Prospects for new drug treatment in epilepsy: a review

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Introduction

Epilepsy is the commonest of neurological disorders with prevalence rates for active epilepsy of 5 per 1000 of the population[1]. Arguably, it has been the most fruitful of therapeutic fields for the neurologist during the course of this century, but one has to question how far we have advanced in our ability to treat patients with epilepsy over the last 20 years. In the field of pharmacology the clinician is still largely dependent on those drugs that were developed in the first half of this century. When epilepsy is compared with other major therapeutic areas such as cardiovascular or gastrointestinal medicine, the neurologist must be depressed by the knowledge that no new major antiepileptic drugs have become established as firstline agents during the last decade. Indeed, many patients continue to take phenobarbitone, a drug introduced into clinical practice in 1912, and phenytoin, an agent that has recently celebrated 50 years in clinical use![2]. In the United States, even valproate is only fully licensed for the treatment of simple absence (petit mal) seizures in spite of its well-recognized properties in the treatment of tonic clonic and partial seizures[3].

Where pharmacological treatment has improved most is in the area of more sophisticated use of the agents that we possess. Thus, whilst major questions still remain, we are better able to decide when to start and when to stop treatment with antiepileptic drugs[4] and the superiority of monotherapy to polytherapy is widely recognized[5]. Our understanding of the pharmacokinetics of the drugs we use has also benefited patients, though to some degree serum blood level estimations are overvalued and in some cases abused[6].

How then can we expect to make progress in identifying and establishing new antiepileptic drugs? No neurologist could surely doubt the need for such agents. Whilst overall the prognosis for patients developing epilepsy is good with up to 70% achieving long-term remissions[7], a significant number of people with epilepsy have a chronic intractable disorder causing disability with significant socio-economic implications. More potent and effective antiepileptic drugs are particularly needed for the treatment of partial epilepsies and drugs with similar efficacy to those available would be of value if they have more specific actions with fewer CNS side effects[8]. Fortunately, major advances in the basic neurophysiology, neuropathology, and neuropharmacology of epilepsy would now suggest that by the end of the century new groups of antiepileptic drugs should be available for routine clinical use. There seems every hope that such drugs will be developed rationally from an understanding of the basic mechanisms of the epilepsies rather than by the chance discovery of antiepileptic drugs through empirical screening programmes.

A century ago, Hughlings Jackson[9] recognized epilepsy as a disorder of hyper-excitability of the nervous system. While Jackson's original physiological definition of epilepsy holds true today, clinical definitions of seizures and epilepsy are more difficult because of the enormous heterogeneity of the clinical disorder. In pursuing the aim of controlling the abnormal electrical activity that leads to epileptic seizures two differing philosophies could be utilized. The first would recognize that epilepsy is a heterogenous disorder with many different causes. This approach would attempt to identify individual causes so as to offer specific treatment that may not be relevant to other forms of epilepsy. Whilst there is greater understanding of epileptogenesis in animal models, their relevance to human epilepsy remains uncertain. As yet such an approach cannot easily be utilized. The second approach is to recognize that the many different causes of epilepsy may well converge and operate through a common final pathway. An attack on such a final common pathway might result in a much broader spectrum antiepileptic effect.

This review article will particularly focus on the latter approach and will present a clinician's view of relevant advances in basic neurophysiology and neuropharmacology that lead from studies of individual cells through to animal models and finally to clinical trials of potential antiepileptic drugs.

Cellular mechanisms of epileptogenesis

There is an enormously increased understanding of the basic cellular mechanisms that lead to epileptic discharge. A full review is beyond the scope of this article, but other reviews are available[10,11]. In many focal epileptogenic areas cells exhibit an unusual pattern of firing with bursts of very high frequency discharge followed by periods of relative quiescence. Such burst firing appears to be determined by prolonged depolarization shifts in the cellular membrane (paroxysmal depolarization shift, PDS). When such shifts occur, bursts of action potentials are propagated by pyramidal tract neurones. Groups of neurones that fire in this abnormal way can on occasion recruit surrounding groups of neurones to a similarly abnormal pattern of firing, and this spread of abnormal activity may lead to the propagation of a seizure.

Some of the mechanisms of paroxysmal depolarization shift at a cellular level have been elucidated. The PDS appears to be calcium dependent[12]. This would imply that to a degree changes in voltage dependent ion channels may be important

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in PDS. However, PDS can also be seen with drugs that have effects through neurotransmitter controlled ion channels. Thus penicillin can cause PDS because of its ability to bind to and block the action of GABA, the inhibitory neurotransmitter, at its receptor. Similarly, the action of excitatory neurotransmitter substances (glutamate and aspartate) at some subspecies of excitatory receptor (the NMDA receptor) also lead to PDS.

