ELSEVIER

European Journal of Pharmacology 342 (1998) 1–13

ejp

Review

New visions in the pharmacology of anticonvulsion

Wolfgang Löscher *

Department of Pharmacology, Toxicology and Pharmacy, School of Veterinary Medicine, Bunteweg 17, 30559 Hannover, Germany

Received 18 September 1997; revised 3 November 1997; accepted 11 November 1997

Abstract

Seizures are resistant to treatment with currently available anticonvulsant drugs in about 1 out of 3 patients with epilepsy. Thus, there is a need for new, more effective anticonvulsant drugs for intractable epilepsy. Furthermore, because of the inadequacy of the currently available anticonvulsant armamentarium with respect to safety, newly developed drugs should be less toxic than existing drugs. Previous and current strategies for development of novel anticonvulsants with improved efficacy or safety are critically discussed in this review. 'Old drugs' (or 'first generation' drugs), which were developed and introduced between 1910 and 1970, are compared with new anticonvulsants both in terms of clinical efficacy and safety and in terms of mechanisms of action. The new drugs are referred to as 'second generation' drugs, i.e. anticonvulsants which have been introduced into clinical practice in recent years, or 'third generation' drugs, i.e. compounds in the pipeline of development. In spite of some 30 years of 'modern' neuroscientific epilepsy research, most novel, clinically effective second generation anticonvulsants have been found by screening (i.e. serendipity) or structural variation of known drugs and not by rational strategies based on knowledge of processes involved in generation of seizures or in development of epilepsy. An exception are only the GABA(γ-aminobutyrate)-mimetic drugs vigabatrin and tiagabine and, to some extent, gabapentin, which have been developed by a rational strategy, i.e. the 'GABA hypothesis' of epilepsy. The fact that preclinical seizure models used for identification and development of novel drugs have been originally validated by old drugs, i.e. conventional anticonvulsants, may explain that several of the new drugs possess mechanisms which do not differ from those of the standard drugs. This may also explain that none of the new drugs seems to offer any marked advantage towards the old, first generation drugs with respect to the ultimate goal of drug treatment of epilepsy, i.e. complete control of seizures, although some of the second generation drugs may have benefits in terms of side effects and tolerability. It is to be hoped that the various novel currently used or planned strategies for drug development produce more effective and safe anticonvulsants than previous strategies. This goal can only be achieved by strengthening our understanding of the fundamental pathophysiology of seizure expression and epileptogenesis as theoretical substrates for new pharmacological strategies, and by devising and refining laboratory models for studying new agents obtained by such strategies.

Keywords: Epilepsy; Seizure; Antiepileptic drug; GABA(γ-aminobutyric acid); Glutamate

1. Introduction

Epilepsy is one of the most common diseases of the brain, affecting at least 50 million persons worldwide (Scheuer and Pedley, 1990). Epilepsy is a chronic and often progressive disorder characterized by the periodic and unpredictable occurrence of epileptic seizures which are caused by an abnormal discharge of cerebral neurons. Many different types of seizures can be identified on the basis of their clinical phenomena. These clinical characteristics, along with their electroencephalographic (EEG) features, can be used to categorize seizures (Commission, 1981). Seizures are fundamentally divided into two major groups: partial and generalized. Partial (focal, local) seizures are those in which clinical or electrographic evidence exists to suggest that the attacks have a localized onset in the brain, usually in a portion of one hemisphere, while generalized seizures are those in which evidence for a localized onset is lacking. Partial seizures are further subdivided into simple partial, complex partial, and partial seizures evolving to secondarily generalized seizures, while generalized seizures are categorized into absence (nonconvulsive), myoclonic, clonic, tonic, tonic–clonic and atonic seizures. In addition to classifying the seizures that occur in patients with epilepsy, patients are classified into appropriate types of epilepsy or epileptic syndromes characterized by different seizure types, etiologies, ages of onset and EEG features (Commission, 1989). More than 40 distinct epileptic syndromes have been identified, making

* Corresponding author. Tel.: +49-511-8568721; fax: +49-511-9538581; e-mail: wloscher@pharma.tiho-hannover.de

epilepsy a remarkably diverse collection of disorders. The first major division of epilepsy are localization-related (focal, local, partial) epilepsies, which account for roughly 60% of all epilepsies, and generalized epilepsies, which account for approximately 40% of all epilepsies. An epilepsy or epileptic syndrome is either idiopathic, which is virtually synonymous with genetic epilepsy, or symptomatic, i.e. due to structural lesion or major identifiable metabolic derangements. Both type of seizure and epilepsy determine the choice and prognosis of therapy. For instance, the most common and most difficult-to-treat type of seizures in adult patients are complex partial seizures, while primary generalized tonic–clonic ('grand mal') seizures respond in most patients to treatment with anticonvulsants. For many of the seizure types and epilepsy syndromes we have little information about their pathophysiological basis. Yet our insight into how partial seizures, generalized tonic–clonic seizures and generalized absence seizures arise is substantial, which is fortunate since these constitute around 90% of seizures (Lothman, 1996).

In the absence of a specific etiological understanding in any of the epilepsies or epileptic syndromes, approaches to drug therapy of epilepsy must necessarily be directed at the control of symptoms, i.e. the suppression of seizures. In fact, all currently available drugs are anticonvulsant (antiseizure) rather than antiepileptic. The latter term should only be used for drugs which prevent or treat epilepsy and not solely its symptoms (see Section 4). The goal of therapy with an anticonvulsant drug is to keep the patient free of seizures without interfering with normal brain function. The selection of an anticonvulsant drug is based primarily on its efficacy for specific types of seizures and epilepsy (Mattson, 1995). For instance, valproic acid is usually the drug of choice for the generalized idiopathic epilepsies, while carbamazepine and phenytoin show the best balance of seizure control with relatively few adverse effects for the treatment of partial epilepsy (Mattson, 1995). In most patients with epilepsy the prognosis for seizure control is very good. However, a significant proportion of individuals with epilepsy suffer from intractable, i.e. pharmacoresistant epilepsy despite early treatment and an optimum daily dosage of an adequate anticonvulsant drug (Dam, 1986; Dreifuss, 1992; Leppik, 1992; Forsgren, 1995; Sillanpää, 1995). Thus, there is a clear need for new drugs or new strategies of therapeutic management. Although surgical treatment of epilepsy may be an alternative if anticonvulsant drugs fail, surgery for epilepsy might not be needed if we knew more about ways to prevent medical intractability or if we had more effective and less toxic anticonvulsant drugs (Theodore, 1992).

In addition to the need for new drugs for epileptic patients whose seizures are resistant to available anticonvulsants, new drugs with benefits in terms of side effects and tolerability are needed even if they do not demonstrate greater efficacy than established anticonvulsants (Richens, 1991; Schmidt and Krämer, 1994). Furthermore, in view of the fact that the therapeutic effectiveness of the older anticonvulsant drugs has usually been limited by their narrow therapeutic ratio, i.e. the ratio of toxic dose against the effective dose, it is hoped that an improved therapeutic ratio may be seen with some of the novel compounds currently being developed.

2. Spectrum of anticonvulsant activity and mechanism of action of old and new anticonvulsant drugs

The 20th century has witnessed considerable progress in anticonvulsant drug development (Löscher and Schmidt, 1994). The major drugs in clinical use, i.e. phenytoin, carbamazepine, valproate, benzodiazepines, ethosuximide, phenobarbital and primidone, were developed and introduced between 1910 and 1970 and will be referred to as 'old drugs' (or 'first generation' drugs) in the following. After a hiatus of over 20 years, several new anticonvulsant drugs, i.e. vigabatrin, gabapentin, felbamate, lamotrigine, oxcarbazepine, tiagabine and topiramate, have been introduced into clinical practice, referred to as 'new drugs' (or 'second generation' drugs) in the following. More recent anticonvulsants which are in preclinical or clinical development will be referred to as 'third generation' drugs.

