Drugs of the Future 2003, 28(9): 925-936

CCC: 0377-8282/2003

**Review Article**

# The treatment of epilepsy: future possibilities

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**Abstract**

Epilepsy is the most common serious brain disorder and comprises a wide range of conditions with varying etiologies. As researchers gain more understanding of the cellular, molecular and genetic mechanisms underlying seizure propagation, we should be able to develop better therapeutic agents designed to suppress seizure-provoking processes, to enhance the brain's natural protective mechanisms and to improve antiepileptogensis. In recent years several new drugs (oxcarbazepine, lamotrigine, topiramate, gabapentin, zonisamide, tiagabine, fosphenytoin, vigabatrin and felbamate) have been added to the therapeutic armamentarium against epilepsy. The new drugs have arisen either from a modification of already marketed drugs and formulations or from the effectiveness on the excitatory/inhibitory balance of the major neurotransmitters involved in the pathogenesis of seizures, *i.e.*, γ-aminobutyric acid (GABA) as the inhibitory neurotransmitter and glutamate as the excitatory one. Potassium channel openers have been developed successfully as well. It is also likely that some novel targets will be found in the next few years, and corresponding novel drugs will represent additional improvements of the existing therapy of epilepsy.

## Introduction

Epilepsy is a major public health issue, one reason being the ageing population in many developed countries and the known increase in the frequency of epilepsy and seizures in later life. Epilepsy is a common neurological condition, affecting 0.5-to 1% of the population worldwide (1-3). Epilepsy also poses a considerable economic burden on society. The direct costs of epilepsy vary significantly depending on the severity of the disease and the response to treatment; however, they generally amount to thousands of Euros annually per patient (4, 5).

Despite the enormity of the problem and continuous, intensive research, epilepsy remains poorly understood. The long-established antiepileptic drugs (AEDs) control seizures in 50% of patients developing partial seizures and in 60-70% of those developing generalized seizures (6). In other words, up to 30% of patients are still refractory to treatment, indicating that there is an urgent need to develop new AEDs.

Following a century of pharmacotherapy and neuroscience research, rational design of AEDs is only now beginning to yield results because of the heterogeneity of the disease and our still limited understanding of it. In addition, there is a need for new drugs that can halt epileptogenesis. Treatment with standard anticonvulsants such as phenytoin, carbamazepine, valproic acid and phenobarbital is often complicated by side effects and failure to adequately control seizures. Moreover, several AEDs possess substantial toxicity problems, often neurotoxic effects. Thus, the side effect profile of new AEDs should also be improved in the future.

Additionally, and this makes the development of new AEDs even more interesting, there is growing evidence that AEDs cover a broad spectrum of pathological conditions ranging from seizures following congenital or acquired brain disorders to behavioral and psychiatric disorders and, recently, neuropathic pain (7).

The need for novel antiepileptics arises from the expanding field of indications as well as from the fact that special seizure types are refractory to common AEDs. In

addition, many of the conventional AEDs exhibit an unfavorable side effect profile. The present review describes the possibilities for developing innovative treatments for epilepsy.

## Mechanisms of action of novel antiepileptic drugs

The ultimate aim of epilepsy treatment is to eliminate seizures using drugs with minimal adverse effects. A rational approach to the drug discovery process is necessary in order to lead to a novel effective therapy. There are several ways to achieve this goal. A better understanding of the processes leading to epilepsy and rapid developments in molecular biology will provide a better insight into the molecular mechanisms of epilepsy, resulting in new targets. Pharmaceutical improvements have already contributed to better epilepsy therapy and will continue to do so in the future. The ultimate goal would be a drug able to cure epilepsy (8-10).

### *GABAergic mechanisms*

GABA is perhaps the most comprehensively studied inhibitory neurotransmitter in the mammalian central nervous system (CNS). It is now well recognized that cellular excitability leading to convulsive seizures can be attenuated by GABAergic stimulation in the CNS. GABA agonists (baclofen, γ-vinyl-GABA, γ-acetylenic-GABA, progabide, muscimol, sodium valproate and tetrahydroisoxazolopyridine) are used as therapeutics in several disorders. Vigabatrin and gabapentin belong to the modern antiepileptics.

#### 1) Compounds acting via $GABA_A$ receptors

GABA is considered to be the major inhibitory neurotransmitter in the brain and loss of GABA inhibition has been clearly implicated in epileptogenesis. GABA interacts with 3 types of receptors: $GABA_A$, $GABA_B$ and $GABA_C$. The $GABA_A$ receptor has provided an excellent target for the development of drugs with an anticonvulsant action. Some clinically useful anticonvulsants, such as the benzodiazepines and barbiturates and possibly valproate, act at this receptor.