Thus drugs that have effects in reducing calcium entry into cells by direct membrane effects, or by preventing PDS through increasing gabergic inhibition or interfering with excitatory neurotransmitter function, may potentially be antiepileptic. As more is understood of the structure-function relationships of inhibitory and excitatory neurotransmitters many new potential antiepileptic drugs may be developed.

GABA and epilepsy

When gamma aminobutyric acid (GABA) interacts with GABA receptors at neurone membranes it causes an opening in structurally related chloride ion channels which results in turn in a membrane hyperpolarization. The evidence linking GABA function to control of seizure threshold is convincing. Thus, drugs such as allylglycine that block the synthesis of GABA and others such as bicuculline which block GABA receptors lead to seizures in experimental animals[13]. There is good evidence of a loss of GABA and GABA terminals in focal models of epilepsy as well as in some genetic models, but similar changes in human epilepsy remain to be demonstrated[14]. GABA may be implicated in the therapeutic action of a number of existing antiepileptic drugs that have been developed by empirical means. Thus both benzodiazepines and phenobarbitone can facilitate the actions of GABA at its receptor site[15]. Valproate may have some actions in raising brain GABA concentrations by inhibiting metabolism of GABA, though whether it does so at therapeutic concentrations is doubtful[16].

All these lines of evidence suggest that the pharmacology of GABA may be important in developing new antiepileptic agents. A number of mechanisms of enhancing gabergic activity may be explored. These include drugs which may be:

(1) Direct GABA agonists
(2) Inhibitors of GABA uptake
(3) Increase the release of GABA
(4) Inhibitors of the degradation of GABA by GABA transaminase
(5) Indirect modulation of GABA receptors through other allied receptor sites, eg the benzodiazepine receptor.

Excitatory neurotransmitters and epilepsy

Glutamate and aspartate are found in high concentration throughout the brain and produce excitation when applied iontophoretically to neurones. They can be shown to be released during seizure activity and probably act as excitatory neurotransmitters[17]. The receptors at which glutamate and aspartate are active have been classified into subtypes with different pharmacological properties. They appear to have preferred ligands in the form of n-methyl-d-aspartic acid (NMDA), quisqualic acid and kainic acid[18,19]. The NMDA receptor is of particular interest for its potential epileptogenic properties. It appears to activate calcium entry ion channels which leads to a paroxysmal depolarizing shift and burst firing[20]. Such receptors are found on the dendrites and soma of neurones throughout the cortex so that it may be that their stimulation is capable of producing a burst firing of normal neurones to released excitatory neurotransmitters such as glutamate and aspartate[17].

A variety of structural analogues of glutamate and aspartate can be shown to block the excitatory actions of these neurotransmitters[19]. Meldrum has shown that, when administered intracerebral or intraventricularly, selective NMDA antagonists (2-APV and 2-APH) have potent antiepileptic effects in audio-sensitive mice and photosensitive baboons[17]. They do, however, penetrate the blood brain-barrier poorly and therefore their systemic effects are much less potent. Whilst NMDA receptor antagonists may also produce considerable neurotoxicity including memory impairment, their discovery may well prove a fruitful field for the development of new potential antiepileptic drugs. As yet, such compounds have not been extensively tested in the clinical situation[21].

A number of drugs are now in clinical evaluation that have been developed because of predefined neurotransmitter function. The first of these, Vigabatrin, was released on the UK market at the end of 1989.

New antiepileptic drugs in development

Meldrum and Porter[22] recently reviewed information on some 17 different compounds undergoing clinical evaluation of their antiepileptic properties. Some of these drugs are direct derivatives of existing drugs, eg oxcarbamazepine, or developments from other groups of drugs with some antiepileptic properties (eg sulphonamides). Others have been discovered because of routine screening of newly synthesized molecules for anticonvulsant effects. The following is a brief review of four potential antiepileptic drugs. These have been chosen because they relate to the authors' own experience or have specific interest in that they have been developed along rational lines from knowledge of neurotransmitter mechanisms underlying possible seizure disorders.

Vigabatrin (gamma-vinyl-gaba)

Vigabatrin is an irreversible inhibitor of GABA-transminase the principle metabolic enzyme inactivating GABA. Vigabatrin binds to the enzyme and acts as a 'suicide' substrate. It elevates brain GABA concentrations in animals[23] and increases GABA concentrations in CSF of man in a dose dependent fashion[24]. Whilst the drug has a short half life its pharmacological action is prolonged because of the irreversible nature of its interaction with its target enzyme.

Doses between 1.5 and 3 g per day in double-blind placebo controlled cross-over studies leave no doubt as to the potent antiepileptic properties of this drug[14]. Forty-one per cent of patients in these studies showed a 50% or greater reduction in seizure frequency which would certainly suggest efficacy comparable to that of conventional antiepileptic drugs in patients with partial seizures or perhaps even superior efficacy. Longer term larger multicentre single blind placebo control studies come to similar conclusions.

