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INVITED REVIEW

Disease modification in partial epilepsy

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Summary

With the growth in antiepileptic drug treatment, the question arises as to what extent we are merely treating the symptom (i.e. the seizures) rather than the underlying disease process (i.e. epileptogenesis). Epileptogenicity can be considered as the process whereby structural and functional changes occur following an insult that in some cases result in epilepsy. Epileptogenicity also describes some of the changes and processes that contribute to the progression observed in some epilepsies. These processes have been modelled in animals mostly by the kindling model of epilepsy, in which repetition of subconvulsive stimuli results in a progressive epileptic state and eventually leads to spontaneous seizures. However, it is not clear that kindling has a human correlate, so models in which an initial insult (status epilepticus, hyperthermia, hypoxia, trauma) is followed by the development of lowered seizure threshold and, in some instances, spontaneous seizures have been used. These models seem to support the 'second hit' hypothesis, in which there is an initial insult resulting in lowered seizure threshold, and then a later insult, the 'second hit', that results in the expression of epilepsy. These models also support the concept of a latent period during which there could be targeted therapies to prevent the epileptogenic process. Although the occurrence of neuronal damage is one such target, neuronal damage is not necessary for epileptogenesis, and other mechanisms are at play. At the present time, it is not known whether targeted therapies may also affect compensatory processes, such as brain repair. Clearly, this would be a potential risk of such strategies. Epidemiological evidence and trials indicate that our present antiepileptic drugs are not effective in preventing epileptogenesis; antiepileptic drugs were, however, not designed for this purpose. Data from animal experiments suggest that treatment of non-convulsive status epilepticus following specific insults may prevent epileptogenesis. The relevance of this for the human condition remains uncertain, but non-convulsive status epilepticus is probably an under-recognized and probably under-treated condition. Perhaps one of the most salutary findings has been the observation of decreased childhood epilepsy with improved neonatal care. This highlights the importance of medical care at the time of an insult, and of prevention of the insults. This review discusses the data that support the concepts underlying epileptogenesis and the model systems that are presumed to reflect the human condition. Particular attention is paid to the potential for interrupting the processes underlying epileptogenesis.

Keywords: epileptogenicity; epilepsy; kindling; status epilepticus; antiepileptic drugs

Abbreviations: AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF = brain-derived growth factor; GABA = γ-aminobutyric acid; NMDA = *N*-methyl-D-aspartic acid

Introduction

In recent years, there has been a burgeoning of drug treatment for epilepsy. The drugs have, however, been selected and are used for the suppression of seizures. As such, they specifically prevent the symptom (seizures) rather than address the underlying cause (the disease process). With the exception of epilepsy surgery to remove the 'focus', none of the past

century's innovations have achieved the ultimate goal—a cure. Epilepsy has numerous underlying aetiologies, and it is unlikely that there is a unique and universal process underlying the development of epilepsy. In the idiopathic generalized epilepsies, there is a strong genetic component (Johnson and Sander, 2001), but even in those epilepsies in which a causative gene has been identified penetrance and phenotype are variable, suggesting substantial influence of other modifying factors, such as environment and genetic background (Johnson and Sander, 2001). In acquired partial epilepsies, there may also be a genetic contribution, but this is less well defined (Ottman *et al*., 1996). In partial epilepsy, most evidence points towards a paradigm of epileptogenesis in which seizures are the clinical expression of an underlying disease process. This is initiated by an event that triggers critical modulators that, over months and years, produce structural and functional changes. Such changes may eventually be expressed clinically as recurrent, unprovoked seizures in susceptible individuals, particularly if the individual is subjected to another neurological insult—a 'second hit'—that triggers the clinical expression of epilepsy. Seizures, in turn, can act on this epileptogenic substrate, causing additional structural and functional changes. One question that has arisen is whether it may be possible to modify this disease process to prevent epileptogenesis and the evolution of epilepsy. In order to answer this question, we will address what occurs between an insult and the expression of epilepsy (latent period), and to what extent seizures themselves modify the epileptogenic process. Lastly, we will review the antiepileptogenic potential of our current medications.

The latent period

It is well recognized that there is often a delay (on occasions >20 years) from a specific insult to the occurrence of seizures. This is most evident following febrile seizures, status epilepticus, hypoxic–ischaemic injury or head injury. Thus temporal lobe epilepsy developed an average of 7.5 years after the initial insult, 16% of patients having a latent period of >10 years (French *et al*., 1993). Similarly, the risk of developing epilepsy remains above that of the general population for >10 years after a serious head injury (Annegers *et al*., 1998). This suggests that either there is a prolonged epileptogenic period or that a 'second hit' is required for the manifestation of epilepsy. That the epileptogenic period can be long has been demonstrated in animal models (see below). However, evidence of an epileptogenic period in humans is indirect. Following an insult, immediate seizures within the first week carry a better prognosis than late seizures (Hart *et al*., 1990). Indeed, in the most comprehensive study of non-penetrating head injuries there was no significant increase in risk when other factors were taken into account (i.e. in the multivariate analysis); however, there was an increased risk of seizures following immediate seizures in the univariate analysis (Annegers *et al*., 1998). This suggests that the transient 'hyperexcitability' expressed soon after an insult is indicative of the nature of the insult itself, whilst the 'hyperexcitability' expressed late after an insult is indicative of more permanent changes in the brain.