Pfizer is developing pregabalin [(*S*)-(+)-3-isobutyl-GABA], a GABA derivative and a follow-up compound to its GABA agonist gabapentin, for the potential treatment of several CNS disorders including epilepsy, neuropathic pain, anxiety and social phobia (11). The (*S*)-(+)-enantiomer of 3-isobutyl GABA blocks maximal electroshock seizures in mice and also potently displaces tritiated gabapentin from a novel high-affinity binding site in rat brain membrane fractions. The (*R*)-(–)-enantiomer is much less active in both assays, suggesting that the gabapentin binding site is involved in the anticonvulsant activity of 3-isobutyl GABA (12). The mechanisms underlying the diverse actions of these compounds in the brain have not been well elucidated. Similarly to gabapentin, pregabalin also caused an increase in GABA uptake via altering GABAergic signaling (13). Gabapentin and pregabalin have antihyperalgesic effects in animal models of neuropathic and inflammatory nociception. The two drugs given in low-dose combinations with naproxen interacted synergistically to reverse thermal hyperalgesia in rats (14). From the safety point of view, there is evidence indicating a relatively high incidence (4 of 19) of myoclonus associated with pregabalin therapy. The rate seems to be at least as high as reported in patients receiving the structurally similar anticonvulsant gabapentin (15).

Modulation of the neuroactive steroid site on the $GABA_A$ receptor complex may be an important new direction for pharmaceutical interventions in epilepsy. Ganaxolone belongs to a novel class of neuroactive steroids called epalons, which specifically modulate $GABA_A$ receptor gene expression in the CNS. Chemically related to progesterone but devoid of any hormonal activity, the epalons have potent antiepileptic, anxiolytic, sedative and hypnotic effects in animals. Ganaxolone was effective against chemically induced seizures in mice (16-18). Additionally, inactive doses of this neurosteroid markedly enhanced the anticonvulsant activity of diazepam (17). Interestingly and surprisingly, ganaxolone pretreatment resulted in a significant prolongation of absence seizure in mice, indicating that an augmentation of $GABA_A$ receptor complex function by neurosteroids has the potential to result in or exacerbate absence seizures (19). The profile of its anticonvulsant activity supports clinical evaluation of this drug as an antiepileptic therapy. Its pharmacokinetics appear to be simple and the compound was well tolerated (20). In fact, ganaxolone has demonstrated outstanding efficacy and good tolerability in children with intractable infantile spasms (21).

#### 2) Inhibition of $GABA_B$-receptor-mediated inhibition

CGP-36742, a $GABA_B$ receptor antagonist, effectively reduced the number of spike-wave discharges and shortened their duration in WAG/Rij rats (22). It may prove to be particularly useful in the management of primary generalized absence seizures (23).

#### 3) Enhancement of GABA in the synapse

GABA reuptake from the synaptic cleft is one important mechanism in the regulation of GABA activity. GABA is cleared by specific, high-affinity, sodium- and chloride-dependent transporters. Inhibition of the reuptake of GABA by potent and selective inhibitors of the GABA transporter (GAT) enhances GABA activity. To date, only highly selective GAT-1 inhibitors are available. Tiagabine is a selective inhibitor of GAT-1. A diheteroarylvinyloxy analogue of tiagabine has recently been reported to be

5 times more potent than tiagabine (24). The lipophilic derivatives of (*R*)-nipecotic acid and guvacine are also potent inhibitors of GAT. The most potent inhibitors of the cloned human GAT-1 are NNC-711 ($IC_{50}$ = 0.04 mM) and tiagabine ($IC_{50}$ = 0.07 mM). (*S*)-SNAP-5114 is also a transporter inhibitor with selectivity for GAT-3 (25). Due to its lipophilicity, it can cross the blood-brain barrier. *In vivo*, (*S*)-SNAP-5114 increased thalamic GABA levels, and sound and pentetrazol-induced convulsions in mice were inhibited by the compound (26).

Stiripentol, selected from a series of alpha-ethylene alcohols, demonstrated anticonvulsant activity in studies in rats and rabbits (27). Its exact mechanism of anticonvulsant action has not been fully elucidated. There is evidence that stiripentol inhibits the synoptosomal uptake of GABA and inhibits GABA transaminase (27). Stiripentol showed antiepileptic efficacy in severe myoclonic epilepsy in infancy (28). However, it is an inhibitor of several CYP450 enzymes (29) and thus, interactions with other AEDs are expected.

4) Increased expression of GABA receptor

An antisense oligodeoxynucleotide (ODN), a short synthetic single-stranded DNA molecule, is believed to inhibit the biosynthesis of a particular protein via nucleotide specific hybridization to the mRNA encoding the protein. According to our present knowledge, rats treated with antisense ODN against the $GABA_A$ receptor develop seizures (30). These results indicate not only that the lack of a GABAergic inhibitory neurotransmission is involved in the epileptogenesis but also the possibility that an increased expression of $GABA_A$ receptors may inhibit seizure development (31).

