Cell. Mol. Life Sci. 64 (2007) 2023 – 2041
1420-682X/07/152023-19
DOI 10.1007/s00018-007-7021-2

Cellular and Molecular Life Sciences

Biomedicine & Diseases: Review

Anticonvulsant, antiepileptogenic, and antiictogenic pharmacostrategies

M. Holtkamp* **and H. Meierkord**

Department of Neurology, Charité – Universitätsmedizin Berlin (Campus Mitte), Charitéplatz 1, 10117 Berlin (Germany), Fax: +49 30 450 56 09 32, e-mail: martin.holtkamp@charite.de, hartmut.meierkord@charite.de

Received 16 January 2007; received after revision 7 March 2007; accepted 17 April 2007
Online First 18 May 2007

Abstract. Pharmacological concepts tailored to status epilepticus, to epileptogenesis following acquired brain insults, and to ictogenesis in established epilepsy vary considerably and should ideally be directed at those pathophysiological mechanisms that presumably underly these conditions. Currently known important molecular targets include voltage-gated sodium and calcium channels, the γ-aminobutyric acid (GABA) system and ionotropic glutamate receptors. Metabotropic glutamate receptors, potassium channels, and neurotransmitters such as acetylcholine, glycine, and monoamines are beyond the scope of this review.

In status epilepticus, immediate failure of GABAergic inhibition occurs, and administration of benzodiazepines and barbiturates displays the pharmacostrategic mainstay. In epileptogenesis within limbic structures, the most important underlying pathophysiological mechanisms currently discussed are transient loss of inhibition and aberrant mossy fiber sprouting. Both processes may be facilitated by *N*-methy-D-aspartat (NMDA) receptor regulation. NMDA antagonists may exhibit antiepileptogenic properties in experimental animals, but reliable data in humans are lacking. In established epilepsy, voltage-gated ion channels and impairment of GABAergic functions contribute to mechanisms facilitating ictogenesis. Blockade of sodium and calcium channels and enhancement of GABAergic inhibition are currently the most important tools to prevent the occurrence of seizures.

Keywords. Status epilepticus, epileptogenesis, established epilepsy, ictogenesis, ion channels, GABAergic inhibition, glutamatergic system.

Introduction

In this review, we focus on present and possible future pharmacological approaches relevant to three different, but overlapping situations: emergency treatment of status epilepticus, modification of epileptogenesis following an initial insult in order to prevent chronic epilepsy, and prophylaxis against the occurrence of further seizures in established epilepsy (Fig. 1). Particular attention is paid to what is known of the underlying cellular and molecular mechanisms of each of the three situations the individual pharmacostrategies may interfere with (Table 1).

First, acute seizure disorders such as status epilepticus (SE) urgently need immediate drug treatment to terminate this emergency situation as soon as possible [1]. For reasons of clarity, we term this approach

* Corresponding author.

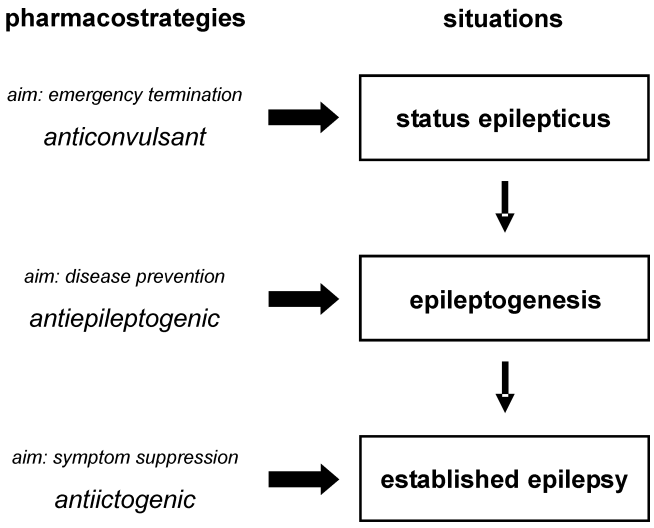

Figure 1. Pharmacological approaches to acute seizure conditions such as status epilepticus (SE), to epileptogenesis following acquired brain insults, and to ictogenesis in established epilepsy are distinctly different. It is the most important aim of the treatment of SE to terminate ongoing epileptic activity as soon as possible. This approach is termed anticonvulsant pharmacostrategy. The prevention or alleviation of the disease chronic epilepsy following brain insults such as SE is termed antiepileptogenesis or disease-modification. In established epilepsy, pharmacological concepts aim at suppression of epileptic seizures as the most prominent symptom and thus are termed antiictogenic. Pharmacological interventions in established epilepsy aiming at modifying the condition itself rather than merely suppressing the symptom epileptic seizure have never been proven to be successful.

'anticonvulsant treatment', although we are aware that not all presentations of this emergency take the form of 'convulsive' status epilepticus.

Second, brain insults acquired postnatally, such as head trauma, stroke, cerebral infectious diseases, and status epilepticus, may induce a variety of neurobiological processes that – after a latent period of days to years – may result in the occurrence of unprovoked epileptic seizures [2]. In this review, we use the term 'antiepileptogenic treatment' to describe pharmacological interventions following an acquired brain insult that are administered with the aim to entirely prevent the complication of unprovoked seizures (established epilepsy). We use the term 'disease-modifying treatment' for interventions following brain insults that may not prevent the development of chronic epilepsy but are supposed to mitigate the process by reducing the frequency of seizures or their severity [3].

Finally, in established epilepsy, the pharmacological strategy is directed at modulation of pathophysiological processes underlying ictogenesis, so that clinically the probability of seizure recurrence is reduced [4]. Therefore, the pharmacological approach in established epilepsy formally presents a secondary prophylaxis against epileptic seizures. In the current review, we term this approach 'antiictogenic treatment'.

This review concentrates on anticonvulsant, antiepileptogenic, and antiictogenic pharmacostrategies in adult epileptic conditions. The effects of these substances on pure neuroprotection [5] and their therapeutical relevance in various non-epileptic conditions [6] are beyond the scope of this review. The pathophysiological mechanisms underlying status epilepticus, epileptogenesis, and ictogenesis in the developing brain are different from those in adults. The interplay between the according substances and brain development was addressed comprehensively in a recent review in this journal [7].

Molecular targets and mechanism of action of substances

The main – but by no means the only – targets of substances important in anticonvulsant, antiepileptogenic, and antiictogenic pharmacostrategies are ionic channels, the inhibitory γ-aminobutyric acid (GABA) system, and excitatory glutamate receptors.

Sodium channels

Voltage-gated sodium channels are responsible for the rising phase of the action potential in excitable cells and membranes. They are of critical importance for the generation and propagation of action potentials. At hyperpolarised potentials, sodium channels are in the resting closed state. With neuronal depolarisation, the sodium channel converts from its closed non-conducting state to the open state that allows increased influx of sodium ions. Then the channel inactivates and the flow of sodium ions is terminated [4, 8]. Changes between the resting, open, and inactivated states occur rapidly in sodium channels of cerebral neurons and thus form the basis for physiological brain function and pathological conditions such as epileptic activity.

Substances such as carbamazepine, lamotrigine, oxcarbazepine [9], and phenytoin [10], and to a lesser extent felbamate [11], topiramate [12], valproate [13], and zonisamide [14] block sodium channels resulting in inhibition of sustained repetitive spike firing that may contribute to propagation of epileptic activity [15]. Carbamazepine, lamotrigine, and phenytoin bind at the inner pore of the sodium channel in its

Table 1. Summary of anticonvulsant, antiepileptogenic, and antiictogenic pharmacostrategies.

Situation	Pathophysiological mechanism	Substance	Main mechanism of action
Status epilepticus	– erosion of GABAergic inhibition due to endocytosis of $GABA_A$-Rs	– benzodiazepines:	increased frequency of Cl^- channel openings
		– barbiturates	prolonged opening of Cl^- channel
		– propofol:	increased Cl^- ion conductance
	– expression of AMPA- and NMDA-Rs	– ketamine?[1]:	non-competitive inhibition at NMDA-R
	– modification of ion channels	– phenytoin:	Na^+ channel blockade
Epileptogenesis	– NMDA-R-regulated inhibitory and excitatory circuit modification	– ketamine?[2]:	non-competitive inhibition at NMDA-R
		– MK-801?[2]:	non-competitive inhibition at NMDA-R
Seizures in established epilepsy	– ion channel alteration	– carbamazepine:	Na^+ channel blockade
		– oxcarbazepine:	Na^+ channel blockade
		– phenytoin:	Na^+ channel blockade
		– lamotrigine:	HVA Ca^{2+} and Na^+ channel blockade
		– zonisamide:	LVA Ca^{2+} and Na^+ channel blockade
		– gabapentin:	HVA ($\alpha 2\delta$ subunit) Ca^{2+} channel blockade
		– topiramate:	HVA Ca^{2+} and Na^+ channel blockade
		– levetiracetam:	SV2A binding
	– reduced GABAergic inhibition	– benzodiazepines:	increased frequency of Cl^- channel openings
		– phenobarbital:	prolonged opening of Cl^- channel
		– tiagabine:	GABA transporter inhibitor
		– valproate:	increases GABA turnover
		– gabapentin:	increases GABA turnover
		– vigabatrin:	GABA transaminase inhibitor (irreversible)
	– increase glutamatergic excitation	– felbamate?[3]:	NMDA-R antagonist
		– topiramate?[3]:	kainate-R and AMPA-R antagonist

$GABA_A$-R/s, γ-aminobutyric $acid_A$ receptor/s; Cl^-, chloride; AMPA-R/s, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor/s; NMDA-R/s, *N*-methy-D-aspartat receptor/s; Na^+, sodium; HVA, high-voltage activated; Ca^{2+}, calcium; LVA, low-voltage-activated; SV2A, synaptic vesicle protein 2A.

[1] anticonvulsant properties of ketamine have been shown in experimental animals but clinical efficacy is unclear.

[2] antiepileptogenic properties of ketamine and MK-801 are contradictory in experimental animals, substances have not been tested in the human condition.

[3] antiictogenic properties of felbamate and topiramate are well-known in patients, it is unclear whether antagonism to glutamate receptors contributes to the clinically relevant mechanisms of action.

inactivated state [16] and delay the transition from the inactivated state to the resting closed state that opens with depolarisation. The prolonged inactivated state and the smaller probability that the channel is in the resting state eventually block high-frequency axonal firing. Interestingly, the inhibitory properties of the above-mentioned substances are 'use-dependent', i.e. repetitive firing results in greater binding of the drugs and thus enhanced inhibition. This property allows protection against occurrence of epileptic seizures without major interference with physiological brain function. Benzodiazepines [17], phenobarbital [18], and propofol [19], which predominantly enhance GABAergic inhibition, at high concentrations also have been demonstrated to exhibit some sodium channel-blocking properties.

Calcium channels

Voltage-gated calcium channels allow ion flux if they are gated open by membrane depolarisation. Calcium channels are categorised into two large groups depending on the extent of hyper- or depolarisation required for activation. L-, R-, P/Q- and N-types are high-voltage-activated (HVA) channels that require significant depolarisation before activation. T-type channels are low-voltage-activated (LVA) and are thus already activated in the hyperpolarised state [20]. L-type channels are mainly located postsynaptically and regulate calcium entry upon neuronal depolarisation. In an animal model of absence epilepsy, blockade of this subgroup of calcium channels with high-dose nimodipine resulted in proictogenic effects [21]. In patients, however, it remains unclear whether the L-type channel antagonistic effect of substances such as phenytoin [22] and carbamazepine [23] contributes to any therapeutic or undesirable effect.

N- and P/Q-type HVA calcium channels represent potential molecular targets, as these channels are required for transmitter release that is inhibited by channel blockade [24, 25]. N-type channels are blocked by lamotrigine [26], levetiractam [27, 28], and topiramate [29]. Lamotrigine may in addition have some inhibitory effects on P-type channels [26]. Gabapentin and its analogue pregabalin strongly bind to the HVA calcium channel auxilliary subunits $\alpha 2\delta$-1 and $\alpha 2\delta$-2 [30, 31]. These subunits enhance current through P/Q-type channels, and their blockade inhibits this subtype of HVA calcium channels [32].

LVA T-type channels play a major role in the generation of thalamic spike-wave discharges as seen

in absence epilepsy [33, 34]. It is important to note that pathophysiological mechanisms underlying the generation of absence seizures are principally different from those underlying all other types of epileptic seizures [35] (see below subchapter "pathophysiology" in chapter "established epilepsy"). Ethosuximide at clinically relevant concentrations selectively blocks T-type calcium channels but does not have any effect on HVA channels [36, 37]. Zonisamide, among other mechanisms of action, also has been reported to block T-type channels [38].

The synaptic vesicle protein 2A (SV2A), which is believed to participate in the regulation of calcium-dependent neurotransmitter release, has been identified as a molecular target for levetiracetam [39]. The synaptic vesicle protein 2 likely influences mechanisms of seizure generation and propagation, as SV2A knockout mice develop an unusually strong seizure phenotype by 1.5 weeks of age. These findings suggest that levetiracetam acts at least in part via binding to SV2A.

