THE NEUROBIOLOGY OF ANTIEPILEPTIC DRUGS

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Antiepileptic drugs (AEDs) provide satisfactory control of seizures for most patients with epilepsy. The drugs have the remarkable ability to protect against seizures while permitting normal functioning of the nervous system. AEDs act on diverse molecular targets to selectively modify the excitability of neurons so that seizure-related firing is blocked without disturbing non-epileptic activity. This occurs largely through effects on voltage-gated sodium and calcium channels, or by promoting inhibition mediated by $GABA_A$ (γ-aminobutyric acid, type A) receptors. The subtle biophysical modifications in channel behaviour that are induced by AEDs are often functionally opposite to defects in channel properties that are caused by mutations associated with epilepsy in humans.

ANTIEPILEPTIC DRUG
A drug that protects against the occurrence of epileptic seizures; an alternative to the term 'anticonvulsant drug'.

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ANTIEPILEPTIC DRUGS (AEDs) are primarily intended to prevent epileptic seizures. They are also beneficial in diverse non-epileptic conditions and are commonly used in the treatment of migraine headache, neuropathic pain and bipolar affective disorder. AEDs can also be useful for treating essential tremor, myotonia, dystonia, anxiety disorders, schizophrenia, restless legs syndrome, social phobia, post-traumatic stress syndrome, and alcohol dependence and withdrawal[1]. Around two-dozen distinct molecular entities are marketed worldwide for epilepsy (BOX 1). To exhibit antiepileptic activity, a drug must act on one or more target molecules in the brain. These targets include ion channels, neurotransmitter transporters and neurotransmitter metabolic enzymes. The ultimate effects of these interactions are to modify the bursting properties of neurons and to reduce synchronization in localized neuronal ensembles. In addition, AEDs inhibit the spread of abnormal firing to distant sites, which is required for the expression of behavioural seizure activity. GENERALIZED ABSENCE SEIZURES, unlike other seizure types, are believed to result from thalamocortical synchronization. Interference with the rhythm-generating mechanisms that underlie the synchronized activity in this circuit is necessary to abort these seizures.

It is convenient to categorize AED actions according to those that involve (1) modulation of voltage-gated ion channels; (2) enhancement of synaptic inhibition; and (3) inhibition of synaptic excitation. Voltage-gated ion channels (including sodium, calcium and potassium channels) shape the subthreshold electrical behaviour of the neuron, allow it to fire action potentials, regulate its responsiveness to synaptic signals, contribute to the PAROXYSMAL DEPOLARIZATION SHIFT, and ultimately are integral to the generation of seizure discharges. In addition, voltage-gated ion channels are crucial elements in neurotransmitter release, which is required for synaptic transmission. Consequently, they are key targets for AEDs that inhibit epileptic bursting, synchronization and seizure spread. Synaptic inhibition and excitation are mediated by neurotransmitter-regulated channels; these channels permit synchronization of neural ensembles and allow propagation of the abnormal discharge to local and distant sites. AEDs that modify excitatory and inhibitory neurotransmission therefore can also suppress bursting and, when they inhibit synaptic excitation, can have prominent effects on seizure spread.

Which ion channels are relevant to the actions of AEDs? Studies in animal models have shown that protection from seizures can be achieved by blockade of sodium or calcium channels, and probably also through facilitation of potassium channels (as might be the case for the novel AED retigabine[2]). Antiepileptic effects are also produced by drugs that enhance inhibition mediated by $GABA_A$ (γ-aminobutyric acid, type A) receptors, or through effects on glycine systems, the regionally specific transmitter systems (including

Box 1 Currently approved antiepileptic drugs

The following antiepileptic drugs are registered in the United States and elsewhere: acetazolamide, carbamazepine, clonazepam, clorazepate, ethosuximide, ethotoin, felbamate, gabapentin, lamotrigine, levetiracetam, mephenytoin, methsuximide, oxcarbazepine, phenobarbital, phenytoin, primidone, tiagabine, topiramate, trimethadione, valproate, vigabatrin (available in Canada, Europe and elsewhere, but not the United States) and zonisamide.

The following additional agents are mainly used for the acute therapy of status epilepticus: diazepam, fosphenytoin, lorazepam, midazolam and propofol.

GENERALIZED ABSENCE SEIZURE A non-convulsive seizure that typically occurs in childhood. It is characterized by a sudden, brief impairment of consciousness, cessation of ongoing activity without loss of postural tone, and 3 Hz rhythmic cortical discharges of geneneralized onset. The usual duration is 5–10 seconds; several episodes can occur daily.

monoamines such as catecholamines, serotonin and histamine, and neuropeptides such as opioid peptides, galanin and neuropeptide Y) and the inhibitory neuromodulator adenosine[3]. In addition, blockade of glutamate receptors (including those of the NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), kainate and group I METABOTROPIC mGluR1 and mGluR5 types) can also protect against seizures in animal models. In principle, it might be possible to prevent seizures by targeting any one or a combination of these systems. In fact, the development of AEDs by screening in animal models that are non-biased with respect to mechanism has uncovered drugs that act by unique combinations of these mechanisms, and in some cases has identified drugs that act by entirely new mechanisms. As a result, marketed AEDs act by a remarkable diversity of actions, and no two marketed drugs work in exactly the same way.

Molecular targets of AED action

Voltage-gated sodium channels. Voltage-gated sodium channels are responsible for the rising phase of neuronal action potentials. When neurons are depolarized to action potential threshold, the sodium channel protein senses the depolarization and, within a few hundred microseconds, undergoes a conformational change that converts the channel from its closed (resting) non-conducting state to the open conducting state that permits sodium flux. Within a few milliseconds, the channel inactivates, terminating the flow of sodium ions. The channel must then be repolarized before it can be activated again by a subsequent depolarization. Brain sodium channels can rapidly cycle through the resting, open and inactivated states, allowing neurons to fire high-frequency trains of action potentials, as is required for normal brain function and for the expression of epileptic activity.

