX binding sites. Both effects enhance membrane hyperpolarization and thus lead to suppression of spontaneous neuronal electrical activity [3]. It is possible that LSG can induce a stabilization of the inactivated state of Na^+ channels leading to a decrease in late channel open probability which was thought to be responsible for the persistent Na^+ current (I_{NaP})[46].

Activity profile in seizure models

In animal studies, LSG was shown to possess anticonvulsant properties both under *in vivo* and *in vitro* conditions [46]. In rodents, LSG inhibited the tonic hindlimb extension produced by either MES or by various chemical convulsants, including PTZ, bicuculine (BIC), nicotine and 4-aminopyridine (4-AP). LSG dose-dependently protected mice against cocaine-induced convulsions with the ED_{50} value of 24.7 mg/kg. At doses between 20 and 80 mg/kg, the drug was also active against audiogenic seizures in rats and gerbils, and PTZ-kindled seizures in mice [46]. In the MES test, the drug occurred more potent than phenytoin (PHT), VPA, and in the PTZ test, it was more effective than VPA [83].

Neuroprotective activity

In *in vitro* models of epileptogenesis in rats, LSG appeared to act on intrinsic neuronal processes. LSG was also shown to block epileptiform activity induced by either PTX addition or Mg^{2+} or Ca^{2+} omission from the perfusion medium of hippocampal slices [46]. It was also shown to block epileptiform discharges in CA1 and CA3 hippocampal areas and in the entorhinal cortex (EC) [46]. Moreover, LSG reduced low Mg^{2+}-induced short recurrent discharges in the hippocampus and seizure-like events in EC. It is tempting to assume that LSG may possess neuroprotective properties [46].

Human studies

The drug at the dose of 500 mg t.i.d. reduced seizure frequency to a significantly greater extent than placebo [46]. Generally, LSG was well tolerated with only mild to moderate side effects, and no interactions with other AEDs were observed. According to Baulac et al. [3], the efficacy of LSG seems to be about average for recently marketed AEDs.

This study confirms that 1500 mg/day is now a well established therapeutic dosage [3]. A single doses of LSG (up to 1000 mg) and its subchronic dosage (500 mg/kg t.i.d. applied for 7 days) were well tolerated [46, 66].

Oxcarbazepine

Mechanisms of action

The anticonvulsant action of oxcarbazepine (OXC) is, like CBZ, thought to be due primarily to blockage of voltage sensitive Na^+ channels resulting in stabilization of hyper-excited neural membranes, inhibition of repetitive neuronal firing and inhibition of the spread of discharges. It also increases K^+ conductance, reduces glutamatergic transmission and modulates Ca^{2+} channel function. A key difference between the two drugs is that OXC unlike CBZ is not metabolized to an epoxide derivative [81].

Activity profile in seizure models

Łuszczki et al. [57] evaluated interactions of OXC and conventional AEDs. In that experiment, OXC (at the highest subthreshold dose that did not significantly influence the electroconvulsive threshold) reinforced the anticonvulsant effects of conventional AEDs, especially when it was combined with CZP, PHT, and VPA. Results of the isobolographic analysis indicated that the experimental combination of CBZ with OXC may sometimes cause unpredictable effects (antagonism) [57].

Because induction or inhibition of the cytochrome P450 system does not considerably affect the metabolism of OXC and 10-monohydroxy derivative (MHD), the potential for interactions with enzyme-inducing or -inhibiting drugs is reduced [7].

Neuroprotective activity

Rekling [76] has proven that OXC at a concentration up to 300 μM reduced cell death induced by OGD. A rise in intracellular Ca^{2+} is a primary event in OGD-induced cell death in hippocampal slices and a reduced Ca^{2+} influx through block of pre- or postsynaptic Ca^{2+} channels is neuroprotective. OXC has a blocking effect on different subtypes of Ca^{2+} channels. Thus, a part of the neuroprotective action seen in the above study with anticonvulsants with a Ca^{2+} channel-blocking profile could be mediated by a reduced influx of Ca^{2+} through voltage-activated Ca^{2+} channels [76].

There is no evidence indicating that OXC is effective in an ischemia test [73]. In contrast to Pitkanen [73], Ambrosio et al. [1] have reported that OXC failed to protect hippocampal neurons against different toxic insults: kainate or veratridine exposure and ischemia-like conditions.