GABA receptors and metabolism

GABA is the most important inhibitory neurotransmitter in the brain, and the GABA system represents an important target for anticonvulsant, antiepileptogenic, and antiictogenic pharmacostrategies. GABA acts on fast chloride-permeable ionotropic $GABA_A$ receptors that are expressed postsynaptically [4]. Receptor activation results in opening of the receptor channels, leading to chloride ion influx and efflux of bicarbonate ions. These eventually hyperpolarise the cell membrane, rendering the cell less excitable [40–42]. It is important to note that the GABAergic system is by no means exclusively inhibitory [43]. Indeed, GABA-mediated excitation of pyramidal cells in rats [44] and in patients with temporal lobe epilepsy [45] has been described. Experimental animal work has allowed better insight into the contribution of the genetic background to GABAergic receptor pharmacology [46]. Rats have been identified that are either seizure prone or seizure resistant to amygdala kindling [47]. The $GABA_A$ receptor $\alpha 1$ subunit upregulation in seizure-resistant rats and downregulation in seizure-prone animals [48] may contribute to the observed diverging receptor pharmacology [46].

Bromide, historically the first antiictogenic substance, has been shown to enhance GABAergic inhibition [49] by increasing sensitivity of $GABA_A$ receptors to GABA [4]. The most relevant molecular target of benzodiazepines is the accordant binding site on the $GABA_A$ receptor. Benzodiazepine binding results in allosteric receptor modulation [4, 50]. Thus, benzodiazepines enhance affinity and binding of GABA to the $GABA_A$ receptor, thereby increasing the frequency of cloride channel openings [51, 52]. Barbiturates act somewhat differently via prolonging the opening of the chloride channel [53–55]. Propofol induces an inward hyperpolarising current carried by chloride ions [56], thus exerting a mechanism of action that is different from that of barbiturates and benzodiazepines. Besides this direct effect on chloride channel conductance [57], propofol enhances the frequency of GABA-induced conductance events [58] and thus potentiates the effect of GABA on neurons [59]. Felbamate and topiramate interfere with multiple molecular targets. They have also been reported to act on $GABA_A$ receptors [60, 61].

Besides receptor modulation, GABAergic inhibition may be enhanced by increasing the amount of GABA available at the synaptic cleft. GABA is converted by glutamic acid decarboxylase from glutamate, and this process has been described to be promoted by gabapentin [62] and valproate [63]. The cerebral concentration of GABA is controlled by the enzyme GABA transaminase, which metabolises GABA to succinic semialdehyde. Vigabatrin irreversibly blocks GABA transaminase, resulting in elevation of cerebral GABA concentrations [64]. GABA is transported from the extracellular space into neurons and glia cells via GABA transporters (GATs). GAT1 is the most abundant GABA transporter, predominantly expressed in presynaptic terminals and glia [65]. Tiagabine is a potent and selective competitive inhibitor of GAT1 that prevents the reuptake of GABA and increases the availability of this inhibitory neurotransmitter [66].

$GABA_B$ receptors are expressed both pre- and postsynaptically [67, 68], and their role in facilitation and inhibition of epileptic activity is complex [42]. Mice lacking functional $GABA_B$ receptors exhibit spontaneous seizures [69], indicating the pathophysiological importance of this receptor subtype in suppressing epilepsy. However, activation of presynaptic $GABA_B$ receptors results in a negative feedback that suppresses GABA release at inhibitory synapses [68]. In addition, there are $GABA_B$ presynaptic heteroreceptors on glutamatergic terminals. Postsynaptic $GABA_B$ receptor activation results in prolonged hyperpolarisation, rendering neuronal networks less excitable. On the other hand, activation of $GABA_B$ receptors in the thalamo-cortical system may contribute to the generation of absence seizures [70]. Tiagabine and vigabatrin, which enhance extracellular GABA concentration, eventually result in $GABA_B$ receptor activation, but it is currently unknown whether this mechanism contributes to any pro- or antiictogenic effects.

Glutamate receptors

Ionotropic glutamate receptors form cation channels mediating fast excitatory neurotransmission in the brain [71]. Glutamate acts at two different ionotropic receptor subtypes: *N*-methy-D-aspartate (NMDA) and non-NMDA receptors. The latter includes α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate sensitive receptors. NMDA receptors can produce channels permeable to calcium and sodium ions, while non-NMDA receptors can build sodium channels [42]. From a pathophysiological point of view, ionotropic glutamate receptors would be ideal molecular candidates for substances administered as part of anticonvulsant, antiepileptogenic, and antiictogenic pharmacostrategies.

Experimental substances have been shown to be competitive (CPP, CGP 40116) [72, 73] or non-competitive (MK-801, TCP, ketamine) [74–76] antagonists at the NMDA receptor. In all *in vitro* animal models of epilepsy, substances such as ketamine and MK-801 demonstrated strong seizure-suppressing properties [77]. In the spectrum of clinically relevant substances, felbamate may act, at least in part, via NMDA receptor blockade [78]. At higher doses the predominantly GABAergic substance propofol inhibits neuronal excitation at the NMDA receptor as well [79].

AMPA receptors mediate most excitatory neuronal transmission and play a major role in seizure spread [4]. Pre- and postsynaptic kainate receptors also contribute to glutamate-mediated neuronal excitation, in particular in limbic structures that are associated with ictogenesis [80]. These non-NMDA receptors therefore display important molecular targets. Besides multiple other mechanisms of action, topiramate in higher concentrations blocks kainate receptors and, to a lesser extent, AMPA receptors [81, 82]. The selective non-competitive AMPA receptor antagonist talampanel, which at present is being tested in clinical trials, has been shown to exhibit a broad spectrum of activity in whole animal and brain slice epilepsy models [83].

Recently identified targets

Beyond the above-mentioned targets for substances used in anticonvulsant, antiepileptogenic, and antiictogenic pharmacostrategies, new targets have been identified that may be addressed by existing or newly developed drugs. Vascular endothelial growth factor (VEGF) was recently demonstrated to suppress epileptic activity *in vitro* [84]. Therefore, VGEF or VGEF-related targets may provide useful endpoints to direct novel pharmacological approaches. Disruption of the blood-brain barrier induced by seizures or inflammation or by both allows the entry of compounds with immunogenic or inflammatory potential [85]. Experimental studies have shown that inflammatory reactions in the brain can enhance neuronal excitability [86], and antiinflammatory treatments may reduce seizures clinically and experimentally [85]. Commonly used substances such as carbamazepine [87] and valproate [88] induce antiinflammatory actions, but it is unknown whether this mechanism contributes to the antiictogenic effect.

Summary and perspectives

Some of the substances currently used in anticonvulsant, antiepileptogenic, and antiictogenic pharmacostrategies in patients mainly exert their action via one defined molecular target such as carbamazepine, oxcarbazepine and phenytoin via sodium channels, levetiracetam via the SV2A protein, and benzodiazepines, tiagabine, and vigabatrin via the $GABA_A$ receptor or GABA metabolism. However, other drugs such as gabapentin, lamotrigine, valproate, and zonisamide act on voltage-gated ion channels and the GABA system, while felbamate and topiramate in addition exert antagonistic properties at glutamatergic receptors. In substances acting at multiple targets, it is often unclear via which of those the most important effects are achieved. Future studies may help to identify even more cellular or molecular targets in epileptic conditions that perspectively developed drugs can interfere with.

Acute seizure disorders

Clinical background

In the vast majority of cases, single tonic clonic generalised epileptic seizures are self-limiting within 2 min after onset [89], and acute pharmacological intervention is not required. Seizure activity that persists or recurs so rapidly that return to clinical baseline conditions is not possible should be treated within 5 min after onset [90] regardless of the academic question whether the condition is termed prolonged epileptic seizure [91] or SE [92]. Besides stroke, SE is the most frequent neurological emergency, with an incidence between 10 and 41/100 000 population [93, 94].

The aim of acute anticonvulsant intervention is to terminate SE in order to prevent lethal systemic or disabling neuronal consequences in generalised convulsive SE [95]. In non-convulsive SE, treatment aims at stopping a highly uncomfortable condition that bears the risk of severe physical injury, in particular, if consciousness is impaired [96]. Anticonvulsant treatment is still hampered by the fact that first- and second-line intravenous substances fail to terminate

SE in about 30–40% of cases. The overall clinical outcome in such patients is therefore still very poor [97–100].

Pathophysiology

Self-termination of most forms of isolated epileptic seizures is hypothesised to be based largely on activation of GABA receptor-mediated inhibition [101]. A breakdown of GABAergic inhibition facilitates the transition from a single epileptic seizure to SE. After brief (< 5 min) electrical stimulation of the perforant path *in vitro* and *in vivo*, prolonged loss of paired-pulse inhibition has been observed, indicating GABAergic impairment [102]. Within minutes of ongoing seizure activity, the number of $GABA_A$ receptors per dentate gyrus granule cell synapse decreases significantly due to endocytosis of $GABA_A$ receptors [103]. The pronounced disappearance of $GABA_A$ receptors likely contributes to the emerging failure of GABAergic inhibition. Such erosion of GABAergic function may also explain the well-known phenomenon of progressive pharmacoresistance to benzodiazepines with ongoing seizure activity (see below subchapter "progressive pharmacoresistance") [104, 105]. Further mechanisms, such as intracellular chloride accumulation and higher bicarbonate permeability, may also contribute to loss of inhibition [106, 107]. If GABA becomes depolarising due to chloride efflux as a result of previous intracellular chloride accumulation, pharmacological increase of GABAergic signalling may increase neuronal excitation [43, 45]. Thus, GABA paradoxically may become excitatory during SE possibly contributing to the develpment of refractoriness. Simultaneously with $GABA_A$ receptor impairment, the number of AMPA and NMDA receptors increases in the wake of movement of receptor subunits to the synaptic membrane [108]. Such antipodal trafficking of inhibitory and excitatory receptors eventually renders the transformed neuron more excitable.

Anticonvulsant pharmacostrategies

Despite the potential paradoxical excitatory effects discussed above, the mainstay of the initial treatment of SE is still enhancement of impaired $GABA_A$-mediated synaptic inhibition. Benzodiazepines are the drugs of choice, as they have a rapid onset of action, exhibit strong anticonvulsant properties, and are generally safe. In patients, a randomised controlled trial revealed that benzodiazepines such as lorazepam and diazepam, with phenytoin co-administered to the latter, and the barbiturate phenobarbital are effective in terminating SE in 55–65% of cases, with lorazepam being significantly more effective than the sodium channel blocker phenytoin (44%) [100].

Pharmacokinetics of GABAergic anticonvulsants. Benzodiazepines have been shown experimentally to rapidly enter the brain. After intravenous administration in cats and dogs, peak brain concentrations of diazepam were achieved 1 min after injection [109]. Peak cerebrospinal fluid concentrations of lorazepam have been described to occur slightly later [110]. Clinical studies on SE, however, have not yet given evidence for a protracted anticonvulsant effect of lorazepam compared to diazepam. The elimination half-life of diazepam (28–54 h) is prolonged compared to the intermediate half-life of lorazepam (8–25 h). Benzodiazepines are highly lipophilic substances and therefore likely redistribute to other lipoid tissues. Thus, the distribution half-life of benzodiazepines is a parameter that is much more significant for the assessment of persistent anticonvulsant effects. The shorter distribution half-life of diazepam (0.3 h) compared to that of lorazepam (2–3 h) is reflected in the clinical effects of these substances. In patients, diazepam prevents recurrence of seizure activity for less than 2 h, while lorazepam is effective for more than 12 h [95, 111]. In the initial treatment of SE, the shorter distribution half-life of diazepam is the rational for co-administration of intravenous long-acting phenytoin, while lorazepam commonly is given in monotherapy [90].

Barbiturates also rapidly enter the brain in SE; however, the elimination half-life is about 100 h in phenobarbital [112] and 8 h after single-dose thiopental, increasing to 18–36 h after prolonged treatment [113].The pharmacokinetic advantage of propofol is the rapid onset of action within minutes [112] and the rapid offset with an elimination half-life of 2–3 h [114].

Progressive pharmacoresistance. The longer SE lasts, the more difficult it becomes to terminate the condition. The clinical variant of subtle SE evolving from untreated or only partially treated overt SE is terminated by phenobarbital or benzodiazepines with or without additional phenytoin in only 8–24% of cases [100]. In a retrospective study of 154 patients, Lowenstein and Alldredge demonstrated that SE treated 30 min after onset was terminated in 80% of cases, while treatment starting 120 min after onset was successful in only 40% [115]. Therefore, pharmacological treatment of SE should be initiated as early as possible. In this context it is important to note that out-of-hospital management of SE with lorazepam, diazepam, and placebo has been assessed in a randomised controlled trial [116]. The dose of intravenous lorazepam required to terminate SE was only 25–50% of that necessary to terminate SE after arrival in the emergency department [100, 116].

In parallel to the clinical data, SE induced by pilocarpine in rats required 10-fold more diazepam if administered 45 min compared to 10 min after seizure onset. This progressive pharmacoresistance against diazepam may be explained by the plasticity of subunits of the $GABA_A$ receptor by ongoing SE as demonstrated in rat dentate gyrus granule cells (see above subchapter "pathophysiology") [105].

Refractory SE. SE and in particular its generalised convulsive form, that is refractory to the initially administered substances, urgently calls for aggressive treatment escalation. Anaesthetics that are commonly administered in refractory status epilepticus (RSE) include propofol, midazolam, and thiopental (marketed in Europe) or its first metabolite pentobarbital (marketed in the US) all of which mainly act via enhancement of synaptic GABAergic inhibition [56]. As yet, it is not well understood to what extent the ion channel-blocking property of these substances contributes to their acute anticonvulsant effects. General anaesthetics are clinically limited by their marked side effects, such as sedation and respiratory depression requiring mechanical ventilation and pressor-requiring cardiovascular depression [117, 118].