Table 1 | Antiepileptic drugs and their molecular targets

Drug	Sodium channels*	Calcium channels*	GABA system*	Glutamate receptors*	Partial seizure‡	GTC seizure‡	Absence seizure‡	Myoclonic seizure‡	Infantile spasms‡§	Lennox-Gastaut‡
Predominant sodium (and calcium) channel activity										
Phenytoin	I_{NaF}, I_{NaP}				+	+	–	–		
Carbamazepine	I_{NaF}				+	+	–	–		
Oxcarbazepine	I_{NaF}				+	+	–	–		
Lamotrigine	I_{NaF}	HVA			+	+	+	(+/–)		+
Zonisamide	I_{NaF}	T-type			+	+	(+)	(+)	(+)	(+)
Mixed, complex or poorly understood actions										
Valproate	I_{NaF}? I_{NaP}?	T-type?	↑ GABA turnover		+	+	+	+		(+)
Felbamate	I_{NaF}	HVA	$GABA_AR$	NMDA	+	+	(+)			+
Topiramate	I_{NaF}, I_{NaP}	HVA	$GABA_AR$	KA/AMPA	+	+	(+)	(+)	(+)	+
Ethosuximide	I_{NaP}?	T-type			–	–	+			
Gabapentin		HVA (α2δ)	↑ GABA turnover		+	+	–	–		
Levetiracetam‖		HVA	Reverses DMCM		+	(+)	(+)	(+)		
Phenobarbital		HVA	$GABA_AR$	AMPA	+	+	–			
GABA-mediated mechanisms										
Benzodiazepines			$GABA_AR$		+	+	+	+		(+)
Vigabatrin			GABAT		+	+	–	–	+	(+)
Tiagabine			GABA-transporter		+	+	–			

*Molecular targets. Not all molecular targets are shown; additional targets are discussed in the text. ‡Clinical efficacy of drugs on symptoms. Clinical evidence: '+' indicates controlled trials or several open-label trials and general acceptance of utility; parentheses indicate less extensive base of evidence. '–' indicates evidence of lack of efficacy or worsening. §A catastrophic epilepsy syndrome usually beginning in the first year of life in which there are typically 'jackknife spasms' (myoclonic seizures involving the muscles of the neck, trunk and limbs, with nodding of the head and stiffening of the arms) and a disorganized cortical discharge termed hypsarrhythmia. ‖ Levetiractam binds with high affinity to synaptic vesicle protein 2A (SV2A), a ubiquitous 90 kDa protein that is associated with synaptic vesicles and is believed to participate in the regulation of Ca^{2+}-dependent neurotransmitter release; SV2A-knockout mice exhibit seizures[138]. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; GABA, γ-aminobutyric acid; $GABA_AR$, $GABA_A$ receptor; GTC, generalized tonic-clonic; HVA, high voltage activated; I_{NaF}, fast sodium current; I_{NaP}, persistent sodium current; KA, kainate; NMDA, *N*-methyl-D-aspartate. DMCM (methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate) is a negative allosteric modulator of $GABA_A$ receptors. Adrenocorticotropic hormone and prednisolone are recognized treatments for infantile spasms. Lamotrigine is also effective in myoclonic astatic epilepsy, but causes worsening of other forms of myoclonic epilepsy. Gabapentin has been associated with focal myoclonus.