Human studies

Friis et al. [32] observed in their study that OXC significantly reduced seizure frequency in 32–48% of patients. In another study [90] in patients switching from CBZ to OXC, 8% of them became seizure free and 32% experienced a greater than 50% reduction in seizure frequency. At a dose of 600–2400 mg/day, OXC turned out to be effective in the treatment of partial seizures [78]. There is an interest in evaluating a potential efficacy of OXC like some other AEDs in conditions beside epilepsy, including neuropathic pain, migraine prophylaxis and psychiatric disorders [8].

Pregabalin

Mechanisms of action

Pregabalin (PGB) is an alpha$_2$-delta (α_2-δ) ligand that has analgesic, anxiolytic, and anticonvulsant activity [8, 25]. Potent binding at this site reduces Ca^{2+} influx at nerve terminals and, thereby, reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P [8]. These activities and effects result in the analgesic, anxiolytic, and anticonvulsant activity. PGB is inactive at $GABA_A$ and

$GABA_B$ receptors [8, 25]. Administration of PGB-active, the enantiomer with antiepileptic properties, results in a significant though very modest decrease (0.6 mM) in forebrain cellular glutamate levels [25]. The PGB enantiomer lacking antiepileptic activity has no apparent effect.

Activity profile in seizure models

Czuczwar and Patsalos [21] have indicated that although PGB has a similar spectrum of activity as GBP in animal seizure models, it appears to be 3 to 10 times more potent. PGB is active in a number of animal models of epileptic seizures including MES seizures, chemical convulsant-induced seizures (PTZ, BIC, PTX), kindled seizures in rats, and audiogenic seizures in genetically susceptible animals [8, 25]. According to Bialer et al. [8] PGB has been also effective in preventing seizures in kindled rats and audiogenic seizures in genetically susceptible mice.

Neuroprotective activity

There is no published evidence about neuroprotection of PGB. However, the potential mechanisms of action and functional consequences of PGB on both the excitatory neurotransmission, including its effects on Ca^{2+} channels, and the inhibitory neurotransmission suggest that PGB can be supposed to act as a potential neuroprotectant [2].

Human studies

Miller et al. [63] have shown a reduction in seizure frequency, usually in 50% of patients treated with PGB. Dworkin et al. [8] have indicated that PGB has been effective in patients with partial seizures with and without secondary generalization, neuropathic pain and generalized anxiety disorder in several placebo-controlled trials. The drug has also shown anxiolytic efficacy in several controlled studies of anxiety disorders [26]. Furthermore, PGB is well tolerated. In the PGB treatment groups [38] dizziness, somnolence and vomiting were the most frequently reported adverse events, usually in patients treated with PGB at a single dose of 300 mg. These study results also suggest that PGB may be an effective analgesic with a duration of action longer than that of ibuprofen.

Remacemide

Mechanisms of action

Remacemide (RCM) and its desglycinyl metabolite (d-REMA) are low-affinity blockers of the NMDA-operated ion channel [69] and have antagonistic action on the fast Na^+ channels [88]. Norris et al. [67] considered a partial blockade of K^+ channels as a possible mechanism of action of RCM.

Activity profile in seizure models

RCM is effective against MES-induced seizures [33, 69] and against seizures induced by NMDA, kainic acid and 4-aminopyridine [33, 88] and affords dose-dependent protection against cocaine-induced seizures [88]. RCM showed little or no protection in seizures chemically induced by PTX, BIC, PTX and strychnine [33, 69]. In cocaine-induced convulsions RCM produced dose-dependent protection. The compound also inhibited convulsions in mice prone to audiogenic seizures [60].

Neuroprotective activity

Neuroprotective action of RCM has been shown by Calabresi et al. [15] who reported that RCM and its active desglycinyl metabolite, d-REMA, induced a concentration-dependent reduction of both repetitive firing discharge and excitatory postsynaptic potentials. RCM and d-REMA decrease glutamate agonist-induced excitotoxicity in isolated chick retina. These findings might have therapeutic implications of possible neuroprotective effect in various neurological disorders. RCM may find use as the NMDA antagonist in chronic type of neurodegeneration like Huntington's or Alzheimer's disease [23].

