Neurotransmitters, Drugs and Brain Function.
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16 The Epilepsies

R. A. WEBSTER

DEFINITION

Epilepsy was defined by Hughlings Jackson as 'An episodic disorder of the nervous system arising from the excessive synchronous and sustained discharge of a group of neurons'. It is a considered and apt definition that highlights important aspects of the disorder that are relevant to our understanding and treatment of it. The fact that it is episodic means that attacks, in whichever form they arise, can occur frequently within minutes or hours of each other or at intervals of weeks, months or years. Such unpredictability complicates treatment. Epilepsy is neither a degenerating nor generally a worsening disorder but therapy needs to be maintained to avoid the possibility, however remote, of a seizure with all its potential personal and social problems.

That an episode arises and spreads from the synchronous as well as excessive discharge of a group of neurons (focus) means that not only must those neurons be in some way predisposed to so discharging but they can also recruit neurons that are otherwise normal. How that discharge manifests itself, i.e. which type of epilepsy occurs, will depend not only on where the abnormal focal neurons are located but also to what extent the activity they initiate can and does spread through the brain. There are consequently a number of different forms of epilepsy, i.e. the epilepsies.

CLASSIFICATION

Epileptic seizures are classified broadly as (a) partial or (b) general:

(a) **Partial seizures or epilepsy (PE)**. As the name implies, these begin and generally remain localised. They may be simple or complex with the symptoms dependent on the cortical area affected. The former may just involve involuntary contractions of a group of muscles or a single limb (Jacksonian motor epilepsy) or abnormal but localised sensory disturbances (Jacksonian sensory epilepsy). They rarely last more than a couple of minutes and consciousness is not impaired.

Complex partial seizures manifest themselves as bizarre behaviours which are also known as psychomotor or temporal lobe epilepsy, since a lesion (focus) is often found in that brain area. Repetitive and apparently purposeful movements vary from simple hand clenching or rubbing to more bizarre hand movements and walking. These can last a few minutes, often disrupt other ongoing activity or speech and the patient has no subsequent memory of them. Complex seizures may develop from simple ones.

(b) **Generalised seizures**. These involve more, or even the whole, of the brain including the reticular system so that consciousness is lost, although in some instances (absence seizures) this is more a loss of awareness rather than any collapse. The two main forms are:

(1) Grand mal (GM) or tonic–clonic seizures (TCS). This is probably what everyone recognises as 'epilepsy'. It starts with a tonic spasm of all musculature and rigid extension of the body, a temporary cessation of respiration, generally salivation and often defecation and micturition. After about one minute this gives way to violent synchronous clonic jerking movements (convulsions) which may continue for a few minutes. The patient may remain unconscious for a longer period before recovering. In some cases the tonic and occasionally the clonic phrase can exist alone.

(2) Petit mal (PM) or absence seizures (AS). These are less dramatic and generally occur in children. They entail a brief and abrupt loss of awareness (consciousness) in which the patient suddenly ceases ongoing activity or speech and stares vacantly for a few seconds before recovering equally quickly. Motor disturbances are rare apart from blinking of the eyes and the patient has no recollection of the event.

In addition to the above main categories seizures can be just myoclonic, isolated clonic jerks, or atonic, loss of postural control with just head drooping or the patient actually falling.

Epileptic seizures affect 0.5% of the population, are more common in the young and, except for partial seizures, often decrease with age. Convulsions associated with metabolic disturbances are not considered to be epileptic.

Many seizures are associated with distinctive EEG patterns (Fig. 16.1). Perhaps the most striking is the 3 per second spike wave activity seen in most leads (cortical areas) in absence seizures, which can be invoked by hyperventilation. Otherwise distinctive EEG patterns are usually only found during an actual seizure, with burst spiking seen alongside clonus in TCS and abnormal discharges with the behavioural patterns of partial epilepsy and in particular that originating in the temporal lobe.

ANIMAL MODELS OF EPILEPSY

These are normally based on the use of either electrical stimulation or chemical convulsants. When applied generally, i.e. an electric shock to the whole brain or convulsants injected systemically, the resulting convulsions are indicative of generalised seizures. If they are applied locally to specific brain areas, the same approaches induce activity indicative of partial seizures. Also some animals can be bred in which seizures either occur spontaneously or can be induced easily by appropriate sensory stimulation.

MODELS OF GENERALISED SEIZURES

(1) Electric shock

In the maximal electric shock (MES) test a supramaximal stimulus is applied bilaterally through corneal or auricular electrodes to induce tonic hind limb extension in rats or

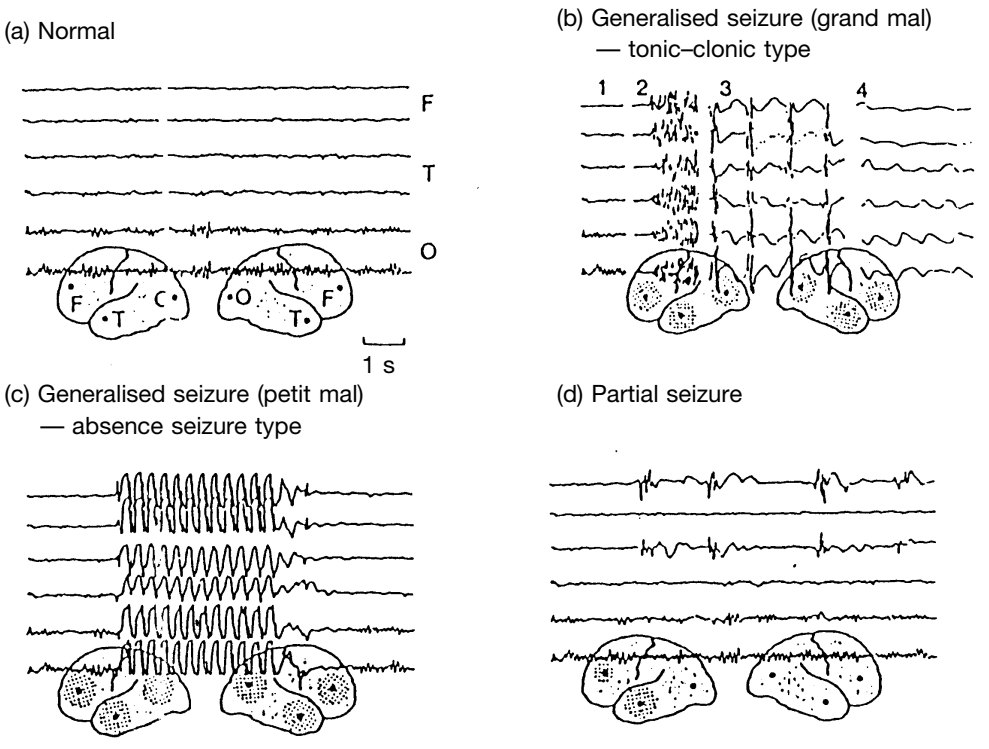

Figure 16.1 EEG patterns in human epilepsies. Electroencephalograms are shown for, a normal subject (a), those suffering from general tonic–clonic seizures (grand mal, (b)), generalised absence seizures (petit mal, (c)), and partial seizures (d). Spikes are seen in both right- and left-sided leads from all three cortical areas, frontal (F), temporal (T) and occipital (C) in the generalised seizures (b, c) but only in the occipital leads in the example of partial seizures (d). In the EEG recorded during the generalised tonic–clonic seizure the normal tracing (1) is followed by the onset of the tonic phase (2), the clonic (convulsive) phase 3 and post-convulsive coma 4. The typical $3\,s^{-1}$ spike and wave discharge of petit mal (c) may be seen during routine recording or induced by procedures such as hyperventilation but the spiking of grand mal and partial epilepsy is only seen during seizures. (Reproduced from Eliesson *et al* (1978), *Neurological Pathophysiology*, 2nd edn, Oxford University Press, New York with permission)

mice. Anticonvulsant activity is determined by measuring the dose of drug required to protect 50% of the stimulated animals (*ED* or PD_{50}) and is predictive of efficacy in TCS.

(2) Chemical convulsants

A number of different chemicals have been used including GABA antagonists such as bicuculline or picrotoxin. Strychnine convulsions have no predictive value since they arise through antagonism of spinal (glycine-mediated) rather than cortical inhibition. The most commonly used agent is pentylenetetrazol (PTZ), also called leptazol. Anticonvulsant activity is again assessed as the dose required to protect 50% of animals, usually mice, against the clonic seizures induced by a dose of PTZ that would otherwise produce them in almost every mouse injected, the so-called CD_{97} (convulsive dose in

97% of animals). The absence of a marked tonic component to the seizure may be significant since the ability to protect animals against PTZ convulsions is predictive of a drug's potential efficacy in absence seizures rather than TCS, despite the fact that PTZ causes convulsions.

The anticonvulsant activity of a drug may also be evaluated by measuring its ability to raise the convulsive threshold, i.e. the amount of applied current or infused PTZ required to just evoke a seizure. Comparison of the efficacy of drugs in the threshold and maximal seizure tests may distinguish between their abilities to raise seizure threshold or reduce seizure spread and development.

MODELS OF PARTIAL SEIZURES

(3) Focal

Partial seizure activity can be induced by the localised application of chemicals such as cobalt or alumina to the cortex or the injection of chemicals such as PTZ or kainic acid directly into particular brain areas like the hippocampus.

(4) Kindling

If a subconvulsive stimulus is applied, generally in rats, at regular intervals, e.g. daily for some two weeks to a specific brain area, especially the amygdala or hippocampus, then eventually full localised (partial) or secondary generalised seizures develop. A similar effect can be obtained by the repeated localised injection of subconvulsive doses of some convulsants. The ability of a drug to reduce the kindled seizure itself may be indicative of value in partial seizure but if it slows the actual development of kindling that may indicate some ability to retard epileptogenesis.