In spite of some 30 years of 'modern' neuroscientific epilepsy research, most novel, clinically effective anticonvulsants have been found by screening (i.e. serendipity) or structural variation of known drugs and not by rational strategies based on knowledge of processes involved in initiation, elaboration, and extension of seizures (ictogenesis) or in development of epilepsy (epileptogenesis), e.g. in augmented propensity for spontaneous seizures or in the progression in severity of seizures or their resistance to medical therapy (Löscher and Schmidt, 1994). An exception are only the GABA (γ-aminobutyrate)-mimetic drugs vigabatrin and tiagabine and, to some extent, gabapentin, which have been developed by a rational strategy, i.e. the 'GABA hypothesis' of epilepsy (Löscher, 1989b, 1993; Olsen and Avoli, 1997).

The fact that preclinical models used for identification and development of novel drugs have been originally validated by 'old' drugs, i.e. conventional anticonvulsants, may explain that several of the new drugs possess mechanisms which do not differ from those of the standard drugs. The most commonly employed animal models in the search for new anticonvulsant drugs are the maximal electroshock seizure test and the pentylenetetrazole seizure test (Löscher and Schmidt, 1988). The maximal electroshock seizure test, in which tonic hindlimb seizures are induced by bilateral corneal or transauricular electrical stimulation, is thought to be predictive of anticonvulsant drug efficacy against generalized tonic–clonic seizures, while the pentylenetetrazole test, in which generalized

myoclonic and clonic seizures are induced by systemic (usually s.c.) administration of convulsant doses of pentylenetetrazole, is thought to represent a valid model for generalized absence and/or myoclonic seizures in humans (Löscher and Schmidt, 1988). As shown in Table 1, the anticonvulsant activity of the old drugs in these models is in accordance with their anticonvulsant efficacy against tonic–clonic or absence/myoclonic seizures. It has been repeatedly proposed that the maximal electroshock seizure test might be also predictive of anticonvulsant efficacy against partial seizures. However, more recent experimental and clinical studies on novel anticonvulsant drugs, such as vigabatrin or glutamate receptor antagonists (see below), have demonstrated that the maximal electroshock seizure test is not suited in this respect (Table 1). Indeed, the relative ineffectiveness of most standard anticonvulsant drugs against ictal events such as complex partial seizures might be attributed to the fact that these drugs were developed in the absence of appropriate experimental models for drug screening (Engel, 1992). Thus, true models of partial seizures, such as amygdala-kindling (see Table 1), should be used to test anticonvulsant efficacy against partial epileptic activity (Löscher and Schmidt, 1988).

As shown in Table 1, the kindling model correctly predicts the clinical effect of both old and new drugs against partial seizures. However, the pentylenetetrazole test did not predict the effect of lamotrigine against absence and myoclonic seizures and yielded false positive data in case of vigabatrin and tiagabine. Genetic animal models of non-convulsive seizures,such as the lethargic (*lh/lh*) mouse, seem to be more predictive in this regard (Hosford and Wang, 1997; Löscher, 1997a).

With respect to mechanisms of action of old drugs, Macdonald has proposed that anticonvulsant drugs can be divided mechanistically into at least three classes based on ability to block sustained high-frequency repetitive firing of action potentials by blockade of voltage-dependent Na^+ channels, to enhance GABAergic inhibition and to block slow, pacemaker-driven, repetitive firing by blocking T-Ca^{2+} current (Macdonald, 1989; Macdonald and Kelly, 1995; Macdonald and Meldrum, 1995). Macdonald (1989) further suggested that the ability of an anticonvulsant drug to block generalized tonic-clonic seizures and some forms of partial seizures may correlate with the ability of the drug to block sustained repetitive firing, while drugs with a broader spectrum of anticonvulsant activity block both sustained repetitive firing and enhance GABAergic inhibition (Table 2). Anti-absence drugs such as ethosuximide may act via their effect on thalamic T-Ca^{2+} current (Table 2). However, by this concept it is difficult to explain how valproate and benzodiazepines act on absence seizures. Furthermore, the concept ignores several additional cellular mechanisms of the old drugs which could explain the differences in pharmacology between drugs in the same class (Rogawski and Porter, 1990; Löscher and Schmidt, 1994; Schachter, 1995; White, 1997). For instance, while carbamazepine and phenytoin are generally thought to act

Table 1
Anticonvulsant effect of old and new drugs against different types of seizures in animal models and in human epilepsy

Drug	Anticonvulsant activity in experimental models			Clinical efficacy			
	MES test (mice or rats, tonic seizures)	s.c. PTZ test (mice or rats, clonic seizures)	Amygdala-kindling (rats, focal seizures)	Partial seizures	Generalized seizures		
					tonic–clonic	absence	myoclonic
Old drugs							
Carbamazepine	+	NE	+	+	+	NE	NE
Phenytoin	+	NE	+	+	+	NE	NE
Phenobarbital	+	+	+	+	+	NE	+
Primidone	+	+	+	+	+	NE	+
Valproate	+	+	+	+	+	+	+
Benzodiazepines	+	+	+	+	+	+	+
Ethosuximide	NE	+	NE	NE	NE	+	+/−
New drugs							
Lamotrigine	+	NE	+	+	+	+	+
Topiramate	+	NE	+	+	+	+/−	+
Oxcarbazepine	+	+/−	?	+	?	NE	NE
Felbamate	+	+	+	+	+	+/−	+
Vigabatrin	NE	+	+	+	?	NE	NE
Tiagabine	NE	+	+	+	?	?	NE
Gabapentin	+/−	+/−	+	+	?	NE	NE
NMDA antagonists	+	+/−	NE	NE	?	?	?

Effect is indicated by + = effective; +/− = inconsistent data; NE = not effective; ? = no data available (or found). MES, maximal electroshock seizure; PTZ, pentylenetetrazole.
For detailed data see Löscher (1997a).

Table 2
Proposed cellular mechanisms of action of old drugs (based on Macdonald, 1989; Macdonald and Kelly, 1995)

Seizure type/anticonvulsant drug	Blockade of voltage-dependent Na^+ channels	Potentiation of GABAergic mechanisms	Blockade of thalamic T-type CA^{2+} channels
Generalized tonic–clonic and partial seizures			
Phenytoin	+ +	NE	NE
Carbamazepine	+ +	NE	?
Phenobarbital	+	+	NE
Broad spectrum			
Valproate	+ +	+	NE
Benzodiazepines	+	+ +	NE
Absence seizures			
Ethosuximide	NE	NE	+

Effect is indicated by +, + + = effective; + / − = inconsistent data; NE = not effective in therapeutically relevant concentrations; ? = no data available (or found).

by their effect on Na^+ channels (Macdonald and Meldrum, 1995), an epileptic patient being resistant to one of these drugs may respond favorably to alternative treatment with the other of the two drugs, clearly indicating that these drugs act by more than one mechanism (Schmidt and Gram, 1995). Similarly, subgroups of amygdala-kindled rats resistant to phenytoin ('phenytoin nonresponders') respond to the anticonvulsant activity of carbamazepine (Löscher and Rundfeldt, 1991; Löscher et al., 1993c), again demonstrating that the concept illustrated in Table 2 oversimplifies the complex effects of these and other anticonvulsant drugs both experimentally and clinically. If one uses this concept for the new anticonvulsant drugs, most of these drugs act on Na^+ channels (Table 3). This is not astonishing in view of the fact that the anticonvulsant effect of most of these compounds was first detected with the maximal electroshock seizure test, which is particularly sensitive to Na^+ channel blockers and may thus preselect drugs with such mechanism of action (Meldrum, 1996). Interestingly, lamotrigine does not effect GABAergic inhibition or T-type Ca^{2+} channels (Table 3), but is a broad acting anticonvulsant drug against different seizure types in patients (Table 1), thus casting doubt that the concept shown in Table 2 is useful for the new anticonvulsant drugs.

In addition to effects on Na^+ channels, several of the new drugs, i.e. topiramate, felbamate, vigabatrin, tiagabine and gabapentin act on GABAergic inhibition, although by different mechanisms (Löscher and Schmidt, 1994; White, 1997). None of the new drugs examined so far exerts an effect on T-type Ca^{2+} channels (Table 3).