It is noteworthy that in another experiment [72] d-REMA was protective against acute cell damage (e.g. occurring within 30 min) induced by NMDA exposure. Apart from epilepsy, this action might prove useful in acute neurological situations, such as stroke and brain trauma [72]. Indeed, an acute protective effect of RCM against damage induced by SE and brain trauma has been demonstrated in rats. Leker et al. [51] have recently underlined that RCM is effective both in focal and in global ischemia.

Human studies

RCM has been investigated in several clinical studies as an add-on therapy in refractory epilepsy. Jones et al. [42] in a double-blind study have proven the safety and efficacy of adjunctive RCM hydrochloride in adult patients with refractory epilepsy who were already taking up to three AEDs [16, 24]. RCM was also tested in animal models of focal ischemia where it was shown to reduce infarct volumes significantly and to improve functional outcome [50]. Thus, in patients undergoing coronary artery bypass surgery, RCM was able to reduce neuropsychological deficits as compared with placebo. However, RCM did not show clinical efficacy in them in comparison to placebo-treated patients [51].

Talampanel (LY 300164)

Mechanisms of action

Talampanel (TLP) is a selective non-competitive antagonist of AMPA subtype of glutamate excitatory amino acid receptors. TLP is an orally active, broad-spectrum anticonvulsant with a novel mechanism of action [7]. However, so far it has not been registered as an AED.

Activity profile in seizure models

TLP is effective against chemically (PTZ, aminophylline) [22, 86] and electrically (MES) induced seizures [18], however, aminophylline and strychnine attenuate the anticonvulsant activity of TLP by raising the ED_{50} values of TLP against MES in mice [13]. Neither BIC nor PTX affect the protective action of TLP [13]. TLP used at the lowest protective dose of 1.0 mg/kg enhances the anticonvulsant activity of all AEDs tested in aminophylline-induced seizures [86]. In their study, Borowicz et al. [13] revealed that aminophylline reduced the anticonvulsant potential of LY 300164 (termed as TLP) in the MES test [13]. In addition, Swiader et al. [84] have indicated that dantrolene did not affect the electroconvulsive threshold whereas it elevated the protective activity of LY 300164 against MES. It was suggested that the inhibition of Ca^{2+} release from the intracellular pool might have potentiated the efficacy of this AMPA/kainate receptor antagonist [84].

Neuroprotective activity

TLP was found protective against ischemic neuronal damage *in vivo*. Perinatal ischemia/hypoxia-induced brain injuries are major potential targets of such agents, thus neuroprotection studies in neonatal animals have particular significance [55, 91]. However, some data have indicated that TLP possesses some neuroprotective properties *in vitro* as well when neuronal cultures or brain slices were directly exposed to glutamate agonists. It protects animals from brain damage by AMPA-induced striatal neurotoxicity in neonatal rats [91]. In the experiments, TLP attenuated neurotoxicity induced by intrastriatal injection of AMPA. TLP therapy instituted 30 min after trauma significantly reduces histological damage in a rat model of traumatic brain injury (TBI) [4]. Furthermore, the drug enhanced the akinesia- and decreased the dyskinesia-inducing effect of levodopa in an *in vivo* primate model of parkinsonism, which suggests an antiparkinson potential [8].

Human studies

TLP has shown an effect in reducing the frequency of all seizures as well as simple partial seizures [8, 17]. TLP dosing strategies may be reliant on concomitant AED medication, as enzyme-inducing AEDs enhance, whereas VPA inhibits its metabolism. TLP is well tolerated, although adverse events occur at lower doses compared with those in healthy subjects, probably because of the additive effect of concomitant AEDs [49].

Tiagabine

Mechanisms of action

Tiagabine (TGB) inhibits neuronal and glial uptake of GABA, thus leading to the enhancement and prolongation of GABA-mediated synaptic events [21]. The GABA uptake inhibitor is structurally related to the prototypic GABA uptake blocker nipecotic acid, but has an improved ability to cross the blood-brain barrier. TGB temporarily prolongs the presence of GABA in the synaptic cleft by delayed clearance [75]. It increases synaptic GABA availability via inhibition of the GAT-1, GABA transporter, on presynaptic neu-

rons and glial cells [8]. GAT-1 is strongly expressed in axon terminals of inhibitory interneurons [29].