SPONTANEOUSLY EPILEPTIC (GENETIC) ANIMALS

Various animals show spontaneous epilepsy or seizures that can be readily induced by sensory stimulation (see Jobe *et al*. 1991). Tottering mice display seizures that resemble absence attacks behaviourally, in their EEG pattern and response to drugs. DBA/2 mice show reflex seizures to audiogenic stimuli while photically-induced seizures can be obtained in the Senegalese baboon, *Papiopapio*, which are similar to generalised tonic–clonic epilepsy.

PREDICTIVE VALUE

It has become clear that drugs which are effective in protecting mice against PTZ are effective in absence seizures while those able to control the tonic response to maximal electroshock are effective in tonic–clonic seizure. Some drugs are effective in only one test and clinical condition whilst a few are active in both (Table 16.1). Experimental focal seizures are indicative of partial seizures.

It could be argued that an antiepileptic drug should really stop the development of epilepsy, i.e. epileptogenesis, and not merely control seizures which would make them just anticonvulsant. If the development of kindling reflects the process of epileptogenesis then drugs effective against its progression should stop the development of

Table 16.1 Comparison of the experimental and clinical activities of established antiepileptic drugs

	Activity against convulsions induced by		Effectiveness clinically in	
	Electroshock	Pentylene tetrazol	Clonic–tonic seizures	Absence seizures
Phenytoin	++	−	+	−
Carbamazepine	++	−	+	−
Phenobarbitone	+(+)	+	(+)	−
Na valproate	+	+	+	+
Clonazepam	(+)	++	(+)	+
Ethosuximide	−	+	−	+

Notes:
The data for the experimental studies gives a semi-quantitative guide to relative activities based on ED_{50} values, i.e. ++ = active, + = some effect, − = not active at non-toxic doses. Clinical comparisons are not related to recommended doses but simply indicate whether a drug is effective (+) or not (−). Generally, drugs that are to be used clinically to control tonic–clonic seizures control electroshock but not pentylenetetrazol-induced convulsions in rats and mice, whilst the converse applies to drugs effective in absence seizures. Na valproate is effective in both experimental models and is used in both clinical conditions, although in all cases higher doses have to be used than for any other drug.

human seizures. Phenytoin and carbamazepine do not stop the development of kindling, although acutely they reduce the fully kindled seizure, and in studies of post-traumatic epilepsy following brain damage in humans (car accidents) these drugs stop the appearance of seizures in the first week or so but do not control epileptogenesis, since seizures can develop subsequently in those patients after therapy has stopped. Generally drugs that increase GABA function or block NMDA receptors retard kindling.

CAUSE AND PATHOLOGY

With such a diversity of seizures it would be surprising if a common cause of epilepsy had been found or even existed, although it is conceivable that a focus might arise in the same way wherever it was found. The actual symptoms would then be determined simply by the location of the focus and their extent, partial or general, by how easily or widely the influence of the focal neurons spread. Other factors might then control that spread and could vary from one region to another depending on local neuronal circuitry and NT utilisation. The fact that different drugs with different mechanisms of action are effective in different epilepsies may support that view.

There is, however, no clear neuropathology. Epilepsy may be secondary to focal lesions such as congenital malformations, infarcts, tumours, cysts or inflections but fortunately many patients with these problems do not develop epilepsy. Again epileptic seizures may occur in those suffering from Huntington's Chorea or Alzheimer's disease. Brain damage such as neuronal loss and glial proliferation may in fact be seen in epileptics but these changes may be secondary to, rather than the cause of, epilepsy. They probably reflect the consequences of intense neuronal activation since in patients dying in status epilepticus they appear to be of recent origin and can be induced in animals by systemic or locally administered convulsant (see Meldrum and Corsellis 1984).

Extensive brain damage or lesions are certainly not essential for convulsions. These merely require appropriate conditions. Everyone is capable of having a convulsion, indeed their induction has been a common treatment for depression. The convulsive threshold of an epileptic, or more precisely that of some of their neurons, is just lower than normal.

There is no known genetic basis for most of the common epilepsies apart from juvenile myoclonic epilepsy and childhood absence epilepsy which are dependent on inheritance of two or more susceptible genes, although genetic factors might more generally determine predisposition. Single distinct mutant genes have been established, however, in three rare forms of epilepsy (less than 1% of total), namely generalised epilepsy with febrile seizures, benign familial neonatal convulsions and autosomal dominant epilepsy (see McNamara 1999). These each encode a part of some voltage-gated ion channel which are believed to be respectively the β subunit of a Na^+ channel (SCNIB), novel K^+ channels and the α subunit of cholinergic nicotinic receptors (CHRNA4). All could lead to increased neuronal excitability and in fact co-expression in oocytes of the Na channel α subunit with the β subunit found in febrile convulsions produces a channel that inactivates more slowly than when it is expressed with normal β subunits.

DEVELOPMENT OF AN EPILEPTIC SEIZURE

A seizure is accompanied by a burst of spikes in the EEG. Between these so-called *ictal* phases are solitary EEG *interictal* spikes. Each of them represents the field potential associated with a burst of action potentials in a group of neurons within the epileptic focus (Fig. 16.2).

Focal neurons when activated show an abnormal excitatory postsynaptic potential (EPSP) called the paroxysmal depolarising shift (PDS) (Fig. 16.2) which leads to an abnormal burst of action potentials at frequencies up to $200\,s^{-1}$. While such neurons can be found anywhere they are more common in the CA3 region of the hippocampus and layer 4 of the cerebral cortex. Neurons showing this burst firing are also called Group I, pacemaker or epileptic neurons and their activation always results in a burst discharge and not a single impulse. Thus they could have a persisting abnormality in membrane or ion channel excitability. What we need to know is not only how such neurons arise but how their influence can spread to affect neighbouring neurons to produce the interictal spike and, more importantly, how this can sometimes, and at immensely variable intervals, develop into a full ictal discharge and seizure (Fig. 16.3) (see Prince 1992; Prince and Connors 1986). There is obviously a graduation in excitability from the group I focal neurons through group II neurons, found either in or immediately adjacent to the focus that may fire normally but can be recruited to display abnormal firing, and their surrounding normal neurons. The gradual progression of an epileptic EEG during the infusion of PTZ in a rat is shown in Fig. 16.4.

The development of a focus is likely to be determined by one or more of the following:

(1) changes in the intrinsic properties and excitability of the focal neuron
(2) a reduction in normal GABA-mediated inhibitory controls
(3) an increase in excitatory coupling between neurons

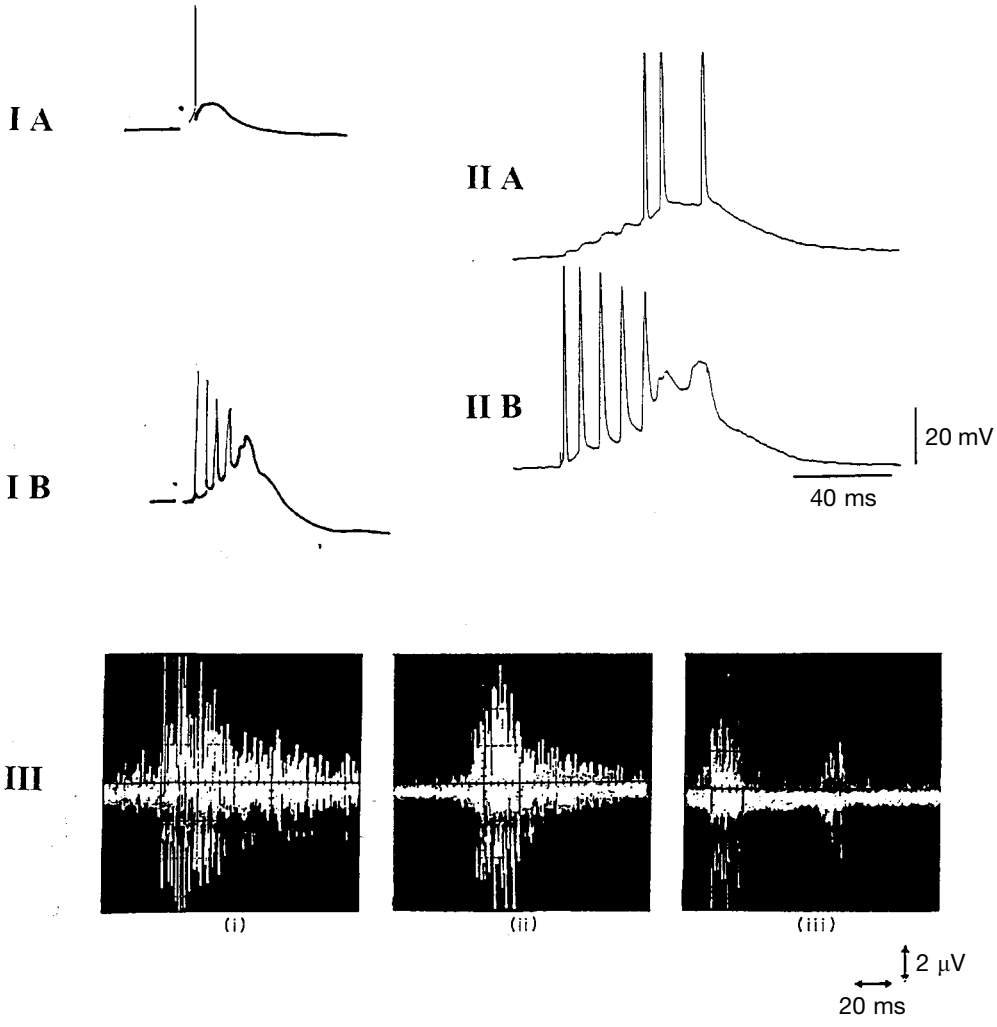

Figure 16.2 Electrophysiological events in the development of an epileptic focus and EEG interictal spike. Intracellular recordings generally show that afferent stimulation of a normal cortical neuron produces one action potential superimposed on a small depolarisation (approx. 10 mV), the excitatory postsynaptic potential of the form drawn in (IA). In a focal type-I epileptic neuron, as found in the CA3 region, the same stimulus can produce a much larger depolarisation, the paroxysmal depolarising shift (PDS) and a burst of spikes (IB). Other neurons must then be recruited and this is shown to be possible in the intracellular recording from two monosynaptically connected CA3 neurons in the hippocampal slice preparation in which each action potential in the presynaptic neuron (IIA) elicits an excitatory potential in the postsynaptic cell which eventually shows a burst of potentials (IIB). Once a number of neurons are recruited there is an almost synchronous discharge of cortical neurons which give rise to an EEG interictal spike. This can be seen from the extracellular recording made with a glass-coated tungsten microelectrode in the cortex of an anaesthetised rat after topical application of the GABA antagonist bicuculline (III). The burst shown in (i) gives rise to a large EEG spike while the other discharges (ii and iii) correspond to medium and small EEG spikes respectively. (II reproduced from Wong *et al.* 1986 and III from Neuropharmacology **30**: Zia-Gharib and Webster 1991 with permission from Elsevier Science.) See also Fig. 2.14

