Mechanisms of Action of Antiepileptic Drugs

Piotr Czapiński[1], Barbara Blaszczyk[2], Stanislaw J. Czuczwar[3,4,*]

[1]*Center for Treatment of Epilepsy and Migraine, Kielecka 25, 31-523 Kraków,* [2]*Department of Neurology, Neuropsychiatric Care Unit, Grunwaldzka 47, 25-736 Kielce,* [3]*Department of Pathophysiology, Skubiszewski Medical University, Jaczewskiego 8, 20-090 Lublin,* [4]*Isotope Laboratory, Institute of Agricultural Medicine, Jaczewskiego 2, 20-950 Lublin, Poland*

Abstract: γ-Aminobutyric acid (GABA), one of the main inhibitory neurotransmitters in the brain, interacts with three types of receptors for GABA - $GABA_A$, $GABA_B$ and $GABA_C$. $GABA_A$ receptors, associated with binding sites for benzodiazepines and barbiturates in the form of a receptor complex, control opening of the chloride channel. When GABA binds to the receptor complex, the channel is opened and chloride anions enter the neuron, which is finally hyperpolarized. $GABA_B$ receptors are metabotropic, linked to a cascade of second messengers whilst the physiological meaning of ionotropic $GABA_C$ receptors, mainly located in the retina, is generally unknown. Novel antiepileptic drugs acting selectively through the GABA-ergic system are tiagabine and vigabatrin. The former inhibits neuronal and glial uptake of GABA whilst the latter increases the synaptic concentration of GABA by inhibition of GABA-aminotransferase. Gabapentin, designed as a precursor of GABA easily entering the brain, was shown to increase brain synaptic GABA. This antiepileptic drug also decreases influx of calcium ions into neurons via a specific subunit of voltage-dependent calcium channels. Conventional antiepileptics generally inhibit sodium currents (carbamazepine, phenobarbital, phenytoin, valproate) or enhance GABA-ergic inhibition (benzodiazepines, phenobarbital, valproate). Ethosuximide, mainly controlling absences, reduces calcium currents via T-type calcium channels. Novel antiepileptic drugs, mainly associated with an inhibition of voltage-dependent sodium channels are lamotrigine and oxcarbazepine. Since glutamate-mediated excitation is involved in the generation of seizure activity, some antiepileptics are targeting glutamatergic receptors – for instance, felbamate, phenobarbital, and topiramate. Besides, they also inhibit sodium currents. Zonisamide, apparently sharing this common mechanism, also reduces the concentration of free radicals.

Novel antiepileptic drugs are better tolerated by epileptic patients and practically are devoid of important pharmacokinetic drug interactions.

Key Words: Antiepileptic drugs, GABA, glutamate, ion channels, epilepsy.

INTRODUCTORY REMARKS

There is no doubt that epilepsy belongs to the most encountered neurological conditions since the disease affects approximately 1% of the population. Around 75-80% of epileptic patients may be provided with adequate seizure control with the help of conventional antiepileptic drugs. Carbamazepine, ethosuximide, phenobarbital, phenytoin, and valproate are the most frequently used conventional antiepileptics. The therapeutic failure in 20-25% of patients has stimulated intensive research on novel antiepileptic drugs and so far nine of them have been developed and licensed mainly as add-on treatment in patients poorly responding to conventional therapy. These are felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, and zonisamide [1].

Majority of antiepileptic drugs possesses more than one mechanism of action. Deckers *et al*. [2] have proposed a classification of antiepileptic drugs based upon these mechanisms. First group consists of antiepileptics (f.e.: carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate) which block sustained repetitive firing in individual neurons, this effect being mainly due to the blockade of voltage-dependent sodium or calcium channels. These drugs are effective against generalized tonic-clonic and partial seizures. The second group includes drugs enhancing inhibitory events mediated by γ-aminobutyric acid (GABA): benzodiazepines, gabapentin, phenobarbital, tiagabine, topiramate, vigabatrin, and valproate. Some of these drugs may be used in all seizure types (absence, generalized tonic-clonic, and partial seizures) – see below. The third group practically consists of one drug – ethosuximide which blocks T-type calcium channels and is active against absences. Recent evidence suggests that also zonisamide may be a T-type calcium channel inhibitor [3]. A separate category of drugs may be also suggested – these antiepileptic drugs reduce events mediated by excitatory amino acids (f.e.: glutamate) and at present three antiepileptics meet these criteria: felbamate, phenobarbital, and topiramate [2].

RECEPTORS FOR GAMMA-AMINOBUTYRIC ACID (GABA)

GABA may mediate its synaptic events through two types of receptors - ionotropic and metabotropic. Among ionotropic receptors associated with a chloride channel so called $GABA_A$ and $GABA_C$ receptors are distinguished - metabotropic ones linked to the cascade of second

*Address correspondence to this author at Isotope Laboratory, Institute of Agricultural Medicine, Jaczewskiego 2, 20-950 Lublin, Poland; E-mail: czuczwar@galen.imw.lublin.pl

1568-0266/05 $50.00+.00

intraneuronal messengers are $GABA_B$ receptors [4,5]. $GABA_A$ receptor complex consists of a number of binding sites for GABA itself, benzodiazepines, barbiturates, ethanol and picrotoxin which is a chloride channel blocker. When GABA binds to its recognition site on the $GABA_A$ receptor complex, an opening of the chloride channel occurs with the subsequent influx of chloride anions into a neuron, resulting in its hyperpolarization. Benzodiazepine derivatives (f.e.: diazepam, clonazepam) increase the frequency of the channel openings whilst barbiturates (f.e.: phenobarbital) prolong the opening time of the channel. Both, benzodiazepines and barbiturates also enhance the affinity of $GABA_A$ receptors for the neurotransmitter [4,5]. In contrast, binding GABA to the $GABA_B$ receptors results in the activation of phospholipase A-2 and the following synthesis of arachidonic acid from phospholipids. Arachidonic acid via regulatory G_i proteins is likely to modulate the activity of adenyl cyclase and cyclic AMP levels. Through the $GABA_B$ receptors GABA affects the release of other important for the neuronal activity neurotransmitters. $GABA_C$ receptors are mainly encountered in the retina and their physiological significance is a matter of dispute [6].

Occurrence of GABA in the central nervous system was demonstrated in 1950 and in the same decade GABA was shown to inhibit seizure activity after its direct cerebral application in dogs [7]. Certainly, this gave rise to the assumption that GABA-ergic inhibition may be an important factor in the suppression of seizure activity in epileptic patients. GABA itself was not a good candidate for an antiepileptic drug since it very poorly entered the brain through the blood- brain barrier. Much attention was paid to a synthesis of GABA-ergic agonists, which would easily penetrate into the central nervous system. Such substances were soon available, for instance agents increasing brain GABA concentration due to the inhibition of GABA metabolism: aminooxyacetic acid, γ-acetylenic-GABA, γ-vinyl-GABA or direct agonists, for example - muscimol. Actually, these substances were found to exert anticonvulsant effects in a variety of experimental models of epilepsy [7,8-10]. The initial enthusiasm was, however, not fully justified - it soon would come out that muscimol displayed a proconvulsant activity in primates and humans [7]. This was understood in terms of an undesired effects of the diffuse stimulation of $GABA_A$ receptors within the brain. Consequently, the subsequent search for GABA-ergic agents as potential antiepileptic drugs would focus on substances indirectly enhancing GABA functions - via inhibition of its metabolism or reduction of its neuronal uptake. This strategy led to the discovery of potent anticonvulsant substances - some of them are nowadays potent antiepileptic drugs.

ANTIEPILEPTIC DRUGS AND GABA-MEDIATED INHIBITION

Valproic acid in the form of sodium salt was introduced to the therapy of epilepsy in the early 60s. One of the most likely mechanisms responsible for its anticonvulsant activity may be inhibition of its metabolic degradation resulting in the elevation of GABA level in the synaptic cleft [11]. However, there are also data indicating no correlation between the protective action of valproate and GABA increase - in fact, valproate clearly reduced seizure activity produced by the inhibitor of GABA synthesis, izoniazid, but did not restore the reduced GABA level [12]. As already mentioned, benzodiazepines (fe.: diazepam, clonazepam) and barbiturates (fe.: phenobarbital) potentiate GABA-mediated inhibition via the increase in the affinity of this inhibitory neurotransmitter to its recognition sites within the $GABA_A$ receptor complex and via the direct influence upon the chloride channel which leads to the enhanced influx of chloride anions into the neuron and subsequent hyper-polarization. Among novel antiepileptic drugs, tiagabine and vigabatrin seem to express their anticonvulsant activity mainly through the GABA-ergic system. Other novel antiepileptics associated with GABA-mediated inhibition, which also share additional mechanisms of action, are: felbamate, gabapentin, and topiramate. Tiagabine and vigabatrin, and to a certain degree - gabapentin, may be considered as drugs whose development was associated with so called GABA hypothesis of epilepsy [13]. Vigabatrin is an irreversible inhibitor of GABA transaminase and its administration in animals or humans results in the 3-fold increase in synaptic GABA level [14-16]. Tiagabine inhibits neuronal and glial GABA uptake, leading thus to the enhancement and prolongation of GABA synaptic events [16,17]. The anticonvulsant activity of inhibitors of GABA uptake in various models of experimental epilepsy was shown much earlier but these substances did not cross the blood-brain barrier. This certainly disqualified their possible use as antiepileptic drugs [18]. Probably, as already mentioned, tiagabine and vigabatrin possess mechanisms of action closely related to GABA-mediated events in the synaptic cleft, in contrast to conventional and some novel antiepileptics which may block voltage-dependent sodium and calcium channels and impair glutamate-induced excitation. For instance, sodium channels are blocked by a variety of antiepileptic drugs, including benzodiazepines (at high concentrations), carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, topiramate, and valproate. Ethosuximide or zonisamide mainly affect T-type calcium channels, and felbamate, phenobarbital, and topiramate inhibit glutamate excitation [19]. Interestingly, gabapentin, a cyclic analogue of GABA, was designed as a GABA agonist easily passing the blood-brain barrier. However, no receptor activity of gabapentin was detected on the $GABA_A$ receptor complex, only increased GABA turnover being found in some rat brain regions [20,21]. Also, gabapentin was documented to increase GABA level in brains of epileptic patients [15]. It is evident now, that this antiepileptic drug binds to the specific unit of voltage-dependent calcium channel and inhibits intraneuronal calcium ion flux from the extraneuronal space [22]. Two novel antiepileptic drugs, topiramate and felbamate, although possessing multiple mechanisms of action (see below), affect GABA-mediated inhibition as well. Specifically, the former seems to potentiate effects of endogenous GABA through a novel binding site on the $GABA_A$ receptor complex [21,23]. The latter enhanced GABA-dependent chloride currents in rat hippocampal neurons [24]. However, such effect *in vitro* was no longer evident in the absence of GABA and, moreover, felbamate was not shown to interact directly with the $GABA_A$ receptor complex [25]. Among conventional and novel