That a second hit may be involved is supported by the very long delay that can occur between an insult and seizures. The necessity of a second hit could also explain why, following most of these initial insults, not all patients proceed to develop epilepsy. Although approximately 30% of affected children have recurrent febrile convulsions, only 7% with febrile convulsions go on to develop unprovoked seizures by the age of 25 years (Annegers *et al*., 1987). For single febrile convulsions lasting 10–29 min and in the absence of focal features, the risk is 3%, and even with very prolonged (⩾30 min) febrile convulsions with no focal features, the risk is 7% (Annegers *et al*., 1987). Similarly, following a serious non-missile, traumatic head injury only 20% develop epilepsy over the following 30 years, and if the head injury is moderate this figure falls to 4% (Annegers *et al*., 1998). There is, however, evidence for a further explanation of this phenomenon. Almost 80% of patients with mesial temporal lobe epilepsy have a prior history of febrile convulsions (French *et al*., 1993), and hippocampal sclerosis has been demonstrated to occur following prolonged febrile convulsions (VanLandingham *et al*., 1998). Thus, febrile seizures are considered to be causative. That other factors are at play is suggested by an increased risk of developing epilepsy for those with febrile seizures, particularly if there is a family history of epilepsy (Nelson and Ellenberg, 1990). Furthermore, developmental abnormalities have been noted in up to 15% of patients with hippocampal sclerosis (Raymond *et al*., 1994); this raises the possibility that febrile seizures and hippocampal sclerosis are not causal, but rather share an aetiology. This may explain why effective prevention of recurrent febrile convulsions with antiepileptic drugs does not decrease the risk of subsequent epilepsy (Berg and Shinnar, 1997). There are also familial forms of temporal lobe epilepsy (Berkovic *et al*., 1996) and familial abnormalities of the hippocampus that are associated with hippocampal sclerosis and temporal lobe epilepsy (Raymond *et al*., 1994; Sisodiya *et al*., 1999).

The human evidence indicates that not only is there an epileptogenic, latent period following an insult, but that other genetic and environmental factors modify (in some instances considerably) the risk of developing epilepsy. Is there experimental evidence of this epileptogenic process? A number of animal models have been used to address this question, and we will concentrate on five of these models: kindling, post-status epilepticus, hyperthermic seizures, neonatal hypoxia–ischaemia and traumatic brain injury.

Kindling

Kindling is the repetition of stimuli that initially evoke afterdischarges but not seizures (Goddard, 1967; McNamara *et al*., 1993). The stimuli usually consist of electrical stimulation of a specific brain structure, but local drug

application has also been used. Repetition of the same stimuli results in a gradual lengthening of the afterdischarges, eventually leading to progressively more severe seizures and finally convulsions. Once an animal has been kindled, the heightened response to the stimulus seems to be permanent and spontaneous seizures occur (McNamara *et al*., 1993). This experimental paradigm has been crucial to our understanding of the epileptogenic process. A high degree of reproducibility has facilitated careful characterization of the effects of drugs on this epileptogenic process, but to what degree does kindling reproduce human epileptogenesis? The origin of kindling was as an observation in rats rather than a model of human epileptogenesis, and since its first description researchers have been searching for a human correlate (Majkowski, 1999). It is not even certain whether such a process can occur in humans, as it takes much longer and is more arduous to induce kindling in primates than in rodents (Wada *et al*., 1978). There has been no direct evidence of kindling in humans, apart from two case reports of seizures occurring in the setting of thalamic stimulation for treatment of chronic pain—a rare occurrence (Majkowski, 1999). Furthermore, even in rodents, there is great variation in the ease with which specific structures can be kindled (McNamara *et al*., 1993). Thus, even if kindling were to occur in humans, it is unlikely to be a ubiquitous explanation of epileptogenesis in partial epilepsy. Kindling in humans has been used to explain a mirror focus in which one epileptic focus results in the appearance of a second focus (Morrell and de Toledo-Morrell, 1999). Kindling alone is unable to explain the occurrence of hippocampal sclerosis in association with other pathology, because kindling itself usually results in no or minimal hippocampal damage and sclerosis (Tuunanen and Pitkanen, 2000). Rather it is the generalized seizures that occur following kindling that may result in neuronal damage (Cavazos *et al*., 1994). Dual pathology is more likely to be due either to an association between extrahippocampal pathologies and pathology within the hippocampus (e.g. in cases of cortical dysplasia) or to hippocampal sclerosis as the result of febrile convulsions, head injuries, hypoxia or status epilepticus secondary to the extrahippocampal pathology (Cendes *et al*., 1995*a*). Even if the kindling model were to hold true in humans, most evidence indicates that the emergence of mirror foci in association with isolated pathologies, such as extratemporal tumours, is uncommon (Cendes *et al*., 1995*a*). A second process that has been argued to occur via a kindling process is the emergence of epilepsy in alcoholics (this has been proposed to be a form of chemical kindling) (Kokka *et al*., 1993). Thus, repetitive episodes of alcohol withdrawal (the 'insult') eventually lead to an epileptic state that persists despite abstinence. This is a familiar clinical situation, but this hypothesis is not supported by epidemiological data as there is no association between the occurrence of epilepsy and the frequency or number of alcohol withdrawals or the length of withdrawals (Wojnar *et al*., 1999). As such, kindling is a model of epileptogenesis in laboratory animals that possibly has no direct human correlate. Because the emergence of epilepsy can arise through many different processes, it is not surprising that the efficacy of drugs that prevent kindling does not necessarily correlate with their ability to influence epileptogenic processes following specific insults in humans (see below).

Rather than seeking a model of epileptogenesis, an alternative approach has been to develop models of specific insults and then to investigate the development of seizures following the insult.