5) Transplantation of GABAergic cells

Embryonic porcine lateral ganglionic eminence cells, which are predominantly GABAergic, demonstrated long-term survival when transplanted into the hippocampus of immunosuppressed adult rats (32). Additional data in animal models are urgently needed to determine the role of cell grafts in the suppression of seizures.

*Glutamatergic mechanisms*

Glutamate is the principal excitatory neurotransmitter of the vertebrate CNS: 70% of the fast excitatory synapses use glutamate as a mediator. Like $GABA_A$ receptors ($Cl^-$ ion channel-gated) and $GABA_B$ receptors (G-protein-coupled), glutamate receptors are also classified as ligand-gated ion channel receptors and metabotropic G-protein-coupled receptors. The ionotropic receptors are further divided into NMDA and non-NMDA (AMPA and kainate) receptors. In addition to its important physiological role in many CNS functions (*e.g.*, learning and memory processes, synaptic plasticity, *etc.*), under pathological conditions, marked release of glutamate activates the excitotoxic cascade and induces excessive cytoplasmic calcium leading to apoptosis and neuronal death. Excess release of glutamate has been observed in animal studies and also in human brain during seizures and glutamate receptor agonists induce epileptiform activity and seizures. Modification of glutamate receptor function in transgenic animals can induce epilepsy (33, 34). Glutamate antagonists have been shown to reduce neuronal loss after ischemic insults (35) and to exhibit anticonvulsive properties in animal studies. Therefore, glutamate antagonists not only have potential to inhibit seizures but also, because of their neuroprotective effects, to prevent the progression of epilepsy. According to the disappointing results of meta-analyses of 12 different drug combinations, “old” antiepileptics (phenobarbital, phenytoin, valproate, carbamazepine) do not prevent epileptogenesis. Unfortunately, none of the newer drugs have been evaluated in antiepileptogenic clinical trials (36).

There are various ways to measure antiepileptogenic potential in animal studies. Recently Rubaj *et al.* (37) published results of a study on the epileptogenic effect of hypoxic seizures hypoxic seizures. Interestingly, while the NMDA antagonist MK-801 appeared to be ineffective, the AMPA antagonist NBQX effectively prolonged seizure latency to hypoxic seizures and prevented an epileptogenic effect. Although further confirmation is needed using other AMPA anatgonists, this finding may be of great importance for the design of antiepileptogenic therapy of patients suffering from epileptogenic insult.

Besides not being able to prevent disease progression, commonly used antiepileptics have another major drawback. Maximum benefit in quality of life of epilepsy patients is achieved when they are seizure-free. However, 40% of patients are inadequately controlled and, even if seizure-free, experience serious side effects, the most common being cognitive impairment and decrease in overall activity (38). It is not surprising that during the past years intensive research has focused on the development of compounds that restore the imbalanced inhibitory-excitatory homeostasis by suppressing the excitatory circuitry, such as glutamate antagonists.

1) NMDA antagonists

From among the ionotropic receptors, the tetrameric NMDA receptors consisting of two different subtypes ($NR_1$ and $NR_2$) were the primary therapeutic targets. Unfortunately, the first NMDA antagonists showed an unacceptable side effect profile (neuronal vacuolization, confusion, hallucination, agitation *etc.*).

In order to reduce the adverse effects of NMDA antagonists, research has focused on low-affinity, use-dependent antagonists, especially the $NR_2$ subtype. In this respect, Co-101244, a novel potent and selective $NR_1/NR_{2B}$ NMDA receptor antagonist, may be a promising lead for new antiepileptic compounds.

From among the low-affinity compounds, remacemide entered phase III clinical trials. Remacemide was compared with carbamazepine as monotherapy in an international double-blind study. However, according to the first results, its efficacy was inferior to that of carbamazepine (39).

Ro-63-1908 is a novel $NR_{2B}$-selective NMDA antagonist that has good anticonvulsive efficacy, as well as neuroprotective effects. Its side effect profile appears to be better than that of the first series of NMDA antagonists (*e.g.*, MK-801) (40).

ADCI (SGB-017), a low-affinity noncompetitive NMDA antagonist, is a broad-spectrum anticonvulsant with a favorable side effect profile. ADCI was protective against chemically and electrically induced seizures in mice (41-43). There is also evidence that ADCI blocks sodium channels as well (44).