Due to the loss of potency of GABAergic substances with ongoing seizure activity, substances that act predominantly via non-GABAergic mechanisms may be of interest in later stages of SE. Two of the 'new-generation' drugs known in the treatment of established epilepsy, topiramate and levetiracetam, have recently been described to be successful in terminating RSE without relevant side effects [119–123]. Levetiracetam is of particular interest in the treatment of SE, as this substance is now available for intravenous administration in more than 50 countries.

A rational strategy in the pharmacological management of RSE that is based on interference with pathophysiological mechanisms underlying ongoing seizure activity would be a reduction of excitatory synaptic mechanisms by blockade of the NMDA receptor that is overexpressed with persistent SE. In the electrical stimulation model of SE, the NMDA antagonist ketamine did not affect SE within the first 15 min after onset, but effectively controlled seizures after 60 min when phenobarbital had already lost its anticonvulsant potency [124]. The NMDA antagonist MK-801 also showed a trend to increased efficiency when administered 4 h after electrically induced SE compared to 1 h, while phenobarbital lost efficiency over time [125]. In contrast to these convincing experimental data, clinical reports on the successful use of NMDA antagonists such as ketamine are sparse [126, 127], and neurotoxic side effects have been described [128].

Summary and perspectives

The predominant molecular target in the anticonvulsant pharmacostrategy of SE is the $GABA_A$ receptor, which rapidly loses its inhibitory efficacy with ongoing seizure activity. Experimental data indicate that blockade of excitatory NMDA receptors that increase in number during SE is an efficient approach in later stages, but so far convincing clinical data are lacking. Future pharmacological approaches may address prevention or reversal of receptor trafficking that seems to present the major pathophysiological mechanism underlying ongoing seizure activity in SE. Furthermore, research may focus on substances that display anticonvulsant mechanisms of action beyond GABAergic inhibition and act on various targets, also including non-NMDA receptors and ion channels.

Epileptogenesis

Clinical background

A variety of acquired brain insults are known to be associated with the development of chronic epilepsy. Following traumatic brain injury (TBI), 2–25% of patients have been reported to exhibit unprovoked epileptic seizures, depending on the severity of the initial trauma [129–131]. While the risk is highest in the months directly after TBI, it remains elevated for more than 5 years in patients with moderate to severe injuries and for more than 15 years in patients with penetrating missile wounds to the brain [129, 132, 133]. This indicates that neurobiological processes underlying posttraumatic epileptogenesis may occur in a very protracted fashion. Stroke is reported to cause subsequent chronic epilepsy within the next 5 years in 2–4% of cases, and the risk of seizures is increased in patients with subarachnoid and intracerebral haemorrhage [134–137]. Chronic epilepsy has been reported in about 10% of patients following cerebral vein and dural sinus thrombosis [138] and in about 7% of patients within 20 years after central nervous system (CNS) infections, with a 4-fold higher risk after viral encephalitis compared to bacterial meningitis [139]. The development of chronic epilepsy following SE is not rare, but in individual cases it may be difficult to discern whether epileptogenesis is the consequence of SE or of the underlying brain disease. The 10-year risk of developing epilepsy after acute symptomatic SE has been reported to be 41% and thus 3.3 fold higher than after a single epileptic seizure with comparable aetiology [140], giving evidence for the major impact of SE itself on epileptogenesis.

It would be a fascinating therapeutic aim to prevent the development of epilepsy after acquired brain injuries rather than to suppress epileptic seizures in established epilepsy. However, a thorough understanding of the pathophysiological mechanisms underlying epileptogenesis is the prerequisite for the development of specific antiepileptogenic pharmacostrategies. These approaches first need consistent proof in experimental animal studies before they can be incorporated in perspective human treatment trials.

Pathophysiology

Animal models. Neurobiological processes underlying epileptogenesis after brain injuries have been studied extensively in experimental animal models of SE [141], and to some extent in models of brain trauma [142, 143] and ischaemic stroke [144].

Experimental SE can be induced in rats by systemic or local administration of chemoconvulsants such as kainic acid [145] or pilocarpine [146, 147], or by continuous or intermittent electrical stimulation of the amygdala [148], the ventral hippocampus [149], or the perforant path [150]. After a latent period of several weeks, 50–100% of animals develop recurrent spontaneous seizures ([149, 151–157].

A new animal model of posttraumatic epileptogenesis has recently been reported [143]. Following severe, non-penetrating lateral fluid-percussion brain injury in rats, 43–50% of injured animals developed epilepsy after a latent period from 7 weeks to 1 year.

Following experimental focal ischaemia induced by cortical photothrombosis [158–160] or permanent occlusion of the middle cerebral artery [161], small studies with no more than 10 rats reported that 25–100% of animals developed spontaneous seizures after 2–10 months. A recent study on rats with middle cerebral artery occlusion induced by intracerebral injection of endothelin 1 demonstrated that only 1 out of 26 animals developed late spontaneous seizures within 6–12 months [144].

Eventually, there may be differences in the epileptogenic processes in the various models described, and it is rather unclear whether these model systems reliably reflect processes in the human condition.

Pathophysiological concepts of epileptogenesis. Following SE, NMDA receptor-regulated circuit modifications in the hippocampal formation resulting in transient loss of inhibition and in increased excitation are currently assumed to represent the pathophysiological basis for epileptogenesis. GABAergic inhibition in the dentate gyrus (DG) has repeatedly been shown to be markedly impaired shortly after SE and to be fully restored and sometimes even hypercompensated within 4–8 weeks after SE [157, 162, 163]. The initial GABAergic disinhibition may be due to loss of specific GABAergic interneurons [156, 164] or a reduced number and sensitivity of postsynaptic $GABA_A$ receptors [165, 166]. As antagonists to the NMDA receptor immediately reverse GABAergic disinhibition [167], it is likely that impaired GABAergic inhibition is in part regulated by NMDA receptors, probably via a Ca^{2+}-dependent dephosphorylation process [2]. However, loss of inhibition does not explain the development of chronic epilepsy sufficiently, as spontaneous seizures occur several weeks later when inhibition has recovered [149, 155–157]. Therefore, we assume that there are two major steps towards the process of epileptogenesis. Disinhibition of the DG results in a loss of the filter function of this structure, allowing physiological stimuli to affect highly vulnerable downstream structures of the hippocampus proper [168–170]. In a second step, excitatory transmission in the hippocampus proper is enhanced, resulting in the generation of spontaneous epileptic seizures. Though DG inhibition at this point is restored by compensatory upregulation of post-synaptic $GABA_A$ receptor subunits [171–173] or by axonal sprouting of the remaining GABAergic interneurons [155, 174, 175], it is too weak to suppress spontaneous seizures, as robust epileptogenic excitatory circuits are already established.

Aberrant sprouting of DG granule cell axons that are termed mossy fibers allows new excitatory connections to be established with granule cell dendrites in the DG inner molecular layer [176–179]. This results in an expansion in the number of recurrent excitatory synapses between granule cells likely playing a major role in epileptogenesis following SE. Suppression of mossy fiber sprouting by cycloheximide was reported not to prevent subsequent epileptogenesis in rats [180, 181], but SE in these studies was induced by chemoconvulsants that act ubiquitously and result in epileptogenic alterations in limbic and neocortical structures. Therefore, in that model, development of chronic epilepsy after blockade of mossy fiber sprouting does not confute that DG sprouting contributes to epileptogenesis. The molecular basis for mossy fiber sprouting again seems to be activation of the NMDA receptor and subsequent Ca^{2+} influx. Increased intracellular Ca^{2+} concentration mediates the expression of the immediate Ca^{2+} dependent early gene, c-*fos* [182], which may regulate mossy fiber sprouting [183]. NMDA receptor blockade has been shown to impair aberrant sprouting [184].

Following experimental brain trauma, epileptogenesis may also have been facilitated by mossy fiber sprouting that was increased in the ipsilateral hippocampus

of animals with fluid-percussion-induced posttraumatic epilepsy compared to those subjected to traumatic brain injury without epilepsy [143]. Furthermore, in mice with fluid percussion-induced brain injury, impaired DG inhibitory efficacy has been demonstrated [185] that may contribute to epileptogenesis along the pathophysiological lines discussed above for the post-SE model.

The pathophysiological basis of post-stroke epileptogenesis has not been investigated thoroughly so far, but molecular mechanisms with modifications of channels and cellular alterations with loss of inhibitory neurons and growth of aberrant excitatory reinnervation to surviving neurons in periinfarct tissue have been discussed [144, 186, 187].

Antiepileptogenic pharmacostrategies

In experimental animals models, antiepileptogenic or disease-modifying pharmacostrategies following SE have been studied extensively, but so far experimental data on preventive approaches after other epileptogenic aetiologies, such as traumatic brain injury or ischaemic stroke, are lacking.

Initial insult modification. Antiepileptogenic effects can be assessed reliably only if substances are given after the end of SE, as administration prior to or during SE may result in 'initial insult modification' [3]. Duration of SE seems to be one of the most important factors for the development of epilepsy [154]. The administration of diazepam 2 h after onset of electrically induced SE in rats significantly reduced the number of animals that eventually developed chronic epilepsy compared to controls [188]. However, such data do not indicate 'true' antiepileptogenesis, as the pharmacological effect was first and foremost anticonvulsant and modified the potentially epileptogenic brain injury.

Dissociated anticonvulsant and antiepileptogenic effects. Some experimental studies reported dissociated anticonvulsant and antiepileptogenic drug effects, i.e. the substances given during SE had limited impact on acute seizure activity but prevented or attenuated subsequent development of chronic epilepsy. Prasad and colleagues administered GABAergic phenobarbital, the sodium channel blocker phenytoin, and the NMDA receptor antagonist MK-801 at 1, 2, and 4 h after onset of electrically induced SE and assessed acute anticonvulsant and late antiepileptogenic effects [125]. Phenobarbital and MK-801 were superior to phenytoin in suppressing SE, but MK-801 was less efficient compared to phenobarbital. Nevertheless, both phenobarbital and MK-801 reduced the number of animals that eventually developed chronic epilepsy significantly when given 1 h after seizure onset, and in addition, MK-801 administered after 2 h rendered fewer animals epileptic. Though MK-801 definitely modified the initial insult, the substance had fewer anticonvulsant but more pronounced epilepsy-preventing properties as compared to phenobarbital, giving rise to indirect evidence for possible antiepileptogenic effects. Interestingly, both phenobarbital and MK-801 administered 4 h after seizure onset did not have any effect on long-term development of epilepsy, indicating that at least in this model system the window for prevention of epilepsy may be rather narrow.

In a similar methodological approach in immature P15 rats, topiramate was less effective than diazepam in terminating acute pilocarpine-induced SE, but it was more effective than diazepam in preventing the development of chronic epilepsy [189]. This finding was not reproduced in adult rats, as comparable doses of topiramate injected at the onset of pilocarpine SE did indeed not affect acute seizure activity, but topiramate did not exhibit any antiepileptogenic or disease-modifying effects either [190]. Pregabalin administered during and after pilocarpine SE was reported to delay onset of spontaneous recurrent seizures without demonstrating acute anticonvulsant effects, but the substance was given during the whole post-SE period studied and therefore it was impossible to discern antiepileptogenic from antiictogenic effects [191].

When substances are administered during SE, a modifying impact on the initial insult can never be completely excluded. Therefore, the only reliable approach to assess antiepileptogenic effects is based on study of drugs that were administered after causing events such as SE had definitely been terminated.

Antiepileptogenesis in experimental post-SE models. As a number of relevant processes underlying epileptogenesis are believed to be NMDA receptor regulated, pharmacological blockade of these receptors seems to be areasonable antiepileptogenic treatment approach.

In a model system of kainite-induced SE, administration of the NMDA receptor antagonist MK-801 immediately after termination of seizure activity lasting 90 min did not prevent or attenuate the development of chronic epilepsy [192]. The dose, however, was 0.1 mg/kg and thus 40 times smaller compared to the study described above that successfully prevented epilepsy when MK-801 was given 1 and 2 h after unterminated seizure activity induced by electrical stimulation [125]. Furthermore, the contra-

dictory results may be due to the different SE models used that may induce heterogeneous epileptogenic mechanisms. Model discrepancies may also explain the conflicting results regarding the antiepileptogenic effect of valproate that completely prevented the development of epilepsy following kainate SE [193], while spontaneous seizures following electrically induced SE were not affected at all [194]. Carbamazepine administered for 8 weeks starting 24 h after termination of pilocarpine-induced SE did not prevent the development of chronic epilepsy; however, spontaneous recurrent seizures occurred less frequently, and duration was shorter compared to vehicle-treated controls [195]. This study demonstrates disease-modifying effects of carbamazepine, which is one of the most common drugs with strong antiictogenic properties in patients with partial epilepsies. However, these findings have to date not been reproduced by other authors. Other substances tested, such as lamotrigine [196], vigabatrin [197, 198], phenobarbital [193], ketamine [199], and levetiracetam [200], did not prove to exhibit antiepileptogenic or disease-modifying properties.