Post-status epilepticus

Seizures are usually self-terminating and brief. Occasionally seizures can persist unabated, or repeated seizures can occur without recovery; this situation is termed status epilepticus. While status epilepticus may occur in individuals with pre-existing epilepsy, more than half of the patients who present with status epilepticus have no history of seizures (DeLorenzo *et al*., 1996). In these patients, the status epilepticus is often acutely precipitated by CNS infection, ischaemia, hypoxia or alcohol. The probability of developing epilepsy (unprecipitated seizures) is 41% within 2 years following acutely precipitated status epilepticus compared with 13% for those with acute symptomatic seizures but no status epilepticus (Hesdorffer *et al*., 1998). This suggests a relationship between the prolonged seizures of status epilepticus and subsequent epileptogenesis, although a relationship between the length of seizure and the nature and severity of the precipitant cannot be discounted. Animal models of acutely precipitated status epilepticus support these clinical findings. Status epilepticus can be induced in animal models using either electrical stimulation or chemoconvulsants. Importantly, it has been possible to induce non-convulsive status epilepticus in animals, thus avoiding confounding factors, such as hypoxia, hyperthermia and acidosis, that occur during convulsive status epilepticus. The animal models that have received greatest attention have been those that have used systemic or local administration of kainic acid (a potent glutamate receptor agonist and inhibitor of glutamate uptake) (Ben-Ari, 1985), systemic administration of pilocarpine (a muscarinic receptor agonist) (Turski *et al*., 1989) or protocols using electrical stimulation of specific brain areas (invariably within the limbic system) (Lothman *et al*., 1990). Following the acute episode of status epilepticus, many of the animals develop spontaneous seizures (epilepsy) after a latent period lasting days to weeks (Ben-Ari, 1985; Turski *et al*., 1989; Lothman *et al*., 1990). Despite significant progress, the mechanisms underlying the epileptogenic process in humans and animal models remain undefined. Much attention has centred on status epilepticus-induced neuronal damage. Post-mortem studies of individuals who died during status epilepticus have revealed patterns of neuronal injury—neuronal necrosis in CA1, CA3 and the subiculum of the hippocampus—that resemble those of mesial temporal sclerosis, the hallmark lesion of temporal lobe epilepsy (DeGiorgio *et al*., 1992). Furthermore, levels of

neurone-specific enolase, a marker of neuronal injury, were found to be elevated immediately after status epilepticus (DeGiorgio *et al*., 1995), and there have been case reports describing the development of hippocampal atrophy and sclerosis in patients followed with neuroimaging after status epilepticus (Cendes *et al*., 1995*b*; Meierkord *et al*., 1997; Wieshmann *et al*., 1997). The interpretation of the human data is confounded by other factors, such as aetiology, physiological compromise and treatment. Thus, experimenters have turned to animal models to determine the role of status epilepticus in the development of neuronal damage, the mechanisms underlying this damage and the role of the neuronal damage *per se* in the development of epilepsy. Critical animal experiments were carried out by Meldrum and co-workers in the 1970s in adolescent baboons using systemically administered bicuculline (Meldrum *et al*., 1973; Meldrum and Brierley, 1973; Meldrum and Horton, 1973). Bicuculline is a potent GABA(A) receptor antagonist and produces convulsive seizures through inhibition of inhibitory neurotransmission. These initial experiments demonstrated a correlation between neuronal damage and duration of the status epilepticus, duration of the hyperpyrexia, severe hypotension and profound hypoglycaemia. Later experiments showed that paralysed and artificially ventilated baboons, in which the hypotension, acidosis, hypoxia and hypoglycaemia were prevented, still sustained significant neuronal damage. Similarly, flurothyl (a volatile convulsant agent that produces seizures by diffusely opening neuronal sodium channels) induces generalized seizures in ventilated rats, producing widespread lesions in the pars reticulata of the substantia nigra, neocortex (layers 3 and 4), amygdala and thalamus as well as CA4 and CA1 hippocampal pyramidal cells (Nevander *et al*., 1985).

Both of these models involved the induction of generalized status epilepticus, but similar damage has been seen in models involving limbic status epilepticus, a model of partial status epilepticus. Early work producing limbic status epilepticus-induced neuronal damage was accomplished with models using kainic acid that produced seizures when either given systemically or injected into the brain (Collins *et al*., 1983). Kainic acid is a powerful excitant and excitotoxin, which when injected directly into the brain produces not only a local lesion but also a seizure-linked pattern of disseminated lesions in brain regions far from the injection site (Olney *et al*., 1974). The administration of anticonvulsants blocks seizure activity as well as the distant neuronal damage, but has no effect on the local lesion (Ben-Ari *et al*., 1979). Similar results were obtained in status epilepticus following systemic administration of the muscarinic agonist pilocarpine (Turski *et al*., 1984). Furthermore, prolonged repetitive stimulation of the perforant path (i.e. the pathway from the entorhinal cortex to the dentate gyrus) in anaesthetized animals resulted in comparable neuronal damage (Sloviter, 1987). From these experiments certain conclusions can be drawn: (i) both generalized and limbic status epilepticus result in neuronal damage; (ii) even without the systemic disturbance associated with status epilepticus, neuronal damage still occurs (although it is less severe); and (iii) neuronal damage is not necessarily due to the administration of the convulsant *per se*, but to the resultant seizure activity.