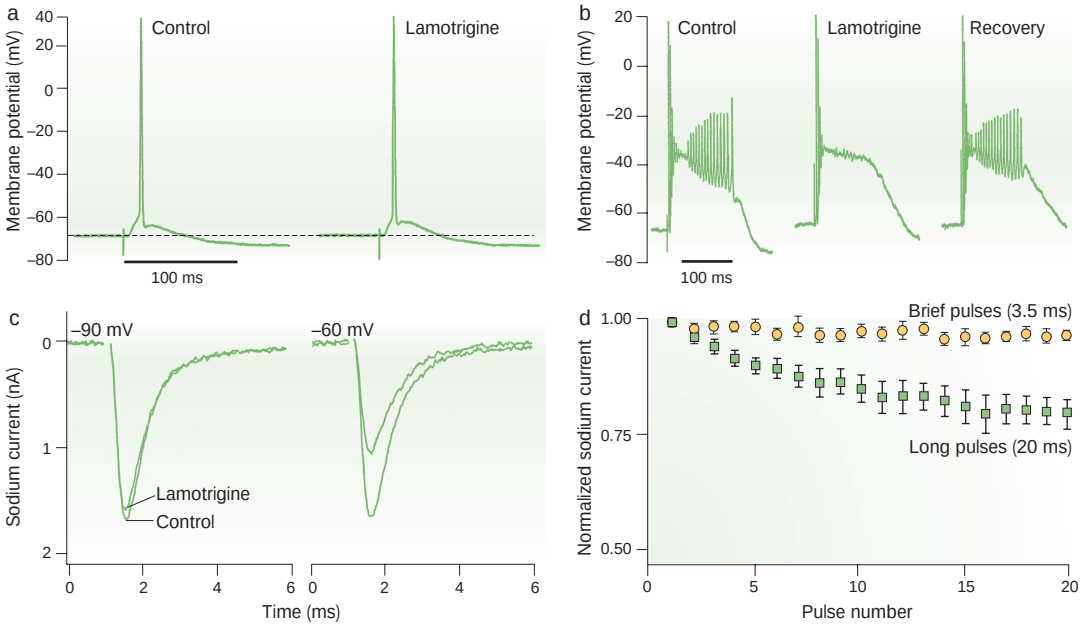

Figure 1 | **Lamotrigine selectively blocks epileptiform discharges without affecting ordinary action potential firing.** **a** | Intracellular recording showing lack of effect of lamotrigine (50 μM) on evoked excitatory synaptic response with superimposed sodium-dependent action potentials. **b** | Recording under magnesium-free conditions (to enhance NMDA (*N*-methyl-D-aspartate) receptor responses) and in the presence of 20 μM bicuculline (to block $GABA_A$ (γ-aminobutyric acid, type A) receptors) showing that lamotrigine selectively inhibits late epileptiform after-discharges without affecting initial action potential responses. Intracellular recordings are from rat CA1 hippocampal neurons evoked with Schaffer collateral/commissural fibre stimulation. **c** | Whole-cell voltage-clamp recording from CNaIIA-1 cells (CHO-K1 cells stably transfected with cDNA encoding rat brain type IIA sodium channels) illustrating voltage-dependent inhibition of sodium current by lamotrigine (50 μM). Currents were activated by step-depolarization to 0 mV from a 30 s conditioning prepulse at the indicated membrane potentials. **d** | Accumulation of block of sodium current with repetitive depolarization (11 Hz) from –90 to 0 mV with pulses of two durations illustrating use-dependence. Modified, with permission, from REF. 17 © (1995) Springer-Verlag.

PAROXYSMAL DEPOLARIZATION SHIFT
Abnormal prolonged depolarization with repetitive spiking characteristic of neurons in epileptic cortical zones that are reflected as interictal discharges in the electroencephalogram.

METABOTROPIC RECEPTOR
A G-protein-coupled receptor that may indirectly influence the activity of ion channels but does not itself serve as a channel.

GENERALIZED TONIC-CLONIC SEIZURE
A convulsive seizure involving the entire body, usually characterized by muscle rigidity, violent rhythmic muscle contractions and loss of consciousness.

PARTIAL SEIZURE
Seizure resulting from a localized brain disturbance; also referred to as 'focal seizure'.

SODIUM CHANNEL INACTIVATION
Entry of the sodium channel into a set of states that are distinct from the open and closed states that prevents the channel from reopening until there has been sufficient time for recovery, thereby preventing persistent sodium flux during long depolarizations.

Modulation of the gating of brain sodium channels is believed to account, at least in part, for the ability of several AEDs to protect against GENERALIZED TONIC-CLONIC and PARTIAL SEIZURES. These AEDs include phenytoin, lamotrigine, carbamazepine, oxcarbazepine[4,5] and zonisamide[6], and possibly felbamate[7], topiramate[8] and valproate[9–13] (TABLE 1). These drugs block high-frequency repetitive spike firing, which is believed to occur during the spread of seizure activity, without affecting ordinary ongoing neural activity (FIG. 1a,b). This accounts for their ability to protect against seizures without causing a generalized impairment of brain function. At hyper-polarized membrane potentials, clinically relevant concentrations of sodium channel-blocking AEDs such as phenytoin, carabamazepine and lamotrigine block sodium channels only weakly[13–17]. However, when the membrane is depolarized, there is a marked increase in the degree of tonic inhibition (FIG. 1c). Moreover, the inhibitory potency is strongly 'use-dependent', so the block accumulates with prolonged or repetitive activation (FIG. 1d). These properties are explained by preferential binding of the drugs to inactivated conformations of the channel. These agents act mainly on action potential firing; the drugs do not directly alter excitatory or inhibitory synaptic responses. However, the effect on action potentials translates into reduced transmitter output at synapses, and glutamate release might be inhibited more strongly than that of other neurotransmitters, including GABA[18,19].

In recent years, the mechanism of SODIUM CHANNEL INACTIVATION has been elucidated and this has provided an opportunity to clarify the way in which phenytoin and other sodium channel-blocking AEDs promote channel inactivation. The normal predominant (fast) inactivation process results from occlusion of the intracellular mouth of the channel by a short loop of amino-acid residues between domains III and IV of the sodium channel α-subunit that serves as a 'hinged lid'[20] (FIG. 2). An additional inactivation process, referred to as 'slow inactivation', begins to come into play with more prolonged depolarizations, such as might occur in association with epileptiform activity[21]. Whereas fast sodium channel inactivation is characterized by rapid (millisecond timescale) onset and recovery, leading to changes in the available pool of sodium channels over the time course of a single action potential, onset and recovery of slow inactivation require several seconds. Slow inactivation contributes to slow spike-frequency adaptation and to the termination of action potential bursts occurring as a result of prolonged or repetitive neuronal depolarization.

The molecular rearrangement that leads to slow inactivation is unknown, but it is distinct from that of fast inactivation. Single channel recordings show that phenytoin does not alter the conductance of the open state of sodium channels[22]. Phenytoin also does not seem to 'stabilize' the normal process of fast inactivation of the sodium channel; in fact, the drug can block