ORIGIN OF FOCAL NEURONS (A in Fig. 16.3)

(i) Properties of focal neurons

Focal neurons must either possess inherent abnormal electrophysiological characteristics or develop them as a result of morphological changes induced in them or around them following some event. There is little evidence of any abnormality in the intrinsic electrophysiological properties of individual neurons studied in brain slices from human focal cortical or hippocampal tissue, although the possibility of some unidentified genetic change in the characteristics of certain ion channels remains possible. By contrast, in electrically kindled rats, NMDA receptors on dentate gyrus granule cells show some plasticity, which at the channel level is manifest by prolonged bursts, clusters and increased agonist potency. Although these changes persist through the kindled state and must therefore be transferred to new receptors, the molecular basis is not known (see Mody 1998). Brain damage can, however, modify neuron function and so possibly make some of them hyperexcitable and focal.

(ii) Reduced inhibition

It has been known for many years that inhibitory interneurons in the spinal cord are very vulnerable and easily destroyed by a reduction in blood supply and that in their absence motoneurons become much more excitable. So it is possible that localised ischemia or hypoxia in the brain could equally well cause a selective loss of GABA inhibitory interneurons and increased excitability of some pyramidal cells. Certainly there is morphological evidence for the loss of such interneurons from occlusion experiments in rodents, as well as a loss of GABA nerve terminals around a cortical alumina focus in monkeys and reduced GABA uptake, and probably therefore GABA nerve terminals, during brain dialysis in epileptic patients. Despite these findings, any neuronal loss reported in human epilepsy appears to be confined to the larger pyramidal neurons, and these do not release GABA.

(iii) Increased excitation

It is equally well known that if a neuron dies, or is destroyed, then any other neuron, which had been innervated by it, gradually becomes supersensitive to the NT it released. In the case of degenerating pyramidal cells this would be glutamate, the excitatory NT. Not surprisingly, undercutting the cortex in animals to produce a deafferentation of some of its neurons not only renders them more likely to show epileptic-like discharges but neurons in hippocampal slices from kindled rats and human focal cortex show supersensitivity to the excitatory amino acids. Such supersensitivity could make some neurons so easily activated that they become ‘epileptic’.

The rate of development of such experimentally induced supersensitivity following denervation or hypoxia is similar to that seen in animals with focal (alumina) lesions but quicker than epileptogenesis following focal pathology (injuries) in humans. Also it must be remembered that although neurons may become supersensitive to glutamate this will no longer be released synaptically from the afferent terminals of the degenerating neurons although its release from others could produce inappropriate, disorganised and extended activation. Indeed there are some morphological changes that would support this.

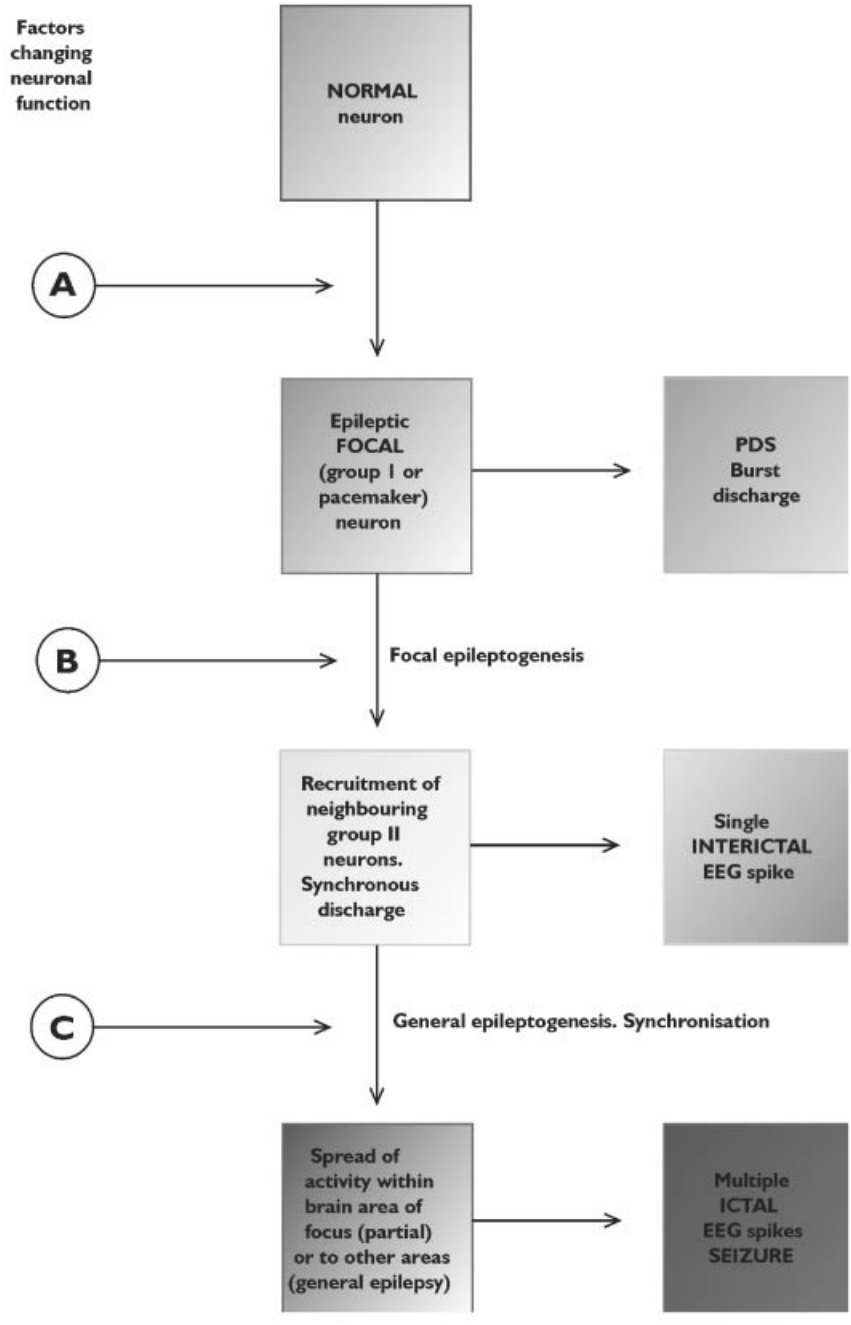

Figure 16.3 Changes in neuronal function required for the development of epileptic seizures. The factors that may control or induce the changes in neuronal function that turn a normal neuron into a focal one (A) recruit other neurons (focal epileptogenesis) to produce an interictal EEG spike (B) and ensure the spread of activity (general epileptogenesis) to full ictal activity (C) are discussed in the text. They include alterations to various ion channels, especially those for Na^+, a reduction in local inhibitory activity or an increase in local excitatory drive. The electrophysiological counterparts of some of the events involved are shown in Fig. 16.2

The dendrites of neurons adjacent to those which degenerate also show extensive growth and sprouting which could facilitate abnormal and disorganised synaptic transmission and cause hyperactivity. It is also known that the dendrites of cells around an alumina focus in monkeys, as well as in human epileptic brain, lose their spinous processes, which might contribute to the paroxysmal discharge by facilitating the spread of depolarisation to the neuron soma. Certainly an increase in the number of Na^+ channels on the dendrites of spinal motoneurons, which would facilitate the occurrence of reactive dendritic Na^+ spikes, has been seen after axotomy.

ORIGIN OF INTERICTAL AND ICTAL SPIKES (B and C in Fig. 16.3)

There are many studies on the induction and spread of spiking in animals both *in vivo* and in isolated brain slices, generally initiated by the use of GABA antagonists or removal of Mg^{2+} ions (*in vitro*). Unfortunately since neither of these events is likely to occur in or around a human epileptic focus the results do not tell us much about how focal activity arises and spreads in humans. This needs to be achieved by the use of human epileptic tissue even though the procedures found to control experimentally induced spiking may well be applicable to humans.

There have been a number of observations which show increased excitation and/or reduced inhibition in slices prepared from human epileptic brain tissue. Thus burst discharges can be evoked with stimuli that would not do so in normal animal tissue and these can be blocked by NMDA receptor antagonists. The inhibitory postsynaptic currents (IPSCs) in hippocampal dentate granule cells in slices prepared from temporal lobe epileptic tissue are in fact reduced by stimulation that activates NMDA currents (Isokawa 1996), which are more prolonged than usual and show changes in slope conductance.

It is perhaps not surprising that NMDA and AMPA receptor mechanisms are important in epileptogenesis. The summation of EPSPs through activation of recurrent polysynaptic excitatory pathways is necessary to mediate the large depolarisation of neurons in and around a focus and the intense discharge and extracellular field potentials of the interactal EEG spike, although these may only occur if counteracting inhibition is reduced. There is in fact some evidence of morphological changes in human epileptic hippocampal tissue that would facilitate such excitatory circuits with aberrant networks of collaterals from axons of individual mossy fibre neurons ramifying through to the CA3 and other regions (Isokawa *et al*. 1993). Also the increase in extracellular K^+ following increasing neuronal activity may itself reinforce the activity by directly depolarising nerve terminals and neurons. High extracellular K^+ would also counteract K^+ efflux and so initiate a prolonged low depolarisation that would facilitate repetitive firing.