Activity profile in seizure models

The isobolographic analysis showed that combinations of TGB with GBP exerted supraadditive (synergistic) interactions in the MES-test in mice. Łuszczki et al. [58] have suggested that from a preclinical point of view, the interactions observed experimentally showed that the combination of TGB and GBP, due to a synergistic anti-seizure activity of the drugs, might provide adequate seizure control in patients with refractory epilepsy.

Neuroprotective activity

According to Trojnar et al. [88] TGB, tested in a perforant pathway stimulation model of SE, did not change GABA levels in the cerebrospinal fluid, it prevented the appearance of seizures during stimulation, reduced CA1 and CA3c pyramidal cell loss as well as the spatial memory impairment in animals.

Also, postischemic treatment with TGB improves neurobehavioral outcome and reduces brain infarction volume in focal ischemia model in rats. The neuroprotective effect of TGB is dose-dependent [88]. According to Pitkanen [73], TGB (36 mg/kg *ip*) administered 30 min before, and 1, 24, 48, and 72 h after ischemia (five administrations altogether) reduced ischemia-induced damage to CA1 pyramidal cells in a four vessel occlusion model of transient global ischemia (10 min) in rats in a dose-dependent manner when assessed 8 days later. Because a single preischemic TGB administration did not protect neurons, it was concluded that the administration of TGB during the postischemic reperfusion phase was critical for the neuroprotection [73]. Leker et al. [51] have recently underlined that TGB is effective both in focal and in global ischemia. Two separate studies [51] have shown the reduction of CA1 hippocampal cell mortality by up to 80% in animal models of global ischemia after TGB administration.

Trojnar et al. [88] have concluded that postischemic hypotermia is partially responsible for the neuroprotective action of TGB. They have also proven that TGB inhibits the development of hippocampal degeneration in the CA1 pyramidal cell layer. The results may suggest that enhancement of GABAergic neurotransmission may protect vulnerable neurons from death.

Reckling [76] has summarized that apart from CBZ, FBM and LTG, also TGB had significant neuroprotective effects in the OGD model but GBP and VPA were not neuroprotective in the model at a concentration up to 300 μM and 10 mM, respectively. Among other next generation anticonvulsants, only OXC has shown neuroprotective effects, whereas LEV did not reduce cell death induced by OGD at a concentration up to 300 μM [76].

Human studies

TGB is effective as add-on therapy in the management of patients with refractory partial epilepsy [75]. TGB has been targeted largely at the management of partial seizures and infantile spasms and was frequently used until the late 1990s when isolated reports of concentric peripheral visual field loss and visual electrophysiological abnormalities began to emerge [8, 39]. TGB has been assessed in small case series in anxiety and mood disorders [7]. Bialer et al. [7] have also described the use of TGB in the treatment of neuropathic pain, especially painful diabetic neuropathy, headache/migraine, and sleep disorders.

Topiramate

Mechanisms of action

The anticonvulsant effect of topiramate (TPM) depends on multifactorial mechanisms.

TPM inhibits several carbonic anhydrase isosymes and modulates AMPA/kainate- and $GABA_A$-activated ion channels as well as voltage activated Na^+ and Ca^{2+} channels. TPM may also activate K^+ conductance and inhibit depolarizing $GABA_A$-mediated responses, which may be due to intra- and/or extracellular pH shifts secondary to carbonic anhydrase inhibition [7]. TPM seems to potentiate the effects of endogenous GABA through a novel binding site on the $GABA_A$ receptor complex [21]. One possible mechanism of action may be the alteration of the phosphorylation state of the kainate receptor [61]. These effects may make it a useful potential neuro-

protectant acting by reducing excitatory amino acid release and ischemic depolarizations as well as by reducing calcium overload in the ischemic cells and increasing the brain's GABAergic activity.

Activity profile in seizure models

In animal models, TPM shows broad spectrum of anticonvulsant activity. It has been documented to exert antiseizure activity in the MES [82, 85, 88], in spontaneously epileptic rats and genetically seizure-prone DBA/2 mice [88] and the amygdala-kindled rats [88]. It is, however, inactive or weakly active in seizures chemically induced by PTX, PTZ, BIC and strychnine [82, 88]. It attenuates seizure-induced hippocampal neuronal injury after experimental SE in rats [88].