Antiepileptogenesis: human data. In patients, several pharmacological substances have prevented the (re-)occurrence of provoked seizures in acute medical conditions [201]. Phenobarbital and valproate have successfully prevented recurrent febrile seizures [202–205], phenobarbital prevented seizures with cerebral malaria [206], lorazepam prevented alcohol-related seizures [207], and phenytoin and carbamazepine prevented seizures early after TBI and cranial surgery [208–210]. However, these findings on provoked acute-symptomatic seizures do not give any evidence for antiepileptogenic effects, as epilepsy is defined by the occurrence of unprovoked seizures [211]. These substances were administered when the risk of provoked epileptic seizures was high; thus seizures were simply suppressed rather than prevented due to pharmacological modification of an underlying epileptogenic process.

Seizures are defined to be unprovoked when they occur more than 7 days after an aetiological incident [212]. Therefore, antiepileptogenic pharmacostrategies methodologically can be assessed only when substances that were administered for a defined period of time after a potentially epileptogenic event prevent the occurrence of late unprovoked epileptic seizures. Unfortunately, available clinical trials on carbamazepine, phenobarbital, phenytoin, and valproate thus far have revealed unsatisfactory results [201]. A Cochrane review incorporating six randomised controlled trials with more than 1400 patients showed that seizure-suppressing drugs after TBI are effective in reducing early fits (see above), but that there is no evidence for an antiepileptogenic or disease-modifying effect regarding the development of chronic epilepsy [213]. In patients, the available evidence is insufficient to establish the net benefit of antiepileptogenic treatment at any time after brain injury.

Summary and perspectives

A major problem of research into substances with antiepileptogenic properties results from the fact that tested drugs are not chosen according to the pathophysiological mechanisms epileptogenesis relies on. Currently, substances that exhibit antiictogenic properties in patients are assessed in experimental animals much like a fishing expedition concerning their additional antiepileptogenic potential. Specific molecular targets of epileptogenesis, such as ionotropic glutamate receptors or Ca^{2+}-dependent intracellular second-messenger systems, have not been studied exhaustively and should present future research pathways.

Established epilepsy

Clinical background

Epilepsy is one of the most common neurological diseases, with a prevalence of 0.5–1% [214]. Current approaches to drug therapy in established epilepsy aim at controlling seizures as the major symptom of the condition. Though antiictogenic pharmacostrategies render the majority of patients with established epilepsy free of seizures, in approximately one-third of all cases seizures cannot be controlled [215]. The discussion of mechanisms and concepts of pharmacoresistance in established epilepsy is beyond the scope of this review and has well been covered previously [216–218].

A diagnosis of epilepsy is made if a patient suffers from recurrent and unprovoked epileptic seizures [211]. The classification of seizures is based on clinical and EEG features, whereas brain pathology, age, and aetiology are not considered [219]. Central to the current classification is the dichotomy of generalised and focal seizures. In generalised seizures, the origin is in both hemispheres simultaneously, while focal seizures involve only a portion of the brain at their onset, most commonly structures in the temporal or frontal lobes.

Pathophysiology

An epileptic seizure represents an acute event that may be a reaction of a normal brain to a noxious insult.

In patients with epilepsy, an underlying epileptogenic abnormality of the brain is responsible for recurrent epileptic seizures. This review concentrates on the latter situation only.

Ictogenesis is a term used to denote processes underlying the induction, propagation, and termination of seizures against the background of an interictal state in established epilepsy [220]. The interictal state may be regarded as a period of relative inactivity. The underlying epileptogenic abnormality that predisposes to spontaneous seizures at this stage is kept in check by seizure-suppressing mechanisms such as drugs.

Voltage-gated ion channels are of major importance as targets for antiictogenic drugs. Sodium and calcium channels form the basis for the transition to ictus since they regulate firing of action potentials and contribute to the paroxysmal depolarisation shift, and they also regulate neurotransmitter release that is required for synaptic transmission [4]. In this context, it is interesting to note that in an increasing number of hereditary epilepsies, ion channel mutations encoding genes are found that are associated with increased excitability [221]. Besides inherited channelopathies, in experimental models of epilepsy acquired alterations of h-channels [222], A-type potassium channels [223], and T-type calcium channels [224] have been reported. Channels regulated by the neurotransmitters GABA or glutamate mediate synaptic inhibition and excitation and thus allow neuronal synchronisation and propagation of epileptic discharges [4].

In keeping with the dichotomy of generalised and focal seizures on which the current seizure classification is based is the finding that the mechanisms and processes associated with a typical absence seizure are quite different from those seen during onset of a focal seizure [35]. At the onset of typical absence seizures, high-voltage 3/s spike-slow-wave discharges can be seen. Experimental studies in the feline penicillin model have indicated that the persisting prominent slow-wave activity suggests preservation of inhibition [225]. The slow-wave activity reflects chloride-sensitive afterhyperpolarisation, indicating intact GABAergic inhibition. Because of this and since synchronisation is central, this form of ictogenesis has been termed the 'hypersynchronous' type [226]. The generation of absence seizures is believed to result from thalamocortical interactions, and spike-slow-wave discharges in absence epilepsy are facilitated by T-type low-voltage-activated calcium channels [33].

In contrast, onset of focal seizures with or without generalisation is associated with a buildup of low-voltage widespread activity. Intracellular recordings have shown that afterhyperpolarisations disappear and are replaced by rapid action potentials in this situation. Because inhibitory processes are eroded, this variant has been termed the 'disinhibitory' type of transition to ictus [226]. The concept of various types of transition to seizure – although currently still in its infancy – may be helpful in the future design of improved antiictogenic pharmacostrategies.

In contrast to absence seizures, focal attacks usually display an evolution in time, with propagation of the epileptic activity from its origin to regions more or less distant from the focus [227, 228]. Such propagation patterns can be studied in the laboratory in various model systems. A combination of intrinsic optical imaging and electrophysiological approaches represents an excellent tool to analyse seizure spread and the way substances may interfere with ictogenesis [229].

There is some evidence that ictal termination, too, may be heterogeneous in different seizure types. It is assumed that generalised convulsions are terminated as a result of active inhibitory processes, but depolarisation block, electrogenic pumps, or changes in the extracellular ional environment may also account for massive postictal neuronal depression [230, 231]. Postictal depression is absent in the hypersynchronous type of ictus as in absence seizures. Positron emission tomography (PET) studies have shown that postictal hypometabolism seen in complex focal seizures is lacking in absence attacks [232, 233]. It would be plausible to assume that some kind of desynchronising mechanisms operate at ictal termination in absence seizures, although robust data are lacking.

Experimental animal models. Most substances that are currently administered in human established epilepsy have been tested before in model systems of elicited seizures. The systems most importantly include the acute maximal electroshock seizure (MES), the pentylenetetrazole (PTZ) seizure test, and the kindling model [234]. The latter relies on repeated application of short electrical stimuli to limbic structures, resulting in a progressive increase in electrographic and behavioural seizure activity [235]. It is important to keep in mind that naive animals are used in these models, and this may not optimally reflect the transition from the interictal to the ictal state in patients with established epilepsy. Substances also have been assessed in models following brain injuries and other initial insults. The problem with this approach is that antiepileptogenic properties are analysed but not antiictogenic features. Therefore, such results cannot simply be translated to established epilepsy, as the pathophysiological mechanisms of epileptogenesis differ from those of ictogenesis (see above). Therefore, better animal models that are more close to the clinical condition have been suggested [236]. A rat model of established partial epilepsy

following electrically induced SE seems to be promising [237]. However, there is no doubt that further animal models of intractable chronic epilepsy are urgently needed.

Antiictogenic pharmacostrategies

Almost all drugs with antiictogenic properties have been identified either by screening in animal models or by chance. A rational strategy for the development of new antiictogenic drugs has so far played only a minor role. The GABAergic substances vigabatrin and tiagabine are two examples that have been developed on the basis of assumed pathophysiological processes. Unfortunately, major side effects, such as irreversible visual field restrictions with vigabatrin [238] and pronounced proictogenic effects with tiagabine [239], heavily restrict the use of these drugs in clinical practice.

A number of currently used antiictogenic substances have multiple molecular targets, but in most cases, it is unknown which of these are the most relevant regarding suppression of seizures.

Pharmacological blockade of voltage-gated ion channels inhibits epileptic bursting, synchronisation, and seizure spread [4]. The potency to modify sodium or HVA calcium channels is shared by carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, topiramate, valproate, and zonisamide. This property of substances is important in the antiictogenic treatment of partial and generalised tonic-clonic seizures. Low-voltage-activated calcium T-type channels are involved in the generation of absence seizures and are selectively blocked by ethosuximide [36, 37]. The clinical efficacy of zonisamide in absence seizures is also explained by its T-type channel blocking property [38]. Lamotrigine does not block T-type calcium channels, and therefore the mechanism of its pronounced antiictogenic potency in absence seizures is still elusive.

Pharmacological enhancement of GABAergic synaptic inhibition reduces the probability of bursting behaviour of neurons. Substances acting at $GABA_A$ receptors are efficient in all types of seizures but – with the exception of benzodiazepines – do not suppress absence seizures [4]. The efficacy of benzodiazepines in suppressing 'hypersynchronous' ictogenesis of absence seizures may result from their ability to 'desynchronise' oscillations in thalamocortical circuits [240]. The chronic use of benzodiazepines is limited by their sedative side effects and by development of dependence and tolerance. Valproate is also highly effective against absence seizures and in addition to gabapentin, tiagabine, and vigabatrin, which also all act on enzymes and transporters and eventually increase the availability of GABA in the synaptic cleft, efficiently suppresses partial and generalised tonic-clonic seizures. The success of substances that enhance GABAergic inhibition in a broad spectrum of seizures may be explained by their counteracting effect on the 'disinhibitory' type of ictogenesis in such seizures.

Pharmacological blockade of synaptic excitation is antiictogenic by suppressing bursting and seizure spread. Substances with antagonistic effects on the NMDA receptor have been demonstrated in *in vitro* and *in vivo* model systems of epilepsy to exhibit strong antiictogenic properties (see above). Unfortunately, none of these substances plays an essential role in the treatment of patients with established epilepsy. An exception may be felbamate, which interferes with the NMDA receptor [241]. However, it is unclear whether this property contributes at all to the drug's antiictogenic effect. MK-801, in high dosage, has strong antiictogenic properties, but untolerable side effects such psychosis severely limit its use in the treatment of epilepsy. In lower dosage, limited efficacy against seizures was demonstrated [242].

Topiramate is presumably the only AMPA and kainate receptor antagonistic drug currently in clinical use [81, 82]. Again, it is unclear whether this pharmacological feature contributes to the antiictogenic properties of the drug. The selective AMPA antagonist talampanel has undergone extensive preclinical testing and early clinical studies [83]. In patients with partial refractory epilepsy, the substance has been shown to reduce the frequency of seizures significantly [243]. Future clinical studies, however, must prove that talampanel will be tolerable at therapeutic doses. At present, evidence is lacking that blockade of NMDA, AMPA or kainate receptors is of major importance in antiictogenic pharmacostrategies in clinical practice.

Summary and perspectives

Voltage-gated ion channels and the GABAergic system represent the main molecular targets in antiictogenic pharmacostrategies in human established epilepsy. The exact mechanisms of action of most clinically used substances are as yet not completely understood. The majority of substances have not been developed following a rational strategy but were found by screening in animal models or by chance. A better understanding of the pathophysiological mechanisms of ictogenesis underlying the various types of epileptic seizures may help to develop future pharmacostrategies that are tailored to individual patients.