antiepileptic drugs, carbamazepine, ethosuximide, lamotrigine, oxcarbazepine, and phenytoin (within therapeutic concentrations) seem to have nothing to do with GABA-mediated inhibition [19].

IS GABA-MEDIATED INHIBITION ALWAYS BENEFICIAL IN EPILEPSY?

Increasing GABA-mediated inhibition may not be always advantageous - both, experimental and clinical data provide evidences that enhancement of the GABA-ergic neurotransmission exacerbates absences. Drugs acting through potentiation of GABA-mediated synaptic events led to an increase in the number and severity of absence seizures in WAG/Rij rats [26]. Vigabatrin was also verified clinically in this respect and it turned out that this drug worsened absence seizures in children [27]. It is very likely that this proconvulsive effect of GABA-mimetic drugs may be related to $GABA_B$ receptors [26]. Actually, the antagonist of $GABA_B$ receptors, compound CGP 35348, potently inhibited spike and wave discharges in WAG/Rij rats [28]. The involvement of the $GABA_A$ receptor complex in this particular effect of GABA agonists must not be ignored since bicuculline, a $GABA_A$ receptor antagonist, also displayed anticonvulsant activity in this model of absence seizures [29]. It is thus likely that enhanced GABA-mediated inhibition may be closely related to the induction of absence seizures. However, many antiepileptic drugs, known to increase GABA-ergic functions are good anti-absence drugs, for instance - benzodiazepines and valproate. A possible explanation must consider an option assuming that these antiepileptic drugs are likely to possess alternative mechanisms of action, responsible for their anti-absence effects. After all, these so far unidentified mechanisms seem to efficiently counteract the GABA-mimetic profile of benzodiazepines and valproate.

RECEPTORS FOR EXCITATORY AMINO ACIDS

Excitatory amino acids (e.g. glutamate or aspartate) are undoubtedly involved in the generation of seizure events [30]. Glutamate and related excitants induce seizure activity upon systemic or intracerebral administration [31-35]. Bearing in mind that some cases of human epilepsy may be accompanied by marked increases in plasma excitatory amino acids or their extracellular concentrations [36], it is likely that excitation mediated by glutamate or other excitatory amino acids in the brain may be causally related to the occurrence of epilepsy in humans. The effectiveness of excitatory amino acid antagonists, especially these blocking ionotropic receptors for glutamate, in various experimental models of epilepsy (electroconvulsions, chemically- or sound-induced seizures) seems to support such an assumption [31, 37-42]. Ionotropic glutamatergic receptors can be subdivided in those sensitive to N-methyl-D-aspartate (NMDA) and those sensitive to α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate/kainate which are regarded as non-NMDA receptors [43]. NMDA receptors increase predominantly sodium and calcium conductances and non-NMDA receptor mediated excitation results in elevated sodium permeability [44-45]. These findings were confirmed *in vivo* since BAY k-8644 reduced the anticonvulsive activity of competitive NMDA receptor antagonists, being ineffective upon AMPA/kainate receptor antagonists [46].

Out of the conventional antiepileptic drugs, only valproate (300 - 400 mg/kg) and diazepam (at doses exceeding 10 mg/kg) were able to inhibit convulsions evoked by systemic N-methyl-D,L-aspartate in mice. Phenobarbital, phenytoin, carbamazepine, and ethosuximide, in the high dose range, were totally ineffective [33]. Similar results were reported by Turski *et al*. [47] - only valproate and diazepam were effective against intracerebroventricular NMDA in mice. On the other hand, all major antiepileptic drugs, except ethosuximide [35] could control seizures produced by intracerebral glutamate.

It has come out during the last decade that apart from ionotropic receptors for glutamate, there exists a population of metabotropic glutamate receptors (mGluRs). The eight mGluRs known so far are divided into three groups, according to their sequence homology, signal transduction mechanisms, and agonist selectivity [48]. Group I includes mGluR1 and mGluR5, which are linked to the activation of phospholipase C. Groups II and III include all other types, negatively coupled to adenylyl cyclase [49]. Recent studies revealed separate functions for two group I receptor subtypes. Glutamate stimulation produces a single peak of intracellular Ca^{2+} mobilization through mGluR1, but Ca^{2+} oscillations through mGluR5 receptors [50]. So far, there is no antiepileptic drug acting via mGluRs.

PROFILE OF NOVEL ANTIEPILEPTIC DRUGS MAINLY ASSOCIATED WITH GABA-MEDIATED INHIBITION

Tiagabine

This antiepileptic drug is marketed in many European countries, USA, and Australia as an adjuvant for the treatment of partial seizures (also with secondary generalization) in patients starting from 13 years of age [16]. This is a derivative of nipecotic acid, easily crossing the blood-brain barrier and potently increasing the level of GABA in the synaptic cleft via inhibition of its neuronal and glial uptake [16,51]. Tiagabine efficiently antagonized tonic seizures induced by pentylenetetrazol, DMCM, and sound in mice and was also effective against amygdala-kindled seizures in rats, reducing both the kindling process (an antiepileptogenic effect) and the expression of the fully kindled seizure [52-55]. This antiepileptic drug antagonized also the clonic phase of pentylenetetrazol-induced convulsions [53]. According to Dalby and Nielsen [54] and Löscher [19], it was ineffective against maximal electroshock-induced convulsions in mice, although at a high dose of 40 mg/kg it was reported to block maximal electroshock in rats [16] and to reduce the incidence of maximal electroshock seizures in mice [55]. In the perforant pathway stimulation model of status epilepticus in rats tiagabine clearly diminished the severity of seizures and reduced seizure-related brain damage to hippocampal pyramidal cells. Also, the impairment of spatial memory, dependent on hippocampal damage, was prevented by tiagabine administration [52]. Interestingly, carbamazepine was much less effective in this respect [56,57]. In the lethargic mouse model of absence seizures, tiagabine

distinctly increased seizure frequency and duration [58]. Clinical trials indicate that tiagabine (up to 64 mg/day), in the form of add-on therapy, reduced complex partial and simple partial seizure frequency by 50% in 28-32% and 8-31%, respectively. This effect was quite consistent with no tendency to fade away for the treatment period of up to 12 months [51]. According to Bialer *et al*. [16], tiagabine evaluated in six open long-term studies at an average daily dose of 30-40 mg decreased partial seizure rate in 30.5% of patients. The adverse potential of tiagabine was mainly associated with the central nervous system - dizziness, asthenia, somnolence, nervousness and tremor (mild to moderate) were noted usually during the titration period [16,51,59]. So far, there is no evidence that administration of tiagabine may result in non-convulsive status epilepticus [16] although some single reports suggest such a possibility [16,60]. Occurrence of other side effects, such as skin rash or psychosis, did not differ significantly among tiagabine- or placebo-treated patients [51].

Vigabatrin

Vigabatrin, as a structural GABA analogue, binds irreversibly to GABA-transaminase which results in the inhibition of this enzyme and reduced metabolism of this inhibitory neurotransmitter. This certainly leads to a considerable increase in the brain GABA level [17]. Although, similarly to tiagabine, vigabatrin also affects GABA-ergic neurotransmission, its pharmacological profile of activity is not, however, identical. This inhibitor of GABA-transaminase was ineffective against maximal electroshock and pentylenetetrazol-induced convulsions but it inhibited seizures produced by DMCM, sound and amygdala-kindling [53,55]. Vigabatrin also decreased the number of seizure episodes and their severity in the perforant path stimulation model, reducing brain damage as well [57]. This GABA enhancer (at 1000 and 1500 mg/kg) was particularly effective against kainate-induced seizure activity and mortality in pubescent rats - it is remarkable that carbamazepine and phenytoin were not anticonvulsant in this model, the former exerted even a proconvulsive action [61]. Engelborghs *et al*. [62] are of opinion that the anticonvulsant activity of vigabatrin may be not exclusively related to the increased GABA level. Actually, they observed maximal protective activity of this drug 4 h after its administration to audiogenic sensitive rats whilst GABA-transaminase was maximally inhibited 24 h after the single dose of vigabatrin. These authors consider other probable mechanisms and suggest that this antiepileptic may as well act through reduction of excitatory amino acid concentration in the brain and/or elevation of glycine content. At anticonvulsive doses, vigabatrin did not impair working memory in rats [63]. Similarly to tiagabine, however, it exacerbated seizure activity in the lethargic mouse model [58]. In addition, chronic vigabatrin (at a relatively high dose of 200 mg/kg/day) was documented to produce reversible myelin vacuolation in adult rats [64]. Moreover, in the range of doses similar to this used clinically (15-50 mg/kg/day) vigabatrin decreased myelin staining in the external capsule and produced axonal degeneration in the white matter and reactive astrogliosis in the frontal cortex in young rats. These irreversible effects could be either directly linked to vigabatrin toxicity or might be a result of increased GABA levels [64].