Side effects noted with the drug include some dizziness, unsteadiness and drowsiness, but serious reactions appear uncommon with over 1200 patients treated worldwide. Major concern has, however, arisen because of problems with animal toxicology. High dose chronic studies, initially in rats and subsequently in dogs, showed pathological evidence of microvacuolation due to apparent intramyelinic oedema[25,26]. Other GABA transaminase inhibitors may produce similar changes[27]. In animals, the pathological change may be associated with encephalopathy and seizures. Whilst there is no evidence that similar changes are found in man these findings have slowed the clinical development of the drug.

Progabide

Progabide has been assessed as an antiepileptic drug because of its direct agonist effects on GABA receptors as well as the fact that its metabolite has similar actions. It is active against a wide variety of animal models of seizures and epilepsy[28]. It has undergone extensive clinical testing[29]. A number of studies have suggested statistically significant antiepileptic efficacy in double-blind studies whilst others have failed to detect an effect. An overview of similar double-blind cross-over studies has suggested that the observed effect in some studies is genuine but more recently published negative studies detract from this hypothesis[30,31]. Crawford and Chadwick[30] also compared valproate to progabide and found valproate superior to progabide in the treatment of partial and tonic clonic seizures.

Progabide has been associated with elevation of liver transaminase. This may occur in up to 8% of patients treated and cases of clinically significant hepatotoxicity are well recognized[32]. The frequency with which elevation of transaminase enzymes was noted led to the cessation of one clinical trial[30]. The combination of doubtful clinical efficacy and hepatotoxicity make it unlikely that this drug will be marketed widely.

Gabapentin

Gabapentin is a GABA-analogue that is rapidly absorbed and unlike GABA penetrates the blood-brain barrier. It is excreted unchanged and is not protein bound. It has been shown to be effective against a variety of seizure models in animals particularly those associated with interference in gabergic transmission or provoked by excitatory aminoacids. In spite of this the mechanism of action of gabapentin remains uncertain. It does not bind to specific receptor sites and has no observable action in altering GABA concentrations or influencing GABA metabolism in pharmacologically relevant doses[33]. A pilot open dose titrating study showed that doses up to 1800 mg per day resulted in 28% of 52 evaluable patients showing a 50% reduction in seizures, both partial and generalized seizures being responsive[34]. A dose-related antiepileptic effect has been observed during a double-blind cross-over study comparing three doses of gabapentin (300 mg, 600 mg, and 900 mg per day) for 2 months each as add on to one or two other anticonvulsant drugs in 25 patients with severe partial or generalized epilepsies[35]. A formal proof of efficacy study has now been undertaken in 127 patients with drug resistant partial epilepsy using a parallel group design with randomization either to placebo or gabapentin 1200 mg per day as add-on treatment. Three months' treatment with gabapentin resulted in a 29% reduction in median partial seizure frequency compared to a reduction of 12.5% with placebo. Twenty-five per cent of patients receiving gabapentin had seizures reduced by 50% or more compared to 10% of patients receiving placebo[36].

Side effects with the drug as add-on therapy appear mild, usually consisting of non-specific complaints of drowsiness and lethargy. Symptoms are more commonly observed with gabapentin than with placebo. Gabapentin appears not to interact with existing antiepileptic drugs.

Whilst further evidence of proof of efficacy is required, gabapentin may be of value, not in possessing greater antiepileptic potency than drugs currently available, but as one having similar antiepileptic properties but with few significant side-effects.

Lamotrigine

This drug has undergone development and testing because of its weak antifolate properties[37]. Reynolds *et al.*[38] suggested that as folate itself is convulsant and some anticonvulsants have antifolate action that antifolate effects may be anticonvulsant. In fact, the antiepileptic properties of lamotrigine may be related to its ability to reduce the release of glutamate, the excitatory neurotransmitter[37]. Lamotrigine is active in a number of animal models of seizures and epilepsy and has a spectrum of activity similar to that of phenytoin. Short-term administration has been shown to reduce photosensitivity in the EEG of susceptible patients[39] and interictal spike activity[40]. Two clinical studies in institutionalized severely epileptic patients have shown mild antiepileptic effects and one double-blind cross-over study in outpatients showed an impressive antiepileptic response[40]. Further proof of efficacy studies are required.

From this brief review it can be appreciated that we may now be approaching a new era in antiepileptic drug development. This is being stimulated by the advances in basic neuroscience which make possible the rational development of new drugs with specific, clearly identified modes of action. Vigabatrin, which has now received CSM approval, is likely to be the first of several new drugs becoming available in the next few years. It is to be hoped that this will improve the drug treatment of epilepsy by offering more effective targeted treatment with fewer side effects for patients with epilepsy.

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