1 Chen, J. W. and Wasterlain, C. G. (2006) Status epilepticus: pathophysiology and management in adults. Lancet Neurol. 5, 246 – 256.
2 McNamara, J. O., Huang, Y. Z. and Leonard, A. S. (2006) Molecular signaling mechanisms underlying epileptogenesis. Sci. STKE. re12.
3 Pitkanen, A. (2002) Drug-mediated neuroprotection and antiepileptogenesis: animal data. Neurology 59 Suppl. 5, S27-S33.
4 Rogawski, M. A. and Loscher, W. (2004) The neurobiology of antiepileptic drugs. Nat. Rev. Neurosci. 5, 553 – 564.
5 Pitkanen, A. and Kubova, H. (2004) Antiepileptic drugs in neuroprotection. Expert. Opin. Pharmacother. 5, 777 – 798.
6 Rogawski, M. A. and Loscher, W. (2004) The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. Nat. Med. 10, 685 – 692.
7 Kaindl, A. M., Asimiadou, S., Manthey, D., Hagen, M. V., Turski, L. and Ikonomidou, C. (2006) Antiepileptic drugs and the developing brain. Cell Mol. Life Sci. 63, 399 – 413.
8 Catterall, W. A. (2000) From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. Neuron 6, 13 – 25.
9 McLean, M. J., Schmutz, M., Wamil, A. W., Olpe, H. R., Portet, C. and Feldmann, K. F. (1994) Oxcarbazepine: mechanisms of action. Epilepsia 35 Suppl. 3, S5-S9.
10 McLean, M. J. and Macdonald, R. L. (1983) Multiple actions of phenytoin on mouse spinal cord neurons in cell culture. J. Pharmacol. Exp. Ther. 227, 779 – 789.
11 Taglialatela, M., Ongini, E., Brown, A. M., Di Renzo, G. and Annunziato, L. (1996) Felbamate inhibits cloned voltage-dependent Na+ channels from human and rat brain. Eur. J. Pharmacol. 316, 373 – 377.
12 Taverna, S., Sancini, G., Mantegazza, M., Franceschetti, S. and Avanzini, G. (1999) Inhibition of transient and persistent Na+ current fractions by the new anticonvulsant topiramate. J. Pharmacol. Exp. Ther. 288, 960 – 968.
13 Albus, H. and Williamson, R. (1998) Electrophysiologic analysis of the actions of valproate on pyramidal neurons in the rat hippocampal slice. Epilepsia 39, 124 – 139.
14 Schauf, C. L. (1987) Zonisamide enhances slow sodium inactivation in Myxicola. Brain Res. 413, 185 – 188.
15 Macdonald, R. L. and Kelly, K. M. (1995) Antiepileptic drug mechanisms of action. Epilepsia 36 Suppl. 2, S2-S12.
16 Kuo, C. C. (1998) A common anticonvulsant binding site for phenytoin, carbamazepine, and lamotrigine in neuronal Na+ channels. Mol. Pharmacol. 54, 712 – 721.
17 Backus, K. H., Pflimlin, P. and Trube, G. (1991) Action of diazepam on the voltage-dependent Na+ current. Comparison with the effects of phenytoin, carbamazepine, lidocaine and flumazenil. Brain Res. 548, 41 – 49.
18 Kendig, J. J. (1981) Barbiturates: active form and site of action at node of Ranvier sodium channels. J. Pharmacol. Exp. Ther. 218, 175 – 181.
19 Martella, G., De Persis, C., Bonsi, P., Natoli, S., Cuomo, D., Bernardi, G., Calabresi, P. and Pisani, A. (2005) Inhibition of persistent sodium current fraction and voltage-gated L-type calcium current by propofol in cortical neurons: implications for its antiepileptic activity. Epilepsia 46, 624 – 635.
20 Catterall, W. A. (2000) Structure and regulation of voltage-gated Ca2+ channels. Annu. Rev Cell Dev. Biol. 16, 521 – 555.
21 van Luijtelaar, E. L., Ates, N. and Coenen, A. M. (1995) Role of L-type calcium channel modulation in nonconvulsive epilepsy in rats. Epilepsia 36, 86 – 92.
22 Tanabe, M., Gahwiler, B. H. and Gerber, U. (1998) L-Type Ca2+ channels mediate the slow Ca2+-dependent afterhyperpolarization current in rat CA3 pyramidal cells in vitro. J. Neurophysiol. 80, 2268 – 2273.
23 Ambrosio, A. F., Silva, A. P., Malva, J. O., Soares-da-Silva, P., Carvalho, A. P. and Carvalho, C. M. (1999) Carbamazepine inhibits L-type Ca2+ channels in cultured rat hippocampal neurons stimulated with glutamate receptor agonists. Neuropharmacology 38, 1349 – 1359.
24 Elliott, E. M., Malouf, A. T. and Catterall, W. A. (1995) Role of calcium channel subtypes in calcium transients in hippocampal CA3 neurons. J. Neurosci. 15, 6433 – 6444.
25 Turner, T. J. (1998) Calcium channels coupled to glutamate release. Prog. Brain Res. 116, 3 – 14.
26 Stefani, A., Spadoni, F., Siniscalchi, A. and Bernardi, G. (1996) Lamotrigine inhibits Ca2+ currents in cortical neurons: functional implications. Eur. J. Pharmacol. 307, 113 – 116.
27 Lukyanetz, E. A., Shkryl, V. M. and Kostyuk, P. G. (2002) Selective blockade of N-type calcium channels by levetiracetam. Epilepsia 43, 9 – 18.
28 Niespodziany, I., Klitgaard, H. and Margineanu, D. G. (2001) Levetiracetam inhibits the high-voltage-activated Ca(2+) current in pyramidal neurones of rat hippocampal slices. Neurosci. Lett. 306, 5 – 8.
29 Zhang, X., Velumian, A. A., Jones, O. T. and Carlen, P. L. (2000) Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. Epilepsia 41 Suppl. 1, S52-S60.
30 Gee, N. S., Brown, J. P., Dissanayake, V. U., Offord, J., Thurlow, R. and Woodruff, G. N. (1996) The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2-delta subunit of a calcium channel. J. Biol. Chem. 271, 5768 – 5776.
31 Marais, E., Klugbauer, N. and Hofmann, F. (2001) Calcium channel alpha(2)delta subunits-structure and Gabapentin binding. Mol. Pharmacol. 59, 1243 – 1248.
32 Fink, K., Meder, W., Dooley, D. J. and Gothert, M. (2000) Inhibition of neuronal Ca(2+) influx by gabapentin and subsequent reduction of neurotransmitter release from rat neocortical slices. Br. J. Pharmacol. 130, 900 – 906.
33 McCormick, D. A. and Contreras, D. (2001) On the cellular and network bases of epileptic seizures. Annu. Rev. Physiol. 63, 815 – 846.
34 Huguenard, J. R. (1996) Low-threshold calcium currents in central nervous system neurons. Annu. Rev. Physiol. 58, 329 – 348.
35 Gloor, P. and Fariello, R. G. (1988) Generalized epilepsy: some of its cellular mechanisms differ from those of focal epilepsy. Trends Neurosci. 11, 63 – 68.
36 Coulter, D. A., Huguenard, J. R. and Prince, D. A. (1989) Characterization of ethosuximide reduction of low-threshold calcium current in thalamic neurons. Ann. Neurol 25, 582 – 593.
37 Gomora, J. C., Daud, A. N., Weiergraber, M. and Perez-Reyes, E. (2001) Block of cloned human T-type calcium channels by succinimide antiepileptic drugs. Mol. Pharmacol. 60, 1121 – 1132.
38 Kito, M., Maehara, M. and Watanabe, K. (1996) Mechanisms of T-type calcium channel blockade by zonisamide. Seizure 5, 115 – 119.
39 Lynch, B. A., Lambeng, N., Nocka, K., Kensel-Hammes, P., Bajjalieh, S. M., Matagne, A. and Fuks, B. (2004) The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc. Natl. Acad. Sci., USA 101, 9861 – 9866.
40 Cossart, R., Bernard, C. and Ben Ari, Y. (2005) Multiple facets of GABAergic neurons and synapses: multiple fates of GABA signalling in epilepsies. Trends Neurosci. 28, 108 – 115.
41 Rogers, C. J., Twyman, R. E. and Macdonald, R. L. (1994) Benzodiazepine and beta-carboline regulation of single GABAA receptor channels of mouse spinal neurones in culture. J. Physiol. 475, 69 – 82.
42 Walker, M. C. and Fisher, A. (2004) Mechanisms of antiepileptic drug action. In: The Treatment of Epilepsy, pp. 96 – 119, Shorvon, S., Perucca, E., Fish, D. and Dodson, E. (eds.), Blackwell Publishing, Oxford.
43 Bernard, C. (2005) Dogma and dreams: experimental lessons for epilepsy mechanism chasers. Cell. Mol. Life Sci. 62, 1177 – 1181.

44 Szabadics, J., Varga, C., Molnar, G., Olah, S., Barzo, P. and Tamas, G. (2006) Excitatory effect of GABAergic axo-axonic cells in cortical microcircuits. Science 311, 233 – 235.
45 Cohen, I., Navarro, V., Clemenceau, S., Baulac, M. and Miles, R. (2002) On the origin of interictal activity in human temporal lobe epilepsy in vitro. Science 298, 1418 – 1421.
46 McIntyre, D. C. and Gilby, K. L. (2006) Parahippocampal networks, intractability, and the chronic epilepsy of kindling. Adv. Neurol. 97, 77 – 83.
47 Racine, R. J., Steingart, M. and McIntyre, D. C. (1999) Development of kindling-prone and kindling-resistant rats: selective breeding and electrophysiological studies. Epilepsy Res. 35, 183 – 195.
48 Golden, G. T., Smith, G. G., Ferraro, T. N. and Reyes, P. F. (1995) Rat strain and age differences in kainic acid induced seizures. Epilepsy Res. 20, 151 – 159.
49 Meierkord, H., Grunig, F., Gutschmidt, U., Gutierrez, R., Pfeiffer, M., Draguhn, A., Bruckner, C. and Heinemann, U. (2000) Sodium bromide: effects on different patterns of epileptiform activity, extracellular pH changes and GABAergic inhibition. Naunyn Schmiedebergs Arch. Pharmacol. 361, 25 – 32.
50 Haefely, W. (1990) Benzodiazepine receptor and ligands: structural and functional differences. In: Benzodiazepines: Current Concepts, pp. 1 – 18, Hindmarch, I., Beaumont, G., Brandon, S. and Leonard, B. E. (eds.), John Wiley & Sons, Chichester, U.K.
51 Macdonald, R. L. (1983) Mechanisms of anticonvulsant drug action. In: Recent Advances in Epilepsy I, pp. 1 – 23, Pedley, T. A. and Meldrum, B. S. (eds.), Churchill Livingstone, Edinburgh.
52 Barker, J. and Owen, D. G. (1986) Electrophysiological pharmacology of GABA and diazepam in cultured CNS neurons. In: Benzodiazepine/GABA Receptors and Chloride Channels: Structural and Functional Properties, pp. 135 – 165, Olsen, R. W. and Venter, J. C. (eds.), Alan R. Liss, New York.
53 Macdonald, R. L. and Olsen, R. W. (1994) GABAA receptor channels. Annu. Rev. Neurosci. 17, 569 – 602.
54 Study, R. E. and Barker, J. L. (1981) Diazepam and (–)-pentobarbital: fluctuation analysis reveals different mechanisms for potentiation of gamma-aminobutyric acid responses in cultured central neurons. Proc. Natl. Acad. Sci. USA 78, 7180 – 7184.
55 Twyman, R. E., Rogers, C. J. and Macdonald, R. L. (1989) Differential regulation of gamma-aminobutyric acid receptor channels by diazepam and phenobarbital. Ann. Neurol. 25, 213 – 220.
56 Hara, M., Kai, Y. and Ikemoto, Y. (1993) Propofol activates GABAA receptor-chloride ionophore complex in dissociated hippocampal pyramidal neurons of the rat. Anesthesiology 79, 781 – 788.
57 Adodra, S. and Hales, T. G. (1995) Potentiation, activation and blockade of GABAA receptors of clonal murine hypothalamic GT1 – 7 neurones by propofol. Br. J. Pharmacol. 115, 953 – 960.
58 Orser, B. A., Wang, L. Y., Pennefather, P. S. and MacDonald, J. F. (1994) Propofol modulates activation and desensitization of GABAA receptors in cultured murine hippocampal neurons. J. Neurosci. 14, 7747 – 7760.
59 Hara, M., Kai, Y. and Ikemoto, Y. (1994) Enhancement by propofol of the gamma-aminobutyric acidA response in dissociated hippocampal pyramidal neurons of the rat. Anesthesiology 81, 988 – 994.
60 Rho, J. M., Donevan, S. D. and Rogawski, M. A. (1997) Barbiturate-like actions of the propanediol dicarbamates felbamate and meprobamate. J. Pharmacol. Exp. Ther. 280, 1383 – 1391.
61 White, H. S., Brown, S. D., Woodhead, J. H., Skeen, G. A. and Wolf, H. H. (1997) Topiramate enhances GABA-mediated chloride flux and GABA-evoked chloride currents in murine brain neurons and increases seizure threshold. Epilepsy Res. 28, 167 – 179.
62 Loscher, W., Honack, D. and Taylor, C. P. (1991) Gabapentin increases aminooxyacetic acid-induced GABA accumulation in several regions of rat brain. Neurosci. Lett. 128, 150 – 154.
63 Loscher, W. (1982) Anticonvulsant and biochemical effects of inhibitors of GABA aminotransferase and valproic acid during subchronic treatment in mice. Biochem. Pharmacol. 31, 837 – 842.
64 Loscher, W. and Horstermann, D. (1994) Differential effects of vigabatrin, gamma-acetylenic GABA, aminooxyacetic acid, and valproate on levels of various amino acids in rat brain regions and plasma. Naunyn Schmiedebergs Arch. Pharmacol. 349, 270 – 278.
65 Sarup, A., Larsson, O. M. and Schousboe, A. (2003) GABA transporters and GABA-transaminase as drug targets. Curr. Drug Targets CNS Neurol. Disord. 2, 269 – 277.
66 Suzdak, P. D. and Jansen, J. A. (1995) A review of the preclinical pharmacology of tiagabine: a potent and selective anticonvulsant GABA uptake inhibitor. Epilepsia 36, 612 – 626.
67 Couve, A., Moss, S. J. and Pangalos, M. N. (2000) GABAB receptors: a new paradigm in G protein signaling. Mol. Cell. Neurosci. 16, 296 – 312.
68 Mott, D. D. and Lewis, D. V. (1994) The pharmacology and function of central GABAB receptors. Int. Rev Neurobiol. 36, 97 – 223.
69 Schuler, V., Luscher, C., Blanchet, C., Klix, N., Sansig, G., Klebs, K., Schmutz, M., Heid, J., Gentry, C., Urban, L. et al. (2001) Epilepsy, hyperalgesia, impaired memory, and loss of pre- and postsynaptic GABA(B) responses in mice lacking GABA(B(1)). Neuron 31, 47 – 58.
70 von Krosigk, M., Bal, T. and McCormick, D. A. (1993) Cellular mechanisms of a synchronized oscillation in the thalamus. Science 261, 361 – 364.
71 Dingledine, R., Borges, K., Bowie, D. and Traynelis, S. F. (1999) The glutamate receptor ion channels. Pharmacol. Rev. 51, 7 – 61.
72 Bertram, E. H. and Lothman, E. W. (1990) NMDA receptor antagonists and limbic status epilepticus: a comparison with standard anticonvulsants. Epilepsy Res. 5, 177 – 184.
73 Fujikawa, D. G., Daniels, A. H. and Kim, J. S. (1994) The competitive NMDA receptor antagonist CGP 40116 protects against status epilepticus-induced neuronal damage. Epilepsy Res. 17, 207 – 219.
74 Rice, A. C. and DeLorenzo, R. J. (1998) NMDA receptor activation during status epilepticus is required for the development of epilepsy. Brain Res. 782, 240 – 247.
75 Lerner-Natoli, M., Rondouin, G., Belaidi, M., Baldy-Moulinier, M. and Kamenka, J., M. (1991) N-[1-(2-thienyl)cyclohexyl]-piperidine (TCP) does not block kainic acid-induced status epilepticus but reduces secondary hippocampal damage. Neurosci. Lett. 122, 174 – 178.
76 Fujikawa, D. G. (1995) Neuroprotective effect of ketamine administered after status epilepticus onset. Epilepsia 36, 186 – 195.
77 Wong, E. H., Kemp, J. A., Priestley, T., Knight, A. R., Woodruff, G. N. and Iversen, L. L. (1986) The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. Proc. Natl. Acad. Sci. U.SA 83, 7104 – 7108.
78 Kuo, C. C., Lin, B., J., Chang, H. R. and Hsieh, C. P. (2004) Use-dependent inhibition of the N-methyl-D-aspartate currents by felbamate: a gating modifier with selective binding to the desensitized channels. Mol. Pharmacol. 65, 370 – 380.
79 Yamakura, T., Mori, H., Masaki, H., Shimoji, K. and Mishina, M. (1993) Different sensitivities of NMDA receptor channel subtypes to non-competitive antagonists. Neuroreport 4, 687 – 690.
80 Bleakman, D. (1999) Kainate receptor pharmacology and physiology. Cell Mol. Life Sci. 56, 558 – 566.
81 Gibbs, J. W., III, Sombati, S., DeLorenzo, R. J. and Coulter, D. A. (2000) Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. Epilepsia 41 Suppl. 1, S10-S16.