Neuroprotective activity

Follett et al. [28] have demonstrated that the clinically-available anticonvulsant TPM, when administered post-insult *in vivo*, is protective against selective hypoxic-ischemic white matter injury and decreases the subsequent neuromotor deficits. It has also been shown that TPM attenuates AMPA/kainate receptor-mediated cell death and Ca^{2+} influx, as well as kainate-evoked currents in developing oligodendrocytes, similar to the AMPA/kainate receptor antagonist 6-nitro-7-sulfamoylbenzo-(f)quinoxaline-2,3-dione (NBQX). Notably, protective doses of NBQX and TPM do not affect normal maturation and proliferation of oligodendrocytes either *in vivo* or *in vitro*. It suggests that AMPA/kainate receptor blockade may have potential for translation as a therapeutic strategy for periventricular leukomalacia and that the mechanism of protective efficacy of TPM is caused at least in part by attenuation of excitotoxic injury to premyelinating oligodendrocytes in developing white matter [28].

Recent studies [70] suggest that TPM can have anti-excitotoxic properties, because it protects against motor neuron degeneration. Moreover, TPM enhances neuroprotection and reduces hemorrhagic incidence in focal cerebral ischemia [70]. Leker et al. [51] have recently underlined that TPM is effective both in focal and global ischemia.

Liu et al. [54] have hypothesized that early administration of a neuroprotective agent in combination with later-onset cooling could represent an effective therapeutic intervention after neonatal hypoxia-ischemia (HI). They have evaluated whether treatment with TPM increased the efficacy of delayed post-HI hypothermia in a neonatal rat stroke model. Neither TPM nor delayed hypothermia alone conferred protection. Combined treatment with TPM and delayed hypothermia improved both performance and pathological outcome in rats compared with phosphate-buffered saline (PBS)-treated animals that underwent delayed hypothermia concurrently. The data provided the impetus for further evaluation of therapeutic approaches that combine drug therapy with delayed-onset cooling after neonatal HI brain injury [54].

Rigoulot et al. [77] have proven that in DZP-treated rats, the number of neurons was dramatically reduced after SE in all subregions of the hippocampus and layers II–IV of the ventral cortices. TPM induced a 24 to 30% neuroprotection in layer CA1 of the hippocampus. In CA3b, its 30-mg/kg dose prevented neuronal death. All rats subjected to SE became epileptic. In conclusion, TPM displayed neuroprotective properties only in CA1 and CA3 that were not sufficient to prevent epileptogenesis.

Pitkanen [73] has indicated that a single dose of TPM (20, 40, or 80 mg/kg, *ip*) administered 140 min after onset of SE, induced by unilateral hippocampal stimulation in rats, reduced neuronal damage bilaterally in the hilus and CA1 and contralaterally in the CA3 when assessed from silver-stained sections 3 days later [73].

Human studies

TPM has been proven to be effective in patients with refractory chronic partial epilepsies in short-term controlled clinical trials [88] but the long-term retention, long-term efficacy and long-term side-effect profile have not been sufficiently investigated [9]. Bootsma et al. [9] concluded that TPM was associated with a high incidence of side effects in clinical practice, affecting long-term retention. On the other hand, Lhatoo et al. [53], basing upon Cox regression analysis, have come to the conclusion that the retention rate for TPM in patients with partial chronic epilepsy reached 28%, whilst that for LTG was 12% and for GBP – only 2%. French et al. [31], however, stated that TPM has efficacy as monotherapy in newly diagnosed adolescents and adults with either partial or mixed seizure disorders. Evidence for effectiveness of TPM in newly diagnosed patients with other generalized epilepsy syndromes is lacking [30]. TPM has been found to be appropriate for adjunctive treatment of refractory partial seizures in adults and effective for the treatment of

refractory partial seizures in children [31]. It may precipitate both psychosis and depression [5].

Vigabatrin

Mechanisms of action

Vigabatrin (VGB) is an AED that irreversibly inhibits GABA transaminase and thus increases GABA concentration, affecting both $GABA_A$ and $GABA_B$ conductances [14].