Conantokins are NMDA receptor antagonist peptides found in the venom of marine cone snails. Current imterest in this peptide family stems from the discovery of their therapeutic potential as anticonvulsants. The four members of the conantokin peptide family identified to date are conantokin (Con)-G, -T, -L and -R. Con-R was recently reported to be a highly potent anticonvulsant compound, with a protective index of 17.5 when tested in the audiogenic mouse model of epilepsy. Con-L was less potent as an anticonvulsant, with a protective index of 1.2 in the same animal model (45, 46). CGX-1007 (Con-G) was previously shown to possess potent neuroprotective properties when administered intracranially following experimental ischemic brain injury. Using the same model of middle cerebral artery occlusion in rats, brain infarction was significantly reduced when CGX-1007 was administered intrathecally after occlusion (47). Con-G is a 17-amino acid peptide antagonist of NMDA receptors isolated from the venom of the marine cone snail, *Conus geographus*. Its mechanism of action has not been well defined, although both competitive and noncompetitive interactions with the NMDA binding site have been proposed. There is evidence that Con-G is a subtype-specific competitive antagonist of NMDA receptors (48). The unique subtype selectivity profile of Con-G may explain its favorable *in vivo* profile compared with nonselective NMDA antagonists.

Fluorofelbamate, a felbamate analog, showed anticonvulsant effects on acute and chronic seizures in an experimental rat model of self-sustaining status epilepticus. In this model, it also displayed antiepileptogenic properties (49). Felbamate causes aplastic anemia and liver dysfunction due to a toxic metabolite, atropaldehyde. The fluorine in fluorofelbamate prevents the toxic formation of this type of metabolite.

Japanese authors have published very impressive data on the glycine-site antagonist SM-31900 but no clinical efficacy data are available at present (50). Jansen *et al.* recently (51) published a series of novel 3-indolylmethyl derivatives with open ring and cyclic substituents showing high activity for the glycine binding site of the NMDA receptor. *In vivo* data are needed to judge their therapeutic potential. Harkoseride (SPM-927, ADD-234037) belongs to a class of functionalized amino acid AED candidates. Harkoseride also displays affinity for the glycine-strychnine-insensitive recognition site of the NMDA receptor complex. It shows potent anticonvulsant activity in several animal models, including models of status epilepticus (8, 39).

The tetronic acid derivative losigamone (AO-33) displays anticonvulsant activity both *in vivo* and *in vitro* (52). Although its exact mode of action is not known, there is *in vitro* evidence that NMDA antagonism and inhibition of excitatory amino acid release may contribute to the anticonvulsant effect of losigamone (53). However, losigamone significantly reduced spontaneous epileptiform events in rat hippocampal slices treated with the noncompetitive $GABA_A$ antagonist picrotoxin (54). Another suggested possible mechanism is $K^+$ channel activation (55). It is also likely that losigamone decreases neuronal excitability via a decrease in the persistent $Na^+$ current (56). Preclinical data indicate that (*S*)-(+)-losigamone may be more effective clinically than losigamone or its (*R*)-(–)-enantiomer (57). In healthy volunteers, losigamone has demonstrated relatively uncomplicated pharmacokinetics and was well tolerated. Losigamone proved to be an effective and well tolerated anticonvulsant drug for the treatment of chronic partial seizures (58, 59). In some subjects a reversible increase in transaminases was observed (60).

### 2) AMPA antagonists

The other very promising therapeutic target is the AMPA subtype of glutamate receptors because AMPA receptors play a pivotal role in epileptogenesis, seizure generation and therefore seizure-induced brain damage (61, 62). Although it was retrospectively found that pentobarbital, thiopental, topiramate and valproate are able to inhibit AMPA receptors, they all have multiple mechanisms of action and no clear correlation has been found between their anticonvulsant effects and AMPA receptor inhibiton. Therefore, their action on AMPA receptors most probably plays only a minor part in their anticonvulsant activity (63).

Sufficient evidence has emerged indicating that the subtype composition of AMPA receptors alters their ion permeability. Normally, AMPA receptors are permeable to $Na^+$ and $K^+$ ions; however, those receptors lacking the $GluR_2$ subtype become $Ca^{2+}$ permeable (64-66). The expression of this subtype is decreased under ischemic conditions. Double-labeling experiments for AMPA and GABA receptors have shown that $Ca^{2+}$ permeable AMPA receptors are mainly expressed on GABAergic inhibitory interneurons (65, 67-69). Therefore, the hypothesis has arisen that reduced GABA inhibition is of glutamatergic origin as a result of AMPA receptor-mediated excitotoxic death of these neurons. It should be mentioned that not only GABA but also NMDA receptors are colocalized with AMPA receptors (70). Inward current via non-NMDA

receptors depolarizes the postsynaptic membrane to remove the block of NMDA receptors by $Mg^{2+}$ (71). Actually, in many cases the activity of AMPA receptors is a prerequisite for activation of NMDA receptors. Interestingly, AMPA antagonists can potentiate the antiseizure activity of both GABA agonists and NMDA antagonists.