It has been proposed that new anticonvulsant drugs act by new mechanisms (Macdonald and Meldrum, 1995). In this respect, inhibition of glutamatergic excitation, particularly that mediated by the *N*-methyl-D-aspartate (NMDA) and non-NMDA types of glutamate receptors, has been suggested to play a significant role (Macdonald and Meldrum, 1995). Indeed, as shown in Table 4, for most of the new anticonvulsant drugs there is evidence for an antiglutamatergic action. However, as also shown in Table 4, there is increasing evidence that several of the old drugs may affect glutamatergic excitation, too. Thus, apparently there is no real difference in mechanisms between the old and new drugs. Except the GABAmimetics vigabatrin and tiagabine, all of the new drugs appear to act by several cellular mechanisms and so do most of the old drugs.

Table 3
Some cellular mechanisms of action of new drugs

Drug	Blockade of voltage-dependent Na^+ channels	Potentiation of GABAergic mechanisms	Blockade of thalamic T-type Ca^{2+} channels
Lamotrigine	+ +	NE	NE
Oxcarbazepine	+ +	NE	?
Topiramate	+	+	?
Felbamate	+	+	?
Vigabatrin	?	+ +	?
Tiagabine	?	+ +	?
Gabapentin	+ / −	+	NE

Effect is indicated by +, + + = effective; + / − = inconsistent data; NE = not effective in therapeutically relevant concentrations; ? = no data available (or found).
For details see Rogawski and Porter (1990), Löscher and Schmidt (1994), Upton (1994), Macdonald and Meldrum (1995), Schachter (1995), Bialer et al. (1996) and White (1997).

Indeed, this combination of several mechanisms may be the explanation for the clinical efficacy of these drugs in human epilepsy, because epilepsy is certainly a disease with multiple etiologies (Löscher and Schmidt, 1994).

In summary, the available data show that blockade of voltage-dependent Na^+ channels, which is thought to be involved in the anticonvulsant effect of phenytoin, carbamazepine and valproate, is also found with lamotrigine, oxcarbazepine, topiramate and felbamate. Potentiation of GABAergic inhibition, which is thought to be involved in the anticonvulsant effect of valproate, barbiturates and benzodiazepines, is also found with vigabatrin, tiagabine, gabapentin, felbamate and topiramate. Furthermore, an effect on glutamatergic mechanisms is found with several old and new drugs. Apart from these cellular mechanisms, both old and new drugs exert additional effects on other neurotransmitters or ion channels which may be important for their pharmacodynamic effects (Rogawski and Porter, 1990; Löscher and Schmidt, 1994; Schachter, 1995; White, 1997). In view of the fact that most of the old and new drugs possess more than one mechanism, the individual combination of the 'old' mechanisms might be the real difference between old and new drugs.

3. Experience with existing strategies of anticonvulsant drug development

There are at least three preclinical strategies which are used for development of new anticonvulsant drugs: (1) random screening of newly synthesised chemical compounds of diverse structural categories for anticonvulsant activity in animal models, (2) structural variation of known anticonvulsant drugs and (3) mechanism-based rational drug development, based on knowledge of the basic pathophysiological events involved in seizures or epilepsy (Löscher and Schmidt, 1994; Upton, 1994). All three strategies have generated clinically effective anticonvulsant drugs, although many scientists currently believe that the strategy of rational ('modern') drug development has important advantages over the more traditional other strategies.

Historically, all old anticonvulsant drugs have been found by serendipity, screening or structural variation of known drugs. Except the bromides and phenobarbital, the anticonvulsant effect of all standard anticonvulsant drugs was first determined in animal models, such as the maximal electroshock seizure or the pentylenetetrazole seizure tests, demonstrating that clinical activity can be predicted by such laboratory models (Löscher and Schmidt, 1994). Therefore, seizure models in laboratory animals are still the most important prerequisite in preclinical search for new anticonvulsant drugs.

If one reviews the new clinically effective and introduced anticonvulsant drugs and groups them according to the existing preclinical strategy by which each drug has been developed, then screening or serendipity led to the development of felbamate, topiramate and lamotrigine, while oxcarbazepine and clobazam were developed by structural variation of known drugs (Löscher and Schmidt, 1994). Only three of the seven new, second generation anticonvulsants with proven clinical efficacy have been developed by mechanism-based rational development, namely vigabatrin, tiagabine and gabapentin (Löscher and Schmidt, 1994). Various other novel 'third generation' anticonvulsant drugs are in preclinical or clinical develop-

Table 4
Some cellular mechanisms of action of old and new drugs

Anticonvulsant drug	Blockade of voltage-dependent Na^+ channels	Potentiation of GABAergic mechanisms	Blockade of glutamatergic mechanisms
Old drugs			
Phenytoin	++	+/−	+/−
Carbamazepine	++	+/−	+/−
Phenobarbital	+	+	+
Valproate	++	+	+/−
Benzodiazepines	+	++	NE
Ethosuximide	NE	NE	NE
New drugs			
Lamotrigine	++	NE	+/−
Oxcarbazepine	++	NE	?
Topiramate	+	+	+
Felbamate	+	+	++
Vigabatrin	?	++	?
Tiagabine	?	++	?
Gabapentin	+/−	+	+/−

Effect is indicated by +, ++ = effective; +/− = inconsistent data; NE = not effective in therapeutically relevant concentrations; ? = no data available (or found).

For details see Rogawski and Porter (1990), Löscher and Schmidt (1994), Upton (1994), Macdonald and Meldrum (1995), Schachter (1995), Bialer et al. (1996) and White (1997).

ment (Löscher and Schmidt, 1994; Bialer et al., 1996; White, 1997). All drugs with already demonstrated clinical activity (e.g. levetiracetam, remacemide, fosphenytoin, dezinamide, loreclozole, losigamone) have been found by screening or structural variation (Löscher and Schmidt, 1994). As with the old anticonvulsant drugs, the anticonvulsant effect of the novel clinically effective compounds was determined by seizure models in laboratory animals, substantiating that clinical activity can be predicted in this way.

The past decades have witnessed an increase in our knowledge on the pathophysiology of brain diseases and the basic mechanisms of drug activity that is without precedent (Dichter, 1994; McNamara, 1994). This knowledge generated several rational strategies for drug development, aimed to identify new anticonvulsant drugs with high specificity/selectivity of action. The most important strategies of rational design of anticonvulsant drugs have been (1) enhancement of GABA-mediated neuronal inhibition, (2) diminution of glutamate-mediated neuronal excitation and (3) modulation of Na^+, K^+ and particularly Ca^{2+} ion channels (cf. Löscher and Schmidt, 1994; Upton, 1994). All three targets for anticonvulsant drug development, i.e. GABAergic inhibition, glutamatergic excitation and intrinsic, voltage-dependent currents are thought to be critically involved in the pathophysiology of epileptic processes (Dichter, 1994).

3.1. Increase of GABAergic neurotransmission

The most successful of these rational strategies in terms of producing new clinically effective anticonvulsant drugs has been pharmacological enhancement of GABAergic neurotransmission. Of the various GABAmimetic drugs produced by this strategy, i.e. inhibitors of GABA aminotransferase such as vigabatrin, GABA uptake blockers such as tiagabine, $GABA_A$ receptor agonists such as progabide and THIP (gaboxadol), and $GABA_A$ receptor modulators, e.g. novel benzodiazepine receptor ligands such as partial agonists (e.g. bretazenil), subtype selective agonists (e.g. abecarnil) or neurosteroids, so far only vigabatrin and tiagabine proved to be effective in epileptic patients (Table 1). Both drugs, which act by increasing GABA levels in the synaptic cleft, are effective treatments for partial seizures in patients with pharmacoresistance to the old drugs (Schmidt and Krämer, 1994; Chadwick, 1997). A third GABAmimetic drug with proven efficacy in partial epilepsy is gabapentin (Schmidt and Krämer, 1994; Chadwick, 1997). Gabapentin has recently been shown to increase GABA turnover in some brain regions of laboratory animals (Löscher et al., 1991), presumably by activation of glutamate decarboxylase (Taylor et al., 1992), and to enhance brain GABA levels in patients (Petroff et al., 1996b), but in contrast to vigabatrin and tiagabine, gabapentin also exerts several other cellular action not related to GABA (see Table 4 and Taylor, 1995).