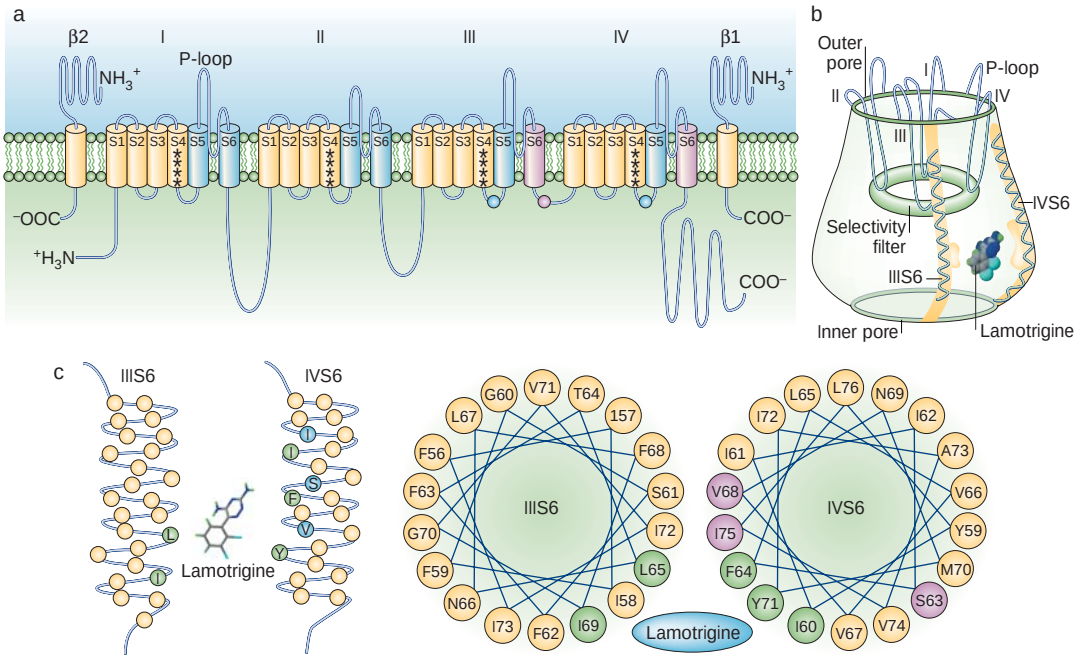

Figure 2 | **Antiepileptic drugs (AEDs) and sodium channels. a** | Primary structures of the subunits of brain type II voltage-gated sodium channels. The main α-subunit, consisting of four homologous repeats (I–IV), is shown flanked by the two auxiliary β-subunits. Cylinders represent probable α-helical transmembrane segments. Blue α-helical segments (S5, S6) form the pore region. Asterisks, S4 voltage sensor; pink circle, inactivation particle in inactivation gate loop ('tethered pore blocker'); blue circles, sites implicated in forming the receptor for the inactivation gate; IIIS6 and IVS6 (pink segments) are regions of modulatory drug binding, including sodium channel-blocking AEDs. **b** | Schematic illustration of the sodium channel pore. The S5 and S6 transmembrane α-helical segments from each homologous repeat (I–IV) form the four walls of the pore. The outer pore mouth and ion selectivity filter are formed by re-entrant P-loops. The key α-helical S6 segments in repeat III and IV, which contain the AED binding sites, are highlighted in yellow. A lamotrigine molecule is illustrated in association with its binding sites. **c** | Amino-acid residues that constitute the lamotrigine binding site in transmembrane segments IIIS6 and IVS6. Left, extended view of the α-helical segments. Substitution of the green residues by alanine results in greater than fivefold reduction in lamotrigine binding affinity for the inactivated state of the channel; substitution of blue residues reduces binding by two- to fivefold. Lamotrigine is shown within the channel pore. Right, axial view (helical wheel representation) of amino-acid side chains according to ideal α-helix with 3.6 residues per turn. Modified, with permission, from REF. 35 © (2001) American Society for Biochemistry and Molecular Biology.

enzymatically treated channels that lack fast inactivation[23]. Rather, phenytoin induces a non-conducting state of the channel that is similar to channel inactivation. Recovery from drug block of the channel occurs much more slowly than does recovery from block by the intrinsic pore blocker[23]. This, in part, accounts for phenytoin's selective ability to block high-frequency firing: when recovery is slow, the block can accumulate during repetitive activation of the channel.

Interestingly, sodium channel mutations that are associated with accelerated recovery from inactivation and increased sodium channel activity (producing a 'gain-of-function') can lead to enhanced seizure susceptibility, as in the epilepsy syndrome GEFS+ type 2 (REF. 24). However, the syndrome is associated with a mutation (T875M) that paradoxically promotes slow inactivation[25]. Computational modelling, with the assumption that recovery from slow inactivation is also promoted, has shown that the mutation can be associated with an enhanced propensity to fire repetitive action potentials[26]. Alternatively, it is conceivable that the mutation does reduce excitability and that the epileptic phenotype results because the firing of inhibitory neurons is affected. It is notable that pharmacologically induced impairment of sodium channel inactivation with AEDs such as phenytoin can also promote seizure activity in some circumstances[27,28]; whether this occurs as a result of effects on inhibitory neurons remains to be determined.

Another important feature of the block of sodium channels by phenytoin and lamotrigine (and one that distinguishes these drugs from local anaesthetics) is its slow onset[29,30]. However, once binding occurs it is tight, and unbinding (recovery from block) is slow. Slow binding has two important implications. First, it implies that the time course of sodium currents are not altered in the presence of the drug and therefore the kinetic properties of normal action potentials are not perturbed. Second, slow binding means that inhibition of action potentials does not occur with firing that has been induced by synaptic depolarizations of ordinary length. Rather, long depolarizations are required, possibly as long as a few seconds or more. In focal epilepsies, the cellular events that characterize ICTAL discharges are sustained depolarizations that evoke intermittent high-frequency bursts of action potentials. Such depolarizations provide the conditions required for drug binding and block. On the other hand, cortical INTERICTAL DISCHARGES are shorter and their frequency is generally not reduced by sodium

GEFS+
A pleotropic autosomal dominant epilepsy syndrome in which there are febrile seizures in childhood and afebrile generalized seizures that persist beyond 6 years of age, including absences, myoclonic seizures, atonic seizures and myoclonic-astatic seizures. The syndrome is distinct from common benign febrile seizures.

ICTAL
Relating to an epileptic seizure.