82 Gryder, D. S. and Rogawski, M. A. (2003) Selective antagonism of GluR5 kainate-receptor-mediated synaptic currents by topiramate in rat basolateral amygdala neurons. J. Neurosci. 23, 7069 – 7074.

83 Bialer, M., Johannessen, S. I., Kupferberg, H. J., Levy, R. H., Perucca, E. and Tomson, T. (2007) Progress report on new antiepileptic drugs: a summary of the Eigth Eilat Conference (EILAT VIII). Epilepsy Res. 73, 1 – 52.

84 McCloskey, D. P., Croll, S. D. and Scharfman, H. E. (2005) Depression of synaptic transmission by vascular endothelial growth factor in adult rat hippocampus and evidence for increased efficacy after chronic seizures. J. Neurosci. 25, 8889 – 8897.

85 Vezzani, A. and Granata, T. (2005) Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia 46, 1724 – 1743.

86 Vezzani, A., Conti, M., De Luigi, A., Ravizza, T., Moneta, D., Marchesi, F. and De Simoni, M. G. (1999) Interleukin-1beta immunoreactivity and microglia are enhanced in the rat hippocampus by focal kainate application: functional evidence for enhancement of electrographic seizures. J. Neurosci. 19, 5054 – 5065.

87 Matoth, I., Pinto, F., Sicsic, C. and Brenner, T. (2000) Inhibitory effect of carbamazepine on inflammatory mediators produced by stimulated glial cells. Neurosci. Res. 38, 209 – 212.

88 Ichiyama, T., Okada, K., Lipton, J. M., Matsubara, T., Hayashi, T. and Furukawa, S. (2000) Sodium valproate inhibits production of TNF-alpha and IL-6 and activation of NF-kappaB. Brain Res. 857, 246 – 251.

89 Theodore, W. H., Porter, R. J., Albert, P., Kelley, K., Bromfield, E., Devinsky, O. and Sato, S. (1994) The secondarily generalized tonic-clonic seizure: a videotape analysis. Neurology 44, 1403 – 1407.

90 Meierkord, H., Boon, P., Engelsen, B., Gocke, K., Shorvon, S., Tinuper, P. and Holtkamp, M. (2006) EFNS guideline on the management of status epilepticus. Eur. J. Neurol 13, 445 – 450.

91 DeLorenzo, R. J., Garnett, L. K., Towne, A. R., Waterhouse, E. J., Boggs, J. G., Morton, L., Choudhry, M. A., Barnes, T. and Ko, D. (1999) Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. Epilepsia 40, 164 – 169.

92 Lowenstein, D. H., Bleck, T. and Macdonald, R. L. (1999) It's time to revise the definition of status epilepticus. Epilepsia 40, 120 – 122.

93 Coeytaux, A., Jallon, P., Galobardes, B. and Morabia, A. (2000) Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology 55, 693 – 697.

94 DeLorenzo, R. J., Hauser, W. A., Towne, A. R., Boggs, J. G., Pellock, J. M., Penberthy, L., Garnett, L., Fortner, C. A. and Ko, D. (1996) A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 46, 1029 – 1035.

95 Lowenstein, D. H. and Alldredge, B. K. (1998) Status epilepticus. N. Engl. J. Med. 338, 970 – 976.

96 Meierkord, H. and Holtkamp, M. (2007) Non-convulsive status epilepticus in adults: clinical forms and treatment. Lancet Neurol. 6, 329 – 339.

97 Mayer, S. A., Claassen, J., Lokin, J., Mendelsohn, F., Dennis, L. J. and Fitzsimmons, B. F. (2002) Refractory status epilepticus: frequency, risk factors, and impact on outcome. Arch. Neurol. 59, 205 – 210.

98 Holtkamp, M., Othman, J., Buchheim, K. and Meierkord, H. (2005) Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. J. Neurol. Neurosurg. Psychiatry 76, 534 – 539.

99 Rossetti, A. O., Logroscino, G. and Bromfield, E. B. (2005) Refractory status epilepticus: effect of treatment aggressiveness on prognosis. Arch. Neurol. 62, 1698 – 1702.

100 Treiman, D. M., Meyers, P. D., Walton, N. Y., Collins, J. F., Colling, C., Rowan, A. J., Handforth, A., Faught, E., Calabrese, V. P., Uthman, B. M., et al. (1998) A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N. Engl. J. Med. 339, 792 – 798.

101 Macdonald, R., L. and Kapur, J. (2006) Role of $GABA_A$ receptors in status epilepticus. In: Status Epilepticus – Mechanisms and Management, pp. 267–280, Wasterlain, C. G. and Treiman, D. M. (eds.), The MIT Press, Cambridge, MA.

102 Naylor, D. E. and Wasterlain, C. G. (2005) GABA synapses and the rapid loss of inhibition to dentate gyrus granule cells after brief perforant-path stimulation. Epilepsia 46 Suppl. 5, 142 – 147.

103 Naylor, D. E., Liu, H. and Wasterlain, C. G. (2005) Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. J. Neurosci. 25, 7724 – 7733.

104 Mazarati, A. M., Baldwin, R. A., Sankar, R. and Wasterlain, C. G. (1998) Time-dependent decrease in the effectiveness of antiepileptic drugs during the course of self-sustaining status epilepticus. Brain Res. 814, 179 – 185.

105 Kapur, J. and Macdonald, R. L. (1997) Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. J. Neurosci. 17, 7532 – 7540.

106 Kaila, K. and Voipio, J. (1987) Postsynaptic fall in intracellular pH induced by GABA-activated bicarbonate conductance. Nature 330, 163 – 165.

107 Staley, K. J., Soldo, B. L. and Proctor, W. R. (1995) Ionic mechanisms of neuronal excitation by inhibitory GABAA receptors. Science 269, 977 – 981.

108 Wasterlain, C. G., Liu, H., Mazarati, A. and Baldwin, R. (2002) NMDA receptor trafficking during the transition from single seizures to status epilepticus. Ann. Neurol. 52 Suppl. 1, 16 (abstract).

109 Ramsay, R. E., Hammond, E. J., Perchalski, R. J. and Wilder, B. J. (1979) Brain uptake of phenytoin, phenobarbital, and diazepam. Arch. Neurol. 36, 535 – 539.

110 Arendt, R. M., Greenblatt, D. J., deJong, R. H., Bonin, J. D., Abernethy, D. R., Ehrenberg, B. L., Giles, H. G., Sellers, E. M. and Shader, R. I. (1983) In vitro correlates of benzodiazepine cerebrospinal fluid uptake, pharmacodynamic action and peripheral distribution. J. Pharmacol. Exp. Ther. 227, 98 – 106.

111 Cock, H. R. and Schapira, A. H. (2002) A comparison of lorazepam and diazepam as initial therapy in convulsive status epilepticus. QJM 95, 225 – 231.

112 Shorvon, S. (1994) Status Epilepticus: Its Clinical Features and Treatment in Children and Adults, Cambridge University Press, Cambridge.

113 Turcant, A., Delhumeau, A., Premel-Cabic, A., Granry, J. C., Cottineau, C., Six, P. and Allain, P. (1985) Thiopental pharmacokinetics under conditions of long-term infusion. Anesthesiology 63, 50 – 54.

114 Wessen, A., Persson, P.M., Nilsson, A. and Hartvig, P. (1994) Clinical pharmacokinetics of propofol given as a constant-rate infusion and in combination with epidural blockade. J. Clin. Anesth. 6, 193 – 198.

115 Lowenstein, D. H. and Alldredge, B. K. (1993) Status epilepticus at an urban public hospital in the 1980s. Neurology 43, 483 – 488.

116 Alldredge, B. K., Gelb, A. M., Isaacs, S. M., Corry, M. D., Allen, F., Ulrich, S., Gottwald, M. D., O'Neil, N., Neuhaus, J. M., Segal, M. R. et al. (2001) A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N. Engl. J. Med. 345, 631 – 637.

117 Claassen, J., Hirsch, L. J., Emerson, R. G. and Mayer, S. A. (2002) Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia 43, 146 – 153.