Activity profile in seizure models

Kang et al. [43] have suggested that VGB increased Na^+/H^+ exchanger (NHE1) and Na^+/HCO_3^- cotransporter (NBC) protein expressions in the gerbil hippocampus. This indicates that GABA receptor-mediated regulation of NHE1 and NBC expressions may participate in acid-base balance in the gerbil hippocampus. Schwabe et al. [79] have shown that microinjection of VGB into the central piriform cortex markedly inhibits the progression and secondary generalization of focal seizures [79]. Świąder et al. [87] have presented studies which have indicated that acute treatment with VGB enhanced the anticonvulsant activity of ESM against PTZ-induced seizures due to a pharmacokinetic interaction. Chronic treatment with VGB would be necessary to specifically characterize the nature of interactions of this antiepileptic with conventional AEDs. In the pharmacodynamic study, Łuszczki et al. [59] have revealed that VGB might potentiate the antiseizure effects of some conventional AEDs [59].

Neuroprotective activity

Trojnar et al. [88] have suggested that in the lithium-pilocarpine model of temporal epilepsy VGB protected against neuronal damage. This analysis has shown that treatment with the drug induced almost total neuroprotection in CA3, efficient protection in CA1 and moderate in the hillus of the dentate gyrus. The drug was also found effective in preventing the effects of transcient global ischemia in gerbils [88]. However, they also have suggested adverse effects of VGB on the brain. Chronic administration was associated with myelin vacuolization, decreased myelin staining in the external capsule, axonal degeneration and glial cell death in the white matter as well as reactive astrogliosis in the frontal cortex. Direct toxicity of VGB or an indirect effect mediated through elevated GABA levels could constitute the mechanisms of damage.

Pitkanen [73] has underlined that there was no neuroprotective effect of VGB on CA1 cell damage, when administered for 4 weeks after SE induction by electrical stimulation of the hippocampus for 90 min. However, Pitkanen [73] has indicated that some other data substantiated a clear neuroprotective effect of VGB treatment when initiated (250 mg/kg) 10 min after induction of SE with pilocarpine in rats and continued for 45 days.

Human studies

Clinically, VGB is effectively used as an adjunctive anticonvulsant for the treatment of multidrug-refractory complex partial seizures in adults. It has also been effective in the management of resistant partial seizures and infantile spasms in both children and adolescents [8]. It has been estimated that VGB contributes to visual field loss by from 14 to 92% [8]. VGB is an effective [64], well-tolerated treatment for infantile spasms. The response is dose-independent.

Zonisamide

Mechanisms of action

Zonisamide (ZNS) has several potential mechanisms of action. It blocks of voltage-sensitive Na^+ channels and T-type Ca^{2+} currents, modulates of GABAergic and dopaminergic (DA) systems, and is a free-radical scavenger [68]. ZNS does not potentiate the synaptic activity of GABA. Moreover, ZNS biphasically facilitates dopaminergic and serotoninergic (5-HT) transmission. At effective concentrations, the drug enhances, whereas at supraeffective concentrations it reduces DA and 5-HT neurotransmission [80].

Activity profile in seizure models

In animal models, ZNS has activities comparable both with those of PTH and CBZ and those of VPA. Thus, it is predicted to have a broad spectrum of antiepileptic activity [52]. Immobilization stress markedly en-

hanced anticonvulsant action of ZNS in mice [37]. Interestingly, stress and forced-swimming stress have been reported to increase blood-brain barrier permeability. The drug did not appear to affect the spontaneous alternation behavior, active avoidance performance, and relative power of cortical EEG [80].

Neuroprotective activity

Sobieszek et al. [80] have summarized that ZNS is an anticonvulsant compound that reduces infarct volume in ischemia-induced neuronal damage. Neuroprotective efficacy of ZNS pretreatment was also shown in hypoxic-ischemic damage in neonatal rats [80].

Reduction of neuronal damage caused by ZNS pretreatment in global forebrain ischemia model in gerbils was also underlined in the above-mentioned article [80]. It should be emphasized that ZNS posttreatment did not exhibit such histological or behavioral effects, as when the drug was administered before the ischemic stimulus. Leker et al. [51] have recently underlined that ZNS is effective only in focal, not in global, ischemia. Its suggested mode of neuroprotection involves a decreased secretion of excitatory amino acids and reduction in post-anoxic depolarizations as well as a reduction in the toxic effects of free radicals. However, because no other studies have been conducted on this drug, it cannot be recommended for neuroprotective purposes. Further trials are warranted to evaluate the potential value of this promising drug [51].