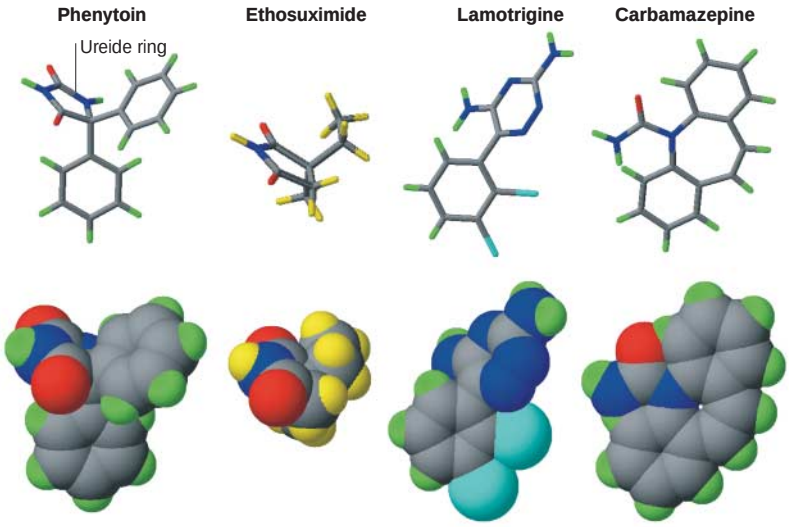

Figure 3 | **Stick and space-filling views showing diphenyl moiety common to the sodium-channel-blocking antiepileptic drugs phenytoin, lamotrigine and carbamazepine.** Although ethosuximide has a heterocyclic five-member ring comparable to the ureide ring of phenytoin, it is not a diphenyl structure and does not block fast sodium currents.

channel-blocking AEDs (except lamotrigine)[31]. Overall, sodium channel-blocking AEDs are expected to have little effect on the physiological generation of action potentials in neurons at normal resting potential levels. The voltage- and use-dependent characteristics of the block would come into play only during pathological, sustained depolarizing events associated with high-frequency discharges, therefore allowing protection against seizures without interference with normal function.

Studies using mixtures of phenytoin, carbamazepine and lamotrigine have revealed that these drugs bind to a common recognition site on sodium channels[32]. Although these three compounds are structurally dissimilar, they do contain a common motif of two phenyl groups separated by one or two C–C or C–N single bonds (1.5–3 Å) (FIG. 3). These two phenyl groups are probably crucial binding elements. Mutational analysis has provided evidence for the location of the AED binding domain. As illustrated in FIG. 2, the S5 and S6 segments are believed to form the lining of the sodium channel pore. Specific phenylalanine (F1764) and tyrosine (Y1771) residues in the S6 segment of domain IV are crucial for use-dependent block by phenytoin and lamotrigine[33,34]. Indeed, adjacent residues spread across 160° of the circumference of the IVS6 segment that flanks F1764 (FIG. 2c) are all relevant to the interaction. When the sodium channel is inactivated, the structure of the channel pore is altered, making the interaction with these residues more favourable. Channel gating is believed to be associated with rotation of the segment containing F1764, Y1771 and the surrounding amino acids so that these residues are brought into the pore, thereby facilitating drug binding. In addition, mutational analysis has revealed that the pore-lining residues leucine 1465 and isoleucine 1469 in IIIS6 also form a portion of the high-affinity binding site for sodium channel-blocking AEDs[35]. The aromatic rings in the antiepileptic molecules might interact with the aromatic side chains of the crucial residues in the IVS6 segment or with the nonpolar side chains of the IIIS6 residues. It is noteworthy that this region of the sodium channel is also implicated in inactivation gating[36].

In addition to effects on the fast sodium current that is responsible for action potentials, AEDs might also act by blocking the PERSISTENT SODIUM CURRENT. The persistent sodium current is ascribed to the current that flows as a result of the overlap between the voltage ranges for sodium channel activation and inactivation ('window' current)[37] and probably arises from alternate gating of the channels that are responsible for fast sodium currents[38], although certain sodium channel isoforms, most notably $Na_v1.6$, exhibit greater non-inactivating current and probably contribute more significantly to the persistent current[37,39]. The current carried by the persistent openings is a minute fraction (0.7–4%) of the fast current. However, this current might have a key role in regulating excitability near firing threshold because it is largely unopposed by other voltage-activated currents in this range of membrane potentials. Moreover, there is evidence that the persistent sodium current contributes to the initiation and maintenance of epileptiform activity[40]. Several authors have reported that phenytoin[40–43], valproate[11] and topiramate[8] inhibit the persistent sodium current at concentrations lower than those that block fast sodium current. The selective reduction of late, persistent sodium channel openings might contribute to the ability of these drugs to protect against seizures with minimal interference in normal function.

Changes in sodium channels that augment the persistent sodium current might contribute to epileptogenesis. In animal models of epileptogenesis, the voltage-dependent properties of sodium channels are altered so that there is greater persistent sodium current[44–46]. This has been attributed to reduced expression of the β1 and β2 auxiliary sodium channel subunits, which is predicted to lead to a depolarizing shift in sodium channel inactivation and greater overlap between the activation and inactivation curves so that the window current is amplified[47]. Moreover, sodium channel mutations that are associated with epilepsy in mice and humans (GEFS+) have been found to enhance the persistent sodium current[48].

Voltage-gated calcium channels. Voltage-gated calcium channels, like sodium channels, are multisubunit protein complexes that permit ion flux when they are gated open by membrane depolarization[49]. Calcium channels are broadly grouped into high voltage-activated (HVA) and low voltage-activated families. HVA channels — which are further subgrouped as L-, R-, P/Q- and N-types — require strong membrane depolarization for gating and are largely responsible for the regulation of calcium entry and neurotransmitter release from presynaptic nerve terminals. HVA calcium channels represent potential AED targets, as blockade of these channels inhibits neurotransmitter release[50]. These channels consist of an α1 protein (encoded by one of seven genes) that forms the channel pore and voltage sensor, along with several auxiliary subunits.

INTERICTAL DISCHARGES
Distinctive waves or complexes that can be recorded between seizures in the electroencephalogram of individuals with epilepsy. Generally brief in duration, but can have various morphologies described as 'sharp wave', 'spike' or 'spike-and-slow-wave'.