From this survey it is clear that just as normal neuronal function requires appropriately balanced inhibitory and excitatory controls so the generation of interictal spikes depends on disturbances in both. Clearly activity cannot spread without the activation of excitatory circuits, in which NMDA receptors play an important role, but it will be much facilitated by reduced inhibition (Masukawa *et al*. 1989). These observations may help to explain the establishment of a focus and the development of the interictal spike, but why activity can only spread to seizure proportions, at certain times, is less clear. It will, however, again require overactivity of excitatory circuits inadequately controlled by inhibitory processes. Since these controls are mediated by

NTs it is now appropriate to consider what evidence there is for a malfunction of NT activity in epilepsy, particularly in those responsible for primary excitation and inhibition, i.e. the amino acids. Before doing so the epileptogenesis of absence seizures (petit mal) justifies separate consideration.

ORIGIN OF ABSENCE SEIZURES

There is much evidence that absence seizures originate in the thalamus probably due to some malfunction of neuronal Ca^{2+} channels. The sudden synchronous bilateral nature of the slow-wave discharge (SWD) in the EEG which typifies this condition was justifiably considered by Jasper (see Jasper and Drooglewer-Fortuyn 1997) to require a subcortical focus and he was able to reproduce them in anaesthetised cats by 3 Hz stimulation of the intralamina thalamus, which in conscious animals also produced absence-like behavioural symptoms such as staring and unresponsiveness. Also in rats with genetic absence epilepsy (GAER) such symptoms are not only accompanied by a synchronous 7–9 Hz SWD but this coincides with high-amplitude discharges in the lateral part of the thalamus, the lesion of which inhibits SWDs.

Within the thalamus the reticular nucleus, which contains predominantly GABA neurons, sends axons to all the other thalamic muclei and although it does not appear to directly drive any thalamic projection to the cortex it receives collaterals from both thalamo-cortical and cortico-thalamic pathways and is well positioned to influence cortico-thalamic activity. If its neurons are stimulated while slightly hyperpolarised they show repetitive burst discharges in rat brain slices followed by a marked after-hyperpolarisation, i.e. oscillatory activity (Avanzini *et al.* 1992). Pharmacological studies *in vivo* in the genetically prone rat show that this depends on the activity of certain Ca^{2+} and Ca^{2+}-activated K^+ conductances and that blocking Ca^{2+} channels just in the reticular nucleus reduces the cortical SWDs. In fact cloning studies in mutant mice strains with features of absence epilepsy show defects in the subunit structure of these channels (Fletcher *et al.* 1996), although why such an effect on channels that have a very widespread distribution should manifest itself in rhythmic activity only in thalamic neurons is uncertain. It may, however, depend on a particular inhibitory control and hyperpolarisation induced locally by GABA, which certainly invokes rhythmic activity when applied to firing neurons and potentiates SWDs in GAERs. In fact this response is probably mediated by $GABA_B$ rather than $GABA_A$ receptors since not only does baclofen ($GABA_B$ agonist) have a similar effect to GABA but when GABA is applied to thalamic neurons it produces a bicuculline-insensitive long-lasting but slight hyperpolarisation which is followed by a low-threshold calcium potential (LTCP) and spike. This T-type Ca^{2+} channel is common in GAERs and larger than normal in thalamic GABA neurons.

NEUROTRANSMITTERS IN EPILEPTIC ACTIVITY

Changes in NT levels and function have been

(1) Looked for in

   (a) human epileptic tissue
   (b) animals in which convulsions have been induced experimentally

(c) animals with spontaneous (genetically disposed) epilepsy

(2) Induced in animals to see how they modify convulsive threshold and intensity

These approaches will be considered in respect of the different NTs although most interest has centred on the amino acids not only because of their possible involvement in the pathology, as already emphasised, but because increased neuronal activity in epilepsy must reflect, even if it is not initiated by, augmented glutamate and/or reduced GABA function.

AMINO ACID MEASUREMENTS

Human studies

Reduced GABA uptake during microdialysis has been mentioned and there are reports of reduced levels of GABA in the CSF of chronic epileptics and of its synthesising enzyme glutamic acid decarboxylase (GAD) in some samples of temporal lobe tissue removed during surgery to alleviate focal seizures. Other reports find no change in GAD but an increase in $GABA_A$ receptors.

Animal studies

In addition to the loss of GAD staining (i.e. GABA) neurons and inhibitory symmetrical synapses around an alumina focus in primates (see above), studies with a chronically implanted cortical cup over a cobalt lesion (focus) in rats show an increased release of glutamate that is associated with spiking (Dodd and Bradford 1976).

Numerous acute experiments with cortical cups show that systemic convulsants increase the release of ACh but rarely that of glutamate. Even the marked convulsant EEG seen after PTZ infusion in the rat (Fig. 16.4) is not accompanied by any rise in glutamate release. This may not mean that it does not occur but that the avid uptake mechanism for glutamate ensures that levels do not rise above basal, unless the stimulation is very extreme. This may explain why perfusates of the lateral ventricle, obtained during kindled seizures induced by the stimulation of the amygdala, showed elevated glutamate levels, but only after very intense neuronal disharges. Basal GABA levels are often too low to even detect in such studies.

If kindling is regarded as a model of the development of epilepsy (epileptogenesis) then following changes in NT function, after or through its development, may be of more value than merely monitoring release during convulsions. Unfortunately results have been inconclusive. Kindling induced by the intraventricular injection of folic acid in rats produced significant increases in cortical glutamate and aspartate, but only the latter correlated directly with increased spiking. With kindling induced by electrical stimulation of the frontal cortex the only change observed alongside the increase in after-discharge was a reduction in glutamine, although this could reflect its utilisation in providing the extra glutamate required for spiking and epileptic activity.

Animals with spontaneous epilepsy

These have yielded few data apart from reports of reduced GABA and taurine in the CSF of baboons with spontaneous seizures.

AMINO ACIDS, MANIPULATION

GABA

Experimentally all GABA antagonists induce convulsions. These include the genuine receptor antagonist bicuculline, which competes with GABA for its recognition site on the $GABA_A$ receptor and picrotoxin, which binds to a different site more closely related to the chloride ion channel.

Reducing the availability of GABA by blocking the synthesising enzyme GAD also promotes convulsions. This may be achieved by substrate competition (e.g. 3-mercapto propionic acid), irreversible inhibition (e.g. allylglycine) or reducing the action or availability of its co-factor pyridoxal phosphate (e.g. various hydrazides such as semicarbazide). In fact pyridoxal phosphate deficiency has been shown to be the cause of convulsions in children.

Clearly since a reduction in GABA function causes convulsions, then augmenting its function should provide an anticonvulsant action. This may be achieved in a number of ways as listed in Table 16.2 and indicated in Fig. 16.6. For more detail see Chapter 9.

Agonists and prodrugs

$GABA_A$ receptor agonists like muscimol and (Fig. 16.7) are active against PTZ in mice and amygdala kindling in rats but ineffective in the photosensitive baboon and in fact produce rhythmic spike and wave discharges in the EEG despite poor brain penetration. These discharges have also been seen in the few humans on which the drugs have been tested unsuccessfully.

The reason for this disappointing response is uncertain but may be due to desensitisation of the $GABA_A$ receptors, or the actual inhibition of GABA inhibitory neurons through somatic autoreceptors which could disrupt the precise timing of physiological inhibition. Activation of the $GABA_B$ receptor with baclofen has no

Table 16.2 Drug augmentation of GABA function

A	B
1 GABA receptor, agonists	$GABA_A$ — muscimol $GABA_B$ — baclofen
2 Gabamimetics	Progabide
Prodrugs	Gabapentin
3 GABA-t inhibitors	Ethanolamine-*o*-sulphate (EOS) Na^+ valproate γ vinyl-GABA (vigabatrin)
4 Uptake inhibitors	
Neuronal	DABA.ACHC
Glial	Nipecotic acid-tiagabine
5 Allosteric enhancement	Benzodiazepines
6 Chloride channel openers	Barbiturates

Notes:
Mechanisms are listed under A and examples of drugs that utilise them under B. All compounds that increase the action of endogenous GABA (1–5) augment neuronal inhibition and have an anticonvulsant action. Drugs that act directly on GABA receptors have not so far proved effective. Barbiturates do not really augment GABA function; they do not act on GABA receptors or modify its destruction, but can open Cl^- channels and so increase neuronal inhibition and thus the action of GABA.

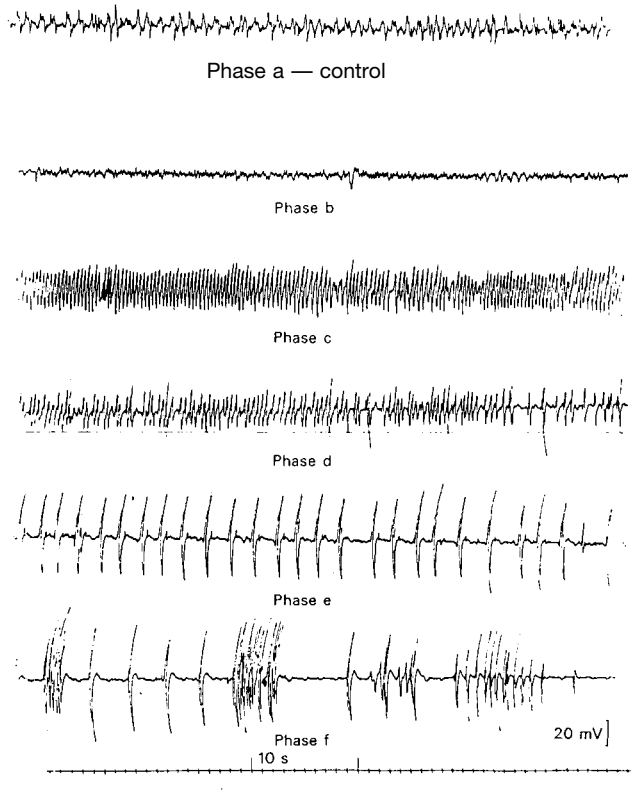

Figure 16.4 Changes in the pattern of EEG activity accompanying the development of a full ictal seizure in the anaesthetised rat during the slow intravenous infusion of pentylenetetrazol. The normal control pattern (phase a) quickly takes on an arousal state (phase b, 2–5 min). This gives way to waves of steadily increasing amplitude but low frequency (2 Hz) for 8–18 min (phase c) on which a few spikes gradually appear at 20 min (phase d). Spikes gradually predominate after some 26 min (phase e) until they group to give a full ictal seizure at 30 min (phase f). Pentylenetetrazol (0.5 M) infused at 30 $\mu l\,min^{-1}$, EEG recorded from skull screw electrodes over the parietal cortex. While this study does not mimic seizure development from a specific focus, since PTZ given systemically can act throughout the brain, it illustrates how cortical activity can become synchronised even without a primary focus. (Reproduced with permission of Macmillan Press Limited from Kent and Webster 1983)

general anticonvulsant effect even though it reduces reflex epilepsy in photosensitive baboons and spiking in hippocampal slices. That GABA function is important, however, in the control of epileptogenic activity is illustrated in Fig. 16.5 which shows that spiking induced in the cortex of the anaesthetised rat by leptazol occurs more readily if GABA function is reduced by the local application of its antagonist bicuculline but retarded if GABA itself is applied.