118 Ropper, A. H. (2003) Neurological and Neurosurgical Intensive Care, Lippincott Williams & Wilkins, Boston.

119 Towne, A. R., Garnett, L. K., Waterhouse, E. J., Morton, L. D. and DeLorenzo, R. J. (2003) The use of topiramate in refractory status epilepticus. Neurology 60, 332 – 334.
120 Bensalem, M. K. and Fakhoury, T. A. (2003) Topiramate and status epilepticus: report of three cases. Epilepsy Behav. 4, 757 – 760.
121 Reuber, M., Evans, J. and Bamford, J. M. (2002) Topiramate in drug-resistant complex partial status epilepticus. Eur. J. Neurol. 9, 111 – 112.
122 Patel, N. C., Landan, I. R., Levin, J., Szaflarski, J. and Wilner, A. N. (2006) The use of levetiracetam in refractory status epilepticus. Seizure. 15, 137 – 141.
123 Rossetti, A. O. and Bromfield, E. B. (2006) Determinants of success in the use of oral levetiracetam in status epilepticus. Epilepsy Behav. 8, 651 – 654.
124 Borris, D. J., Bertram, E. H. and Kapur, J. (2000) Ketamine controls prolonged status epilepticus. Epilepsy Res. 42, 117 – 122.
125 Prasad, A., Williamson, J. M. and Bertram, E. H. (2002) Phenobarbital and MK-801, but not phenytoin, improve the long-term outcome of status epilepticus. Ann. Neurol. 51, 175 – 181.
126 Sheth, R. D. and Gidal, B. E. (1998) Refractory status epilepticus: response to ketamine. Neurology 51, 1765 – 1766.
127 Bleck, T., Quigg, M., Nathan, B. R., Smith, T. L. and Kapur, J. (2002) Electroencephalographic effects of ketamine treatment for refractory status epilepticus. Epilepsia 43 Suppl. 7, 282. 2002 (abstract).
128 Ubogu, E. E., Sagar, S. M., Lerner, A. J., Maddux, B. N., Suarez, J. I. and Werz, M. A. (2003) Ketamine for refractory status epilepticus: a case of possible ketamine-induced neurotoxicity. Epilepsy Behav. 4, 70 – 75.
129 Annegers, J. F., Hauser, W. A., Coan, S. P. and Rocca, W. A. (1998) A population-based study of seizures after traumatic brain injuries. N. Engl. J. Med. 338, 20 – 24.
130 Asikainen, I., Kaste, M. and Sarna, S. (1999) Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome. Epilepsia 40, 584 – 589.
131 Jennett, W. B. and Lewin, W. (1960) Traumatic epilepsy after closed head injuries. J. Neurol. Neurosurg. Psychiatry 23, 295 – 301.
132 Salazar, A. M., Jabbari, B., Vance, S. C., Grafman, J., Amin, D. and Dillon, J. D. (1985) Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. Neurology 35, 1406 – 1414.
133 Caveness, W. F., Meirowsky, A. M., Rish, B. L., Mohr, J. P., Kistler, J. P., Dillon, J. D. and Weiss, G. H. (1979) The nature of posttraumatic epilepsy. J. Neurosurg. 50, 545 – 553.
134 Lamy, C., Domigo, V., Semah, F., Arquizan, C., Trystram, D., Coste, J. and Mas, J. L. (2003) Early and late seizures after cryptogenic ischemic stroke in young adults. Neurology 60, 400 – 404.
135 Bladin, C. F., Alexandrov, A. V., Bellavance, A., Bornstein, N., Chambers, B., Cote, R., Lebrun, L., Pirisi, A. and Norris, J. W. (2000) Seizures after stroke: a prospective multicenter study. Arch. Neurol. 57, 1617 – 1622.
136 Burn, J., Dennis, M., Bamford, J., Sandercock, P., Wade, D. and Warlow, C. (1997) Epileptic seizures after a first stroke: the Oxfordshire Community Stroke Project. BMJ 315, 1582–1587.
137 So, E. L., Annegers, J. F., Hauser, W. A., O'Brien, P. C. and Whisnant, J. P. (1996) Population-based study of seizure disorders after cerebral infarction. Neurology 46, 350 – 355.
138 Ferro, J. M., Correia, M., Rosas, M. J., Pinto, A. N. and Neves, G. (2003) Seizures in cerebral vein and dural sinus thrombosis. Cerebrovasc. Dis. 15, 78 – 83.
139 Annegers, J. F., Hauser, W. A., Beghi, E., Nicolosi, A. and Kurland, L. T. (1988) The risk of unprovoked seizures after encephalitis and meningitis. Neurology 38, 1407 – 1410.
140 Hesdorffer, D. C., Logroscino, G., Cascino, G., Annegers, J. F. and Hauser, W. A. (1998) Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. Ann. Neurol. 44, 908 – 912.
141 Pitkanen, A. and Halonen, T. (1998) Prevention of epilepsy. Trends Pharmacol. Sci. 19, 253 – 255.
142 Pitkanen, A. and McIntosh, T. K. (2006) Animal models of post-traumatic epilepsy. J. Neurotrauma 23, 241 – 261.
143 Kharatishvili, I., Nissinen, J. P., McIntosh, T. K. and Pitkanen, A. (2006) A model of posttraumatic epilepsy induced by lateral fluid-percussion brain injury in rats. Neuroscience 140, 685 – 697.
144 Karhunen, H., Jolkkonen, J., Sivenius, J. and Pitkanen, A. (2005) Epileptogenesis after experimental focal cerebral ischemia. Neurochem. Res. 30, 1529 – 1542.
145 Ben Ari, Y. (1985) Limbic seizure and brain damage produced by kainic acid: mechanisms and relevance to human temporal lobe epilepsy. Neuroscience 14, 375 – 403.
146 Olney, J. W., de Gubareff, T. and Labruyere, J. (1983) Seizure-related brain damage induced by cholinergic agents. Nature 301, 520 – 522.
147 Turski, L., Cavalheiro, E. A., Sieklucka-Dziuba, M., Ikonomidou-Turski, C., Czuczwar, S. J. and Turski, W. A. (1986) Seizures produced by pilocarpine: neuropathological sequelae and activity of glutamate decarboxylase in the rat forebrain. Brain Res. 398, 37 – 48.
148 Nissinen, J., Halonen, T., Koivisto, E. and Pitkanen, A. (2000) A new model of chronic temporal lobe epilepsy induced by electrical stimulation of the amygdala in rat. Epilepsy Res. 38, 177 – 205.
149 Lothman, E. W., Bertram, E. H., Kapur, J. and Stringer, J. L. (1990) Recurrent spontaneous hippocampal seizures in the rat as a chronic sequela to limbic status epilepticus. Epilepsy Res. 6, 110 – 118.
150 Mazarati, A. M., Wasterlain, C. G., Sankar, R. and Shin, D. (1998) Self-sustaining status epilepticus after brief electrical stimulation of the perforant path. Brain Res. 801, 251 – 253.
151 Hellier, J. L., Patrylo, P. R., Dou, P., Nett, M., Rose, G. M. and Dudek, F. E. (1999) Assessment of inhibition and epileptiform activity in the septal dentate gyrus of freely behaving rats during the first week after kainate treatment. J. Neurosci. 19, 10053 – 10064.
152 Cavalheiro, E. A., Riche, D. A. and Le Gal, L. S. (1982) Long-term effects of intrahippocampal kainic acid injection in rats: a method for inducing spontaneous recurrent seizures. Electroencephalogr. Clin. Neurophysiol. 53, 581 – 589.
153 Cavalheiro, E. A., Leite, J. P., Bortolotto, Z. A., Turski, W. A., Ikonomidou, C. and Turski, L. (1991) Long-term effects of pilocarpine in rats: structural damage of the brain triggers kindling and spontaneous recurrent seizures. Epilepsia 32, 778 – 782.
154 Klitgaard, H., Matagne, A., Vanneste-Goemaere, J. and Margineanu, D. G. (2002) Pilocarpine-induced epileptogenesis in the rat: impact of initial duration of status epilepticus on electrophysiological and neuropathological alterations. Epilepsy Res. 51, 93 – 107.
155 Mathern, G. W., Bertram, E. H., III, Babb, T. L., Pretorius, J. K., Kuhlman, P. A., Spradlin, S. and Mendoza, D. (1997) In contrast to kindled seizures, the frequency of spontaneous epilepsy in the limbic status model correlates with greater aberrant fascia dentata excitatory and inhibitory axon sprouting, and increased staining for N-methyl-D-aspartate, AMPA and GABA(A) receptors. Neuroscience 77, 1003 – 1019.
156 Gorter, J. A., van Vliet, E. A., Aronica, E. and Lopes da Silva, F. H. (2001) Progression of spontaneous seizures after status epilepticus is associated with mossy fibre sprouting and extensive bilateral loss of hilar parvalbumin and somatostatin-immunoreactive neurons. Eur. J. Neurosci. 13, 657 – 669.
157 Holtkamp, M., Matzen, J., van Landeghem, F., Buchheim, K. and Meierkord, H. (2005) Transient loss of inhibition precedes spontaneous seizures after experimental status epilepticus. Neurobiol. Dis. 19, 162 – 170.
158 Kelly, K. M., Kharlamov, A., Hentosz, T. M., Kharlamova, E. A., Williamson, J. M., Bertram, E. H., III, Kapur, J. and

Armstrong, D. M. (2001) Photothrombotic brain infarction results in seizure activity in aging Fischer 344 and Sprague Dawley rats. Epilepsy Res. 47, 189 – 203.
159 Kharlamov, E. A., Jukkola, P. I., Schmitt, K. L. and Kelly, K. M. (2003) Electrobehavioral characteristics of epileptic rats following photothrombotic brain infarction. Epilepsy Res. 56, 185 – 203.
160 Liu, J., Schmitt, K. L., Kharlamov, E. A., Stolarski, C. J., Grayson, D. R. and Kelly, K. M. (2002) Quantitative reverse transcription-polymerase chain reaction of GABA(A) alpha1, beta1 and gamma2S subunits in epileptic rats following photothrombotic infarction of neocortex. Epilepsy Res. 52, 85 – 95.
161 Kelly, K. M. (2006) Stroke. In: Animal Models of Epilepsy, pp. 501 – 520, Pitkanen, A., Moshe, S. L. and Schwartzkroin, P. A. (eds.), Elsevier Academic Press, London.
162 Shirasaka, Y. and Wasterlain, C. G. (1994) Chronic epileptogenicity following focal status epilepticus. Brain Res. 655, 33 – 44.
163 Gorter, J. A., van Vliet, E. A., Aronica, E. and Lopes da Silva, F. H. (2002) Long-lasting increased excitability differs in dentate gyrus vs. CA1 in freely moving chronic epileptic rats after electrically induced status epilepticus. Hippocampus 12, 311 – 324.
164 Kobayashi, M. and Buckmaster, P. S. (2003) Reduced inhibition of dentate granule cells in a model of temporal lobe epilepsy. J. Neurosci. 23, 2440 – 2452.
165 Cohen, A. S., Lin, D. D., Quirk, G. L. and Coulter, D. A. (2003) Dentate granule cell GABA(A) receptors in epileptic hippocampus: enhanced synaptic efficacy and altered pharmacology. Eur. J. Neurosci. 17, 1607 – 1616.
166 Leroy, C., Poisbeau, P., Keller, A. F. and Nehlig, A. (2004) Pharmacological plasticity of GABA(A) receptors at dentate gyrus synapses in a rat model of temporal lobe epilepsy. J. Physiol 557, 473 – 487.
167 Mazarati, A. M. and Wasterlain, C. G. (1997) Blockers of NMDA receptor restore paired-pulse inhibition in the rat dentate gyrus lesioned by perforant path stimulation. Neurosci. Lett. 234, 135 – 138.
168 Heinemann, U., Beck, H., Dreier, J. P., Ficker, E., Stabel, J. and Zhang, C. L. (1992) The dentate gyrus as a regulated gate for the propagation of epileptiform activity. Epilepsy Res. Suppl. 7, 273 – 280.
169 Lothman, E. W., Stringer, J. L. and Bertram, E. H. (1992) The dentate gyrus as a control point for seizures in the hippocampus and beyond. Epilepsy Res. Suppl. 7, 301 – 313.
170 Behr, J., Gloveli, T., Gutierrez, R. and Heinemann, U. (1996) Spread of low Mg2+ induced epileptiform activity from the rat entorhinal cortex to the hippocampus after kindling studied in vitro. Neurosci. Lett. 216, 41 – 44.
171 Schwarzer, C., Tsunashima, K., Wanzenbock, C., Fuchs, K., Sieghart, W. and Sperk, G. (1997) GABA(A) receptor subunits in the rat hippocampus II: altered distribution in kainic acid-induced temporal lobe epilepsy. Neuroscience 80, 1001 – 1017.
172 Brooks-Kayal, A. R., Shumate, M. D., Jin, H., Rikhter, T. Y. and Coulter, D. A. (1998) Selective changes in single cell GABA(A) receptor subunit expression and function in temporal lobe epilepsy. Nat. Med. 4, 1166 – 1172.
173 Fritschy, J. M., Kiener, T., Bouilleret, V. and Loup, F. (1999) GABAergic neurons and GABA(A)-receptors in temporal lobe epilepsy. Neurochem. Int. 34, 435 – 445.
174 Davenport, C. J., Brown, W. J. and Babb, T. L. (1990) Sprouting of GABAergic and mossy fiber axons in dentate gyrus following intrahippocampal kainate in the rat. Exp. Neurol. 109, 180 – 190.
175 Esclapez, M. and Houser, C. R. (1999) Up-regulation of GAD65 and GAD67 in remaining hippocampal GABA neurons in a model of temporal lobe epilepsy. J. Comp. Neurol. 412, 488 – 505.
176 Cavazos, J. E., Zhang, P., Qazi, R. and Sutula, T. P. (2003) Ultrastructural features of sprouted mossy fiber synapses in kindled and kainic acid-treated rats. J. Comp. Neurol. 458, 272 – 292.
177 Wuarin, J. P. and Dudek, F. E. (1996) Electrographic seizures and new recurrent excitatory circuits in the dentate gyrus of hippocampal slices from kainate-treated epileptic rats. J. Neurosci. 16, 4438 – 4448.
178 Okazaki, M. M., Molnar, P. and Nadler, J. V. (1999) Recurrent mossy fiber pathway in rat dentate gyrus: synaptic currents evoked in presence and absence of seizure-induced growth. J. Neurophysiol. 81, 1645 – 1660.
179 Feng, L., Molnar, P. and Nadler, J. V. (2003) Short-term frequency-dependent plasticity at recurrent mossy fiber synapses of the epileptic brain. J. Neurosci. 23, 5381 – 5390.
180 Longo, B. M. and Mello, L. E. (1997) Blockade of pilocarpine- or kainate-induced mossy fiber sprouting by cycloheximide does not prevent subsequent epileptogenesis in rats. Neurosci. Lett. 226, 163 – 166.
181 Longo, B. M. and Mello, L. E. (1998) Supragranular mossy fiber sprouting is not necessary for spontaneous seizures in the intrahippocampal kainate model of epilepsy in the rat. Epilepsy Res. 32, 172 – 182.
182 Labiner, D. M., Butler, L. S., Cao, Z., Hosford, D. A., Shin, C. and McNamara, J. O. (1993) Induction of c-fos mRNA by kindled seizures: complex relationship with neuronal burst firing. J. Neurosci. 13, 744 – 751.
183 Watanabe, Y., Johnson, R. S., Butler, L. S., Binder, D. K., Spiegelman, B. M., Papaioannou, V. E. and McNamara, J. O. (1996) Null mutation of c-fos impairs structural and functional plasticities in the kindling model of epilepsy. J. Neurosci. 16, 3827 – 3836.
184 Sutula, T., Koch, J., Golarai, G., Watanabe, Y. and McNamara, J. O. (1996) NMDA receptor dependence of kindling and mossy fiber sprouting: evidence that the NMDA receptor regulates patterning of hippocampal circuits in the adult brain. J. Neurosci. 16, 7398 – 7406.
185 Bonislawski, D. P., Schwarzbach, E. P. and Cohen, A. S. (2007) Brain injury impairs dentate gyrus inhibitory efficacy. Neurobiol. Dis. 25, 163 – 169.
186 Slapo, G. D., Lossius, M. I. and Gjerstad, L. (2006) Poststroke epilepsy: occurrence, predictors and treatment. Expert. Rev Neurother. 6, 1801 – 1809.
187 Camilo, O. and Goldstein, L. B. (2004) Seizures and epilepsy after ischemic stroke. Stroke 35, 1769 – 1775.
188 Pitkanen, A., Kharatishvili, I., Narkilahti, S., Lukasiuk, K. and Nissinen, J. (2005) Administration of diazepam during status epilepticus reduces development and severity of epilepsy in rat. Epilepsy Res. 63, 27 – 42.
189 Suchomelova, L., Baldwin, R. A., Kubova, H., Thompson, K. W., Sankar, R. and Wasterlain, C. G. (2006) Treatment of experimental status epilepticus in immature rats: dissociation between anticonvulsant and antiepileptogenic effects. Pediatr. Res. 59, 237 – 243.
190 Francois, J., Koning, E., Ferrandon, A. and Nehlig, A. (2006) The combination of topiramate and diazepam is partially neuroprotective in the hippocampus but not antiepileptogenic in the lithium-pilocarpine model of temporal lobe epilepsy. Epilepsy Res. 72, 147 – 163.
191 Andre, V., Rigoulot, M. A., Koning, E., Ferrandon, A. and Nehlig, A. (2003) Long-term pregabalin treatment protects basal cortices and delays the occurrence of spontaneous seizures in the lithium-pilocarpine model in the rat. Epilepsia 44, 893 – 903.
192 Brandt, C., Potschka, H., Loscher, W. and Ebert, U. (2003) N-methyl-D-aspartate receptor blockade after status epilepticus protects against limbic brain damage but not against epilepsy in the kainate model of temporal lobe epilepsy. Neuroscience 118, 727 – 740.
193 Bolanos, A. R., Sarkisian, M., Yang, Y., Hori, A., Helmers, S. L., Mikati, M., Tandon, P., Stafstrom, C. E. and Holmes, G. L. (1998) Comparison of valproate and phenobarbital treatment after status epilepticus in rats. Neurology 51, 41 – 48.