Since this neuronal damage is easily and rapidly quantifiable, considerable effort has been made to determine the effects of interventions on this damage. Thus, *N*-methyl-D-aspartic acid (NMDA) receptor antagonists given before or shortly after status epilepticus are neuroprotectant (Lason *et al*., 1988; Fariello *et al*., 1989; Clifford *et al*., 1990; Lerner-Natoli *et al*., 1991), and certain antiepileptic drugs have neuroprotective effects if given prior to the induction of status epilepticus (Pitkanen *et al*., 1996). Since these interventions are pre-emptive, they have little clinical applicability, but they do raise a separate issue. How does status-induced neuronal damage relate to epileptogenesis? That there may be a distinction between neuronal damage and epileptogenesis is indicated by kindling, in which epileptogenesis occurs in the setting of little or no neuronal damage. Indeed, kindling may protect against kainate-induced neuronal damage (Kelly and McIntyre, 1994), raising the intriguing possibility that epilepsy itself is neuroprotective. Conversely, damaging the hippocampus through severe hypoxic injury can inhibit epileptogenesis (Milward *et al*., 1999). Furthermore, there have been instances in which a drug that confers neuroprotection during status epilepticus does not prevent epileptogenesis (Andre *et al*., 2001); it could be argued, however, that this is due to incomplete neuroprotection. So if neuronal damage *per se* may not be critical for epileptogenesis following status epilepticus, what are the critical changes and what is the relevance of the neuronal damage? The neuronal damage possibly relates more closely to other pathologies post-status epilepticus, such as memory and behavioural problems (Stafstrom *et al*., 1993). The main epileptogenic changes following status epilepticus have yet to be clearly defined. Changes have been reported in intrinsic properties of neurones (Sanabria *et al*., 2001), the rate of neurogenesis (Parent *et al*., 1997), receptor function (Brooks-Kayal *et al*., 1998), inhibitory interneurones (Cossart *et al*., 2001), synaptic arrangements (Okazaki *et al*., 1995) and the extracellular space. All of these could be epileptogenic; however, it has been difficult to identify one critical or necessary process. It would be appealing to direct therapy at preventing these changes; however, these processes may also have a compensatory role. Indeed, the successful prevention of epileptogenesis could incur a cost such as greater memory or behavioural sequelae following an insult.

Hyperthermic seizures

Although 80% of patients with hippocampal sclerosis have a history of febrile convulsions (French *et al*., 1993), febrile convulsions rarely lead to epilepsy (Annegers *et al*., 1987; Verity and Golding, 1991). Hyperthermic seizure can be induced in rats by blasts of hot air or water. The similarities

between the animal model and the human condition are that seizures occur in response to high body temperature and that increasing age confers resistance to these seizures (Baram *et al*., 1997; Walker and Kullmann, 1999). Although fever in humans is associated with other physiological changes, reducing the body temperature is an effective way of reducing the likelihood of seizures and thus the hyperpyrexia is probably the main trigger. There are, however, major differences between hyperthermic seizures in rats and febrile convulsions in humans. Hyperthermia apparently results in seizures in the vast majority of young Sprague–Dawley rats (Baram *et al*., 1997) but febrile convulsions are relatively rare in children. In humans there may be predisposing factors, such as hippocampal malformations and heredity, and indeed genes have been identified that predispose to febrile convulsions (Wallace *et al*., 1998). In experimental models, prolonged hyperthermic seizures in immature rats did not cause spontaneous seizures in adulthood but did increase seizure susceptibility to a second hit (Dube *et al*., 2000). For example, seizures were induced by exposing rat pups to hyperthermia for 30 min; pentobarbital was used to prevent seizures in a control group of hyperthermic animals (Dube *et al*., 2000). Spontaneous seizures did not develop in adult rats from either group. However, a subsequent insult with low-dose kainate triggered seizures in 100% of adult animals that had previously displayed neonatal hyperthermic seizures (Dube *et al*., 2000). Of those displaying seizure activity, most progressed to status epilepticus. In contrast, few (17%) hyperthermic pentobarbital-treated controls developed seizures after low-dose kainate treatment. Using electrical stimulation as a different insult, hippocampal–entorhinal cortex slices from rats with hyperthermic seizures produced prolonged, self-sustaining discharges (Dube *et al*., 2000).

These results suggest that prolonged hyperthermic seizures early in life increased seizure susceptibility later in life but did not cause spontaneous seizures ('epilepsy'). An alternative view is that, since febrile convulsions rarely lead to epilepsy, the changes that occur following febrile convulsions could be predominantly protective against epilepsy rather than epileptogenic (Walker and Kullmann, 1999). Since many children with febrile convulsions probably have a predisposing susceptibility to seizures, the low incidence of subsequent epilepsy could be explained by an antiepileptogenic effect of febrile seizures. Thus, those changes that have been reported to occur in animal models that have been interpreted as epileptogenic, such as changes in GABAergic inhibition (Chen *et al*., 1999) or changes in particular cationic channels (Chen *et al*., 2001), could be antiepileptogenic.

Neonatal hypoxia–ischaemia

Like the immature rat model of hyperthermic seizures, the rat model of neonatal hypoxia–ischaemia employs an initiating event that closely resembles a common precipitating injury in humans. In this model, neonatal rats exposed to a perinatal hypoxic insult display both acute seizures and subsequent seizure susceptibility and seizure-induced neuronal injury (Jensen *et al*., 1992). Oxygen deprivation increased seizure susceptibility to a chemical convulsant when hypoxic seizures were induced in rat pups on postnatal day 10 (P10), whose development roughly correlates to a human term newborn, but not in rats aged 5 or 60 days, suggesting age-specific changes (Jensen *et al*., 1992). Indeed, hypoxic injury in adult animals can reduce seizure susceptibility (Milward *et al*., 1999). This is perhaps due to a reduction of neuronal densities to levels lower than those that can sustain seizure activity.

There are developmental factors that may predispose the neonatal brain to seizures. One such age-specific change may be related to glutamate receptor subtypes. NMDA receptor density peaks late in the first postnatal week, whilst the density of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors peaks later, in the second postnatal week around P10 (Jensen *et al*., 1995). There are also age-related changes in NMDA and AMPA receptor subtypes. NMDA receptors have more prolonged opening times, enhancing NMDA receptor-mediated neurotransmission at early ages (Monyer *et al*., 1994). At early developmental stages there is also a higher proportion of calcium-permeable AMPA receptors due to lack of the glutamate receptor 2 subunit (Pickard *et al*., 2000). In addition, glutamate uptake is under developmental regulation, with decreased expression of glutamate transporters in the neonatal brain (Ullensvang *et al*., 1997), which could contribute to enhanced excitability. Indeed, exposure of hippocampal cultures to glutamate pulses can result in the development of hyperexcitability (Sun *et al*., 2001).