Unfortunately, there is a number of potential problems with increasing GABAergic neurotransmission as a strategy in anticonvulsant drug development. At least in laboratory animals, most GABAmimetic drugs produce tolerance and dependence (Löscher, 1986; Löscher and Schmidt, 1994; Costa and Guidotti, 1996), which is well known from both experimental and clinical experience with barbiturates and traditional benzodiazepines. If drugs such as vigabatrin and tiagabine produce tolerance and dependence in patients has to await more clinical experience with these drugs, particularly in terms of monotherapy. Drugs which increase GABA concentrations, such as vigabatrin and tiagabine, are likely to aggravate non-convulsive (absence, myoclonic) seizures, most probable by an effect of enhanced GABA levels on $GABA_B$ receptors (Marescaux et al., 1992). As a consequence, the spectrum of clinical efficacy of such compounds is relatively small, although vigabatrin is also effective against infantile spasms, i.e. in West syndrome (Löscher and Schmidt, 1994). Another potential disadvantage of some new GABAmimetic drugs, e.g. vigabatrin, is the induction of psychotic reactions (Grant and Heel, 1991; Löscher and Schmidt, 1994; Thomas et al., 1996). Indeed, a hyperactive GABA system has been involved as a common etiological factor in both schizophrenia and affective psychoses (Squires and Saederup, 1991).

3.2. Decrease of glutamatergic neurotransmission

Another strategy, which has been used by several drug companies for development of anticonvulsant and neuroprotective compounds during recent years, is drug-induced decrease of glutamatergic neurotransmission (Löscher and Schmidt, 1994). Drugs developed by rational drug design include NMDA receptor antagonists, such as the noncompetitive antagonist MK-801 (dizocilpine) or the competitive antagonist D-CPPene (3-(2-carboxypiperazin-4-yl)propenyl-1-phosphonate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonists, such as NBQX (2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(F)quinoxaline) and GYKI 52466 (1-(4-aminophenyl)-4-methyl-7,8-methylendioxy-5H-2,3-benzodiazepine). As yet, clinical data are only available for NMDA receptor antagonists, including dextrorphan, an active metabolite of the antitussive dextromethorphan, which acts as a noncompetitive NMDA receptor antagonist (Löscher and Schmidt, 1994). In view of the increasing evidence that an abnormality of glutamate-mediated neurotransmission may critically contribute to the pathophysiology of seizures and epilepsy, development of glutamate receptor antagonists, particularly drugs blocking NMDA receptors, was thought to be one of the most promising strategies for rational anticonvulsant drug development (Dingledine et al., 1990; Löscher, 1993). However, both the clinical trials and more recent data from animal models demonstrated a number of severe problems associated with the mechanism (Löscher

and Schmidt, 1994), so that further development of NMDA receptor antagonists for treatment of epilepsy has been subsided. The few clinical trials with MK-801, D-CPPene and dextrorphan did not yield any significant anticonvulsant effect of the drugs in patients with partial seizures (Löscher and Schmidt, 1994). Instead, treatment was associated with marked adverse effects, such as psychosis, impairment of learning and memory and impairment of motor function. This was unexpected because all these drugs had been well tolerated in phase I studies in healthy volunteers. Interestingly, several previous experimental observations indicated that limbic epileptogenesis enhances the adverse effect potential of NMDA receptor antagonists, leading to induction of proconvulsant effects, motor impairment and psychotomimetic effects (Löscher and Hönack, 1991; Löscher and Schmidt, 1994). Examples of relevant observations in this respect are as follows (reviewed by Löscher and Schmidt, 1994). Pre-existing susceptibility to focal seizures was suggested to be a prerequisite for proconvulsant effects of the noncompetitive NMDA receptor antagonist ketamine in rats (Leccese et al., 1988). The noncompetitive NMDA receptor antagonist memantine induced seizures in kindled rats at doses that were anticonvulsant in non-kindled rats (Löscher and Hönack, 1990). Kindled rats were more sensitive than non-kindled rats to the induction of behavioral adverse effects (e.g. stereotypies) by competitive NMDA antagonists (Löscher and Hönack, 1991). The glycine/NMDA receptor antagonist (+)-HA-966 ((+)-3-amino-1-hydroxypyrrolid-2-one) induced paroxysmal activity in limbic brain regions of kindled but not non-kindled rats (Wlaz et al., 1994). The reasons for this functional difference between kindled and non-kindled rats remain to be elucidated (for discussion see Wlaz et al., 1994), but all these data strongly suggest that models of chronic epilepsy, such as the kindling model, should be added to the preclinical assessment of adverse effects of NMDA receptor antagonists and probably also other investigational drugs in order to enhance the predictive value of such data for adverse effects occurring in patients with chronic brain disease (Wlaz and Löscher, 1997).

It remains to be seen whether other strategies of glutamate antagonism, e.g. AMPA receptor antagonists or ligands for the metabotropic glutamate receptor provide advantages in terms of risk–benefit ratio for treatment of epilepsy (see Section 4). Drugs, such as lamotrigine or riluzole, which reduce glutamate release by blockade of Na^+ channels, clearly differ in their pharmacology from selective glutamate receptor antagonists and should not be assigned to this category. Recent in vitro experiments with other Na^+ channel blockers, i.e. carbamazepine and oxcarbazepine, have shown that these drugs, as lamotrigine, inhibit veratrine-induced glutamate release from rat brain slices at therapeutically relevant concentrations (Waldmeier et al., 1996). However, experiments in conscious rats with determination of veratrine-enhanced extracellular glutamate levels by microdialysis led to the conclusion that neither of these drugs in relevant doses inhibits physiological glutamate release in vivo (Waldmeier et al., 1996).

3.3. Modulation of ion channels

Similar to the glutamate-directed strategy, the ion channel-directed strategy of developing new anticonvulsant drugs failed to produce any clinically effective drugs with advantages over existing drug treatments. With respect to Na^+ channels, ralitoline was developed as a state dependent blocker of voltage sensitive Na^+ channels, but both experimental and clinical studies failed to demonstrate any clear advantage over standard drugs, such as phenytoin and carbamazepine, so that further development was terminated (Löscher and Schmidt, 1994; Bialer et al., 1996). With respect to Ca^{2+} channels, several Ca^{2+} channel (L-type) blockers, such as verapamil, nifedipine, diltiazem and flunarizine have been clinically evaluated in epileptic patients, but only low or absent anticonvulsant efficacy was demonstrated by controlled trials (Löscher and Schmidt, 1994). However, as new antagonists for various Ca^{2+} channel subtypes are discovered, it remains possible that effective new anticonvulsants may emerge. A third, possibly more promising target could be K^+ channels, which will be discussed in Section 4.

3.4. Should selectivity of action be pursued?

The disappointing experience with most rational strategies has led to a debate on whether (and how) we should pursue rational drug development to identify new anticonvulsant drugs with high specificity/selectivity of action. The most important arguments against the idea of pursuing selectivity of action as a potentially profitable approach to anticonvulsant drug development are the lack of success of several previous attempts of 'rational' drug development and the success of various previous attempts of 'non-rational' anticonvulsant drug development, i.e. development by random screening or structural variation. Several inherent reasons may explain the failure of rational strategies: (1) most of the old, first generation anticonvulsants already act by several of the mechanisms on which rational strategies are based, making it unlikely that a novel drug developed by such strategy has significant clinical advantages. (2) Most first generation drugs exert more than one mechanism, while novel agents developed by mechanism-directed strategies are often selective for one type of mechanism. Since epileptic seizures must be viewed as multifactorial, anticonvulsants with several mechanisms (e.g. valproate) have advantages compared to drugs with a selective effect, e.g. on one type of ion channel or neurotransmitter. (3) The optimal use of a drug with a single mechanism would ideally require the development of predictive markers that this particular mechanism is operative in the epilepsy of the individual patient, but such markers

do not exist as yet. (4) Most of the events that contribute to epileptogenesis and/or ictogenesis appear to be exaggerated aspects of normal physiology so that drugs rationally developed to selectively act on such events may interfere with normal excitability or synaptic transmission. (5) The way in which modern approaches are applied to drug discovery are still too simplistic, ignoring the complex alterations of brain functions, particularly the disturbances of behavior and cognitive function, induced by chronic epilepsy. Indeed, much of our classification into separate entities may be more a reflection of how our brains work than a true description of reality.