Talampanel (GYKI-53773; formerly LY-300164), a 2,3-benzodiazepine derivative, is the active (–)-isomer of (±)-GYKI-53405 that acts at a negative modulatory site of glutamatergic AMPA receptors ("GYKI site") in a noncompetitive manner. Although the chemical structure of talampanel is that of a benzodiazepine, its pharmacological effect is dissociated from the benzodiazepine/GABA receptor complex. Preclinical studies confirmed its unusually broad anticonvulsant spectrum, being effective in severe seizure models that are resistant to treatment with classic anticonvulsant agents (Table I). Talampanel is also active in the kindling model which is thought to be an animal model of epileptogenesis. According to both preclinical and clinical results, there is no tolerance to its activity.

It was also demonstrated in animal studies that the protective activity of valproate, diphenylhydantoin and phenobarbital is enhanced by talampanel (72) in the electroshock assay, similar to the findings obtained with valproate, carbamazepine and diazepam in aminophylline-induced convulsions in mice (73). The same synergy was observed when talampanel was used in combination with diazepam in different electrically and chemically induced seizure models in rodents. More importantly, this effect was especially marked in kindled rats (74), a model known to distinguish between the antiepileptogenic and antiseizure efficacy of drugs. On the other hand, the combination did not induce adverse effects with regard to motor coordination and long-term memory.

The anticonvulsant and neuroprotective effects of talampanel were demonstrated in various stroke and trauma models. Its neuroprotective effect was studied *in vivo* in the Mongolian gerbil carotid artery occlusion model (75) and in the middle carotid artery occlusion model of focal ischemia in rats (76). Belayev *et al.* found the drug to be neuroprotective in traumatic brain injury in rats (77). All of these findings indicate that talampanel may be able to prevent and/or retard the development of epilepsy.

Talampanel showed efficacy in reducing seizure frequency in a crossover, add-on trial in patients with refractory partial seizures, with 80% of talampanel-treated patients having fewer seizures compared to placebo. Talampanel was well tolerated, and dizziness and ataxia were the only significant adverse events (78). On ongoing multicenter, double-blind phase II clinical trial is evaluating talampanel in approximately 250 epilepsy patients.

YM-872 is a selective, potent inhibitor of [$^3$H]-AMPA binding with a $K_i$ value of 0.096 μM. The compound significantly improved neurological deficit in middle carotid artery occlusion model in rats (79) and in cats, and is currently undergoing clinical trials in the U.S. (AMPA Receptor Antagonist Treatment in Ischemic Stroke - ARTIST) (80). YM-928 is another noncompetitive AMPA antagonist that was recently reported to inhibit AMPA-mediated toxicity in primary rat cultures and has oral anticonvulsant activity in DBA/2 mice (81). AMP-397A is a water-soluble, orally active quinoxalinedione with a long duration of action (63). BIIR-561-CL is a novel combined antagonist of the AMPA receptors and voltage-dependent sodium channels with *in vivo* efficacy in electroshock and focal ischemia mouse models (82). The Scandinavian company, NeuroSearch A/S is in the early stages of developing NS-1209 (SPD-502), a competitive AMPA antagonist.

*Table I: Oral efficacy of talampanel in mouse seizure models induced by electroshock and different chemoconvulsants.*

| Seizure models | $ED_{50}$ mg/kg p.o.* |
|---|---|
| Maximal electroshock | 8.6 |
| Metrazole | 16.8 |
| Strychnine | 17.4 |
| Bemegride | 23.9 |
| Bicuculline | 14.6 |
| Nicotine | 22.7 |
| 4-AP | 8.4 |
| 3-MPA | 17.1 |

*1-h pretreatment time

*Influencing membrane channels*

1) Potassium channels

The discovery in 1998 of two novel genes (KCNQ2 and KCNQ3) mutated in a rare inherited form of epilepsy known as benign familial neonatal convulsions enabled insight into the molecular etiology of a human idiopathic generalized epilepsy syndrome for the first time. These disease genes encode subunits of neuronal M-type $K^+$ channels, key regulators of brain excitability (83). KCNQ4 channels, stably expressed in HEK293 cells, are activated by retigabine and BMS-204352. Activation of potassium channels generally reduces cellular excitability, making potassium channel openers potential drug candidates for the treatment of diseases related to hyperexcitabilty such as epilepsy, neuropathic pain, acute ischemic stroke and neurodegeneration (84).