Inhibition is also developmentally regulated. GABA(A) receptors undergo marked developmental regulation (Brooks-Kayal *et al*., 2001) but, importantly, GABA(A) receptors in immature neurones may be excitatory rather than inhibitory (Rivera *et al*., 1999). GABA(A) receptors on opening are permeable to chloride and their function is dependent on the chloride gradient across the cell membrane. Lack of a chloride pump in immature neurones results in intracellular accumulation of chloride, and a depolarizing effect of GABA(A) receptor activation (Rivera *et al*., 1999). These changes in GABA(A) receptor mediated inhibition could also affect the pharmacodynamics of antiepileptic drugs, such as benzodiazepines and phenobarbital, that act on these receptors.

Hypoxia-induced seizures can be prevented by an AMPA receptor antagonist but not by an NMDA receptor antagonist, suggesting that the main mediator of these seizures is AMPA receptor activation. Importantly, preventing hypoxia-induced seizures prevented the late epileptogenic effects of perinatal hypoxia in immature rats (Jensen *et al*., 1995).

Traumatic brain injury

There are at least three animal models of post-traumatic hyperexcitability, and these models consider three different

phenomena that occur with traumatic brain injury. Undercut areas of cortex with maintained pial blood supply *in vivo* become hyperexcitable over a period of a few weeks (Sharpless and Halpern, 1962; Echlin and Battista, 1963). Spontaneous interictal discharges develop and ictal discharges are easily evoked. The mechanisms underlying this hyperexcitability are uncertain. GABAergic inhibition seems if anything to be increased, with the development of new inhibitory connections (Prince and Jacobs, 1998). It has been hypothesized that increased neuronal excitability through changes in membrane properties along with increased conductance of NMDA receptors could explain this hyperexcitability, regardless of whether GABAergic inhibition remains intact (Bush *et al*., 1999). This model does reflect some of the pathology that is seen following head injury, in which white matter lesions and cavitation can effectively undercut the cortex.

A critical clinical observation following stroke and head injury is the high risk of epilepsy associated with intracerebral haemorrhage. This can be modelled by the injection of iron chloride (Willmore *et al*., 1978). Again over a period of weeks, animals develop spontaneous seizure activity (Willmore *et al*., 1978). The mechanisms underlying hyperexcitability in this model are different and possibly result from abnormalities that occur in glutamate transport (Engstrom *et al*., 2001).

A third model has been fluid percussion injury to the dura that results in hilar interneurone loss in the hippocampus (Lowenstein *et al*., 1992). The mechanism by which this occurs is unknown. In the short-term, the neuronal loss is accompanied by enhanced excitability of the hippocampus, but no spontaneous seizures (Lowenstein *et al*., 1992). However, months after the injury the hippocampus has a lower threshold for the generation of seizure-like activity, and there is sprouting of excitatory axons (mossy fibre sprouting) that may contribute to hyperexcitability (Santhakumar *et al*., 2001). Despite this, there is no evidence of spontaneous seizures, perhaps due to a concomitant increase in inhibition (Santhakumar *et al*., 2001).

These models demonstrate that head injury may result in at least three different epileptogenic pathways, which lead to hyperexcitability often without overt seizures. There is a latent period for the development of this hyperexcitability, and the occurrence of a second insult is probably necessary for the manifestation of epilepsy.

Seizures and epileptogenesis

Much of the modern approach to treatment has been based on the adage of Gower that 'seizures beget seizures' and that the progression of untreated epilepsy is one of progressive worsening and more frequent seizures. This observation can relate to the progression of an underlying disease process, such as occurs with tumours or the progressive myoclonic epilepsies, but is it a necessary consequence of seizures themselves or seizure discharges, as kindling would seem to indicate (see above)? That this is unlikely is suggested by the occurrence of benign childhood epilepsy syndromes in which there is usually spontaneous remission despite frequent, often untreated seizures (Berg and Shinnar, 1997). However, in a series of hospital-based epidemiological studies, Reynolds and colleagues found that the greater the number of seizures that occurred prior to treatment, the worse the prognosis of the epilepsy, and that in untreated populations there was a tendency for progressively shorter seizure-free intervals (Reynolds, 1987; Elwes *et al*., 1988). This has been used as supportive evidence that seizures themselves are epileptogenic. There are, however, many criticisms of these studies (Berg and Shinnar, 1997). More recent reports have supported the finding that a large number of seizures and a poor initial response to treatment predict intractability. For example, in a community-based study, the most robust predictor of poor prognosis was the number of seizures during the first 6 months after presentation to a doctor (MacDonald *et al*., 2000). Furthermore, in a hospital-based study, >20 seizures prior to treatment and failure to respond to the first drug therapy were predictive of a poor prognosis (Kwan and Brodie, 2000). There is, however, an alternative explanation for these findings. From the onset, epilepsy could have an inherent severity and prognosis that is reflected in the early response to treatment (Sander, 1993; Berg and Shinnar, 1997). The explanation for a greater number of seizures prior to treatment having an influence on prognosis could also be interpreted as: (i) less severe seizures (complex partial and simple partial seizures compared against generalized seizures) are likely to be associated with a greater delay before seeking medical attention, and may have an intrinsically poorer response to treatment (as has been observed in some drug studies); or (ii) more frequent seizures and seizure clustering could be associated with epilepsies that have an inherently poorer prognosis. Since these various interpretations are at odds with Gower's hypothesis, it becomes important to ask whether there is any other method of investigating this critical question. One such approach has been the study of untreated populations in developing countries (Feksi *et al*., 1991*a*, *b*; Placencia *et al*., 1993, 1994). The main finding in these studies is that the prognosis for resolution of the epilepsy in untreated populations is similar to that for treated populations from developed countries. Furthermore, the response to treatment in previously untreated populations (i.e. late treatment) was the same as the response to treatment in patients from developing countries, who are treated earlier in the course of the epilepsy. Although these are not placebo-controlled studies, they provide powerful evidence that the prognosis for epilepsy is not influenced by early treatment. This has received further support from a first seizure study in which patients with their first unprovoked tonic–clonic seizure were randomized to drug treatment or placebo, but all would receive treatment following a second seizure (Musicco *et al*., 1997). There was no difference in eventual remission rate between these two groups, although the group that had their first seizure treated were less likely to have a