Drug development traditionally aims towards more and more selective targets, but there is accumulating evidence that an absolute selectivity in a drug may in fact not be desirable in a clinical situation that involves complex adaptive changes. Thus, there are various recent examples from different fields of pharmacotherapy where the development of drugs with a more selective action has proved disappointing in providing a more selective therapy with fewer adverse effects and improved clinical efficacy (Fredholm and Abbott, 1990). This throws up the question whether we should be thinking about the development of nonselective drugs as a potentially more successful strategy.

Greater understanding of basic brain pharmacology and mechanisms of epilepsy may allow the development of new treatment strategies. In view of the fact that patients with the same type of clinical seizure may differentially respond to anticonvulsant drugs, the pathophysiological events underlying epileptic seizures apparently not only differ between different seizure types but are also multifactorial for the same type. In order to achieve improved therapy of epilepsy, the real challenge for the future will be to create novel broadly acting anticonvulsant drugs with multiple mechanisms of action but decreased adverse effect potential in comparison to currently used medical therapies. With respect to novel pharmacological strategies, newly developed laboratory models for pharmaco-resistant seizures may help to develop drugs with efficacy in intractable epilepsy (Heinemann et al., 1994; Löscher, 1997b).

4. Perspectives for new developments

Traditionally, pharmacological strategies for the treatment of epilepsy have aimed at seizure initiation and propagation rather than the processes leading to epilepsy. As a result, none of the currently available anticonvulsant drugs is capable of preventing epilepsy, e.g. after brain injury (Hernandez, 1997). Furthermore, there is increasing evidence that, despite early onset of treatment and suppression of seizures, anticonvulsant drugs do not affect the progression or underlying natural history of epilepsy (Shinnar and Berg, 1996). Thus, one important goal for the future will be to develop anti-epileptogenic drugs, i.e. drugs which prevent or treat epilepsy and not only its symptoms and thus can be referred to as truly antiepileptic. For this goal, interdisciplinary research and communication between clinical and basic scientists will be essential and suitable preclinical models are needed. Interesting models in this respect are the kindling model, because kindling involves many processes thought to be important for epileptogenesis and chronic epilepsy, and spontaneous recurrent seizures following acute application of kainate and pilocarpine (Löscher, 1997a). With respect to novel anticonvulsant drugs, it is interesting to note that levetiracetam seems to exert anti-epileptogenic and possibly antiepileptic properties (Löscher et al., 1997a). Levetiracetam does seemingly not act by any of the mechanisms thought to be involved in the mechanism of action of other anticonvulsant drugs (Haria and Balfour, 1997) which might explain its unexpected experimental efficacy against epileptogenesis.

With respect to new mechanisms as targets for drug development, $GABA_B$ receptor antagonists and selective T-type Ca^{2+} channel antagonists may be interesting for treatment of non-convulsive (absence, myoclonic) seizures. However, similar to ethosuximide (Table 1), the disadvantage of such drugs would be their narrow spectrum of clinical activity. For treatment of partial or generalized convulsive seizures, potentially interesting new developments include non-NMDA (AMPA/kainate) receptor antagonists and K^+ channel agonists. In contrast to NMDA receptor antagonists, AMPA receptor antagonists are effective anticonvulsants in the kindling model and do not induce stereotyped behaviors or marked motor impairment at anticonvulsant doses (Lees, 1996), suggesting that these compounds may be clinically effective against partial seizures. In this respect, it is important to note that renal toxicity which led to termination of development of the prototype AMPA receptor antagonist NBQX is not a property of the more recently developed AMPA receptor antagonists (Lees, 1996). In addition to novel AMPA receptor antagonists, our growing understanding of the function and the molecular biology of the NMDA receptor may lead to the discovery of new and valuable anticonvulsants acting at this site, with better efficacy and safety profiles than previous NMDA receptor antagonists.

Apart from glutamate receptors, stimulation of the opening of K^+ channels has repeatedly been proposed as an interesting mechanism of anticonvulsant drug mechanism, but until recently no selective and systemically effective K^+ channel agonists were available (Löscher and Schmidt, 1994). The newly developed anticonvulsant D-23129 (retigabine) has been described to exert an opening effect on K^+ channels at relevant drug concentrations (Bialer et al., 1996). However, the drug exerts also other cellular effects, including potentiation of GABA currents, increase of GABA synthesis, and inhibition of glutamate/kainate currents, which may explain the broad

anticonvulsant activity in diverse preclinical models (Bialer et al., 1996). Of course, the progress of all these new pharmaco-logical strategies will depend on data from clinical evaluation.

In addition to development of new drugs for treatment of epilepsy, the use of two or more available anticonvulsants with different mechanisms of action for 'rational polypharmacy' or 'rational polytherapy' may a useful alternative treatment strategy, particularly if monotherapy fails (Leppik, 1996). In approximately 40% of patients with epilepsy, monotherapy with conventional anticonvulsants is either not tolerated or does not provide optimal seizure control (Pellock, 1995). Polypharmacy may be necessary in as many as 30% of all epileptic patients (Pellock, 1995). The theoretical and/or experimental basis for choosing specific drug combinations is mainly compromised however by the current lack of fully understanding of the chain of events leading from molecular mechanisms to specific seizures and the progression of seizures into human epilepsy syndromes (Schmidt, 1997). Animal models may be useful in both studying basic mechanisms of ictogenesis and epileptogenesis and defining targets for rational drug design and rational polytherapy (Löscher and Ebert, 1996). Furthermore, in view of the fact that the numerous possible combinations of standard and newly developed anticonvulsant drugs cannot be studied in controlled clinical trials, animal models may be used to preselect potentially interesting drug combinations (Löscher and Wauquier, 1996). The goal of rational polytherapy would be to propose drug combinations which are better than either drug alone and even more important are more effective and less toxic than standard drugs (Schmidt, 1997). That this approach is producing effective new treatment strategies is demonstrated by the synergistic effect of combinations of NMDA and AMPA receptor antagonists (Löscher et al., 1993b) or combinations of lamotrigine and valproate (Brodie and Yuen, 1997). After the detection of such synergistic drug interactions, it might be possible to combine the involved mechanisms in a single drug, because monotherapy with a drug that has multiple mechanisms of action is avoid of pharmacokinetic drug–drug interactions often encountered with combined therapy.

For all drug treatment strategies, it would be a major advancement if methods for predictive identification of responders would be developed. The physician needs to know in whom a specific drug or drug combination is ineffective and wishes to identify patients who are most likely to benefit (Schmidt, 1997). Unfortunately, this information is difficult to retrieve from clinical trial data. Although several predictors of poor prognosis and intractability of epilepsy, such as seizure type, high seizure frequency, onset of epilepsy in infancy, symptomatic etiology of seizures, psychotic disturbances, presence of multiple seizure types, and poor short-term results of therapy, have been proposed in human epilepsy (Loiseau, 1986; Sillanpää, 1995), it is not possible to predict with certainty in a given patient whether treatment with an anticonvulsant drug will be effective and which of the available anticonvulsant drugs or which of the pharmacodynamic mechanisms offered by these drugs is best suited for this patient. If non-invasive diagnostic measures would exist that allow to conclude after short treatment whether a chosen drug in a given patient will be effective or not, this would greatly improve current practice of epilepsy treatment. Thus, future efforts for the search for new anticonvulsant drugs should also attempt to establish diagnostic measures which will allow to predict responders.