Retigabine (D-23129, D-20443 [as dihydrochloride salt]) is a novel AED with broad spectrum and potent anticonvulsant properties, both *in vitro* and *in vivo* (85-88). Nickel and Szelenyi (1993, unpublished results) demonstrated that D-20443 was able to suppress 4-aminopyrine-induced seizures in mice. Later, Yonekawa *et al.* (89) observed that the compound tended to reverse to varying degrees the 4-aminopyrine effects, especially the increase in the EPSP duration, indicating a possible involvement of $K^+$ channel opening in its antiepileptic mode of action. Thereafter, the compound was shown to activate a $K^+$ current in neuronal cells, more precisely the

the M-current in Chinese hamster ovary cells transfected with the human KCNQ2/3 $K^+$ channel heteromultimere (90, 91). Cloning studies of the KCNQ2 potassium channel gene suggest that these channels may be important new targets for anticonvulsant therapies (92). Based on experimental results of Dailey *et al.* (87) in genetically epilepsy-prone rats, it is likely that D-20443 will suppress both tonic/clonic and absence seizures in humans. Indeed, retigabine has successfully been used in human epilepsy (8). In addition, there is experimental evidence that retigabine may prove to be effective in the treatment of neuropathic pain (93) and neurodegenerative disorders (8).

BMS-204352, a fluoro-oxindole potassium channel opener, was being developed as a potential neuroprotectant for the treatment of acute ischemic stroke. BMS-204352 is a potent and effective opener of two important subtypes of neuronal potassium channels, the calcium-activated, large conductance potassium channels ($K_{Ca}$ channels) and voltage-dependent, noninactivating potassium channels known as KCNQ channels. Additional investigations demonstrated that the novel maxi-K channel opener BMS-204352 may be selectively beneficial in the treatment of experimental traumatic brain injury (94). In clinical studies, however, the results have been disappointing. In patients with acute stroke, BMS-204352 failed to show superior efficacy compared to placebo (95). However, since the first clinical trials with retigabine have been promising, there is a chance that BMS-204352 may have thereapeutic potential in the treatment of epilepsy, although no clinical results are known at present.

2) Sodium and calcium channels

Low voltage-activated $Ca^{2+}$ channels play an important role in pacing neuronal firing and producing network oscillations, such as those that occur during sleep and epilepsy. Based on the brain distribution and novel gating properties of $\alpha$1I, the new member of the T-type calcium channel family, it was suggested that the channel may have an important role in determining the electroresponsiveness of neurons, and therefore may be a novel drug target (96).

Safinamide (NW-1015; formerly PNU-151774E) has a broad spectrum of activity in a variety of chemically and mechanically induced animal seizure models (97, 98). It is a sodium and calcium channel modulator that also inhibits monoamime oxidase B (97, 99, 100). Safinamide is under development for the treatment of epilepsy, Parkinson's disease, pain and stroke (101).

Rufinamide (CGP-33101) interacts with the inactivated state of the $Na^+$ channel, limiting high-frequency firing of action potentials in neurons. There was no interaction with a number of neurotransmitter systems, including GABA, NMDA, *etc.* binding sites. The protective index of rufinamide, as shown in rodent models of epilepsy, is much higher than that of most common AEDs (102). At steady state, rufinamide reached a peak plasma concentration with a $t_{max}$ of 3.4 h and a mean half-life of 7.3 h. No autoinduction of rufinamide metabolism occurred. Rufinamide did not influence the plasma concentration of carbamazepine, phenytoin or valproate when added to these single AED regimens (103, 104). Rufinamide has been shown to be safe and effective in reducing seizure frequency in epileptic patients (102, 104).

3) Voltage-gated sodium channels

Animal experiments and functional investigations on human chronically epileptic tissue, as well as genetic studies in epilepsy patients and their families, strongly suggest that some forms of epilepsy may share a pathogenetic mechanism, *i.e.*, an alteration of voltage-gated sodium channels. Therefore, drugs modulating sodium currents are still interesting candidates for epilepsy treatment.

Remacemide and its active metabolite, desglycinyl-remacemide, exert their antiepileptic effects, at least in part, via an inhibitory action on voltage-gated $Na^+$ channels (105, 106). Additionally, it may have antagonistic effects at the NMDA receptors (107). The pharmacokinetic profile of remacemide and its desglycinyl metabolite is relatively simple. However, plasma concentrations of remacemide and the desglycinyl metabolite are reduced in the presence of concomitant antiepileptic drugs with hepatic enzyme-inducing activity (108). Clinical studies, however, showed that remacemide is inferior to carbamazepine (109). Due to its modest effect on seizure frequency and significant withdrawal rate, it is unlikely that remacemide will be further developed as an antiepileptic drug (110). Moreover, remacemide had no significant benefit in the treatment of Parkinson's disease (111). At present, an NIH-funded trial of remacemide and Coenzyme Q10 in Huntington's disease is under way to address the glutamate- and mitochondrial-mediated hypotheses of neurodegeneration.