second seizure. Overall, it appears that seizures do not beget seizures. This does not exclude the possibility that there are a minority of epilepsies in which seizures can result in 'progression' of the epilepsy. One such epilepsy is mesial temporal epilepsy resulting from hippocampal sclerosis, in which recurrent seizures may cause further structural and functional changes in the hippocampus. This has been supported by the findings that epilepsy duration correlated with hippocampal volume loss and progressive neuronal loss and dysfunction (Tasch *et al*., 1999; Theodore *et al*., 1999; Fuerst *et al*., 2001). There has also been a case report of hippocampal volume decreasing with time in hippocampal sclerosis (Van Paesschen *et al*., 1998) and the appearance of hippocampal sclerosis *de novo* following secondary generalized brief tonic–clonic seizures (Briellmann *et al*., 2001). Whether this is the cause of the seizures or the result of hypoxia during seizures or some other underlying pathological process remains uncertain (Sutula and Pitkanen, 2001). That hippocampal sclerosis may be progressive is supported mainly by animal data, such as the changes that can be seen in the kindling model of epilepsy in which eventual spontaneous seizures result in progressive neuronal loss within the hippocampus (Cavazos *et al*., 1994). Indeed, following a single seizure there is evidence of both apoptotic cell death and neurogenesis in the dentate granule cell layer (Bengzon *et al*., 1997).

It thus seems likely that the majority of epilepsies are non-progressive; however, there are syndromes that are progressive either because of the nature of the underlying pathology or of the seizures themselves.

Targets to prevent epileptogenesis

A neurological injury sets in motion myriad changes that contribute to epileptogenesis. To interrupt epileptogenesis, disease-modifying interventions will need to target critical processes triggered by the initiating event, changes occurring in the latent period, and/or those underlying disease progression after recurrent unprovoked seizures emerge. Agents with multiple mechanisms of action might be capable of acting at different points in the expanding cascade of biochemical and cellular changes. Interventions that act on the modulators driving the epileptogenic cascade may provide neuroprotection (preventing neuronal injury/death), neurostabilization (preserving/restoring neuronal function) and/or neuronal recovery or regeneration.

A consistent finding in animal models is that stopping prolonged seizure activity at the time of an insult will reduce the neuronal damage and may protect against epileptogenesis. This appears to hold true in animal models of neonatal hypoxia (Jensen *et al*., 1995) and precipitated status epilepticus in animal models (Meldrum and Brierley, 1973; Sloviter, 1983; Nevander *et al*., 1985). Furthermore, there is evidence to suggest that this is also true in human status epilepticus (DeGiorgio *et al*., 1995). What if the seizure cannot be stopped? Are there other targets for preventing neuronal death and epileptogenesis following an insult? Most of the research directed at answering this question has concentrated on neuroprotection.

Neuronal loss is the visible consequence of neurological insult and may occur via both necrosis and apoptosis. Cell death by necrosis can begin within minutes of injury, with alterations in intracellular ion flux, cellular swelling and lysis. In contrast, apoptosis involves a complex cascade of events mediated by intracellular proteins and enzymes that produce programmed cell destruction in which the cell body shrinks and the nuclear material fragments (Kerr, 1971). Apoptosis generally evolves over a longer period of time.

The differences in mechanisms and time course of necrosis versus apoptosis point to potential differences in interventions. Prevention of necrosis may require intervention before or during the insult to stabilize neuronal membranes and prevent alteration of ion fluxes. On the other hand, there may be more time to intervene in apoptotic cell death by targeting later steps in the apoptotic process, such as receptor-mediated messengers and the second messenger systems involved in the mobilization of the intracellular proteins and enzymes that control programmed cell death. However, recent research has suggested that there may not be such a definite distinction. For example, it appears that necrotic mechanisms may activate apoptosis (Roy and Sapolsky, 1999; Fujikawa *et al*., 2000). Thus, strategies aimed at downstream processes may be more effective in reducing the consequences of both apoptotic and necrosis-induced neuronal death.

Excitotoxic cascade

Cell death following a precipitating injury (e.g. hypoxia or seizure activity) involves elevated calcium levels and is mediated mainly by glutamate (Lipton and Rosenberg, 1994; Michaelis, 1998). Decreased energy production following injury stimulates glutamate release from presynaptic terminals. Excessive glutamate binding to NMDA receptors and to AMPA receptors lacking the glutamate receptor 2 subunit can directly cause an influx of calcium and sodium ions that depolarizes the cell, which in turn permits a further influx of calcium. Group I metabotropic glutamate receptors acting via a G-protein-linked second messenger system can also depolarize neurones, but in addition can release calcium from intracellular stores (Bruno *et al*., 2001). High levels of intracellular calcium trigger calcium-dependent processes, such as the activation of proteases, lipid peroxidases and endonucleases and the production of oxygen free radicals, thereby destroying structural proteins, cell membranes and DNA. Intracellular accumulation of zinc may also play a critical role in seizure-induced neuronal death (Weiss *et al*., 2000).