One interesting example in this respect stems from preclinical experiments in the amygdala-kindling model. We have previously shown that repeated testing of fully kindled Wistar rats with phenytoin allows the selection of rats which always react to phenytoin with an increase in focal seizure threshold (phenytoin responders) and rats which never respond (phenytoin nonresponders) (Löscher and Rundfeldt, 1991). As shown by various subsequent studies, phenytoin nonresponders are a useful model of pharmacoresistant partial seizures (Löscher, 1997b). The novel anticonvulsant vigabatrin, which acts by increasing GABA both in the brain and periphery, was demonstrated to be effective in phenytoin responders, but ineffective in nonresponders (Löscher et al., 1993c). After administration of a single anticonvulsant dose of vigabatrin, a significant plasma GABA increase was determined in phenytoin responders but not in nonresponders (Löscher et al., 1993c). Based on these data, we proposed that determination of plasma GABA shortly after onset of vigabatrin therapy is suited to predict whether an epileptic patient will be a responder or nonresponder. If true, this would be the first individual prognostic measure of an anticonvulsant drug's efficacy. In order to prove this clinically important possibility, we undertook a retrospective study in epileptic patients undergoing chronic treatment with vigabatrin. Plasma GABA levels of nonepileptic patients served as control. In epileptic patients not responding to chronic treatment with vigabatrin, plasma GABA levels were not significantly different from control, whereas a significant increase in GABA levels was determined in vigabatrin responders (Löscher et al., 1993a,d), thus confirming our prediction from the experiments in kindled rats. This example illustrates how animal models can be used to develop new concepts for the clinical situation. Interestingly, in addition to plasma GABA determinations, the recent development of ^{1}H magnetic resonance spectroscopic measurement of brain GABA levels in patients allows to determine the effect of vigabatrin on human brain GABA after a single dose administration (Petroff et al., 1996a), which could be used for early identification of nonresponders. Both plasma determinations and magnetic resonance spectroscopy could also be interesting for noninvasive GABA monitoring after other GABA elevating drugs, such as gabapentin (Petroff et al., 1996b) and valproate (Löscher and Schmidt, 1980).

As an alternative to administration of drugs that act in the brain at various sites, novel treatment strategies aimed to suppress seizure propagation through specific brain regions have been proposed (Löscher and Ebert, 1996). While seizure initiation may be in various brain locations, it appears that generalization of seizure activity spreads along relatively universal or 'preferred' propagation pathways. Thus, blockade of generalisation of seizure activity by local manipulation of such preferred propagation pathways could constitute a more rational therapeutic approach with efficacy on various seizure types than targeting the diverse mechanisms involved in initiation of different seizure types. Novel treatment strategies aimed to suppress seizure propagation through specific brain regions could involve targeting of drugs or drug combinations to such 'key structures', e.g. the substantia nigra pars reticulata (Löscher and Ebert, 1996). Possible approaches in this respect are: (1) targeting systemically administered drugs to such regions based on the uneven distribution and regional heterogeneity of enzymes and receptor subtypes involved in inhibitory and excitatory neurotransmission. Examples in this respect are the regionally selective effect of valproate on GABA turnover in substantia nigra (Löscher, 1989a) and the development of new benzodiazepine receptor ligands with selectivity for those α-subunits (e.g. α_1) which exhibit a particular high density in the nigra (Turner et al., 1993). (2) Regional drug targeting based on direct drug infusion into a brain region by the use of mini- or micropumps; this approach has already been discussed with respect to focal application of anticonvulsant drugs in patients in whom the epileptic focus is identified but not resectable (Löscher and Ebert, 1996). (3) Implantation of biocompatible polymer matrices which can be used for the local delivery of transmitters or trophic factors or combinations of both. There is already experience with GABA-, noradrenaline-, dopamine- and neuronal growth factor-releasing polymeric brain implants in models of epilepsy (kindling) or Parkinson (Löscher and Ebert, 1996). (4) An alternative approach apart from drug application is implantation of neural grafts.

Neuronal grafting, particularly using noradrenergic locus coeruleus neurons, has been used as a tool to reduce seizure propagation in seizure models (Lindvall and Björklund, 1992). Until recently, there has been no conclusive experimental evidence that intracerebral grafts of GABAergic neurons can influence epileptic activity. One target region for implantation of GABAergic neurons would be the substantia nigra pars reticulata, because increase of GABAergic inhibition in this region has been shown to suppress seizure propagation in diverse types of experimental epilepsy (Löscher and Ebert, 1996). Recent experiments from our laboratory has demonstrated that implantation of fetal striatal GABAergic neurons into substantia nigra of amygdala-kindled rats induces a marked reduction in seizure severity compared to implantation of non-GABAergic neurons or vehicle, but the anticonvulsant effect of the GABAergic grafts was only transient (Löscher et al., 1997b). It remains to be established whether intracerebral grafting of genetically engineered GABA-producing cells or implantation of polymer matrices with long-term GABA release have advantages in this respect, possibly constituting a further step to develop more efficient strategies for seizure suppression in pharmacoresistant epilepsies.

A further perspective for new therapeutic developments in treatment of epilepsy stems from the identification of genetic defects (Schmidt, 1997). Advances in molecular genetics and molecular pharmacol-ogy may become a source of promise for diseases previously unresponsive to conventional treatments. In the case of the epilepsies, identification of mutant genes underlying familial epilepsies may lead to a new pharmacological treatment strategy, through the development of in vitro expression systems permitting rapid search for novel drugs, creation of specific animal models based on expression of the precise mutation and correction of disease phenotypes by introducing novel and highly specific genetic information into the person with epilepsy (McNamara, 1994; Allen and Walsh, 1996; Schmidt, 1997).

5. Conclusions

Anticonvulsants have greatly improved the lives of people with epilepsy. Approximately 70% of patients can achieve complete freedom from seizures with appropriate treatment (Scheuer and Pedley, 1990). Furthermore, there have been significant advances in the medical treatment of epilepsy in recent years (Sabers and Gram, 1996). Some of the old, first generation anticonvulsants have been marketed in the form of new formulations, e.g. retard preparations of valproate and carbamazepine, or modification of phenytoin to the water soluble phenytoin-prodrug fosphenytoin for parenteral use, resulting in improved efficacy and tolerability. A marked increase in the number of comparative clinical trials of anticonvulsants has also made treatment choice somewhat simpler (Sabers and Gram, 1996). The development strategies described in this review resulted in the introduction of several new, second generation anticonvulsants. Compared with the first generation anticonvulsants, many new drugs exhibit simpler pharmacokinetics and are devoid of liver enzyme inducing or inhibiting properties, thus increasing the ease of use, decreasing the number of drug interactions and improving adverse effect profiles (Perucca, 1996; Sabers and Gram, 1996). Indeed, current evidence suggests that the new, second generation of anticonvulsants is as efficient as the old drugs but exhibits fewer adverse effects, although the scientific evidence from randomized clinical trials comparing established and new anticonvulsants with each other is still pending (Schmidt and Krämer, 1994; Rogvihansen and Gram, 1995; Chadwick, 1997). Furthermore, a com-

plete assessment of the efficacy and adverse effects of the newer agents is not yet possible because of the relative lack of experience with them, such that the potential for infrequent adverse reactions or reactions occurring only after long term use is largely unknown (Loiseau, 1996). An example of how infrequent adverse effects could change the risk–benefit ratio of a novel drug is felbamate, which has induced fatal aplastic anaemia and fatal liver disease in a number of patients (Schmidt and Krämer, 1994). At present, the main use of the new drugs is in patients refractory to first-line old drugs such as valproate or carbamazepine and further studies are required to characterize their activity spectrum as well as their potential value in monotherapy (Perucca, 1996). Novel approaches to the clinical testing of anticonvulsants make it possible to demonstrate unequivocal efficacy, including efficacy as monotherapy, very early in the development of novel compounds (Sabers and Gram, 1996). However, based on current knowledge, in most patients the new, second generation drugs can not be recommended for first-line use until evidence is obtained that potential advantages in tolerability or ease of use outweigh the drawback of their high cost (Perucca, 1996).

With respect to the ultimate goal of drug treatment of epilepsy, i.e. complete control of seizures, none of the new drugs seems to offer any marked advantage towards the old, first generation drugs. In other words, a significant number of patients with chronic epilepsy will not become seizure free despite the availability of several new anticonvulsant drugs (Dam, 1996). The only current alternative for patients with pharmacoresistant partial seizures is epilepsy surgery (Dam, 1996). With regard to the third generation drugs which are currently in the pipeline of development (cf. Löscher and Schmidt, 1994; Bialer et al., 1996) and to future strategies for anticonvulsant drug development, one important goal should be increased efficacy in difficult-to-treat epilepsies, including intractable partial epilepsies and childhood syndromes such as the Lennox–Gastaut syndromes and the West syndrome. Novel animal models for drug resistant seizures, such as phenytoin-resistant subgroups of kindled rats, may help to improve preclinical strategies in this respect (Löscher, 1997b). Furthermore, we need drugs that are truly antiepileptogenic, i.e. which either prevent epilepsy or alter its natural course (Shinnar and Berg, 1996). These goals can only be achieved by strengthening our understanding of the fundamental pathophysiology of seizure expression and epileptogenesis as theoretical substrates for new pharmacological strategies, and by devising and refining laboratory models for studying new agents obtained by such strategies.