Its clinical effectiveness was proved in a number of trials. As underlined by Bialer *et al*. [16], in one of the recent US double-blind, placebo-controlled add-on studies, vigabatrin at 3-4g/day was capable of reducing seizure frequency by at least 50% in ca 40-50% patients suffering from drug resistant complex partial seizures. It is worth stressing that in the placebo group, the responders did not exceed 10%. As an adjuvant antiepileptic drug, vigabatrin was shown in an open trial to be effective in cases of mild to moderate partial epilepsies. At a mean dose of 2.21 ± 0.64 g per day during the fourth month of treatment, almost 40% of patients became seizure free and in further 17% the seizure frequency was diminished by more than 50% [65]. In childhood epilepsy, adjunctive vigabatrin (70 ± 38 mg/kg/ day) produced a 50% (or more) reduction in seizure frequency in cases of generalized myoclonic, atonic, and tonic-clonic as well as partial (with or without secondary generalization) epilepsy [66]. The drug also exerted beneficial effects in West syndrome, both as a monotherapy (150 mg/kg/day) [67] or add-on treatment (mostly to valproate or dexamethasone) [68]. It is remarkable that when added to current antiepileptic medication, vigabatrin did not affect cognitive performances and behavior - as a matter of fact a slight improvement in cognitive functions was observed in patients receiving this GABA enhancer [69]. No evidence for vigabatrin-induced intramyelinic edema in humans [16] and disturbed neuronal conduction in the brain were found [70]. Some cases of psychiatric events were noted but they did not exceed 3.4% in adults and 6% in children, and were usually mild [16,71]. Recently, some reports claim that vigabatrin may induce visual field constriction [72-74].

Lawden *et al*. [73] argue that this adverse effect may be attributed to a toxic influence vigabatrin on the retina and seems to persist after the drug's withdrawal. Others represent a view that this effect may be reversible [75]. Some other authors are of opinion that the visual field effect may be not necessarily attributed to vigabatrin only, since other antiepileptic drugs (carbamazepine, diazepam, gabapentin, phenytoin, and tiagabine) were also linked with this undesired action [76-78].

OTHER NOVEL ANTIEPILEPTIC DRUGS

Gabapentin

As mentioned above, gabapentin has no affinity to GABA-ergic receptors [20,21]. Apart from blockade of the specific subunit of the voltage-dependent calcium channel [22], this antiepileptic drug may increase synthesis of GABA [16,17]. Experimental studies indicate that gabapentin inhibited tonic pentylenetetrazol- and DMCM-induced convulsions and audiogenic seizures in mice [54]. Gabapentin efficiently antagonized all seizure parameters in amygdala-kindled rats but was ineffective against maximal electroshock in mice [54]. However, it raised the threshold for electroconvulsions (at 50-100 mg/kg) and considerably potentiated (at 25 mg/kg) the protective activity of conventional antiepileptic drugs against maximal electroshock in mice [79]. Gabapentin inhibited audiogenic seizures in

DBA/2 mice, the respective ED_{50} (120 min treatment time) against wild running, clonus and tonus being 11.6, 8.1 and 5.4 mg/kg. At the subprotective dose of 2.5 mg/kg, gabapentin enhanced the anticonvulsant action of diazepam, phenobarbital, valproate (to a considerable degree), felbamate, phenytoin (to a moderate degree), carbamazepine and lamotrigine (to a small extent) [80]. Apparently, no pharmacokinetic interaction was responsible for combination therapy of gabapentin with the antiepileptic drugs [79,80], in terms of their free plasma levels at least. In contrast to tiagabine and vigabatrin, gabapentin did not affect the seizure frequency in the lethargic mouse model of absence seizures [58]. Interestingly, gabapentin (20-30 mg/kg) suppressed firing of neurons in substantia nigra pars reticulata which may be crucial to its anticonvulsant activity [81].

Gabapentin is mainly recommended as adjunctive therapy for partial seizures with or without secondary generalization [17,82]. Monotherapy with this drug was also effective in refractory partial seizures at a minimum daily dose of 3.6 g [16]. Gabapentin seems also effective against refractory generalized tonic-clonic seizures [16]. As add-on therapy, gabapentin was given in doses of 26-78 mg/kg/day to children with partial epilepsy. According to Korn-Merker *et al*. [83], the seizure frequency remained unchanged in 65% of patients, whilst 29% benefited from the drug.

Topiramate

Topiramate is a good example of a drug sharing multiple mechanisms of action. Specifically, this antiepileptic inhibits voltage-dependent sodium and calcium currents, potentiates GABA-mediated events, blocks the AMPA/KA receptor and enhances potassium currents [1,84]. The receptor and channel activities of topiramate probably result from its binding to to specific sites phosphorylated by cAMP-dependent protein kinases. This leads to the impaired channel or receptor phosphorylation, which under physiological conditions is necessary for proper receptor/channel functioning [84]. Interestingly, topiramate is also an inhibitor of several carbonic anhydrase isozymes [84]. The drug is effective against all major experimental convulsive procedures, i.e. against maximal electroshock-induced convulsions, amygdala-kindled seizures and pentylenetetrazol-induced convulsions. Its ED_{50} value to protect against maximal electroshock in mice was 62.1 mg/kg [85], however the protection offered against the clonic phase of pentylenetetrazol convulsions was much weaker – at 175 and 200 mg/kg it elevated the convulsive threshold [86]. Significant inhibition of amygdala-kindling parametres in rats was observed with topiramate at 75 and 100 mg/kg [86]. Experimental data indicate that topiramate enhances the protective potential of conventional antiepileptic drugs in different models of rodent epilepsy [85,86]. This reflects its ability to positively interact with other antiepileptic drugs in cases of human refractory partial onset epilepsy [84]. This novel antiepileptic drug is also very efficient as monotherapy (100 or 200 mg daily) when compared to conventional antiepileptics – carbamazepine (600 mg daily) or valproate (1250 mg daily). It is noteworthy that 75% of patients were seizure free after one-year monotherapy [84]. Also, the drug has a very broad spectrum of antiepileptic efficacy, being effective practically against all types of epileptic seizures [1,87].

Initially, high incidence of undesired effects in patients receiving topiramate was clearly associated with too short titration period and excessive doses of the antiepileptic [84]. In some patients topiramate may induce confusion, ataxia, fatigue, and somnolence. Following long-term treatment with the drug, a possibility of renal calculi arises due to the inhibition of carbonic anhydrase [1].

Multiple mechanism of topiramate's activity have made it a real candidate for the treatment of other than epilepsy disorders, including neuropathic pain, bipolar disorder, post-traumatic stress disorder, and obesity [84].

Lamotrigine

This novel antiepileptic drug shares a very similar mechanism of action with conventional antiepileptic drugs, carbamazepine and phenytoin. The drug binds to the inactivated form of voltage-dependent sodium channels, thus limiting the sustained repetitive firing of neurons without any substantial effect upon normal synaptic activity [88]. Also, lamotrigine reduces calcium currents via voltage-sensitive calcium channels [89]. Its reduction of glutamate release is controversial – according to Loscher [19], this effect may be encountered only at supratherapeutic concentrations.

Lamotrigine is effective against two major experimental models of epilepsy – maximal electroshock-induced seizures in mice and amygdala-kindled convulsions in rats. However, it does not offer any protection against pentylenetetrazol seizures [54,90]. Its clinical spectrum is broader – the drug is effective against generalized tonic-clonic, partial, and absence seizures [91-93]. Similarly to other novel antiepi-leptic drugs, lamotrigine posesses comparable anticonvulsant efficacy but exerts much less adverse effects when compared to conventional antiepileptic drugs [94]. This is why the percentage of patients completing the long-term trials is considerably higher with lamotrigine than with valproate [94].

Lamotrigine has been often associated with the incidence Stevens Johnson syndrome or toxic epidermal necrolysis. However, detailed analysis of this problem has revealed that other antiepileptic drugs (carbamazepine, phenobarbital or phenytoin) may also induce this condition to a comparable degree [84]. Lamotrigine may produce rash, an obviously dose-related effect that may in serious cases lead to the discontinuation of lamotrigine treatment in less than 4% of patients [84,94]. As with other novel antiepileptic drugs, the incidence of undesired effects may be reduced with slower titration schedule and lower initial dose of this antiepileptic drug [94].