PERSISTENT SODIUM CURRENT
A small component of the sodium current that does not inactivate.

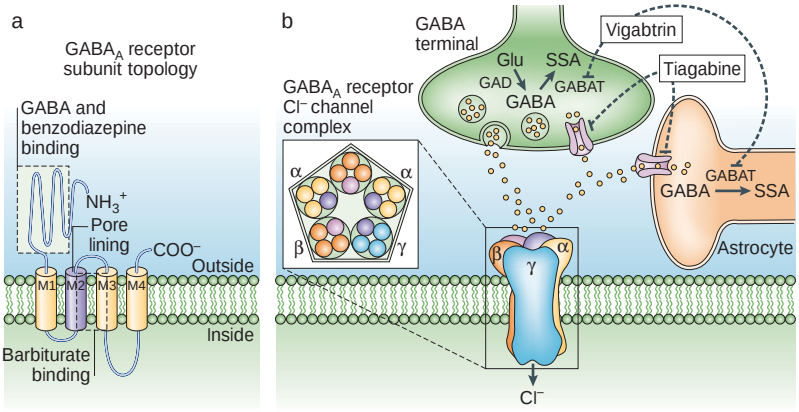

Figure 4 | **GABA receptors and antiepileptic drugs. a** | Membrane topology of GABA$_A$ (γ-aminobutyric acid, type A) receptor subunits. Residues identified as essential for agonist (GABA) and benzodiazepine binding are in the extracellular amino terminus. Barbiturates bind to the membrane-spanning M2 and M3 segments. **b** | Inhibitory GABA synapse illustrating synthesis of GABA in a presynaptic terminal from glutamate through the GABA-shunt of the tricarboxylic acid (Krebs) cycle by glutamate decarboxylase (GAD). In neurons and astrocytes, GABA is degraded by GABA transaminase (GABAT) to succinic semialdehyde (SSA); vigabatrin is an irreversible inhibitor of GABAT. Cylinders represent uptake transporters, which are inhibited by tiagabine. The pentameric structure of GABA$_A$ receptors is represented to the left. Small circles indicate membrane-spanning α-helical segments corresponding to those shown in **a**. M2 segments form the Cl^- channel pore.

Of particular interest from the perspective of AED mechanisms are the α2δ-1 and α2δ-2 auxiliary subunits, which bind the AED gabapentin and its analogues with high affinity[51,52]. Gabapentin, the lipophilic 3-cyclohexyl analogue of GABA, was originally synthesized in an attempt to develop a brain-penetrant GABA agonist. However, gabapentin lacks activity at GABA$_A$ receptors. Rather, the α2δ-binding affinities of gabapentin and analogues such as pregabalin correlate in a stereoselective fashion with their antiepileptic potency, strongly implicating these subunits as a relevant target[53,54]. The α2δ-subunits are highly glycosylated products of a single gene that is post-translationally cleaved into α2- and δ-peptides, which are then covalently linked by a disulphide bridge. α2δ-1 and α2δ-2 are believed to form complexes with many calcium channel types (represented by different α1 isoforms), allosterically enhancing current amplitude and also promoting channel trafficking to the membrane. In particular, the auxiliary subunits markedly augment the current through P/Q-type calcium channels (formed from the α1A/Ca_v2.1 principal calcium channel subunit)[55,56]. Mutagenesis experiments have shown that the gabapentin binding site is probably confined to the α2 protein and the external (rather than the transmembrane or internal) portion of the associated δ component[57,58].

The functional consequences of gabapentin binding to α2δ-1 and α2δ-2 are still not fully defined. Initial studies of the effect of gabapentin on neuronal calcium currents yielded inconsistent effects. However, several recent studies with dorsal root ganglion neurons have confirmed that the drug inhibits HVA calcium current in a concentration-dependent fashion at clinically relevant concentrations (~10–100 μM), although the effect is relatively small[59–61]. Nevertheless, the effect on calcium current probably translates into a reduction in excitatory transmission, as shown by inhibition of potassium-evoked glutamate release from brain slices[62] and suppression of excitatory postsynaptic currents, at least in spinal dorsal horn neurons[63]. Interestingly, increased expression of α2δ-1 in pain-sensitive dorsal root ganglion neurons and in the dorsal spinal cord might contribute to the hyperexcitability of pain pathways in neuropathic pain syndromes, and the ability of gabapentin to inhibit excitatory synaptic responses in the spinal cord is potentiated under such pathological circumstances[1]. It will be of interest to determine whether changes in subunit expression could similarly occur in epilepsy and affect gabapentin responsiveness. Although the α2δ subunit is at present the most plausible target for gabapentin, the drug has been found to increase GABA synthesis and turnover[64], and it seems to elevate GABA levels in the human brain, possibly through competitive inhibition of the system-L branched-chain-amino acid transporter or through reversal of the GABA-uptake transporter[65,66].

In addition to gabapentin, several other AEDs can, in part, act through inhibition of HVA calcium channels. For example, phenobarbital can block these channels, but its effects on GABA$_A$ receptors are probably more important in its antiepileptic activity[67]. Lamotrigine can also inhibit HVA (N- and P/Q-type) calcium channels[68,69]; it does not affect low voltage-activated T-type calcium channels[70]. Similarly, levetiracetam at clinically relevant concentrations has been reported to produce a small inhibition of calcium current[71], with a predominant affect on N-type channels[72].