Soretolide (D-2916) exhibits an anticonvulsant profile similar to carbamazepine. In rats there is a certain sex-related difference in metabolism of this AED. Females hydroxylate the methyl of the isoxazolyl ring forming the active metabolite D-3187, resulting in higher brain concentrations and longer half-lives. The drug is reported to be in phase II trials (112, 113).

*Unknown mechanisms*

The novel compound SB-204269 (carabersat) shows potent anticonvulsant activity in the mouse maximal electroshock seizure threshold test (114). SB-204269 did not interact with many of the well-known mechanistic targets for established antiepileptic drugs (*e.g.*, $Na^+$ channels or GABAergic neurotransmission). Subsequent studies have shown that the anticonvulsant properties of SB-204269 are likely to be mediated via a novel stereospecific binding site present in the CNS (114-116). Trigeminal

parasympathetic reflexes were blocked by tonabersat, carabersat and other anticonvulsants. These agents may, therefore, have therapeutic benefit in conditions where this type of reflex is evident (117).

*Improvements in the chemical structure of available drugs*

1) Valproate derivatives

At present there are three compounds in clinical trials in patients with epilepsy that can be regarded as second-generation valproate: valrocemide, amide derivatives and SPD-421.

Valrocemide (TV-1901) was developed from a pharmacokinetic-based design of a series of *N*-valproyl derivatives of GABA and glycine. It has the ability to protect animals against electrically, chemically or sensorily induced seizures (118, 119), indicating its promising potential in the treatment of epilepsy. The compound is in phase II development.

The use of valproate is limited by its teratogenicity and hepatotoxicity. Amide derivatives of valproate such as *N*-methyl-tetramethylcyclopropane carboxamide, (2*S*,3*S*)-valnoctamide, (*R*)-propylisopropyl acetamide and valproylglycinamide have shown particular value as potential follow-up compounds. They possess a broad-spectrum antiepileptic activity and have been found to nonteratogenic in animals (8, 120, 121).

SPD-421 (formerly DP-VPA) is a new compound where valproic acid is chemically bound to lecithin. The cleavage of DP-VPA and local release of active valproic acid occurs selectively in response to paroxysmal neuronal activity by PLA2 which is elevated in an epileptic seizure. This might result in an improved efficacy to safety ratio (122). SPD-421 is in phase II trials as add-on therapy in the treatment of complex partial seizures.

2) Lamotrigine derivatives

Lamotrigine and the classic antiepileptic agents phenytoin and valproate block the fast-inactivating sodium channel but fail to affect persistent conductance. In contrast, two lamotrigine derivatives (sipatrigine and 202W92) and riluzole inhibit the persistent sodium current at low therapeutic concentrations (123). Consequently, there is a possibility of developing novel AEDs which suppress persistent conductance, resulting in the control of seizures.

3) Levetiracetam derivatives

NPS-1776, a branched-chain, low-molecular-weight aliphatic amide, is an orally active molecule being developed for the treatment of epilepsy and other neurological and psychiatric disorders. The compound exhibited a high margin of safety, rapid onset and a broad spectrum of activity in controlling seizures in preclinical studies (39).

4) Benzodiazepines

Recent research has shown that the density of the peripheral benzodiazepine receptors is significantly increased in several CNS disorders, such as epilepsy, multiple sclerosis, cerebral ischemia, astrocytoma, brain injury and neurodegenerative diseases (124). These benzodiazepine receptors bind selectively to benzodiazepine ligands and an isoquinoline carboxamide derivative PK-11195 with high affinity. Pretreatment with the isoquinoline PK-11195 attenuated the occurrence of seizures and hyperactivity in rats treated with kainic acid (125), indicating again that peripheral benzodiazepine receptors may be interesting targets for future drug develepment.

*Neuropeptide receptor ligands as novel targets*

Biologically active peptides identified in the brain (neuropeptides) modulate the activity of classic neurotransmitters in either positive or negative fashion. The end effect of a neuropeptide depends on the neurotransmitter involved (excitatory or inhibitory) and on the direction in which the activity of a target transmitter is modulated (stimulation or suppression). Overall, those neuropeptides which enhance GABAergic transmission and/or inhibit glutamatergic excitation may be regarded as “antiepileptic” and *vice versa*.

To date, virtually every peptide identified in the brain has been studied with regard to its effects on seizures. However, only a few neuropeptides exhibited potent effects across different seizure models and can be considered as targets for new antiepileptic drugs: somatostatin (SRIF) (126), neuropeptide Y (NPY) (126) and galanin (127).