GABA-t inhibitors

GABA transaminase is a mitochondrial enzyme which, like GAD, requires pyridoxal phosphate as co-factor. It is present in both neurons and glia and while secondary to

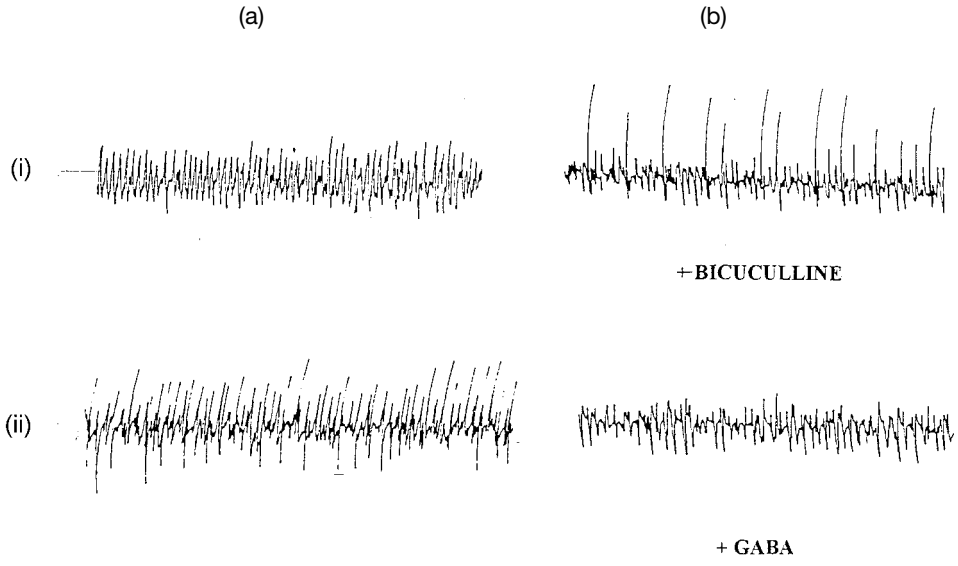

Figure 16.5 The importance of GABA in controlling the development of EEG epileptic spiking. The EEG records shown were taken from the anaesthetised rat during the infusion of pentylenetetrazol (PTZ). They were obtained from screw electrodes (a) in the skull over one parietal cortex and from electrodes within a cortical cup (b) on the other exposed parietal cortex which was superfused with artificial CSF to which drugs could be added. Thus while the whole cortex received PTZ only that area adjacent to the cup could be influenced by the drugs. Under control conditions the developing epileptogenic EEG was identical in both recordings. Records from the screw electrodes (a) showed the expected progressive change from wave-like (i) to spiking (ii) similar to phases c and d in Fig. 16.4. When the cortex under the cup electrodes (b) was exposed to the GABA antagonist bicucilline the EEG had already developed spiking (bi) while that from the screw electrodes (ai) still remained wave-like. By contrast, when GABA was in the cup the EEG within it developed more slowly with wave-like activity (bii) persisting when spiking had already developed in the record from the screw electrodes (aii). Clearly GABA retards the development of spiking. (Unpublished figure but see Kent and Webster 1986 for detail and drug concentrations)

uptake in the degradation of GABA a number of inhibitors have proved effective experimentally and some clinically. Ethanolamine-O-sulphate was one of the first tested. It produces a large (fortyfold) and sustained increase in brain GABA accompanied by a reduction in seizures induced by maximal electroshock. Gabaculine and aminooxyacetic acid are similar but are ineffective in man whereas γ-vinyl GABA (vigabatrin) has proved useful clinically. The use of this and sodium valporate is considered later.

Uptake inhibitors

GABA is removed from the synapse by a high-affinity sodium and chloride-dependent uptake into GABA neurons and surrounding glia. Blocking this process potentiates the inhibitory action of GABA applied directly to neurons *in vivo* and *in vitro*. Some inhibitors show specificity for glia and others for neuronal uptake, although since recent molecular cloning has revealed four distinct GABA transporters (Chapter 9)

this simple classification may require modification. Probably because of structural similarities to GABA, few of these compounds show brain penetration but tiagabin, a lipophilic form of nipecotic acid, has been tried successfully in refractory epilepsy.

Receptor modulators

Benzodiazepines bind to a specific site on the GABA chloride ionophore, which differs from that for GABA itself, but when occupied augments the binding and action of GABA to increase the frequency of opening of chloride ion channels. Thus they augment GABA inhibition. Many of them are potent anticonvulsants, especially when tested against PTZ and retard the development of kindling. Unfortunately their clinical value is limited by the development of tolerance.

Barbiturates also potentiate the action of GABA but as they can do this by directly increasing the duration of opening of the chloride ion channel, independently of the GABA or benzadiazepine receptor sites, they cannot strictly be considered to augment GABA. Some such as phenobarbetone are, however, of proven clinical value.

Glutamate

NMDA receptor antagonists such as AP5 and AP7 were first shown to be anticonvulsant following introcerebroventricular injection into DBA/2 mice susceptable to audiogenic seizures. In addition, they offer protection to PTZ, reduce the afterdischarge in amygdala kindled rats and can actually retard the development of kindling. Although AP7 has some effect in photosensitive baboons, systemically active compounds have proved difficult to synthesise. Recently felbamate, an antagonist at the glycine-sensitive site on the NMDA receptor, has shown systemic anticonvulsant activity and clinical efficacy.

Inhibition of glutamate release was thought to be the mode of action of lamotrigine. It reduces MES and kindling and also glutamate (and to a lesser extent GABA) release induced in brain slices by veratridine, which opens sodium channels. But it now seems likely that the actual block of sodium channels is its primary action (see later).

The epileptic discharges induced in hippocampal slices by tetanic stimulation has been shown to be accompanied by reduced GABA-mediated IPSPs (Stelzer, Slater and Bruggencate 1987). Since AP7 not only reduced the discharges but also restored the response to GABA some linkage between NMDA and $GABA_A$ receptors seems probable. In fact the interaction between glutamate and GABA probably means that both of them and possibly their different receptors may need to be manipulated appropriately to control convulsive activity. This has been shown in fact experimentally when bicuculline was infused intravenously for short periods in the rat to give a burst of epileptic-like spiking in the EEG. Superfusion of the cortex using the cup technique with the glutamate AMPA antagonist CNQX or the $GABA_B$ agonist baclofen reduced the actual number (initiation) of spikes but not their amplitude, while NMDA antagonists (AP7) and the $GABA_A$ agonist muscimal reduced the size (development and spread of excitation) and not the number of spikes (Zia-Gharib and Webster 1991). Clearly more than one aspect of amino acid function may need to be controlled.

Other NTs have been implicated in the aetiology of epilepsy but direct evidence is lacking. They will be considered briefly.

ACETYLCHOLINE (ACh)

Cholinergic agonists, e.g. carbachol, applied to the rat cortex cause focal spiking and even seizures which can also be induced by large doses of CNS-penetrating anti-cholinesterases such as physostigmine (reversible inhibitor) or di-isopropylfluoro-phosphate (irreversible). Many studies have also shown that cortical ACh release increases in proportion to EEG activity during the administration of a wide range of convulsants. Nevertheless while cholinergic-induced seizures can be suppressed by antimuscarinic drugs they have no effect against any epilepsy in humans and ACh release presumably reflects rather than directly causes cortical activity.

MONOAMINES

The widespread and diverging nature of ascending monoamine pathways to the cortex suggest that NA and 5-HT are more likely to have a secondary modifying rather than a primary effect on the initiation of epileptic activity. In reality this is the case and their secondary role is even a minor one. Generally a reduction in monoamine function facilitates experimentally induced seizures (see Meldrum 1989) while increasing it reduces seizure susceptibility. The variability of the procedures used and results obtained do not justify more detailed analysis here.

Some mention should perhaps be made of dopamine, considering its role in the control of motor function. It is perhaps not surprising that DA agonists like apomorphine block the myoclonus induced in photosensitive baboons and audiogenic seizures in DBA/2 mice while neuroleptics (DA antagonists) may have a weak proconvulsant effect in humans. Also in rats with absence seizures dopa, apomorphine and D_1 agonists reduce facial clonus and spike and wave discharges, while the D_1 antagonist SCH 23390 increases them. Nevertheless, there is no evidence of a significant role for DA (or NA and 5-HT) in human epilepsies.

ADENOSINE

A number of studies have shown that adenosine inhibits neuronal firing both *in vitro* and *in vivo* and is itself released during intense neuronal activity. It can protect against PTZ seizures in rodents while the antagonist theophylline is proconvulsant. No clear picture of its role in human epilepsy has emerged.