In contrast to HVA calcium channels, whose main function is regulation of neurotransmitter release, low voltage-activated (T-type) calcium channels are believed to regulate neuronal firing by participating in bursting and intrinsic oscillations[73]. In the thalamus, these channels are crucial for the abnormal oscillatory behaviour that underlies generalized absence seizures[74]. In thalamic relay neurons and thalamic reticular neurons — GABA interneurons that modulate and synchronize thalamic output — T-type calcium channels generate 'low-threshold calcium spikes', which trigger a burst of action potentials mediated by sodium channels[75]. The T-type calcium channel family (Ca_v3) consists of the α1G, α1H and α1I subunits, which are ~30% homologous to HVA subunits in their putative membrane-spanning regions. Thalamic relay neurons express high levels of α1G subunits, whereas thalamic reticular neurons express high levels of α1I and moderate levels of α1H subunits[76]. Thalamic neurons from transgenic mice that lack α1G subunits fail to fire in burst mode and the mice are resistant to pharmacologically induced absence seizures, strongly supporting a role for thalamic neuron bursting mediated by T-type calcium channels in absence epilepsy[77]. Conversely, T-type calcium currents are substantially larger and Ca_v3 mRNA expression is greater in thalamic reticular neurons in a rat strain that exhibits absence seizures (the genetic absence epilepsy rat from Strasbourg or GAERS) than in seizure-free control rats[78,79]. Recently, 12 missense mutations were found in

the α1H gene *CACNA1H* in 14 of 118 patients with childhood absense epilepsy but not in 230 unrelated controls[80]. Khosravani *et al.*[81] induced five of these mutations in the rat α1H ($Ca_v3.2$) T-type channel homologue and found that three were associated with significant gain-of-function effects on T-type channel activity that would predispose to hyperexcitability, including shifts of the activation voltage closer to the resting potential and of the inactivation voltage towards more depolarized potentials (so that there is increased channel availability for opening at the resting potential). Although these alterations in channel gating are compatible with the clinical phenotype, childhood absence epilepsy is likely to be POLYGENIC in origin so that variations in *CACNA1H* might only partially account for the disorder[82].

Ethosuximide, an AED that is highly effective in the treatment of absence seizures but is ineffective in other seizure types, inhibits T-type (but not HVA) calcium channels in thalamic neurons[83]. This blocking action has been confirmed for all three cloned human T-type calcium channel types that are expressed in heterologous cells[84]. The potency is low so that at clinically relevant concentrations only a small fraction of channels are blocked. Nevertheless, the magnitude of the effect seems to be sufficient to reduce the amplitude of low-threshold spikes to an extent that prevents bursting and absence seizure activity. Ethosuximide does not block fast voltage-gated sodium currents at clinically relevant concentrations[85,86] and as a result it has no activity against partial or generalized tonic-clonic seizures (TABLE 1). Indeed, although it shares the UREIDE RING-like structure with phenytoin, it does not have the crucial phenyl groups that seem to be necessary for blockade of fast sodium currents (FIG. 3). Although it is now generally accepted that ethosuximide affects T-type calcium channels in thalamic neurons, blockade of other ionic currents, including the persistent sodium current, might also be relevant[86] (but see REF. 43) and, at least in animal models, it seems that ethosuximide might also interact with neocortical regions that trigger absence seizure activity[87]. It has been reported that zonisamide, which might have activity against absence seizures (TABLE 1), also blocks T-type calcium channels[88]. Lamotrigine is a highly effective anti-absence drug that, as noted above, does not affect T-type calcium channels; the mechanism by which it protects in this seizure type is a mystery.

GABA systems. Potentiation of inhibitory neurotransmission mediated by GABA is a key mechanism of AED action. Neurons that use GABA as their neurotransmitter represent only a small fraction of neurons in regions that are key to epileptic activity, such as the neocortex, hippocampus and amygdala, and in these regions excitatory synapses can be several-fold more common than inhibitory ones[89]. However, these inhibitory connections are vital in restraining the natural tendency of recurrently connected excitatory neurons to undergo the transition through positive feedback into synchronized epileptiform discharges[90].

GABA acts through fast chloride-permeable IONOTROPIC $GABA_A$ receptors and also through slower metabotropic G-protein-coupled $GABA_B$ receptors. Reduction in the efficacy of synaptic inhibition mediated by $GABA_A$ receptors — for example, with drugs that block $GABA_A$ receptors, such as bicuculline and pentylenetetrazol — can lead to seizures. Moreover, mutations in the $GABA_A$ receptor γ2 subunit (GABRG2) have been associated with various epilepsy syndromes including GEFS+ type 3, childhood absence epilepsy and severe MYOCLONIC epilepsy of infancy (DRAVET'S SYNDROME)[91–94] (TABLE 2). These mutations result in reduced $GABA_A$ receptor-mediated inhibitory function by various mechanisms including reduced surface expression of functional receptors and altered kinetics[95]. Similarly, a mutation in the α1 subunit (GABRA1) that markedly reduces the function of heteromeric GABA receptors containing the subunit has been associated with autosomal dominant JUVENILE MYOCLONIC EPILEPSY in one family[96]. Conversely, pharmacological enhancement of $GABA_A$ receptor-mediated inhibition is an effective antiepileptic approach. Indeed, bromide, the first effective epilepsy treatment, augments $GABA_A$ receptor-mediated inhibition by enhancing the sensitivity of $GABA_A$ receptors to GABA and increasing $GABA_A$ receptor currents owing to the threefold increase in permeability of Br^- over Cl^- (REFS 97–99). Although it has long been supplanted in clinical epilepsy therapy by less toxic agents, bromide salts continue to be widely used for treating epileptic dogs and cats in veterinary medicine. Many modern AEDs influence $GABA_A$ receptor inhibition (TABLE 1), either by interacting with $GABA_A$ receptors or by modifying the activity of enzymes and transporters so as to alter the dynamics of GABA. Drugs that act through these mechanisms typically have a broad spectrum of antiepileptic activity in human seizure disorders, although, with the exception of benzodiazepine receptor agonists, they are generally ineffective in absence seizures. Valproate and gabapentin increase GABA synthesis and turnover, and valproate and to a lesser extent gabapentin have a range of activities that overlaps those of drugs that are known to interact with GABA systems.