Levetiracetam

Levetiracetam considerably differs from other novel antiepileptic drugs in that it does not interfere with any known target for anticonvulsant activity. To be true, the drug does not affect voltage-dependent channels or receptors for major inhibitory or excitatory neurotransmitters [95]. Interestingly, levetiracetam is ineffective in acute models of

experimental epilepsy, including maximal electroshock-induced convulsions or clonic phase of pentylenetetrazol (or other chemical convulsants) seizures. In contrast, it is highly effective against amygdala-kindling in rats and a number of genetic models of epilepsy. In the amygdala-kindling model, this antiepileptic drug not only inhibits convulsions in fully kindled animals, but also retards the development of kindling as well, which may speak for its antiepileptogenic efficacy [95,96]. A specific binding site for levetiracetam in the brain has been identified and the drug seems to be displaced from this site to a certain degree by ethosuximide and pentylenetetrazol. However, other antiepileptic drugs (carbamazepine, diazepam, phenobarbital, or valproate) or convulsants (picrotoxin or bicuculline) were completely ineffective in this regard [95].

So far, the drug is recommended as an adjuvant for treatment of partial drug-resistant epilepsy, therefore, it is impossible to state whether the beneficial clinical effects result only from levetiracetam alone. Anyway, the clinical outcome is promising – following introduction of levetiracetam, almost 40% of patients experienced a 50% reduction in seizure frequency and 20% of patients had even a 75% reduction [97]. It is remarkable that monotherapy with levetiracetam, following the add-on phase, also proved very effective in refractory patients, the adverse effects being only minimal [97].

Contrary to antiepileptic drugs as a whole, levetiracetam did not impair cognitive functions in experimental animals or epileptic patients. Most commonly encountered adverse effects were somnolence, headache, asthenia and dizziness [97].

Felbamate

This is also an example of an antiepileptic drug possessing multiple mechanism of anticonvulsant action. To date, the drug has been documented to block voltage-dependent sodium channels and NR2B subunit of NMDA receptor [98,99]. Also, felbamate presumably inhibits glutamatergic neurotransmission via AMPA/kainate receptors [100] and enhances GABA-mediated events through a barbiturate-like modulatory effect on the $GABA_A$ receptor [101].

Felbamate effectively inhibits maximal electroshock-, audiogenic-, pentetrazole-, picrotoxin-, N-methyl-D-aspartate-, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-induced convulsions and amygdala- or pentetrazol-kindled seizures [25,102-105]. Bicuculline- and strychnine-evoked convulsions were, however, not affected by felbamate [25].

Clinical use of this antiepileptic is at present limited since there are reports indicating a possibility of aplastic anemia of idiosyncratic origin and hepatic failure. Although, the incidence of fatal aplastic anemia is in the range of one in 20,000 patients [106]. Also, to a high degree this condition may be eliminated since, generally, patients with felbamate-induced bone marrow failure either had blood dyscrasias or pre-existing immune disorders [107]. Consequently, the proper selection of patients may help avoiding this life-threatening condition. Prevalence of felbamate hepatotoxicity does not significantly differ from that associated with valproate [107]. Anyway, felbamate use is mainly restricted to partial refractory epilepsy and Lennox-Gastaut syndrome, resistant to other antiepileptic medications [108,109]. In contrast to a risk of aplastic anemia, the drug demonstrates very limited adverse effects from the central nervous system [98].

Zonisamide

This antiepileptic drugs, apart from mechanism shared by many antiepileptics, also has a very unique mechanism of action. Similarly to majority of antiepileptic drugs, zonisamide blocks voltage-dependent sodium channels and reduces calcium currents through T-type channels. Also, zonisamide, at therapeutic concentrations, enhances both, dopaminergic and serotonergic neurotransmission and inhibts glutamate-induced excitation. The drugs also shares a very unique mechanism among antiepileptic drugs – it apparently reduces the overproduction of nitric oxide and free radicals, which may be related to its anticonvulsant and neuroprotective effects. However, zonisamide does not seem to interfere with GABA-mediated events [110].

Owing to its multiple mechanism of action, zonisamide possesses a broad spectrum of anticonvulsant activity against experimental seizures. This antiepileptic drug is effective against maximal electroshock and chemical convulsants, pentylenetetrazol or fluorothyl. Although, the data on inhibition of pentylelentetrazol-induced convulsions are inconsistent. There is also some controversy as for the effectiveness of zonisamide against amygdala-kindling in rats. Nevertheless, the drug is effective in the treatment of drug-resistant partial seizures, as well as against generalized tonic-clonic, absence, and myoclonic convulsions. Interestingly, zonisamide has an advantage over carbamazepine or valproate in patients with complex partial epilepsy. Recent clinical data indicate that zonisamide is effective against bipolar disorder and acute mania. There is also evidence that the drug may alleviate symptoms of Parkinson's disease, which is probably dependent on the inhibition by zonisamide of type B monoaminooxidase [110]. Its possible anti-migraine effects are also considered [84].

Undesired effects of zonisamide include somnolence, ataxia, headache, nausea, agitation, irritability or fatigue. Also, loss of appetite or anorexia may complicate the treatment process [110].

Oxcarbazepine

This newer antiepileptic drug, closely related to carbamazepine, possesses also an active metabolite – the monohydroxy derivative. The mechanism of action of the parent drug and metabolite involve blockade of voltage-dependent sodium and calcium channels. Although, in *in vitro* conditions oxcarbazepine was demonstrated to inhibit both, chemically- or electrically-induced release of glutamate, this effect could not be confirmed *in vivo* [111].

Oxcarbazepine efficiently antagonizes maximal electroshock-induced convulsions in rodents, as well as the tonic

phase of pentylenetetrazol convulsions. There are also data avilable on the inhibition by this antiepileptic of pilocarpine-evoked status epilepticus in rats [111].

Clinically, the drug is effective against generalized tonic-clonic and partial seizures. It is remarkable that the adverse effects are rather mild – cognition (or memory) was only minimally affected [111].

Mechanism of action of conventional and new antiepileptic drugs is summarized in Table **1**.

PROFILE OF POTENTIAL ANTIEPILEPTIC DRUGS AFFECTING GABA-MEDIATED INHIBITION

Ganaxolone belongs to neuroactive steroids and its main mechanism of action involves increase in the chloride channel permeability within the $GABA_A$ receptor complex. It is remarkable that this neurosteroid binds to a steroid recognition site of the receptor complex. Although its moiety bears a close similarity to progesterone, the drug possesses no hormonal activity [16,112]. Ganaxolone was found to be active in a variety of convulsive tests in rodents - maximal electroshock, pentylenetetrazol-, bicuculline-, and picrotoxin-induced convulsions. It was, however, ineffective against strychnine- and NMDA-evoked seizures although a clear-cut antilethal activity against NMDA was observed [112]. It is noteworthy that ganaxolone also inhibited pentylenetetrazol convulsions in fully kindled with pentylenetetrazol mice and its potency was even stronger than that of diazepam and valproate [113]. Only ganaxolone exhibited antiepileptogenic activity since it was capable of blocking the development of kindling - this effect was not shared by either diazepam or valproate [113]. Also, the neurosteroid was superior to the conventional antiepileptic drugs in terms of adverse activity since within the range of its anticonvulsant doses, ambulatory activity of mice was not disturbed [113]. From the preclinical profile of the drug its potential activity against myoclonic, tonic-clonic and partial complex seizures is expected [112,113]. This may indicate that ganaxolone may share some more mechanisms of action. Indeed, it may also inhibit voltage-dependent calcium channels and reduce NMDA receptor-mediated events [112]. However, like many GABA-enhancers, ganaxolone exacer-bated seizures in animal models of absence and at doses above 20 mg/kg it did produce synchronous spike and wave discharges [114]. So far, very limited clinical data exist - ganaxolone proved effective against refractory infantile spasms (36 mg/kg/day) and complex partial seizures (1.5-1.8 g/day) [16]. Adverse effects were mainly associated with disturbed functions of the central nervous system – somnolence, asthenia, dizziness or stupor were occasionally observed [16].

Table 1. Mechanisms of Action of Conventional and New Antiepileptic Drugs (AEDs).

AED	Enhancement of GABA- mediated excitation	Blockade of sodium channels	Blockade of calcium channels	Inhibition of glutamate-	Other
Benzodiazepines	+	+*			
Carbamazepine		+			
Ethosuximide			+ (T-type)		
Phenobarbital	+	+		+	
Phenytoin		+			
Valproate	+	+			+
Gabapentin			+ (L-type)		
Felbamate	+	+		+	
Lamotrigine		+	+ (L-type)		
Levetiracetam					+
Oxcarbazepine		+	+ (L-type)		
Tiagabine	+				
Topiramate	+	+	+ (L-type)	+	+
Vigabatrin	+				
Zonisamide		+	+ (T-type)	+	+

+, a documented mechanism of action (except for other mechanisms). Inconsistent data or data observed at supratherapeutic concentrations have not been included.

* This mechanism can work at high concentration of benzodiazepines, encountered at intensive treatment of status epilepticus.

In healthy volunteers, ganaxolone (single doses of 50-800 mg) reached its peak plasma levels after 0.5-6 h and its half-life ranged from 2 to 9 h. The protein binding is high and exceeds 99% - the drug is also metabolized and mainly excreted in the feces [16].