APPROACHES TO THE CONTROL OF EPILEPTIC ACTIVITY

Irrespective of the cause of epilepsy, the spread of seizure activity will be attenuated by either decreasing the excitation or increasing the inhibition of neurons. This may be achieved in a number of ways, either *directly* by

(a) blocking excitatory voltage-gated Na^+ (or possibly Ca^{2+}) channels (1)
(b) increasing the opening of inhibitory Cl^- channels (2)

or *indirectly* by

(c) reducing the release of the excitatory NT, glutamate (3) or its action at NMDA receptors (4)

(d) increasing the availability (and release) of the inhibitory NT, GABA by blocking its reuptake (5) or metabolism (6) or activating the GABA receptor either directly (7) or through the benzodiazepine receptor (8).

These effects, to which the above numbers (1)–(8) refer, are shown in Fig. 16.6.

How the drugs currently available for the treatment of epilepsy may utilise these mechanisms will now be considered.

ANTIEPILEPTIC DRUGS (AEDs)

There is no shortage of AEDs (Fig. 16.7) but it is not appropriate to consider them in detail in this text other than to see how their mechanisms of action comply with and illustrate those proposed above (Fig. 16.6) for the control of epileptic seizures (see Meldrum 1996; Upton 1994). The decision on which drug to use depends not only on their proven efficacy in a particular type of epilepsy (some drugs are inactive in certain forms) but also what side-effects they have — many are sedative — how they interact with other drugs and how often they need to be taken. Compliance is a problem over a long period if dosing is required more than once a day. It is probably acceptable in reality, if not scientifically, to divide the drugs into old-established AEDs and new AEDs. Only the latter have been developed chemically to modify the known synaptic function of the amino acids.

OLD AEDs

Phenobarbitone was the first AED and was introduced in 1912. It was largely replaced in 1932 by phenytoin for the management of tonic–clonic seizures and partial and secondary epilepsy. Carbamazepine followed, then ethosuximide for absence seizures and valproic acid. These remained, apart from the introduction of the benzodiazepines, the mainstay of therapy until the last decade. They were introduced solely on their ability to control experimentally induced seizures. Their mechanisms of action were unknown and no thought was given to the possibility of NT modification and in fact subsequent research has shown that with the exception of the benzodiazepines none of them work primarily through NT manipulation. They act directly on neuronal excitability.

Phenytoin and carbamazepine

An effective AED might control seizures and not be too sedative, by stopping a neuron from firing excessively without affecting its ability to respond normally. This is how phenytoin is believed to work. Studies in cultured spinal cord neurons (Macdonald and McLean 1986) have shown that concentrations of phenytoin equivalent to those occurring clinically do not affect the resting membrane potential or the shape of a single-action potential but reduce the rapid discharge induced by depolarising the neuron, while leaving the first action potential intact (Fig. 16.8). It is believed to block voltage-dependent sodium channels (not those mediating the synaptic currents) after their activation, i.e. when they become inactivated, and so maintains them in that inactivated state and unresponsive. These effects, which are also shown by carbamazepine, would explain their effectiveness experimentally against maximal electroshock-induced

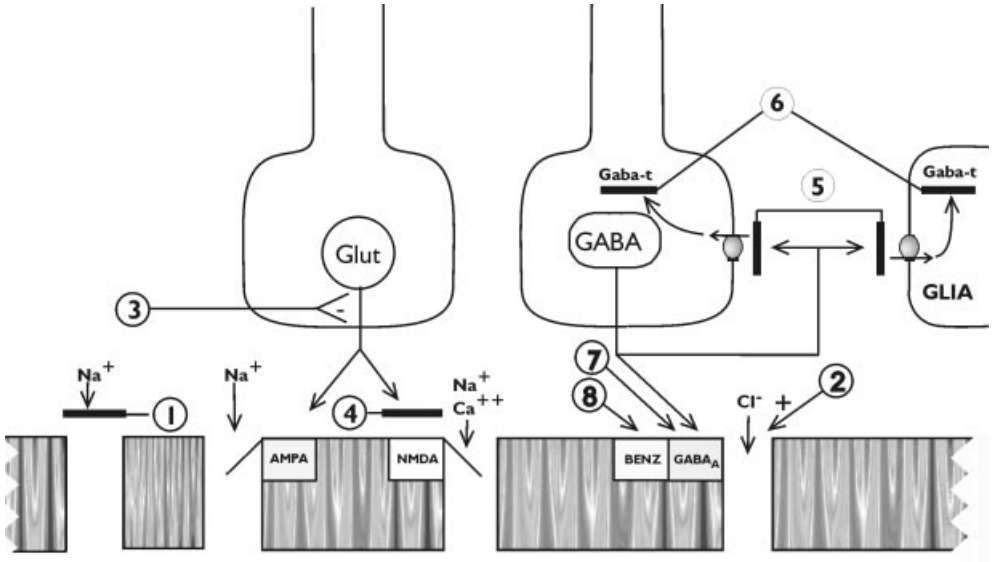

Figure 16.6 Possible sites of action of antiepileptic drugs. Antiepileptic drugs either directly affect ion channels to reduce Na^+ (1) or increase Cl^-(2) influx, depress glutamate release (3) or its action through NMDA receptors (4), or potentiate the effect of GABA by reducing its destruction by uptake (5) or metabolism by GABA transaminase (6), acting directly on $GABA_A$ receptors (7) or potentiating that effect of GABA through an action on benzodiazepine receptors that allosterically alter the $GABA_A$ site (8). Currently there are no clinically useful drugs that act as glutamate receptor antagonists

seizures and clinically in focal and generalised epilepsy. Also, since they act only on the inactivated channel, they will not affect normal neuronal function, which is why in the experimental study, the first action potential remains unaltered. Neither compound is of any value against absence seizures and may exacerbate them. They have no clear effect on NT function although there is some evidence that *in vivo* they may potentiate GABA-induced chloride currents.

Ethosuximide

This is really only effective against absence seizures. Experimentally it has no effect on the voltage-gated sodium channels affected by phenytoin but has been reported to suppress the transient T-type calcium currents in the thalamic neurons which are the origin of the 2–3 Hz spike and wave discharge characteristic of this form of epilepsy (see Mody 1998 for detail). Since these discharges are thought to arise from oscillations in excitability induced by changes in the T-type calcium current (see section above on the origin of absence seizures), this would obviously be a neat explanation of its efficacy in that condition. Unfortunately some workers have not been able to repeat this finding at clinically equivalent concentrations and consider ethosuximide to reduce a special persistent Na^+ channel and a Ca^{2+}-activated K^+ channel.

Barbiturates and benzodiazepines (B & Bs)

As outlined above (see also Chapter 9), these drugs have been found to influence the Cl^- channel of the $GABA_A$ receptor. Phenobarbitone acts directly to prolong its

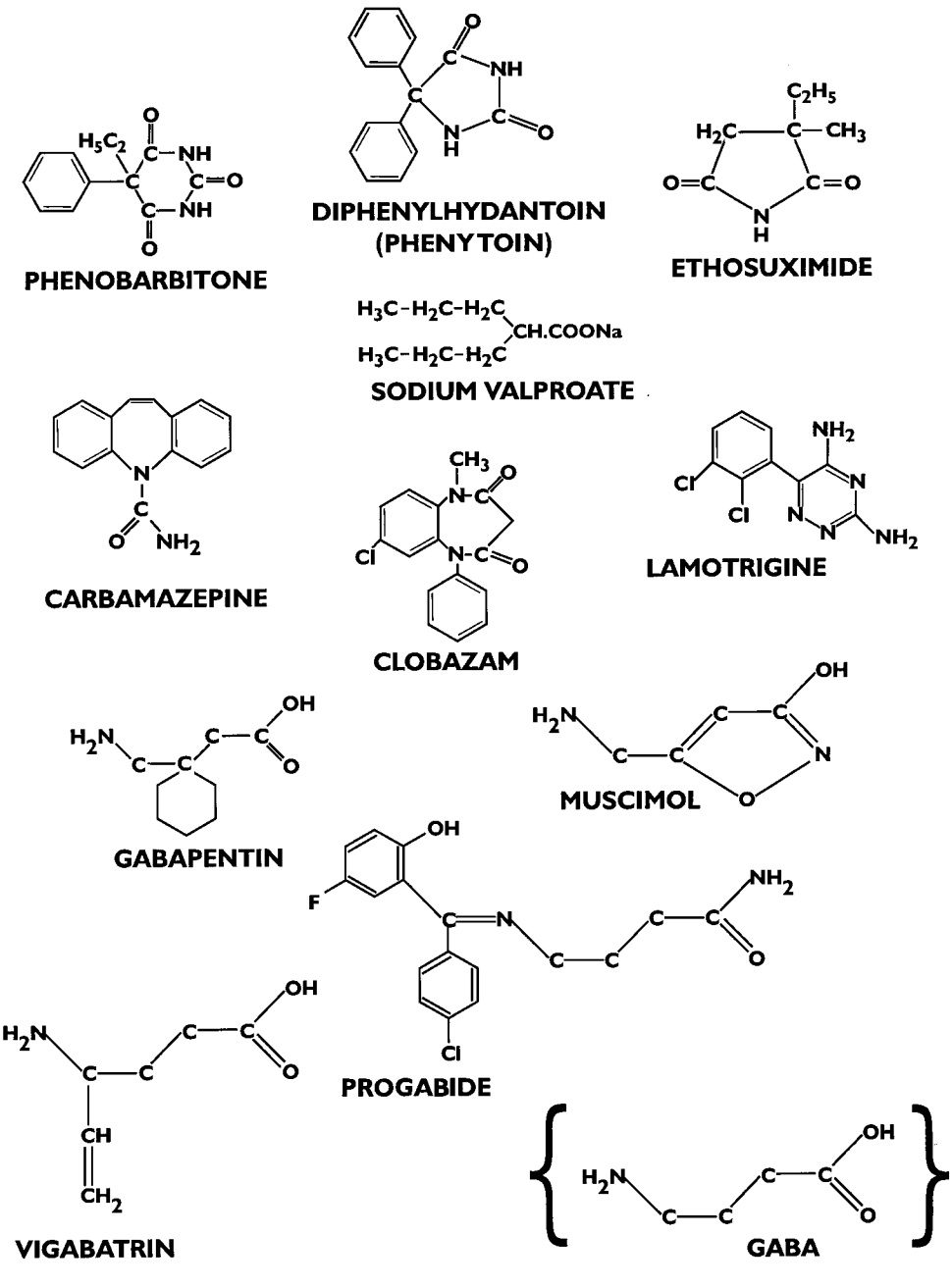

Figure 16.7 The structure of some established antiepileptic drugs (AEDs) and some newer ones. Note that while the structures of phenytoin and ethosuximide are similar and also close to that of phenobarbitone, they are effective in different forms of epilepsy. Vigabatrin, progabide and gabapentin are clearly related to GABA. Muscimol is a $GABA_A$ agonist but is not an effective antiepileptic drug