Human studies

According to Newmark [65], a review of previous studies, including one in children, suggests that ZNS can be effective for otherwise refractory partial seizures. Furthermore, in small studies, generalized tonic-clonic seizures, atypical absences, infantile spasms and myoclonia, particularly the seizures of progressive myoclonic epilepsies, have responded to ZNS, as have the seizures of the Lennox-Gastaut syndrome [65]. Recently, there have been reports of ZNS monotherapy for infantile spasms [45, 80].

Conclusions

In this article we tried to review current available data on new and potential AEDs. Most of them have been, or still are being studied, in respect of their toxicity, neuroprotection and adverse effects.

As Czuczwar et al. have reviewed [19], the pro-apoptotic effect in young rat brains is a significant aspect of the influence of AEDs on CNS. So far there are no other conclusive results in clinical research confirming this. If there had been, the usage of the AEDs would be still seriously limited in children. In her research, Ikonomidou [40] has indicated that, apart from benzodiazepines and barbirurates, such an effect is caused by PHT, VPA and VGB at concentrations corresponding to their anticonvulsant activity in experimental models of epilepsy [40]. One of the above-presented AEDs, TPM, has very promising neuroprotective profile, stemming from the fact that this drug acts on several different yet complementary antiischemic pathways, thereby increasing the likelihood of a positive protective effect. TPM, an AED reducing the excitatory effects of glutamate and enhancing GABA-mediated inhibition, very potently prevented neuronal loss in hippocampus exposed to prolonged seizure activity [73]. It must be emphasized that pro-apoptotic activity of TPM was significantly weaker, which means that it was observed at doses higher than those providing effective experimental epilepsy prevention [40].

Also, some other AEDs, for example TGB, presented neuroprotective effects in experimental models of epilepsy [73]. It seems logical to use AEDs with neuroprotective potential since, by preventing neuronal death, they are likely to stop synaptic reorganization and subsequent epileptogenesis. Strategies preventing neuronal loss suppress the process of forming epileptogenic loops, thus possibly inhibiting epileptogenesis. Furthermore, the two above-mentioned drugs were found to be effective in both global and focal ischemia, and both showed an extended therapeutic window that would enable their use in clinical practice. However, despite these seemingly promising prospects, it is important to understand that currently no individual AED can be viewed as a potential neuroprotectant against ischemic injury.

Drugs mentioned in this review (FBM, GBP, LEV, OXC, TGB, TPM, VGB, ZNS) have been already licensed, whereas some of them: PGB, RCM, TLP and LSG, have not been yet registered as AEDs. They are still a subject of further research. However, recent experiments in animals and clinical trials have shown that they appear to be promising drugs with several applications both in the treatment of seizures and neu-

Tab. 1. Neuroprotective properties of antiepileptic drugs in experimental models of ischemia and seizures in animals

Antiepileptic drugs	Neuroprotection in ischemia	Neuroprotection against convulsants or convulsive prodcedures	Induction of neurodegeneration	References
Felbamate	+	+	ND	[7, 51, 73, 76, 88]
Gabapentin	+	+	ND	[73, 88]
Levetiracetam	+/–	–	ND	[36, 51, 73]
Losigamone	ND	+	ND	[46]
Oxcarbazepine	+/–	+/–	+	[1, 73, 76]
Pregabalin	ND	ND	ND	
Remacemide	+	+	ND	[15, 51, 72]
Talampanel	+	+	+	[4, 91]
Tiagabine	+	+/–	+	[51, 73, 76, 88]
Topiramate	+	+	+*	[28, 51, 70, 73, 77, 88]
Vigabatrin	+	+/–	+	[73, 88]
Zonisamide	+	ND	ND	[51, 80]

* Ikonomidou [39] indicates that pro-apoptotic activity of TPM was evident at doses higher than those providing effective seizure prevention, however, other AEDs induce neurodegeneration at effective doses. ND – non determined

ropathic pain and generalized anxiety disorder. However, new AEDs are initially approved for the adjunctive treatment of epilepsy.

Summarizing, a new approach to drug screening, including the process of epileptogenesis, may yield new classes of drugs that not only suppress seizures but also specifically act to protect against the neurobiological changes that contribute to the development of epilepsy. By preventing or reversing the neuronal circuit reorganizations that produce lowered seizure thresholds following brain injuries such as head trauma or SE, these antiepileptogenic drugs could prevent, or reverse, progressive worsening of the epileptic process.

The neuroprotective properties of the selected AEDs are presented in Tab. 1.

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