References

Allen, K.M., Walsh, C., 1996. Shaking down new epilepsy genes. Nature Med. 2, 516–518.

Bialer, M., Johannessen, S.I., Kupferberg, H.J., Levy, R.H., Loiseau, P., Perucca, E., 1996. Progress report on new antiepileptic drugs: A summary of the Third Eilat Conference. Epilepsy Res. 25, 299–319.

Brodie, M.J., Yuen, A.W.C., 1997. Lamotrigine substitution study: Evidence for synergism with sodium valproate?. Epilepsy Res. 26, 423–432.

Chadwick, D.W., 1997. An overview of the efficacy and tolerability of new antiepileptic drugs. Epilepsia 38, S59–S62.

Commission on Classification and Terminology of the International League Against Epilepsy, 1981. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 22, 489–501.

Commission on Classification and Terminology of the International League Against Epilepsy, 1989. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 30, 389–399.

Costa, E., Guidotti, A., 1996. Benzodiazepines on trial: A research strategy for their rehabilitation. Trends Pharmacol. Sci. 17, 192–200.

Dam, M., 1986. Intractable epilepsy: Introduction. In: Schmidt, D., Morselli, P.L. (Eds.), Intractable Epilepsy: Experimental and Clinical Aspects. Raven Press, New York, pp. 1–3.

Dam, M., 1996. Epilepsy surgery. Acta Neurol. Scand. 94, 81–87.

Dichter, M.A., 1994. Emerging insights into mechanisms of epilepsy: Implications for new antiepileptic drug development. Epilepsia 35, S51–S57.

Dingledine, R., McBain, C.J., McNamara, J.O., 1990. Excitatory amino acid receptors in epilepsy. Trends Pharmacol. Sci. 11, 334–338.

Dreifuss, F.E., 1992. Present status in the treatment of the epilepsies. In: Theodore, W.H. (Ed.), Surgical Treatment of Epilepsy. Elsevier, Amsterdam, pp. 3–5.

Engel, J.J., 1992. Experimental models of epilepsy: classification and relevance to human epileptic phenomena. In: Avanzini, G., Engel, J.J., Fariello, R. and Heinemann, U. (Eds.), Neurotransmitters in Epilepsy. Elsevier, Amsterdam, pp. 9–20.

Forsgren, L., 1995. Epidemiology of intractable epilepsy in adults. In: Johannessen, S.I., Gram, L., Sillanpää, M., Tomson, T. (Eds.), Intractable Epilepsy. Wrightson Biomedical Publishing, Petersfield, pp. 25–40.

Fredholm, B., Abbott, A., 1990. New targets for drug action: Is high selectivity always beneficial?. Trends Pharmacol. Sci. 11, 175–178.

Grant, S.M., Heel, R.C., 1991. Vigabatrin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. Drugs 41, 889–926.

Haria, M., Balfour, J.A., 1997. Levetiracetam. Cns. Drugs 7, 159–164.

Heinemann, U., Draguhn, A., Ficker, E., Stabel, J., Zhang, C.L., 1994. Strategies for the development of drugs for pharmacoresistant epilepsies. Epilepsia 35, S10–S21.

Hernandez, T.D., 1997. Preventing post-traumatic epilepsy after brain injury: Weighing the costs and benefits of anticonvulsant prophylaxis. Trends Pharmacol. Sci. 38, 59–62.

Hosford, D.A., Wang, Y., 1997. 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 38, 408–414.

Leccese, A.P., Marquis, K.L., Mattia, A., Moreton, J.E., 1988. The convulsant and anticonvulsant effects of phencyclidine (PCP) and PCP analogues in the rat. Behav. Brain Res. 19, 163–169.

Lees, G.J., 1996. Therapeutic potential of AMPA receptor ligands in neurological disorders. Cns. Drugs 5, 51–74.

Leppik, I.E., 1992. Intractable epilepsy in adults. In: Theodore, W.H. (Ed.), Surgical Treatment of Epilepsy. Elsevier, Amsterdam, pp. 7–11.

Leppik, I.E., 1996. Rational Polypharmacy. Elsevier, Amsterdam.

Lindvall, O., Björklund, A., 1992. Intracerebral grafting of inhibitory neurons. A new strategy for seizure suppression in the central nervous system. Adv. Neurol. 57, 561–569.

Loiseau, P. (1986) Intractable epilepsy: prognostic evaluation. In: Schmidt, D. and Morselli, P.L. (Eds.), Intractable Epilepsy: Experimental and Clinical Aspects. Raven Press, New York, NY, pp. 227–258.