Table 16.3 Possible mechanisms of action and features of some antiepileptic drugs

	Use	Mode of action	Comments (half-life, hours)
Established drugs			
HYDANTOINS			
Diphenylhdantoin (phenytoin)	GM (PE)	1	Widely used. Hyperplasia of gums. Anti-folate. Teratogenic. Ineffective in PM (20–80)
DIBENZAPINES			
Carbamazepine	GM FE TLE	1	Improves mood. Related to tricyclic antidepressants. Drug of choice in FE (10–20)
SUCCINIMIDES			
Ethosuximide	PM (AS)	1	Drug of choice for PM, with Na valproate (20–60)
BARBITURATES			
Phenobarbitone	GM/FE	2	Sedative. Withdrawal fits. Little used (50–100)
Primidone	GM/PE		Works partly by conversion to phenobarbitone in body
BENZODIAZEPINES			
Diazepam	SE	8	Given intravenously in SE (<100)
Clonazepam	ME SE		Diazepam largely replaced by clonazepam
Clobazam	PM		Adjunct to other anti-epileptics. Partly as an anxiolytic
SHORT-CHAIN FATTY ACIDS			
Sodium valproate	GM PM ME	6 also 1 (and 2)	Inhibition of GABA metabolism too slow to explain initial anti-convulsant effect. Increasing use in ME, PM, GM (5–15)
Newer drugs			
Lamotrigine	PE GM (AS)	4 (1)	Fewer side effects (24)
Gabapentin	PE GM	?	Excreted unchanged
Vigabatrin	PE (GM)	6	Exacerbates AS (PE)

Notes:
The numbers (1–8) refer to their sites of action as shown in Fig. 16.6. All compounds may produce some overt signs of CNS depression, e.g. ataxia, sedation, dizziness.

opening time (mechanism 2 in Fig. 16.8), while the benzodiazepines modify the $GABA_A$ receptor allosterically and increase the likelihood (frequency) of Cl^- channel opening. The benzodiazepines are particularly effective against experimentally induced PTZ seizures.

Phenobarbitone may be as effective as phenytoin and carbamazepine in partial and generalised tonic–clonic seizures but its other central effects such as sedation, depression, listlessness and cognitive impairment mar its usefulness.

Clonazepam, a typical 1:4 benzodiazepine, is effective in absence seizures, myoclonic jerks and tonic–clonic seizures and given intravenously it attenuates status epilepticus. It is less sedative than phenobarbitone but tolerance develops and its withdrawal, as

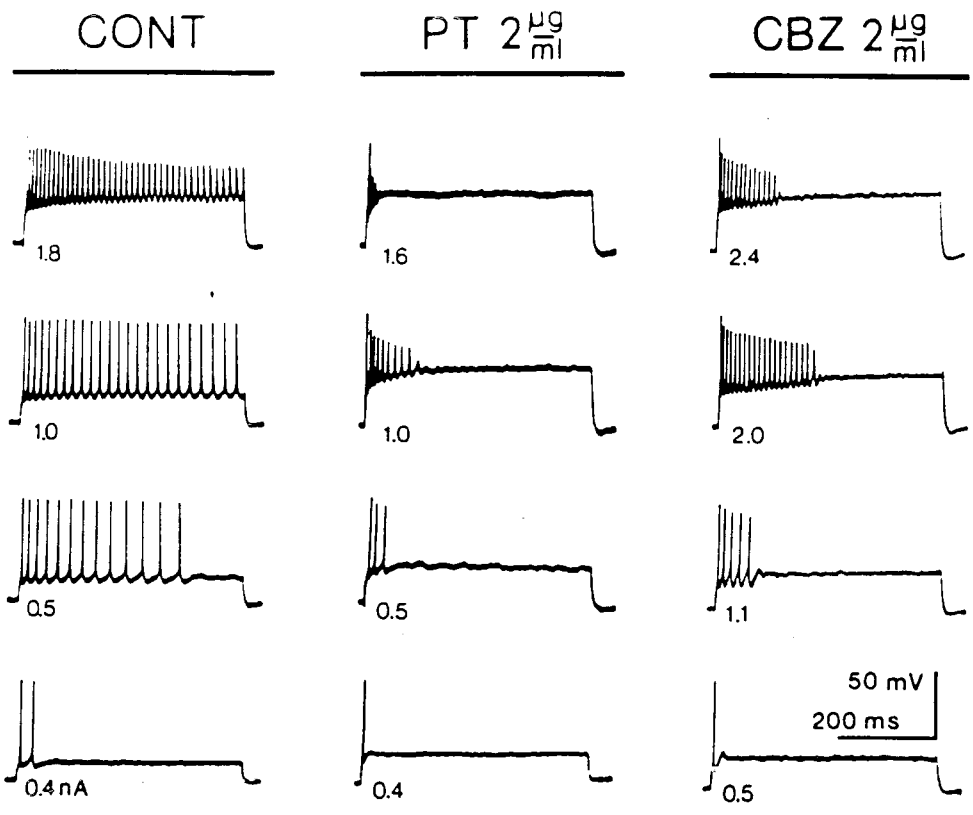

Figure 16.8 Cellular action of phenytoin and carbamazepine. Each column shows the response of a spinal cord neuron in culture to four increasing directly applied current pulses (amplitude in nA given at start of each sweep. Under control conditions (CONT)) the progressive depolarisations (bottom to top of each column of traces) induce increasing sustained discharges, whereas in the presence of phenytoin (PTZ) and carbamazepine (CBZ) firing cannot be maintained although the initial action potential remains. (Reproduced from MacDonald and McLean 1986.) These drugs are thought to bind to Na^+ channels after they have been active (opened) and maintain them in the inactivated state. Thus they do not affect the initial response but stop neurons from maintaining the abnormal sustained discharge that would be characteristic of epileptic activity. Resting membrane potentials (E_m) are shown at the bottom of each column and amplitude (mV) and time (ms) at the bottom right

with phenobarbitone, can precipitate seizures. Although still used in refractory myoclonic epilepsy, when its depressant effect on the spinal cord may be significant, clonazepam, like phenobarbitone, is rarely used now, but the more recently introduced 1:5 benzodiazepine clobazam is quite often used as an adjunct (not in the United States). While there is some belief and evidence that clonazepam and clobazam are more effective than other benzodiazepines as anticonvulsants nothing is known specifically about their modes of action that supports this view. The reported inhibitory effects of B & Bs on a calcium-sensitive NT release in synaptosomes is difficult to evaluate in terms of their *in vivo* anticonvulsant activity.

Valproic acid (sodium valproate)

Introduced initially for absence seizures, this drug is now known to be effective in and used to treat tonic–clonic seizures and most types of epilepsy. It was found to inhibit GABA transaminase and so elevate GABA concentrations and inhibition. This is achieved, however, over a slower time-course than its anti-seizure effect, especially experimentally, which is now thought to be due to its phenytoin-like, use-dependent block of sodium channels. Since, unlike phenytoin, the full effect of valproate takes some weeks to develop, its slower effect on GABA metabolism and activity should not be ignored.

NEW AEDs

Most of these have been used mainly as add-on therapy although some are now being used alone.

Lamotrigine

One unwanted side-effect of phenytoin is its anti-folate activity. A programme of synthetic chemistry to manipulate the structure of the anti-folate compound pyrimethium to try to replace that property with anticonvulsant activity resulted in the synthesis of lamotrigine. It proved to be an effective AED in partial and generalised epilepsy but experience has found it also to be of value in absence seizures.

Experimentally it was shown to reduce the release of glutamate and to a lesser extent GABA, induced in small brain slices by veratridine, a sodium ion channel opener. It now appears that its primary effect is prolonging the inactivation of sodium channels in a use-dependent manner much like phenytoin, although in a recent study of intracellularly recorded activity of striatal neurons in the rat corticostriatal slice preparation some differences emerged. While both drugs reduced experimentally induced repetitive firing, phenytoin was more effective against those induced by direct current activation of the neurons and also inhibited the EPSPs induced by the direct application of glutamate. By contrast, lamotrigine had little effect on the glutamate response but was more active against those induced by corticostriatal tract stimulation, suggesting that part of lamotrigine's action may still reside presynaptically in reducing glutamate release (Calabresi *et al*. 1999).

Vigabatrin (γ vinyl GABA)

This drug is chemically related to GABA, is an irreversible inhibiter of GABA transaminase and appears to produce its antiepileptic effect through that mechanism. Not only does it increase brain GABA levels in animals it also elevates them up to threefold in human CSF and in the occipital cortex of normal and epileptic patients as shown by nuclear magnetic resonance spectroscopy. An interesting decrease in glutamate may be secondary to the rise in GABA. It is effective in partial and secondary generalised epilepsy, but since its mode of action requires the regeneration of new enzyme (GABA-t) its effect far outlasts its plasma life. A worrying intramyelinic oedema in rat nerves has fortunately not been seen in humans or primates.