Retigabine

In *in vitro* experiments, retigabine was documented to enhance GABA-dependent chloride currents and increase the synthesis of GABA [16]. The drug was also capable of opening the potassium channel and weakly block sodium and calcium channels [115,116]. This GABA enhancer proved to be very active in many experimental rodent models of epilepsy - it inhibited maximal electroshock-, sound and pentylenetetrazol-induced seizures as well as penicillin, picrotoxin, kainate and intracerebroventricular NMDA-produced convulsions. Its potent protective activity against amygdala-kindled seizures in rats needs to be underlined [16]. On the other hand, it failed to protect against strychnine and bicuculline [16]. Similarly to ganaxolone, retigabine efficiently suppressed epileptogenesis which can be studied in the amygdala kindling. Valproate was only partially effective whilst carbamazepine or phenytoin were completely ineffective in this respect [16]. So far, retigabine has been tested in epileptic patients at 200 mg twice a day. However, no improvement has been reported which may indicate that higher doses must be used, in the range of 0.6-1.2 g/daily [16]. No major side effects after a daily dose of 0.6 g were noted - the adverse effects were of central origin (dizziness, fatigue and disorders of concentration) [16].

3-amino-propyl-n-butyl-phosphinic Acid (CGP 36742)

This compound differs totally from the previously discussed drugs in that it does not enhance GABA-induced inhibition but blocks $GABA_B$ receptor-mediated events. As shown from animal models of absences, CGP 36742 exerted clear-cut protective effects [117,118]. It is remarkable that CGP 36742 improves cognitive performance in rats [119].

DRUG-RESISTANT EPILEPSY

Around 30% of epileptic patients do not respond properly to antiepileptic drugs. This problem may be overcome in part of them by using combinations of antiepileptic drugs, especially those showing synergy in experimental models of epilepsy [79,120]. Probably, one of the main reasons for drug resistance is over-expression of proteins involved in the active transport through natural barriers – for instance, blood-brain barrier [121]. An alternative reason might be neuronal loss encountered in epileptic patients [121]. Interestingly, more than two decades ago, experimental evidence indicated that mice with hippocampal lesion confined to the CA3 area were less sensitive to the antiseizure effects of antiepileptic drugs enhancing GABA-mediated events [122,123]. It is quite likely that neurodegeneration may impair the expression of anticonvulsant activity of antiepileptic drugs under clinical conditions.

Apart from the pure drug-resistant epilepsy, some epileptic patients may face intractable seizures due to other than pharmacoresistance reasons. During the 90s of the XX century, a number of experimental papers clearly indicated that caffeine, administered in doses far below its convulsive potential, significantly reduced the anticonvulsant activity of conventional antiepileptic drugs against maximal electroshock-induced seizures in mice [124-126]. It is noteworthy, that this untoward effect of caffeine did not undergo any tolerance and actually, was increased upon chronic administration of the methylxanthine derivative [125,126]. Acute caffeine influence upon the protective activity of conventional antiepileptic drugs is shown in Table **2**. Very recent data provide data that a caffeine-like effect may be also shared by nicotine in maximal electroshock test in mice [127]. Clinical research supports experimental data, showing that consumption of caffeine-rich beverages may significantly reduce the effectiveness of antiepileptic drugs in epileptic patients [128]. So far, there is no clinical evidence on the negative effects of nicotine. Interaction of nicotine with a number of antiepileptic drugs is shown in Table **3**.

Its is thus likely that a therapeutic failure in epilepsy may be not always due to pharmacoresistance in properly cured patients. Lack of therapeutic success may be due to caffeine ingested in the form of coffee, tea or caffeinated beverages. Also, the smoking habit is a very likely candidate for therapeutic failures.

Table 2. Impairment by Caffeine of the Protective Activity of Conventional Antiepileptic Drugs (AEDs) Against Maximal Electroshock-induced Tonic Convulsions in Mice.

AED	Caffeine (mmol/kg)		
	0.119	**0.238**	**0.476**
Carbamazepine	0	+	++
Phenobarbital	+	++	+++
Phenytoin	+	+	++
Valproate	0	+	++

Caffeine was given intraperitoneally (i.p.), 30 min prior to maximal electroshock. AEDs were also administered i.p., phenytoin and phenobarbital 120 min, carbamazepine 60 min, and valproate – 30 min before the test.

+, at least 25% increase in the respective ED_{50} value; ++, at least 50% increase; +++, at least 90% increase; 0, no significant effect.

Data were transformed from Czuczwar et al. [124].

Table 3. Nicotine-induced Impairment of the Anticonvulsant Activity of Antiepileptic Drugs (AEDs) in Mice Challenged with Maximal Electroshock-induced Tonic Seizures.

AED	Nicotine (4 mg/kg, i.p.)
Carbamazepine (11.1)	++
Phenobarbital (14.6)	++
Phenytoin (8.5)	++
Valproate (205)	+
Lamotrigine (5.9)	+++
Topiramate (28.9)	++

Nicotine was administered intraperitoneally (i.p.) 5 min before the electroconvulsive test. AEDs were injected i.p., phenytoin 120 min, lamotrigine, phenobarbital, topiramate 60 min, whilst carbamazepine and valproate 30 min prior to the test.

+, at least 40% increase in the respective ED_{50} value; ++, more than a 50% increase; +++, more than an 80% increase. Data were adapted from Czuczwar et al. [127].

GENERAL CONCLUSION

Novel antiepileptic drugs enhancing GABA-mediated events usually possess a better pharmacological profile in experimental epilepsy models than conventional antiepileptic drugs and generally, their pharmacokinetics in humans is more predictable. Drug interactions are rather rare [19,129]. In open label trials, good results have been reported – for instance, at least 50% reduction in seizure frequency was observed in 50% of patients taking vigabatrin, 20-30% - gabapentin and 26-30% - tiagabine (partial seizures) [130]. In cases of drug resistant epilepsies, double-blind placebo-controlled trials indicate that maximum 10% of patients benefit from add-on therapy with these antiepileptics [130].

Seizure activity leads to neuronal cell loss [131] and, as it has been already mentioned, neurodegeneration may affect the protective activity of some antiepileptic drugs [122,123]. It seems of particular importance to select antiepileptic drugs with neuroprotective properties. Experimental data indicate that especially, topiramate, lamotrigine and tiagabine provide considerable neuroprotection in experimental models of epilepsy [131]. As soon as this effect is confirmed in clinical conditions, these drugs should initiate treatment of epilepsy in order to prevent neuronal cell death. Interestingly, experimental data has provided evidence that barbiturates and benzodiazepines induce massive apoptotic response in immature rodents [132]. There is, however, no clinical evidence upon this undesired effect of these antiepileptic drugs.

REFERENCES

[1] Czuczwar, S.J.; Patsalos, P.N. The new generation of GABA enhancers. *CNS Drugs* **2001**, *15*,339-350.

[2] Deckers, C.L.P.; Czuczwar, S.J.; Hekster, Y.A.; Keyser, A.; Kubova, H.; Meinardi, H.; Patsalos, P.; Renier, W.O.; van Rijn, C.M. Selection of antiepileptic drug polytherapy based on mechanism of action: the evidence reviewed. *Epilepsia* **2000**, *41*, 1364-1374.

[3] Sobieszek, G.; Borowicz, K.K.; Kimber-Trojnar, Z.; Malek, R.; Piskorska, B.; Czuczwar, S.J. Zonisamide: A new antiepileptic drug. *Pol. J. Pharmacol.* **2003**, *55*, 683-689.

[4] Antkiewicz-Michaluk, L. Receptor and voltage-operated ion channels in the central nervous system. *Pol. J. Pharmacol.* **1995**, *47*, 253-264

[5] Kostowski, W. Recent advances in the GABA-A-benzodiazepine receptor pharmacology. *Pol. J. Pharmacol.* **1995**, *47*, 237-246.

[6] Enz, R.; Cutting, G.R. Molecular composition of $GABA_C$ receptors. *Vision Res.* **1998**, *38*, 1431-1441.

[7] Meldrum, B.S. Gamma-aminobutyric acid and the search for new anticonvulsant drugs. *Lancet* **1978**, *2*, 304-306

[8] Schechter, P.J.; Tranier, Y.; Jung, M.J.; Böhlen, P. Audiogenic seizure protection by elevated brain GABA concentration in mice: Effects of γ-acetylenic-GABA and γ-vinyl-GABA, two irreversible GABA-T inhibitors. *Eur. J. Pharmacol.* **1977**, *45*, 319-328

[9] Kleinrok, Z.; Czuczwar, S.J.; Kozicka, M. Effect of dopaminergic and GABA-ergic drugs given alone or in combination on the anticonvulsant action of phenobarbital and diphenylhydantoin in the electroshock test in mice. *Epilepsia* **1980**, *21*, 519-529.

[10] Czuczwar, S.J. Effect of combined with dopaminergic and GABA-ergic drugs on the threshold for maximal electroconvulsions in mice. *Pol. J. Pharmacol.* **1981**, *33*, 25-35.

[11] Chapman, A.G.; Keane, A.P.; Meldrum, B.S.; Simiand, J.; Verniers, J.C. Mechanism of action of valproate. *Prog. Neurobiol.* **1982**, *19*, 315-359.

[12] Bernasconi, R.; Klein, M.; Martin, P.; Portet, C.; Maitre, L.; Jones, R.S.G.; Baltzer, V.; Schmutz, M. The specific protective effect of diazepam and valproate against isoniazid-induced seizures is not correlated with increased GABA levels. *J. Neural Transm.* **1985**, *63*, 169-189.

[13] Löscher, W. GABA and the epilepsies. Experimental and clinical considerations. In GABA. *Basic Research and Clinical Applications;* Bovery, N.G.; Nistico, G.; Eds.; Pythagora Press: Roma, 1989; pp 260-300.