Once begun, the excitotoxic cascade can propagate. The normal concentration of extracellular glutamate is about one-thousandth that of the intracellular concentration, but reversal of glutamate uptake and the release of intracellular glutamate from dying cells can raise the ambient concentration around

neighbouring neurones to toxic concentrations (Lipton and Rosenberg, 1994). Furthermore, excitability and neuronal death can be modified by inflammatory mediators, such as the interleukins that are released during and following status epilepticus (De Simoni *et al*., 2000). Thus, strategies aimed at intervention against glutamate-mediated excitotoxicity represent a particularly intriguing possibility for disease modification. These interventions could be aimed at initial processes, such as specific glutamate receptor antagonism, an approach that has met with a certain amount of success but that requires early intervention (see section above headed Post-status epilepticus). Alternatively, interventions aimed downstream could perhaps be used later after an insult, but the many different intracellular pathways involved make it difficult to identify a simple, effective strategy (Henshall *et al*., 2001).

Epileptogenesis

Neurological insult may cause rearrangements in the synaptic circuitry with or without neuronal death. As has been discussed, it is still uncertain whether many of the changes that occur in animal models are compensatory or epileptogenic; more particularly, the mediators of the epileptogenic process have yet to be determined. Genes and kinases are activated, mRNA transcription increases and proteins are synthesized, but it is still not clear which are the critical genes, kinases, mRNAs and proteins.

One model of a putative epileptogenic process is the reactive sprouting of granule cell axons, 'mossy fibres', which has been observed within the dentate gyrus in both humans with mesial temporal epilepsy and in animal models (Sutula *et al*., 1988, 1989; Babb *et al*., 1991; Cavazos *et al*., 1991). The most striking sprouting is that which occurs into the molecular layer of the dentate granule cells, resulting in local excitatory loops. Although it was thought that target cell loss through necrosis and/or apoptosis resulted in these new aberrant synaptic connections, mossy fibre sprouting occurs in the setting of no or minimal neuronal death (Liu *et al*., 1999). When mossy fibre sprouting is associated with seizure activity, it is not clear whether this altered neuronal circuitry is a cause or effect of seizures; however, it is likely that the new pathways exacerbate aberrant seizure activity and do not restore normal function.

Neuronal reorganization may be reduced by seizure suppression. In a rat model of kainic acid-induced continuous seizure activity, uncontrolled seizures were associated with extensive neuronal degeneration and mossy fibre sprouting (Sutula *et al*., 1992). With phenobarbital treatment for 14 days, the degree of mossy fibre synaptic reorganization was significantly less (Sutula *et al*., 1992). This model suggests that mossy fibre sprouting can be reduced by suppressing seizures before synaptic reorganization occurs. Yet it is not clear whether blocking mossy fibre sprouting will prevent latent hyperexcitability. Indeed, blocking mossy fibre sprouting with the protein synthesis inhibitor cycloheximide does not prevent epileptogenesis (Longo and Mello, 1998). However, the interpretation of these experiments is confounded by the likelihood that inhibition of protein synthesis will inhibit other, antiepileptogenic processes. This possibility raises a crucial question, not only about these experiments but also whether therapies will be able to discriminate epileptogenic from concurrent antiepileptogenic processes.

Modification of the epileptogenic process

In models of epileptogenesis induced by prolonged seizures (e.g. febrile seizures, status epilepticus, neonatal hypoxia/ischaemia), preventing or stopping seizure activity attenuates both the neurological damage and the occurrence of epilepsy/hyperexcitability. This observation is indirectly supported by uncontrolled clinical data in which precipitated seizures carry a better prognosis than precipitated status epilepticus for the development of epilepsy (Hesdorffer *et al*., 1998). A further finding in an animal model of status epilepticus is that MK-801, an NMDA receptor antagonist, prevents the occurrence of post-status epilepticus epilepsy without affecting the length or severity of the status epilepticus (Rice and DeLorenzo, 1998). This suggests that, for some models, neuronal death and epileptogenesis may have similar mediators. MK-801 also inhibits the kindling process, demonstrating its antiepileptogenic potential (McNamara *et al*., 1988).

Inhibiting possible seizure activity in other models, such as the iron chloride model of traumatic brain injury, may not prevent epileptogenesis (Willmore and Triggs, 1984). In the iron chloride model, lipid peroxidation and the formation of free radicals via this route is more likely to be the initiating mechanism of epileptogenesis (Willmore and Rubin, 1984). Although there may be different initiating mechanisms, are there similar downstream pathways involved in the epileptogenesis associated with these models? One possibility is the expression of brain-derived neurotrophic factor (BDNF), a growth factor that is induced by neuronal damage from ischaemia, trauma or epilepsy and is also induced by seizures (Lindvall *et al*., 1994). This nerve growth factor is neuroprotective, and thus may be expressed as a physiological response to neuronal injury (Lindvall *et al*., 1994). There is evidence, however, to suggest that BDNF is epileptogenic. Anti-nerve growth factor antibodies and antibodies directed against the BDNF receptor, tyrosine kinase B, infused intraventricularly, inhibit the kindling process (Van der Zee *et al*., 1995; Binder *et al*., 1999). Also, underexpression of BDNF in heterozygous BDNF knockout mice inhibited the rate of kindling (Kokaia *et al*., 1995). The interpretation of these studies is confounded by the observation that BDNF directly infused into the hippocampus paradoxically inhibits kindling (Larmet *et al*., 1995). The mechanism of this is unclear, but the effect could be due to downregulation of BDNF receptors or to some antiepileptogenic process, such as the regulation of modulatory neuropeptides (Croll *et al*., 1994). Once again, this exempli-

fies the dichotomous role of many mediators in initiating both epileptogenic and antiepileptogenic processes.

Are our current antiepileptic drugs antiepileptogenic?