194 Brandt, C., Gastens, A. M., Sun, M., Hausknecht, M. and Loscher, W. (2006) Treatment with valproate after status epilepticus: effect on neuronal damage, epileptogenesis, and behavioral alterations in rats. Neuropharmacology 51, 789 – 804.
195 Capella, H. M. and Lemos, T. (2002) Effect on epileptogenesis of carbamazepine treatment during the silent period of the pilocarpine model of epilepsy. Epilepsia 43 Suppl. 5, 110 – 111.
196 Halonen, T., Nissinen, J. and Pitkanen, A. (2001) Effect of lamotrigine treatment on status epilepticus-induced neuronal damage and memory impairment in rat. Epilepsy Res. 46, 205 – 223.
197 Halonen, T., Nissinen, J. and Pitkanen, A. (2001) Chronic elevation of brain GABA levels beginning two days after status epilepticus does not prevent epileptogenesis in rats. Neuropharmacology 40, 536 – 550.
198 Andre, V., Ferrandon, A., Marescaux, C. and Nehlig, A. (2001) Vigabatrin protects against hippocampal damage but is not antiepileptogenic in the lithium-pilocarpine model of temporal lobe epilepsy. Epilepsy Res. 47, 99 – 117.
199 Hort, J., Brozek, G., Mares, P., Langmeier, M. and Komarek, V. (1999) Cognitive functions after pilocarpine-induced status epilepticus: changes during silent period precede appearance of spontaneous recurrent seizures. Epilepsia 40, 1177 – 1183.
200 Klitgaard, H., Matagne, A., Vanneste-Goemaere, J. and Margineanu, D. G. (2001) Effects of prolonged administration of levetiracetam on pilocarpine-induced epileptogenesis in rat. Epilepsia 42 Suppl. 7, 114 – 115 (abstract).
201 Temkin, N. R. (2001) Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. Epilepsia 42, 515 – 524.
202 Mamelle, N., Mamelle, J. C., Plasse, J. C., Revol, M. and Gilly, R. (1984) Prevention of recurrent febrile convulsions – a randomized therapeutic assay: sodium valproate, phenobarbital and placebo. Neuropediatrics 15, 37 – 42.
203 Camfield, P. R., Camfield, C. S., Shapiro, S. H. and Cummings, C. (1980) The first febrile seizure – antipyretic instruction plus either phenobarbital or placebo to prevent recurrence. J. Pediatr. 97, 16 – 21.
204 Thilothammal, N., Kannan, Krishnamurthy, P. V., Kamala, K. G., Ahamed, S. and Banu, K. (1993) Role of phenobarbitone in preventing recurrence of febrile convulsions. Indian Pediatr. 30, 637 – 642.
205 Wolf, S. M., Carr, A., Davis, D. C., Davidson, S., Dale, E. P., Forsythe, A., Goldenberg, E. D., Hanson, R., Lulejian, G. A., Nelson, M. A., et al. (1977) The value of phenobarbital in the child who has had a single febrile seizure: a controlled prospective study. Pediatrics 59, 378 – 385.
206 White, N. J. (1998) Not much progress in treatment of cerebral malaria. Lancet 352, 594 – 595.
207 D'Onofrio, G., Rathlev, N. K., Ulrich, A. S., Fish, S. S. and Freedland, E. S. (1999) Lorazepam for the prevention of recurrent seizures related to alcohol. N. Engl. J. Med. 340, 915 – 919.
208 Lee, S., T., Lui, T., N., Chang, C. N., Cheng, W. C., Wang, D. J., Heimburger, R. F. and Lin, C. G. (1989) Prophylactic anticonvulsants for prevention of immediate and early postcraniotomy seizures. Surg. Neurol. 31, 361 – 364.
209 North, J. B., Penhall, R. K., Hanieh, A., Frewin, D. B. and Taylor, W. B. (1983) Phenytoin and postoperative epilepsy. A double-blind study., J. Neurosurg. 58, 672 – 677.
210 Temkin, N. R., Dikmen, S. S., Wilensky, A. J., Keihm, J., Chabal, S. and Winn, H. R. (1990) A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N. Engl. J. Med. 323, 497 – 502.
211 Dodson, W. E. (2004) Definitions and classification of epilepsy. In: The Treatment of Epilepsy, pp. 3 – 20, Shorvon, S., Perucca, E., Fish, D. and Dodson, E. (eds.), Blackwell Publishing, Oxford.
212 Jennett, W. B. (1962) Epilepsy after Blunt Head Injuries, William Heinemann Medical Books, London.
213 Schierhout, G. and Roberts, I. (2001) Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane Database Syst. Rev. CD000173.
214 Sander, J. W. (2003) The epidemiology of epilepsy revisited. Curr. Opin. Neurol. 16, 165 – 170.
215 Kwan, P. and Brodie, M. J. (2000) Early identification of refractory epilepsy., N. Engl., J. Med. 342, 314 – 319.
216 Remy, S. and Beck, H. (2006) Molecular and cellular mechanisms of pharmacoresistance in epilepsy. Brain 129, 18 – 35.
217 Sisodiya, S. M. (2003) Mechanisms of antiepileptic drug resistance. Curr. Opin. Neurol. 16, 197 – 201.
218 Loscher, W., Poulter, M. O. and Padjen, A. L. (2006) Major targets and mechanisms of antiepileptic drugs and major reasons for failure. Adv. Neurol. 97, 417 – 427.
219 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.
220 Doman, G. and Pelligra, R. (2003) Ictogenesis: the origin of seizures in humans. A new look at an old theory. Med. Hypotheses 60, 129 – 132.
221 Lerche, H., Jurkat-Rott, K. and Lehmann-Horn, F. (2001) Ion channels and epilepsy. Am. J. Med. Genet. 106, 146 – 159.
222 Chen, K., Aradi, I., Thon, N., Eghbal-Ahmadi, M., Baram, T. Z. and Soltesz, I. (2001) Persistently modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyperexcitability. Nat. Med. 7, 331 – 337.
223 Bernard, C., Anderson, A., Becker, A., Poolos, N. P., Beck, H. and Johnston, D. (2004) Acquired dendritic channelopathy in temporal lobe epilepsy. Science 305, 532 – 535.
224 Su, H., Sochivko, D., Becker, A., Chen, J., Jiang, Y., Yaari, Y. and Beck, H. (2002) Upregulation of a T-type Ca2+ channel causes a long-lasting modification of neuronal firing mode after status epilepticus. J. Neurosci. 22, 3645 – 3655.
225 Giaretta, D., Avoli, M. and Gloor, P. (1987) Intracellular recordings in pericruciate neurons during spike and wave discharges of feline generalized penicillin epilepsy. Brain Res. 405, 68 – 79.
226 Engel, J., Jr., Dichter, M. and Schwartzkroin, P. A. (1997) Basic mechanisms of human epilepsy. In: Epilepsy: A Comprehensive Textbook, pp. 499 – 512, Engel, J., Jr. and Pedley, T.,A. (eds.), Lippincott-Raven, Philadelphia.
227 Holtkamp, M., Buchheim, K., Siegmund, H. and Meierkord, H. (2003) Optical imaging reveals reduced seizure spread and propagation velocities in aged rat brain in vitro. Neurobiol. Aging 24, 345 – 353.
228 Buchheim, K., Schuchmann, S., Siegmund, H., Weissinger, F., Heinemann, U. and Meierkord, H. (2000) Comparison of intrinsic optical signals associated with low Mg2+-and 4-aminopyridine-induced seizure-like events reveals characteristic features in adult rat limbic system. Epilepsia 41, 635 – 641.
229 Salek-Haddadi, A., Merlet, I., Mauguière, F., Meierkord, H., Buchheim, K., Fish, D., Koepp, M. J. and So, E. L. (2004) New physiological and radiological interventions in the presurgical evaluation of epilepsy. In: The Treatment of Epilepsy, pp. 665 – 698, Shorvon, S., Perucca, E., Fish, D. and Dodson, E. (eds.), Blackwell Publishing, Oxford.
230 During, M. J. and Spencer, D. D. (1992) Adenosine: a potential mediator of seizure arrest and postictal refractoriness. Ann. Neurol. 32, 618 – 624.
231 Kostopoulos, G., Drapeau, C., Avoli, M., Olivier, A. and Villemeure, J. G. (1989) Endogenous adenosine can reduce epileptiform activity in the human epileptogenic cortex maintained in vitro. Neurosci. Lett. 106, 119 – 124.
232 Engel, J., Jr., Kuhl, D. E., Phelps, M. E., Rausch, R. and Nuwer, M. (1983) Local cerebral metabolism during partial seizures. Neurology 33, 400 – 413.
233 Engel, J., Jr., Lubens, P., Kuhl, D. E. and Phelps, M. E. (1985) Local cerebral metabolic rate for glucose during petit mal absences. Ann. Neurol. 17, 121 – 128.

234 Loscher, W. (2002) Animal models of epilepsy for the development of antiepileptogenic and disease-modifying drugs. A comparison of the pharmacology of kindling and post-status epilepticus models of temporal lobe epilepsy. Epilepsy Res. 50, 105 – 123.
235 Sato, M., Racine, R. J. and McIntyre, D. C. (1990) Kindling: basic mechanisms and clinical validity. Electroencephalogr. Clin. Neurophysiol. 76, 459 – 472.
236 Stables, J. P., Bertram, E., Dudek, F. E., Holmes, G., Mathern, G., Pitkanen, A. and White, H. S. (2003) Therapy discovery for pharmacoresistant epilepsy and for disease-modifying therapeutics: summary of the NIH/NINDS/AES models II workshop. Epilepsia 44, 1472 – 1478.
237 Nissinen, J. and Pitkanen, A. (2007) Effect of antiepileptic drugs on spontaneous seizures in epileptic rats. Epilepsy Res. 73, 181 – 191.
238 McDonagh, J., Stephen, L. J., Dolan, F. M., Parks, S., Dutton, G. N., Kelly, K., Keating, D., Sills, G. J. and Brodie, M. J. (2003) Peripheral retinal dysfunction in patients taking vigabatrin. Neurology 61, 1690 – 1694.
239 Koepp, M. J., Edwards, M., Collins, J., Farrel, F. and Smith, S. (2005) Status epilepticus and tiagabine therapy revisited. Epilepsia 46, 1625 – 1632.
240 Sohal, V. S., Keist, R., Rudolph, U. and Huguenard, J. R. (2003) Dynamic GABA(A) receptor subtype-specific modulation of the synchrony and duration of thalamic oscillations. J. Neurosci. 23, 3649 – 3657.
241 Subramaniam, S., Rho, J. M., Penix, L., Donevan, S. D., Fielding, R. P. and Rogawski, M., A. (1995) Felbamate block of the N-methyl-D-aspartate receptor. J. Pharmacol. Exp. Ther. 273, 878 – 886.
242 Troupin, A. S., Mendius, J. R., Cheng, F. and Risinger, M. W. (1986) MK-801. In: New Anticonvulsant Drugs, pp. 191 – 201, Meldrum, B., S. and Porter, R., J. (eds.), John Libbey, London.
243 Chappell, A. S., Sander, J. W., Brodie, M. J., Chadwick, D., Lledo, A., Zhang, D., Bjerke, J., Kiesler, G. M. and Arroyo, S. (2002) A crossover, add-on trial of talampanel in patients with refractory partial seizures. Neurology 58, 1680 – 1682.