[14] Kalviainen, R.; Halonen, T.; Pitkanen, A.; Riekkinen, P.J. Amino acid levels in the cerebral fluid of newly diagnosed epileptic patients: effects of vigabatrin and carbamazepine. *J. Neurochem.* **1993**, *60*, 1244-1250

[15] Petroff, O.A.C.; Rothman, D.L.; Behar, K.L.; Lamoreux, D.; Mattson, R.H. The effect of gabapentin on brain gamma-butyric acid in patients with epilepsy. *Ann. Neurol.* **1996**, *39*, 95-99.

[16] Bialer, M.; Johanessen, S.I.; Kupferberg, H.J.; Levy, R.H.; Loisseau, P.; Perucca, E. Progress report on new antiepileptic drugs: a summary of the fourth Eilat conference (EILAT IV). *Epilepsy Res.* **1999**, *34*, 1-41.

[17] Patsalos, P.N. New antiepileptic drugs. *Ann. Clin. Biochem.* **1999**, *36*, 10-19.

[18] Meldrum, B.S.; Croucher, M.J.; Krogsgaard-Larsen, P. GABA-uptake inhibitors as anticonvulsant agents. In *Problems in GABA Research: From Brain to Bacteria;* Okada, Y.; Roberts, E.; Eds.; Excerpta Medica: Amsterdam-Oxford-Princeton, 1981; pp 182-191.

[19] Löscher, W. New visions in the pharmacology of anticonvulsion. *Eur. J. Pharmacol.* **1998**, *342*, 1-13.

[20] Löscher, W.; Hönack, D.; Taylor, C.P. Gabapentin increases aminooxyacetic acid-induced GABA accumulation in several regions of rat brain. *Neurosci. Lett.* **1991**, *120*, 150-154.

[21] Meldrum, B.S. Update on the mechanism of action of antiepileptic drugs. *Epilepsia* **1996**, *37*, Suppl. 6, S4-S11.

[22] Gee, N.S.; Brown, J.P.; Dissanayake, V.U.K.; Offord, J.; Thurlow, R.; Woodruff, G.N. The novel anticonvulsant drug, gabapentin (neurontin), binds to the $\alpha_2\delta$ subunit of a calcium channel. *J. Biol. Chem*. **1996**, *271*, 5768-5776.

[23] Shank, R.P.; Gardocki, J.F.; Vaught, J.L.; Davis, C.B.; Schupsky, J.J.; Raffa, R.B.; Dodgson, S.J.; Nortey, S.O.; Maryanoff, B.E. Topiramate: preclinical evaluation of a structurally novel anticonvulsant. *Epilepsia* **1994**, *35*, 450-460.

[24] Ticku, M.K.; Kamatchi, G.L.; Sofia, R.D. Effect of anticonvulsant felbamate on $GABA_A$ receptor system. *Epilepsia* **1991**, *32*, 389-391.

[25] Swinyard, E.A.; Sofia, R.D.; Kupferberg, H.J. Comparative anticonvulsant activity and neurotoxicity of felbamate and four

prototype antiepileptic drugs in mice and rats. *Epilepsia* **1986**, *27*, 27-34.

[26] Marescaux, C.; Vergnes, M.; Depaulis, A. Genetic absence epilepsy in rats from Strasbourg: A review. *J. Neural Transm.* **1992**, *35*, 37-69.

[27] Parker, A.P.; Agathonikou, A.; Robinson, R.O.; Panayiotopoulos, C.P. Inappropriate use of carbamazepine and vigabatrin in typical absence seizures. *Dev. Med. Child Neurol.* **1998**, *40*, 517-519.

[28] Puigcerver, A.; van Luijtelaar, E.L.J.M.; Drinkenburg, W.H.I.M.; Coenen, A.M.L. Effects of the GABA-B antagonist CGP 35348 on sleep-wake states, behaviour, and spike-wave discharges in old rats. *Brain Res. Bull.* **1996**, *40*, 157-162.

[29] Peeters, B.W.M.M.; van Rijn, C.M.; Vossen, J.M.H.; Coenen, A.M.L. Effects of GABA-ergic agents on spontaneous non-convulsive epilepsy, EEG and behaviour, in the WAG/Rij inbread strain of rats. *Life Sci.* **1989**, *45*, 1171-1176.

[30] Meldrum, B.S. Amino acid neurotransmitters and new approaches to anticonvulsant drug action. *Epilepsia* **1984**, *25*, S140-S149.

[31] Ben-Ari ,Y.; Lagowska, J.; Tremblay, E.; Le Gal LaSalle, G. A new model of focal status epilepticus: Intraamygdaloid application of kainic acid elicits repetitive secondarily generalized convulsive seizures. *Brain Res*. **1979**, *163*, 176-179.

[32] Czuczwar, S.J.; Meldrum, B.S. Protection against chemically induced seizures by 2-amino-7- phosphono-heptanoic acid. Eur. J. Pharmacol. 1982, 83, 335-338.

[33] Czuczwar SJ, Frey H-H, Löscher W. Antagonism of N-methyl-D,L-aspartic acid-induced seizures by antiepileptic drugs and other agents. *Eur. J. Pharmacol.* **1985**, *108*, 273-280.

[34] Kleinrok, Z.; Czuczwar, S.J.; Turski, L. Prevention of kainic acid-induced seizure-like activity by antiepileptic drugs. Pol. J. Pharmacol. **1980**, *32*, 261-264.

[35] Stone, W.E.; Javid, M.J. Effects of anticonvulsants and other agents on seizures induced by intracerebral L-glutamate. *Brain Res*. **1983**, *264*, 165-167.

[36] Huxtable, R.J.; Laird, H.; Lippincott, S.E.; Wolson, P. Epilepsy and the concentration of plasma amino acids in humans. *Neurochem. Int.* **1983**, *5*, 125-135.

[37] Croucher, M.J.; Collins, J.F.; Meldrum, B.S. Anticonvulsant action of excitatory amino acid antagonists. *Science* **1982**, *216*, 899-901.

[38] Czuczwar, S.J.; Cavalheiro, E.A.; Turski, L.; Turski, W.A.; Kleinrok, Z. Phosphonic analogues of excitatory amino acids raise the threshold for maximal electroconvulsions in mice. *Neurosci. Res.* **1985**, *3*, 86-90.

[39] Czuczwar, S.J.; Turski, L.; Schwarz, M.; Turski, W.A.; Kleinrok, Z. Effects of excitatory amino-acid antagonists on the anticonvulsant action of phenobarbital or diphenylhydantoin in mice. *Eur. J. Pharmacol.* **1984**, *100*, 357-362.

[40] Turski ,W.A.; Urba_ska, E.; Dziki, M.; Parada-Turska, J.; Ikonomidou, C. Excitatory amino acid antagonists protect mice against seizures induced by bicuculline. *Brain Res*. **1990**, *514*, 131-134.

[41] Smith, S.E.; Durmuller, N.; Meldrum, B.S. The non-N-methyl-D-aspartate receptor antagonists, GYKI 52466 and NBQX are anticonvulsant in two animal models of reflex epilepsy. *Eur. J. Pharmacol.* **1991**, *201*, 179-183.

[42] Turski, L.; Jacobsen, P.; Honoré, T.; Stephens, D.N. Relief of experimental spasticity and anxiolytic/anticonvulsant actions of the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate antagonist 2, 3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline. *J. Pharmacol. Exp. Ther.* **1992**, *260*, 742-747.

[43] Watkins, J.C.; Krogsgaard-Larsen, P.; Honoré, T. Structure-activity relationships in the development of excitatory amino acid receptor agonists and competitive antagonists. *Trends Pharmacol. Sci.* **1990**, *11*, 25-33.

[44] Monaghan, D.T.; Bridges, R.J.; Cotman, C.W. The excitatory amino-acid receptors: their classes, pharmacology and distinct properties in the function of the central nervous system. *Ann. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365-402.

[45] Zorumski, C.F.; Thio, L.L. Properties of vertebrate glutamate receptors: calcium mobilization and desensitization. *Prog. Neurobiol.* **1992**, *39*, 295-336.

[46] Czuczwar, S.J.; Gasior, M.; Turski, W.A.; Kleinrok, Z. Influence of a Ca^{2+} channel agonist, BAY k-8644, on the anticonvulsant activity of NMDA and non-NMDA receptor antagonists. *Eur. J. Pharmacol.* **1994**, *264*, 103-106.

[47] Turski, L.; Niemann, W.; Stephens DN. Differential effects of antiepileptic drugs and carbolines on seizures induced by excitatory amino acids. *Neuroscience* **1990**, *39*. 799-807.

[48] Pin, J.P.; Duvoisin, R. The metabotropic glutamate receptors: structure and functions. *Neuropharmacology* **1995**, *34*, 1-26.

[49] Bordi, F.; Ugolini, A. Group I metabotropic glutamate receptors: implications for brain diseases. *Prog. Neurobiol.* **1999**, *59*, 55-79.

[50] Nakanishi, S.; Nakajima, Y.; Masu, M.; Ueda, Y.; Nakahara, K.; Watanabe, D.; Yamaguchi, S.; Kawabata, S.; Okada, M. Glutamate receptors: brain function and signal transduction. *Brain Res. Rev.* **1998**, *26*, 230-235.

[51] Adkins, J.C.; Noble, S. Tiagabine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. *Drugs* **1998**, *55*, 437-460.

[52] Halonen, T.; Nissinen, J.; Jansen, J.A.; Pitkanen, A. Tiagabine prevents seizures, neuronal damage and memory impairment in experimental status epilepticus. *Eur. J. Pharmacol.* **1996**, *299*, 69-81.