“Anticonvulsant” neuropeptides share the following basic physiological and pharmacological properties: (i) Receptors for these neuropeptides belong to a superfamily of $G_i$ protein-coupled receptors. (ii) Receptors for these peptides are located on principal excitatory neurons in the hippocampus (dentate granule cells, or pyramidal cells) either pre- or postsynaptically. (iii) Activation of a neuropeptide receptor either blocks glutamate release from presynaptic terminal or hyperpolarizes postsynaptic terminal, resulting in either case in suppression of excitotoxic epileptogenic mechanisms.

Receptors for SRIF, NPY and galanin are heterogeneous. Anticonvulsant effects of peptides are often receptor-subtype specific; moreover, activation of different receptor subtypes may have opposite effects on seizures. Thus, while activation of $Y_2$ or $Y_5$ receptors mediates the anticonvulsant action of NPY, stimulation of $Y_1$ receptors in the hippocampus may have proconvulsant effects

(126). Seizure-suppressing effects of SRIF are mediated by the $sst_2$ subtype of the $SRIF_1$ receptor (126); seizure suppression by galanin involves GAL1 and GAL2 receptor subtypes (127).

Native neuropeptides cannot be used as antiepileptic drugs due to rapid cleavage by peptidases in the bloodstream and poor permeability through the blood-brain barrier. Thus, the notion of neuropeptide receptors as a target for anticonvulsant therapy led to pharmacological studies on the development of low-molecular-weight nonpeptide agents which would bind with reasonable affinity to a neuropeptide receptor, and which can be given systemically. Furthermore, since endogenous peptides do not discriminate between receptor subtypes, functional heterogeneity of receptors in seizure modulation calls for development of synthetic ligands which would prefer "anticonvulsant" receptor subtype (*e.g.*, $Y_5$ over $Y_1$ in the case of NPY).

Modification of the SRIF molecule resulted in the development of SMS-201-995, a protease-resistant cyclic peptide with anticonvulsant properties (128). Rational compound design applied to galanin resulted in the synthesis of galnon, a nonpeptide low-molecular-weight galanin receptor agonist having potent seizure-suppressing effects (129). A selective nonpeptide antagonist for the $Y_1$ receptor subtype, BIBP-3225, was shown to be a viable alternative approach for inhibiting the "proconvulsant" receptor subtype (130).

## Optimization of existing antiepileptic drugs

Approximately 30% of epilepsy patients fail to respond to the first and second antiepileptic drugs. One obvious approach to managing this problem is extending the selection of antiepileptic drugs through the design of novel compounds. An alternative strategy is to enhance the efficacy of currently available anticonvulsant agents.

Transfering the concept of multidrug-resistance (MDR) genes and proteins from cancer research to neurology and epileptology uncovers new perspectives in enhancing the efficacy of some conventional antiepileptic drugs (131).

P-glycoprotein (Pgp), encoded by a multidrug-resistant gene mdr-1, belongs to a superfamily of ATP-binding cassette proteins expressed in brain endothelial cells, thus representing a component of the blood-brain barrier (132). Normal function of Pgp is protecting the brain from xenobiotics (133). In epilepsy, however, Pgp may contribute to failure of an antiepileptic drug to access the brain and exhibit its therapeutic effect (134). A number of antiepileptic drugs are regulated by Pgp, including phenytoin, carbamazepine, phenobarbital, topiramate and probably, lamotrigine (135). Recent advances in oncopharmacology yielded a number of relatively effective Pgp inhibitors, which are being considered as additive agents in pharmacoresistant epilepsies, such as SDZ-PSC-833 (136) and LY-335979 137).

## Outlook

The introduction of the newer AEDs, from felbamate to levetiracetam, has raised hopes of controling epilepsy with fewer adverse effects and improved quality of life. An ideal anticonvulsant drug would prevent or inhibit excessive pathological neuronal discharge without interfering with physiological neuronal activity and without producing side effects. Such an ideal compound is not yet available. Indeed, the search for an ideal AED which would control all types of epilepsy and have a convenient pharmacokinetic profile and few side effects is not just a dream. However, epilepsy therapy will have to focus on strategies for preventing and curing the disease rather than controling symptoms. Techniques for identifying novel AEDs are changing and need to change more. Preclinical *in vivo* screens can be improved by using animals with genetic or acquired epilepsies that have similar modifications in the properties of the target molecules as human epilepsy syndromes. Future work is likely to define molecular targets for AEDs that will block or reverse chronic epileptogenesis. Knowing more about the factors behind individual variability in antiepilepsy drug tolerability and dose response, as well as a general knowledge of implications of epileptogenic processes would represent an important advance in tailoring epilepsy pharmacotherapy. An AED is likely to be successful if it exhibits optimal characteristics, such as drug efficacy, tolerability, pharmacokinetics, interactions and cost-effectiveness. Hopefully, the next decade will bring the breakthroughs.

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