Our current antiepileptic drugs are antiepileptogenic insofar as they can terminate status epilepticus and prolonged seizures. Indeed, there is some experimental evidence in animal models to suggest that certain antiepileptic drugs given prior to the induction of status epilepticus have neuroprotective effects even if they do not modify the status epilepticus (Pitkanen *et al*., 1996). Do these findings hold just for status epilepticus? From the experimental evidence above, it is likely that suppressing seizures associated with hypoxic/ischaemic injury in neonatal rats has a similar antiepileptogenic effect. Indeed, suppression of prolonged seizure activity could also have relevance to head injury. Non-convulsive status epilepticus can occur in the setting of head injury and stroke, and is probably frequently unrecognized (Towne *et al*., 2000). Whether aggressive treatment of this non-convulsive status epilepticus improves prognosis is unknown, but it does open up the possibility of trials of aggressive antiepileptic drug treatment in this patient subgroup. Furthermore, inhibition of neuronal activity with the sodium channel blocker tetrodotoxin prevented epileptogenesis in the isolated cortex model of head injury (Graber and Prince, 1999). The inhibition of neuronal activity in this study is much greater than that achieved with antiepileptic drugs, and it may not be relevant to other models of head injury. Indeed, in human studies, prophylactic treatment with agents tested to date does not change the underlying pathological processes involved in post-traumatic epilepsy (Temkin *et al*., 1990, 1999). The failure of these prophylaxis trials may be due, in part, to study design issues, e.g. inadequate doses and the extent of neuronal injury. It is also possible that successful prophylaxis requires pharmacological mechanisms not present in the two agents tested, phenytoin and valproate (sodium channel blockade, effects on T-type calcium channels, GABA potentiation). Whether seizure suppression in subgroups with putative progressive epilepsies can alter prognosis for the epilepsy is unknown, and is an area that needs further study.

Can antiepileptic drugs have antiepileptogenic effects independent of their effect on seizure suppression? It is likely that such an antiepileptogenic effect is a chance association, as the drugs are neither designed to be antiepileptogenic nor chosen for their antiepileptogenic potential. The main preclinical studies of epileptogenesis have been carried out in the kindling model, although it is difficult to find a human correlate of this process. Agents seem to differ in their effects on different stages of kindling (Wada *et al*., 1976; Leviel and Naquet, 1977; Turner *et al*., 1977; Silver *et al*., 1991; Wauquier and Zhou, 1996; Morimoto *et al*., 1997; Amano *et al*., 1998; Loscher *et al*., 1998; Postma *et al*., 2000). For example, valproate, phenobarbital and benzodiazepines displayed prophylactic effects in kindling models, i.e. these agents inhibited acquisition of the kindled state (Silver *et al*., 1991). Other agents had no such effects or very weak effects on the development of kindling, e.g. phenytoin and carbamazepine (Wada *et al*., 1976; Turner *et al*., 1977; Silver *et al*., 1991). Carbamazepine and diazepam suppressed kindled seizures once they had developed, as did valproate (Wada *et al*., 1976; Leviel and Naquet, 1977). Phenytoin was not effective in suppressing kindled seizures but did prevent spontaneous seizures in kindled animals (Wada *et al*., 1976; Turner *et al*., 1977). Of the newer antiepileptic drugs, topiramate delayed seizure acquisition in kindling and inhibited kindled seizures in a dose-dependent fashion (Morimoto *et al*., 1997; Amano *et al*., 1998). Although lamotrigine did not inhibit amygdala-kindled seizure development at a low dose (5 mg/kg) in rats, a higher dose (15 mg/kg) enhanced the development of kindling, exhibiting a 'pro-epileptogenic' effect (Postma *et al*., 2000). In animals that were not treated with lamotrigine during kindling, kindled seizures were inhibited by lamotrigine. If, however, lamotrigine was administered during the development of kindling, it was ineffective in suppressing kindled seizures and even had proconvulsant effects. With acute treatment, levetiracetam inhibited kindling acquisition (an effect that persisted after acute treatment was discontinued) and suppressed seizures in fully kindled animals (Loscher *et al*., 1998). The persistent effect on kindling development associated with acute levetiracetam treatment may provide a different and as yet unclear parameter for potential antiepileptogenic effects of antiepileptic drugs.

Although these studies demonstrate that antiepileptic drugs can have antiepileptogenic effects, it is not always clear that this effect is independent of their ability to suppress afterdischarges following stimulation (i.e. their anti-seizure effects). Also, their relevance to human epilepsy is unknown.

Conclusion

There is little evidence that our present therapies have strong antiepileptogenic potential, independent of their ability to terminate prolonged seizures. This antiepileptogenic effect through the termination of prolonged seizures may, however, be important. There is substantial animal evidence to suggest that a prolonged seizure may be epileptogenic and that interventions to prevent on-going seizure activity are protective. The possible under-recognition of non-convulsive status epilepticus in association with an acute insult emphasizes the need to investigate all patients with unexplained coma or confusional states with EEG. There is, however, as yet no good human evidence of any benefit from treating non-convulsive status epilepticus in these patients.

The presence of a latent period during which epileptogenic changes occur raises the possibility of other directed therapy to prevent or ameliorate this process. This approach is complicated by the likelihood that many of the processes

underlying epileptogenicity also underlie neuronal repair, physiological compensation and even antiepileptogenic processes. Thus, therapies aimed at these targets could ironically do more harm than good. Epidemiological surveys have supported the possibility that one of the major influences on the incidence of epilepsy in recent years has been improvement in neonatal care, preventing the occurrence of neonatal hypoxia/ischaemia (Cockerell *et al*., 1995). Perhaps treatment during the epileptogenic period is not the Holy Grail, towards which we should all be striving, but, more obviously, we should be considering better medical care at the time of an insult, and, indeed, prevention of the insults themselves.

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