[53] Dalby, N.O.; Nielsen, E.B. Tiagabine exerts an anti-epileptogenic effect in amygdala kindling epileptogenesis in the rat. *Neurosci. Lett.* **1997**, *229*, 135-137.

[54] Dalby, N.O.; Nielsen, E.B. Comparison of the preclinical anticonvulsant profiles of tiagabine, lamotrigine, gabapentin and vigabatrin. *Epilepsy Res.* **1997**, 28, 63-72.

[55] Sills, G.J.; Butler, E.; Thompson, G.G.; Brodie, MJ. Vigabatrin and tiagabine are pharmacologically different drugs. A pre-clinical study. *Seizure* **1999**, *8*, 404-411.

[56] Lahtinen,H.; Ylinen, A.; Lukkarinen, U.; Sirvio, J.; Miettinen, R.; Riekkinen, P. Failure of carbamazepine to prevent behavioral and histopathological sequalae of experimentally-induced status epilepticus. *Eur. J. Pharmacol.* **1996**, *297*, 213-218.

[57] Pitkanen, A.; Tuunanen, J.; Halonen, T. Vigabatrin and carbamazepine have different efficacies in the prevention of status epilepticus induced neuronal damage in the hippocampus and amygdala. *Epilepsy Res.* **1996**, *24*, 29-45.

[58] Hosford, D.A.; Wang, Y. Utility of the lethargic (lh/lh) mouse model of absence seizures in predicting the effects of lamotrigine, vigabatrin, tiagabine, gabapentin, and topiramate against human absence seizures. *Epilepsia* **1997**, *38*, 408-414.

[59] Luer, M.S.; Rhoney, D.H. Tiagabine: a novel antiepileptic drug. *Ann. Pharmacother.* **1998**, *32*, 1173-1180.

[60] Knake, S.; Hamer, H.M.; Schomburg, U.; Oertel, W.H.; Rosenow, F. Tiagabine-induced absence status epilepticus in idiopathic generalized epilepsy. *Seizure* **1999**, *8*, 314-317.

[61] Mecarelli, O.; De Feo, M.R.; Del Priore, D. Vigabatrin versus carbamazepine and phenytoin in kainic acid-treated pubescent rats. *Pharmacol. Res.* **1997**, *36*, 87-93.

[62] Engelborghs, S.; Pickut, B.A.; D'Hooge, R.; Wiechert, P.; Haegele, K.; De Deyn, P.P. Behavioral effects of vigabatrin correlated with whole brain gamma-aminobutyric acid metabolism in audiogenic sensitive rats. *Arzneimittelforschung* **1998**, *48*, 713-716.

[63] Mazurkiewicz, M.; Sirvio, J.; Riekkinen, P. Effects of single and repeated administration of vigabatrin on the performance of non-epileptic rats in a delayed non-matching to position task. *Epilepsy Res.* **1993**, *15*, 221-227.

[64] Sidhu, R.S.; Del Bigio, M.R.; Tuor, U.I.; Seshia, S.S. Low-dose vigabatrin (gamma-vinyl GABA)-induced damage in the immature rat brain. *Exp. Neurol.* **1997**, *144*, 400-405.

[65] Arzimanoglou, A.A.; Dumas, C.; Ghirardi, L. Multicentre clinical evaluation of vigabatrin (Sabril) in mild to moderate partial epilepsies. French Neurologist Sabril Study Group. *Seizure* **1997**, *6*, 225-231.

[66] Sheth, R.D.; Buckley, D.; Penney, S.; Hobbs, G.R. Vigabatrin in childhood epilepsy: comparable efficacy for generalized and partial seizures. *Clin. Neuropharmacol.* **1996**, *19*, 287-304.

[67] Wohlrab, G.; Boltshauser, E.; Schmitt, B. Vigabatrin as a first-line drug in West syndrome: clinical and electroencephalographic outcome. *Neuropediatrics* **1998**, *29*, 133-136.

[68] Siemes, H.; Brandl, U.; Spohr, H.L.; Volger, S.; Weschke, B. Long-term follow-up study of vigabatrin in pretreated children with West syndrome. *Seizure* **1998**, *7*, 293-297.

[69] Provinciali, L.; Bartolini, M.; Mari, F.; Del Pesce, M.; Ceravolo, M.G. Influence of vigabatrin on cognitive performances and

behaviour in patients with drug-resistant epilepsy. *Acta Neurol. Scand.* **1996**, *94*, 12-18.

[70] Mauguiere, F.; Chauvel, P.; Dewailly, J.; Dousse, N. No effect of long-term vigabatrin treatment on central nervous system conduction in patients with refractory epilepsy: results of a multicenter study of somatosensory and visual evoked potentials. PMS Study Multicenter Group. *Epilepsia* **1997**, *38*, 301-308.

[71] Thomas, L.; Trimble, M.; Schmitz, B.; Ring, H. Vigabatrin and behaviour disorders; a retrospective survey. *Epilepsy Res*. **1996**, *25*, 21-27.

[72] Kalviainen, R.; Nousiainen, I.; Mantyjarvi, M.; Nikoskelainen, E.; Partanen, J.; Partanen, K.; Riekkinen, P. Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual field defects. *Neurology* **1999**, *22*, 922-926.

[73] Lawden, MC.; Eke, T.; Degg, C.; Harding, G.F.; Wild, J.M. Visual field defects associated with vigabatrin therapy. *J. Neurol. Neurosurg. Psychiatry* **1999**, *67*, 716-722.

[74] Wild, J.M.; Martinez, C.; Reinshagen, G.; Harding, G.F. Characteristics of a unique visual field defect attributed to vigabatrin. *Epilepsia* **1999**, *40*, 1784-1794.

[75] Versino, M.; Veggiotti, P. Reversibility of vigabatrin-induced visual field defect. *Lancet* **1999**, *354*, 486.

[76] Steinhoff, B.J.; Freudenthaler, N.; Paulus, W. The influence of established and new antiepileptic drugs on visual perception. II. A controlled study in patients with epilepsy under long-term antiepileptic medication. *Epilepsy Res.* **1997**, *29*, 49-58.

[77] Stefan, H.; Bernatik, J.; Knorr, J. Visual field defects due to antiepileptic drugs. *Nervenarzt* **1999**, *70*, 552-555.

[78] Wohlrab,G.; Boltshauser, E.; Schmitt, B.; Schriever, S.; Landau, K. Visual field constriction is not limited to children treated with vigabatrin. *Neuropediatrics* **1999**, *30*, 130-132.

[79] Borowicz, K.K.; Swiader, M.; Luszczki, J.; Czuczwar, S.J. Effect of gabapentin on the anticonvulsant activity of antiepileptic drugs against electroconvulsions in mice: An isobolographic analysis. *Epilepsia* **1992**, *43*, 956-963.

[80] De Sarro, G.; Spagnolo, C.; Gareri, P.; Gallelli, L.; De Sarro, A. Gabapentin potentiates the antiseizure activity of certain anticonvulsants in DBA/2 mice. *Eur. J. Pharmacol. 1998*, **349**,179-185.

[81] Bloms-Funke, P.; Löscher, W. The anticonvulsant gabapentin decreases firing rates of substantia nigra pars reticulata neurons. *Eur. J. Pharmacol.* **1996**, *316*, 211-218.

[82] Kalviainen, R.; Keranen, T.; Riekkinen, P.J. Place of newer antiepileptic drugs in the treatment of epilepsy. *Drugs* **1993**, *46*, 1009-1024.

[83] Korn-Merker, E.; Borusiak, P.; Boenigk, H.E. Gabapentin in childhood epilepsy: a prospective evaluation of efficacy and safety. *Epilepsy Res.* **2000**, *38*, 27-32.

[84] Bialer, M.; Johanessen, S.I.; Kupferberg, H.J.; Levy, R.H.; Louiseau, P.; Perucca, E. Progress report on new antiepileptic drugs: a summary of the Sixth Eilat Conference (EILAT VI). *Epilepsy Res.* **2002**, *51*, 31-71.

[85] Swiader, M.; Kotowski, J.; Gasior, M.; Kleinrok, Z.; Czuczwar, S.J. Interaction of topiramate with conventional antiepileptic drugs in mice. *Eur. J. Pharmacol.* **2000**, *399*, 35-41.

[86] Borowicz, K.K.; Luszczki, J.J.; Duda, A.M.; Czuczwar, S.J. Effect of topiramate on the anticonvulsant activity of conventional antiepileptic drugs in two models of experimental epilepsy. *Epilepsia* **2003**, *44*, 640-646.

[87] Cross, H. Topiramate monotherapy for childhood absence seizures: an open label pilot study. *Seizure* **2002**, *11*, 406-410.

[88] Macdonald, R.L.; Greenfield, L.J. Mechanisms of action of new antiepileptic drugs. *Curr. Opin. Neurol.* **1997**, *10*, 121-128.

[89] Stefani, A.; Spadoni, F.; Bernardi, G. Voltage-activated calcium channels: targets of antiepileptic drug therapy? *Epilepsia* **1997**, *38*, 959-965.

[90] Miller, A.A.; Wheatley, P.; Sawyer, D.A,; Roth, B. Pharmacological studies on lamotrigine, a novel potential antiepileptic drug, I: anticonvulsant profile in mice and rats. *Epilepsia* **1986**, *27*, 483-489.

[91] Binnie, C.D.; Debets, R.M.; Engelsman, M.; Meijer, J.W.; Meinardi, H.; Overweg, J.; Peck, A.W.; Van Wieringen, A.; Yuen, W.C. Double-blind, cross-over trial of lamotrigine (Lamictal) as add-on therapy in intractable epilepsy. *Epilepsy Res.* **1989**, *4*, 222-229.