Tiagabine

Drugs that block the neuronal and in particular the glial uptake of GABA, like diaminobutyric acid and nipecotic acid respectively, proved effective anticonvulsants experimentally but had to be administered directly into the ventricals (intra-cerebroventrically). Attaching nipecotic acid to a lipophilic component to increase brain penetration resulted in tiagabine. Surprisingly, it appears to act preferentially on the GABA transporter GAT_1 which, although found on astrocytes, is more associated with nerve terminals. Microdialysis in rats shows it increases extracellular GABA and prolongs the post-excitatory hyperpolarisation of neurons. It has proved effective in partial and secondary generalised epilepsy but prolonged post- and possibly presynaptic actions of the increased GABA could present problems.

Gabapentin

This drug, which is a cyclohexone analogue of GABA, was synthesised in the hope that it would be an agonist for GABA receptors which could cross the blood–brain barrier. Its efficacy in drug-resistant partial and secondary generalised epilepsy means that it certainly must enter the brain but it does not bind to GABA receptors. Despite this, it appears to increase GABA brain levels in epileptic patients and weak potentiation of GAD and inhibition of GABA-t have been described. It does not appear to affect sodium or calcium channels even though experimentally chronic dosing blocks repetitive neuronal firing. Specific binding sites have been shown for it on neuronal membranes which appear to be a leucine transporter, but their significance is not clear.

OTHER NEW AEDs

The last few years has seen an explosion in AEDs. Some of those mentioned above may fall by the wayside and others appear. At the time of writing, we could include felbamate, zonisamide oxcarbazepine and topiramate. They all appear to have a phenytoin-like action on sodium channels, although topiramate appears to also potentiate the action of GABA on $GABA_A$ receptors like the benzodiazepines but through a different site.

SUMMARY

It will be apparent that all the possible mechanisms of action for anticonvulsant drugs outlined above (Fig. 16.6) have not been realised by those drugs currently available. The efficacy of glutamate NMDA antagonists is still restricted to experimental studies. No clinically useful drug has been developed and its synthesis will depend not only on finding a compound capable of entering the brain but also on the realisation of the hope that focal NMDA receptors may prove to be different from others. It may then be possible to target them specifically and avoid widespread depression. Lamotrigine does reduce the release of glutamate but this may be secondary to the blockade of sodium channels.

No directly acting $GABA_A$ receptor agonists have been found and it is likely that they would be too depressant (widespread in action) unless focal GABA, like NMDA, receptors have undergone some changes to become specifically targetable. Drugs that decrease the destruction of GABA such as GABA-t inhibitors (vigabratrim) and uptake blockers (tiagabine) have, however, been developed.

Despite all these approaches, drugs acting directly on neuronal ions channels are still the most effective AEDS.

Whether one drug with one mechanism of action will ever be adequate in the therapy of epilepsy is uncertain. Even drugs which apparently have a similar mechanism of action on sodium channels, such as phenytoin, carbamazepine, valproic acid and lamotrigine have different uses as only the latter two are effective in absence seizures. This could reflect some action additional to that on sodium channels (e.g. GABA-t inhibition for valproate) or an effect on a particular type of sodium channel that is different by virtue of some change in its α subunits. In fact the additional clinical effect of some new AEDs (e.g. vigabatrin and tiagabine) in patients not properly controlled by old AEDs like phenytoin could indicate the need for increased GABA function as well as sodium channel block for proper seizure control. The obvious complexity of NT and ion channel interactions in the control of neuronal function may well mean that the proper control of seizures may require the appropriate manipulation of more than one NT and one neuronal function.

Newer AEDs do have some advantages in that they tend to have fewer effects on the metabolism of each other or other drugs. By contrast, phenobarbitone is one of the most potent inducers of the microsomal enzyme system (cytochrone P_{450}) responsible for the metabolism of drugs. Phenytoin and carbamazepine have a similar but less marked effect while valproate inhibits the system.

One thing is certain. All the new AEDs are much more expensive than the older ones and one might therefore question the justification of their use. The reason is that the older ones have limited efficacy and not-inconsiderable toxicity. Indeed even with polytherapy the seizures are not always adequately controlled. So are there other approaches?

OTHER TREATMENTS

Surgery

If there is a clear established focus then maybe the best treatment is to remove it. This is, of course, both difficult and expensive but its use is expanding with about 500 operations per year in the UK. It is only considered in cases of partial (not general) epilepsy when conventional drug therapy has failed and a clear focus can be established. The advent of sophisticated assessments, such as MIR, long-term EEG telemetry, in-depth electrode recording and PET studies of blood flow and diazepan binding has now made this possible. Most commonly part of the anterior temperal lobe is removed, 70% of patients become seizure-free and neurological (mainly visual) and psychiatric problems are surprisingly few (5–10%).

Gliosis

This is not really a treatment but there is a view that glial cells can protect against seizures since the enzyme systems they possess (e.g. $Na–K^+$ATPase and carbonic anhydrase) facilitate the regulation of ion movements and reduce the spread of seizures. Certainly ageing, a fatty diet, and phenytoin itself increase glial cell count while decreasing seizure susceptibility. In fact inhibition of carbonic anhydrase and the production of bicarbonate was one of the first treatments for epilepsy and a recent discovery that under certain circumstances intracellular bicarbonate can depolarise neurons has created a fresh interest in it.

REFERENCES

Avanzini, G (1992) Generalised epileptogenesis. In *Epileptogenic and Excitotoxic Mechanisms* (Eds Avanzini, G, Fariello, R, Heinemann, U and Mutani, R), John Libbey, London pp. 29–40.

Avanzini, G, de Curtis, M, Marescaux, C, Panzica, F, Spriefico, R and Vergnes, M (1992) Role of the thalamic reticular nucleus in the generation of rhythmic thalamo-cortical activities subserving spike and waves. *J. Neural Trans.* **35** (Suppl): 85–95.

Calabresi, P, Centonze, D, Marfia, GA, Pisani, A and Bernardi, G (1999) An *in vitro* electrophysiological study on the effects of phenytoin, lamotrigine and gabapentia on striatal neurons. *Brit. J. Pharmacol.* **126**: 689–696.

Dodd, PR and Bradford, HF (1976) Release of amino acids from the mature cobalt induced epileptogenic focus. *Brain Res.* **111**: 377–388.

Fletcher, CF, Lutz, CM, O'Sullivan, TN, Shaughnessy Jr, JD, Hawkes, R, Frankel, WN, Copeland, NG and Jenkins, NA (1996) Absence epilepsy in tottering mutant mice is associated with calcium channel defects. *Cell* **87**: 607–617.

Isokawa, M (1996) Decrement of $GABA_A$ receptor mediated inhibitory postysynaptic currents in dentate granule cells in epileptic hippocampus. *J. Neurophysiol.* **75**: 1901–1908.

Isokawa, M, Levesque, MF, Babb, TL and Engel Jr, J (1993) Single mossy fibre axonal systems of human dentate granule cells studied in hippo-campal slices from patients with temporal lobe epilepsy. *J. Neurosci.* **13**: 1511–1522.

Isokawa, M, Levesque, M, Fried, I and Engel, J Jr (1997) Glutamate currents in morphologically identified human dentate granule cells in temporal lobe epilepsy. *J. Neurophysiol.* **77**: 3355–3369.

Jasper, HH and Drooglewer-Fortuyn, J (1997) Experimental studies of the functional anatomy of petit mal epilepsy. *Ass. Res. Nerv. Ment. Dis. Proc.* **26**: 272–298.

Jobe, PC, Mishra, PK, Ludwig, N and Dailey, JW (1991) Scope and contribution of genetic models to an understanding of the epilepsies. *Crit. Rev. Neurobiol.* **6**: 183–215.

Kent, AP and Webster, RA (1983) The evaluation of different types of anti-convulsant drug activity against leptazol-induced epileptogenic activity in the anaesthetised rat. *Brit. J. Pharmac.* **78**: 553–559.

Kent, AP and Webster, RA (1986) The role of GABA and excitatory amino acids in the development of the leptazol-induced epileptogenic EEG. *Neuropharmacology* **25**: 1023–1030.

McNamara JO (1999) Emerging insights into the genesis of epilepsy. *Nature* **399**: Suppl A15–22.

Macdonald, RL and McLean, MJ (1986) Anticonvulsant drugs: mechanisms of action. *Adv. Neurol.* **44**: 713–736.

Masukawa, LM, Higashima, M, Kim, JH and Spencer, DD (1989) Epileptiform discharges evoked in hippocampal brain slices from epileptic patients. *Brain Res.* **493**: 168–174.

Meldrum, BS (1989) The epilepsies. In *Neurotransmitters, Drugs and Disease* (Eds Webster, RA and Jordan, CC), Blackwell, pp. 301–334.

Meldrum, BS (1996) Update on the mechanism of action of antiepileptic drugs. *Epilepsia* **37** (Suppl. 6): 4–11.

Meldrum, BS and Corsellis, JAN (1984) Epilepsy. In *Greenfield's Neuropathology*, 4th edn (Eds Blackwood, W and Corsellis, JAN), Edward Arnold, London, pp. 921–950.

Mody, I (1998) Ion channels in epilepsy. *Int. Rev. Neurobiol.* **42**: 199–226.

Prince, DA (1992) Basic mechanisms of focal epileptogenesis. In *Epileptogenic and Excitotoxic Mechanisms* (Eds Avanzini, G, Fariello, R, Heinemann, U and Mutani, R), John Libbey, London, pp. 17–27.

Prince, DA and Connors, BW (1986) Mechanisms of interictal epileptogenesis. *Adv. Neurol.* **44**: 275–299.

Stelzer, A, Slater, NT and Bruggencate, G (1987) Activation of NMDA receptors blocks GABA ergic innervation in an *in vitro* model of epilepsy. *Nature* **326**: 698–701.

Upton, N (1994) Mechanisms of action of new anti-epileptic drugs. *Trends Pharmacol. Sci.* **15**: 456–462.

Wong, RKS, Traub, RD and Miles R (1986) *Cellular Basis of Neuronal Syncronyic Epilepsy* **44**: 583–592.

Zia-Gharib, F and Webster, RA (1991) Effects of compounds modulating amino acid transmission on the development and control of bicuculline-induced epileptogenic spiking in the rat. *Neuropharmacology* **30**: 995–1009.