Lothman, E.W., 1996. Basic mechanisms of seizure spread. Epilepsy Res. 11 (Suppl.), 9–16.
Löscher, W., 1986. Development of tolerance to the anticonvulsant effect of GABA-mimetic drugs in animal models of seizure states. In: Frey, H.-H., Fröscher, W., Koella, W.P., Meinardi, H. (Eds.), Tolerance to Beneficial and Adverse Effects of Antiepileptic Drugs. Raven Press, New York, pp. 37–45.
Löscher, W., 1989a. Valproate enhances GABA turnover in the substantia nigra. Brain Res. 501, 198–203.
Löscher, W., 1989b. GABA and the epilepsies. Experimental and clinical considerations. In: Bowery, N.G., Nisticò, G. (Eds.), GABA. Basic Research and Clinical Applications. Pythagora Press, Rome, pp. 260–300.
Löscher, W., 1993. Basic aspects of epilepsy. Curr. Opin. Neurol. Neurosurg. 6, 223–232.
Löscher, W., 1997a. Animal models of epilepsy and epileptic seizures. In: Eadie, M.J., Vajda, F. (Eds.), Antiepileptic Drugs. Handbook of Experimental Pharmacology. Springer, Berlin. In press.
Löscher, W., 1997b. Animal models of intractable epilepsy. Prog. Neurobiol. 53, 239–258.
Löscher, W., Ebert, U., 1996. Basic mechanisms of seizure propagation: Targets for rational drug design and rational polypharmacy. Epilepsy Res. 11 (Suppl.), 17–44.
Löscher, W., Hönack, D., 1990. High doses of memantine (1-amino-3,5-dimethyladamantane) induce seizures in kindled but not in non-kindled rats. Naunyn-Schmiedebergs Arch. Pharmacol. 341, 476–481.
Löscher, W., Hönack, D., 1991. Responses to NMDA receptor antagonists altered by epileptogenesis. Trends Pharmacol. Sci. 12, 52.
Löscher, W., Rundfeldt, C., 1991. Kindling as a model of drug-resistant partial epilepsy: Selection of phenytoin-resistant and nonresistant rats. J. Pharmacol. Exp. Ther. 258, 483–489.
Löscher, W., Schmidt, D., 1980. Increase of human plasma GABA by sodium valproate. Epilepsia 21, 611–615.
Löscher, W., Schmidt, D., 1988. Which animal models should be used in the search for new antiepileptic drugs? A proposal based on experimental and clinical considerations. Epilepsy Res. 2, 145–181.
Löscher, W., Schmidt, D., 1994. Strategies in antiepileptic drug development: Is rational drug design superior to random screening and structural variation?. Epilepsy Res. 17, 95–134.
Löscher, W., Wauquier, A., 1996. Use of animal models in developing guiding principles for polypharmacy in epilepsy. Epilepsy Res. (Suppl.), 61–65.
Löscher, W., Hönack, D., Taylor, C.P., 1991. Gabapentin increases aminooxyacetic acid-induced GABA accumulation in several regions of rat brain. Neurosci. Lett. 128, 150–154.
Löscher, W., Gram, L., Stefan, H., 1993a. Plasma GABA and seizure control with vigabatrin. Lancet 341, 117.
Löscher, W., Rundfeldt, C., Hönack, D., 1993b. Low doses of NMDA receptor antagonists synergistically increase the anticonvulsant effect of the AMPA receptor antagonist NBQX in the kindling model of epilepsy. Eur. J. Neurosci. 5, 1545–1550.
Löscher, W., Rundfeldt, C., Hönack, D., 1993c. Pharmacological characterization of phenytoin-resistant amygdala-kindled rats, a new model of drug-resistant partial epilepsy. Epilepsy Res. 15, 207–219.
Löscher, W., Fassbender, C.P., Gram, L., Gramer, M., Hörstermann, D., Zahner, B., Stefan, H., 1993d. Determination of GABA and vigabatrin in human plasma by a rapid and simple HPLC method: Correlation between clinical response to vigabatrin and increase in plasma GABA. Epilepsy Res. 14, 245–255.
Löscher, W., Hönack, D., Rundfeldt, C., 1997a. Antiepileptogenic effects of the novel anticonvulsant levetiracetam (ucb L059) in the kindling model of temporal lobe epilepsy. J. Pharmacol. Exp. Ther. In press.
Löscher, W., Ebert, U., Lehmann, H., Rosenthal, C., Nikkhah, G., 1997b. Seizure suppression in kindling epilepsy by grafts of fetal GABAergic neurons in rat substantia nigra. J. Neurosci. Res. In press.
Macdonald, R.L., 1989. Antiepileptic drug action. Epilepsia 30 (1), S19–S28.
Macdonald, R.L., Kelly, K.M., 1995. Antiepileptic drug mechanisms of action. Epilepsia 36, S2–S12.
Macdonald, R.L., Meldrum, B.S., 1995. Principles of antiepileptic drug action. In: Levy, R.H., Mattson, R.H., Meldrum, B.S. (Eds.), Antiepileptic Drugs, 4th ed. Raven Press, New York, pp. 61–78.
Marescaux, C., Vergnes, M., Depaulis, A., 1992. Genetic absence epilepsy in rats from Strasbourg: A review. J. Neural Transm. 35, 37–69.
Mattson, R.H., 1995. Selection of antiepileptic drug therapy. In: Levy, R.H., Mattson, R.H., Meldrum, B.S. (Eds.), Antiepileptic Drugs, 4th ed. Raven Press, New York, pp. 123–136.
McNamara, J.O., 1994. Cellular and molecular basis of epilepsy. J. Neurosci. 14, 3413–3425.
Meldrum, B., 1996. Action of established and novel anticonvulsant drugs on the basic mechanisms of epilepsy. Epilepsy Res. 11 (Suppl.), 67–78.
Olsen, R.W., Avoli, M., 1997. GABA and epileptogenesis. Epilepsia 38, 399–407.
Pellock, J.M., 1995. Antiepileptic drug therapy in the United States: A review of clinical studies and unmet needs. Neurology 45, S17–S24.
Perucca, E., 1996. The new generation of antiepileptic drugs: Advantages and disadvantages. Br. J. Clin. Pharmacol. 42, 531–543.
Petroff, O.A.C., Rothman, D.L., Behar, K.L., Collins, T.L., Mattson, R.H., 1996a. Human brain GABA levels rise rapidly after initiation of vigabatrin therapy. Neurology 47, 1567–1571.
Petroff, O.A.C., Rothman, D.L., Behar, K.L., Lamoureux, D., Mattson, R.H., 1996b. The effect of gabapentin on brain gamma-aminobutyric acid in patients with epilepsy. Ann. Neurol. 39, 95–99.
Richens, A., 1991. The efficacy and safety of new antiepileptic drugs. In: Pisani, F., Perucca, E., Avanzini, G., Richens, A. (Eds.), New Antiepileptic Drugs. Elsevier, Amsterdam, pp. 89–96.
Rogawski, M.A., Porter, R.J., 1990. Antiepileptic drugs: Pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. Pharmacol. Rev. 42, 223–286.
Rogvihansen, B.A., Gram, L., 1995. Adverse effects of established and new antiepileptic drugs: An attempted comparison. Pharmacol. Ther. 68, 425–434.
Sabers, A., Gram, L., 1996. Drug treatment of epilepsy in the 1990s: Achievements and new developments. Drugs 52, 483–493.
Schachter, S.C., 1995. Review of the mechanisms of action of antiepileptic drugs. Cns. Drugs 4, 469–477.
Scheuer, M.L., Pedley, T.A., 1990. The evaluation and treatment of seizures. N. Engl. J. Med. 323, 1468–1474.
Schmidt, D., 1997. Search for new anticonvulsants. In: Eadie, M.J., Vajda, F. (Eds.), Antiepileptic Drugs. Handbook of Experimental Pharmacology. Springer, Berlin. In press.
Schmidt, D., Gram, L., 1995. Monotherapy versus polytherapy in epilepsy: A reappraisal. Cns. Drugs 3, 194–208.
Schmidt, D., Krämer, G., 1994. The new anticonvulsant drugs. Implications for avoidance of adverse effects. Drug Safety 11, 422–431.
Shinnar, S., Berg, A.T., 1996. Does antiepileptic drug therapy prevent the development of 'chronic' epilepsy?. Epilepsia 37, 701–708.
Sillanpää, M., 1995. Epidemiology of intractable epilepsy in children. In: Johannessen, S.I., Gram, L., Sillanpää, M., Tomson, T. (Eds.), Intractable Epilepsy. Wrightson Biomedical Publishing, Petersfield, pp. 13–25.
Squires, R.F., Saederup, E., 1991. A review of evidence for GABAergic predominance/glutamatergic deficit as a common etiological factor in both schizophrenia and affective psychoses: More support for a continuum hypothesis of 'functional' psychosis. Neurochem. Res. 16, 1099–1111.
Taylor, C.P., 1995. Gabapentin. Mechanisms of action. In: Levy, R.H., Mattson, R.H., Meldrum, B.S. (Eds.), Antiepileptic Drugs, 4th ed. Raven Press, New York, pp. 829–841.
Taylor, C.P., Vartanian, M.G., Andruszkiewiewicz, R., Silverman, R.B., 1992. 3-Alkyl GABA and 3-alkylglutamic acid analogues: Two new classes of anticonvulsant agents. Epilepsy Res. 11, 103–110.
Theodore, W.H., 1992. National Institutes of Health Consensus Develop-

ment Conference Statement: Surgery for Epilepsy (19–21 March 1990). In: Theodore, W.H. (Ed.), Surgical Treatment of Epilepsy. Elsevier, Amsterdam, pp. 241–246.

Thomas, L., Trimble, M., Schmitz, B., Ring, H., 1996. Vigabatrin and behaviour disorders: A retrospective survey. Epilepsy Res. 25, 21–27.

Turner, J.D., Bodewitz, G., Thompson, C.L., Stephenson, F.A., 1993. Immunohistochemical mapping of gamma-aminobutyric acid type A receptor alpha subunits in rat central nervous system. In: Stephens, D.N. (Ed.), Anxiolytic β-carbolines: From Molecular Biology to the Clinic. Springer-Verlag, Berlin, pp. 29–49.

Upton, N., 1994. Mechanisms of action of new antiepileptic drugs: Rational design and serendipitous findings. Trends Pharmacol. Sci. 15, 456–463.

Waldmeier, P.C., Martin, P., Stocklin, K., Portet, C., Schmutz, M., 1996. Effect of carbamazepine, oxcarbazepine and lamotrigine on the increase in extracellular glutamate elicited by veratridine in rat cortex and striatum. Naunyn-Schmiedebergs Arch. Pharmacol. 354, 164–172.

White, H.S., 1997. Clinical significance of animal seizure models and mechanism of action studies of potential antiepileptic drugs. Epilepsia 38, S9–S17.

Wlaz, P., Löscher, W., 1997. Evaluation of associated behavioral and cognitive deficits in anticonvulsant drug testing. In: Peterson, S., Albertson, T. (Eds.), Neuropharmacology Methods in Epilepsy Research. CRC Press, Boca Raton. In press.

Wlaz, P., Ebert, U., Löscher, W., 1994. Low doses of the glycine/NMDA receptor antagonist *R*-(+)-HA-966 but not D-cycloserine induce paroxysmal activity in limbic brain regions of kindled rats. Eur. J. Neurosci. 6, 1710–1719.