[92] Loiseau, P.; Yuen, A.W.; Duche, B.; Menager, T.; Arne-Bes, M.C. A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment with treatment resistant partial seizures. *Epilepsy Res.* **1990**, *7*, 136-145.

[93] Buchanan, N. Lamotrigine in the treatment of absence seizures. *Acta Neurol. Scand.* **1995**, *92*, 348.

[94] La Roche, S.M.; Helmers, S.L. The new antiepileptic drugs. *JAMA* **2004**, *291*, 605-614.

[95] Klitgaard, H.; Pitkänen, A. Antiepileptogenesis, neuroprotection, and disease modification in the treatment of epilepsy: focus on levetiracetam. *Epileptic Disord.* **2003**, *5(Suppl. 1)*, S9-S16.

[96] Dooley, M.; Plosker, G.L. Levetiracetam. A review of its adjunctive use in the management of partial onset seizures. *Drugs* **2000**, *60*, 871-893.

[97] Abou-Khalil, B.; Lazenby, B. Long-term experience with levetiracetam. *Epileptic Disord.* **2003**, *5 (Suppl. 1)*, S33-S37.

[98] Harty, T.P.; Rogawski, M.A. Felbamate block of recombinant N-methyl-D-aspartate receptors: selectivity for the NR2B subunit. *Epilepsy Res*. **2000**, *39*, 47-55.

[99] Tagliatella, M.; Ongini, E.; Brown, A.M.; Di Renzo, G.; Annunziato, L. Felbamate inhibits cloned voltage-dependent Na^+ channels from human and rat brain. *Eur. J. Pharmacol*. **1996**, *316*, 373-377.

[100] DeSarro, G.; Ongini, E.; Bertorelli, R.; Aguglia, U.; DeSarro, A. Excitatory amino acid neurotransmission through both NMDA and non-NMDA receptors is involved in the anticonvulsant activity of felbamate in DBA/2 mice. *Eur. J. Pharmacol*. **1994**, *262*, 11-15.

[101] Rho, J.M.; Donevan, S.D.; Rogawski, M.A. Mechanism of action of the anticonvulsant felbamate: opposing effects on N-methyl-D-aspartate and α-amino-butyric acid A receptors. *Ann. Neurol.* **1994**, *35*, 229-236.

[102] McNamara, J.O. Kindling: an animal model of complex partial epilepsy. *Ann. Neurol.* **1984**, *16*, S72-S76.

[103] Giorgi, O.; Carboni, G.; Frau, V.; Orlandi, M.; Valentini, V.; Feldman, A.C. Anticonvulsant effect of felbamate in the pentetrazole kindling model of epilepsy in the rat. *Naunyn-Schmiedeberg's Arch. Pharmacol*. **1996**, *354*, 173-178.

[104] Wlaz, P.; Löscher W. Anticonvulsant activity of felbamate in amygdala kindling model of temporal lobe epilepsy in rat. *Epilepsia* **1997**, *38*,1167-1172.

[105] Ebert, U.; Reissmüller, E.; Löscher W. The new antiepileptic drugs lamotrigine and felbamate are effective in phenytoin-resistant kindled rats. *Neuropharmacology* **2000**, *39*, 1893-1903.

[106] Harden, C.L. New antiepileptic drugs. *Neurology* **1994**, *44*, 787-795.

[107] Pellock, J.M. Felbamate in epilepsy therapy: evaluating the risk. *Drug Saf.* **1999**, *21*, 225-239.

[108] Mellick, G.A. Hemifacial spasm: successful treatment with felbamate. *J. Pain Sympt. Manag.* **1995**, *10*, 392-395.

[109] Winkler, S.R.; Luer M.S. Antiepileptic drug review: part 2. *Surg. Neurol.* **1998**, *49*, 566-568.

[110] Sobieszek, G.; Borowicz, K.K.; Bimber-Trojnar, Z.; Malek, R.; Piskorska, B.; Czuczwar, S.J. Zonisamide: A new antiepileptic drug. *Pol. J. Pharmacol*. **2003**, *55*, 683-689.

[111] Wellington, K.; Goa, K.L. Oxcarbazepine. An update of its efficacy in the management of epilepsy. *CNS Drugs* **2001**, *15*, 137-163.

[112] Gasior, M.; Carter, R.B.; Witkin, J.M. Neuroactive steroids: potential therapeutic use in neurological and psychiatric disorders. *Trends Pharmacol. Sci*. **1999**, *20*, 107-112.

[113] Gasior, M.; Beekman, M.; Carter, R.B.; Goldberg, S.R.;Witkin,J.M. Antiepileptogenic effects of the novel synthetic neuroactive steroid, ganaxolone, against pentylenetetrazol-induced kindled seizures: comparison with diazepam and valproate. Drug *Dev. Res.* **1998**, *44*, 21-33.

[114] Snead, O.C. Ganaxolone, a selective, high-affinity steroid modulator of the gamma-aminobutyric acid-A receptor, exacerbates seizures in animal models of absence. *Ann. Neurol.* **1998**, *44*, 688-691.

[115] Rundfeldt. C.; Rohlfs, A.; Netzer, R. Multiple actions of the new anticonvulsant D-23129 on voltage-gated inward currents and GABA-mediated currents in cultured neuronal cells. *Naunyn-Schmiedeberg's Arch. Pharmacol*. **1995**, *351 Suppl.*, R160.

[116] Dost, R.; Rundfeldt, C. The anticonvulsant retigabine potently suppresses epileptiform discharges in the low Ca^{++} and low Mg^{++} model in the hippocampal slice preparation. *Epilepsy Res*. **2000**, *38*, 53-66.

[117] Vergnes, M.; Boehrer, A.; Simler, S.; Bernasconi, R.; Marescaux, C. Opposite effects of $GABA_B$ receptor antagonists on absences and convulsive seizures. *Eur. J. Pharmacol.* **1997**, *332*, 245-255.

[118] Getova, D.; Froestl, W.; Bowery, N.G. Effects of $GABA_B$ receptor antagonism on the development of pentylenetetrazol-induced kindling in mice. *Brain Res.* **1998**, *809*, 182-188.

[119] Getova, D.; Bowery, N.G.; Spassov, V. Effects of $GABA_B$ receptor antagonists on learning and memory retention in a rat model of absence epilepsy. *Eur. J. Pharmacol.* **1997**, *320*, 9-13.

[120] Luszczki, J.J.; Czuczwar, M.; Kis, J.; Krysa, J.; Pasztelan, I.; Swiader, M.; Czuczwar, S.J. Interactions of lamotrigine with topiramate and first-generation antiepileptic drugs in the maximal electroshock test in mice: An isobolographic analysis. *Epilepsia* **2003**, *44*, 1003-1013.

[121] Elger, C.E. Pharmacoresistance: Modern concept and basic data derived from human brain tissue. *Epilepsia* **2003**, *44 (Suppl. 5)*, 9-15.

[122] Czuczwar, S.J.; Turski, L.; Turski, W; Kleinrok, Z. Effects of some antiepileptic drugs in pentetrazol-induced convulsions in mice lesioned with kainic acid. *Epilepsia* **1981**, *22*, 407-414.

[123] Czuczwar, S.J.; Turski, L.; 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.

[124] Czuczwar, S.J.; Gasior, M.; Janusz, W.; Szczepanik, B.; Wlodarczyk, D.; Kleinrok, Z. Influence of different methylxanthines on the anticonvulsant action of common antiepileptic drugs in mice. *Epilepsia* **1990**, *31*, 318-323.

[125] Gasior, M.; Borowicz, K.K.; Buszewicz, G.; Kleinrok, Z.; Czuczwar, S.J. Anticonvulsant activity of phenobarbital and valproate against maximal electroshock in mice during chronic treatment with caffeine and caffeine discontinuation. Epilepsia 1996, 37, 262-268.

[126] Gasior, M.; Borowicz, K.; Kleinrok, Z.; Czuczwar, S.J. Chronic caffeine and the anticonvulsant potency of antiepileptic drugs against maximal electroshock. *Pharmacol. Biochem. Behav.* **1996**, *54*, 639-644.

[127] Czuczwar, M; Kis, J.; Czuczwar, P.; Wielosz, M.; Turski, W. Nicotine diminishes anticonvulsant activity of antiepileptic drugs in mice. *Pol. J. Pharmacol.* **2004**, 55, 799-802.

[128] Kaufman, K.R.; Sachdeo, R.C. Caffeinated beverages and decreased seizure control. *Seizure* **2003**, *12*, 519-521.

[129] Majkowski, J. Interactions between new and old generations of antiepileptic drugs. *Epileptologia* **1994**, *2 (Suppl.1)*, 33-42.

[130] Fröscher, W. Synergistic and additive effects of antiepileptic drugs in epileptic patients. *Epileptologia* **1998**, *6 (Suppl 2)*, 31-42.

[131] Trojnar, M.K.; Malek, R.; Chroscinska, M.; Nowak, S.; Blaszczyk, B.; Czuczwar, S.J. Neuroprotective effects of antiepileptic drugs. Pol. J. Pharmacol. 2003, 54, 557-566.

[132] Olney, J.W.; Farber, N.B.; Wozniak, D.F.; Jevtovic-Todorovic, V.; Ikonomidou, C. Environmental agents that have the potential to trigger massive apoptotic neurodegeneration in the developing brain. *Environ. Health Perspect.* **2000**, *108*, 383-388.