The antiepileptic activity of benzodiazepine-like agents occurs through positive allosteric modulation of $GABA_A$ receptors containing the γ2 subunit, which is necessary for benzodiazepine modulation. $GABA_A$ receptors containing the α1 subunit are an important target for protection against seizures by benzodiazepine[100,101]. The effects of benzodiazepines on tonic $GABA_A$ receptor currents, which originate from GABA acting on extrasynaptic receptors, might be particularly important in their action[102]. In clinical practice, benzodiazepines have an important role in the acute treatment of STATUS EPILEPTICUS. However, their use in chronic therapy is limited by the sedation and muscle relaxation that occurs at doses that are comparable to those that protect against seizures and, more importantly (because the side effects diminish over time), by the development of tolerance and dependence.

POLYGENIC
A characteristic that is controlled by different genes, each of which has only a small role in the phenotype.

UREIDE RING
Heterocyclic ring formed from urea ($CO(NH_2)_2$) as in phenytoin and barbiturates. In ethosuximide, the hydantoin ureide ring of phenytoin is substituted for a succinimide ring with a single nitrogen atom.

IONOTROPIC RECEPTOR
Possessing an intrinsic channel (pore) that mediates transmembrane ion flux.

MYOCLONIC SEIZURE
Sudden, brief, involuntary spasm (contraction–relaxation) of the tongue or muscles of the face, trunk, arms, legs or the entire body.

DRAVET'S SYNDROME
A rare intractable epilepsy syndrome in which prolonged generalized tonic, clonic or tonic-clonic seizures occur between 2 and 9 months of age followed by myoclonic, tonic-clonic, absence and partial seizures in the second year of life. The syndrome is associated with delayed psychomotor and speech development, and ataxia.

JUVENILE MYOCLONIC EPILEPSY
A common generalized epilepsy syndrome presenting between the ages of 8 and 26 years with early morning myoclonus, mainly affecting the upper extremities, and often associated with generalized tonic-clonic seizures and less frequently with absence seizures.

STATUS EPILEPTICUS
Continuous seizure activity without recovery of consciousness or return to neurological function.

Table 2 | Ion channel genes implicated in human epilepsy syndromes

Gene	Functional role of expressed protein	Epilepsy syndrome
Voltage-gated ion channels		
*SCN1A**	Neuronal (type I) voltage-gated sodium channel, α-subunit ($Na_v1.1$)	GEFS+ type 2; severe myoclonic epilepsy of infancy
*SCN2A**	Neuronal (type II) voltage-gated sodium channel, α-subunit ($Na_v1.2$)	Febrile seizures associated with afebrile seizures; benign familial neonatal-infantile seizures
*SCN1B**	Voltage-gated sodium channel, β-subunit	GEFS+ type 1
*CACNA1H**	T-type voltage-gated calcium channel α1H-subunit ($Ca_v3.2$)	Childhood absence epilepsy
*KCNQ2**	M-type potassium channel subunit	Benign neonatal epilepsy, type 1; myokymia with neonatal epilepsy
*KCNQ3**	M-type potassium channel subunit	Benign neonatal epilepsy, type 2
KCNA1	$K_v1.1$ (Shaker-like) voltage-gated potassium channel subunit	Episodic ataxia/myokymia, type 1, sometimes with partial seizures
CLCN2	Voltage-gated chloride channel ClC2	Childhood absence epilepsy, type 3; juvenile absence epilepsy; epilepsy with grand mal seizures on awakening
Neurotransmitter-gated ion channels		
*GABRA1**	$GABA_A$ receptor, α1-subunit	Juvenile myoclonic epilepsy
*GABRG2**	$GABA_A$ receptor, γ2-subunit	GEFS+ type 3; childhood absence epilepsy, type 2
CHRNA4	Neuronal nicotinic acetylcholine receptor, α4-subunit	Nocturnal frontal lobe epilepsy, type 1
CHRNB2	Neuronal nicotinic acetylcholine receptor, β-subunit	Nocturnal frontal lobe epilepsy, type 3

Asterisks indicate subunits of antiepileptic drug (AED) targets. KCNQ2/KCNQ3 are targets of the experimental AED retigabine. $GABA_A$, γ-aminobutyric acid, type A; GEFS+, generalized epilepsy with febrile seizures plus. (Adapted from REF. 139.) A single case report identified a mutation in CACNB4 (voltage-gated calcium channel, β4-subunit gene) in juvenile myoclonic epilepsy and the mutation was associated with other cases of idiopathic generalized epilepsy[140]. In addition, there are several reports of an association of epilepsy with mutations in CACNA1A (voltage-gated calcium channel, α1A subunit)[141–144]. Syndromic nomenclature as defined in Online Mendelian Inheritance in Man, OMIM (McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, Maryland) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, Maryland), 2000).

Hypersynchronous activity in thalamocortical circuits is believed to underlie the 3-Hz spike-and-wave activity that is characteristic of generalized absence seizures. The anti-absence activity of benzodiazepines, such as clonazepam, probably results from their ability to 'desynchronize' these oscillations[103]. This occurs through the enhancement of mutual inhibition in the thalamic reticular nucleus by effects on benzodiazepine-sensitive α3-containing $GABA_A$ receptors. Thalamic reticular neurons exert an inhibitory influence on thalamocortical relay neurons that is necessary for de-inactivation of the T-type calcium currents that underlie bursting. Benzodiazepines reduce the inhibitory output of the reticular neurons and therefore prevent absence seizure activity.

Barbiturates such as phenobarbital also act as positive allosteric modulators of $GABA_A$ receptors, but with a different mode of action from benzodiazepines. At clinically relevant concentrations, phenobarbital does not increase the frequency of GABA-induced channel openings, but rather shifts the relative proportion of openings to favour the longest-lived open state associated with prolonged bursting (brief openings in rapid succession), thereby increasing the overall probability that the channel is open[104]. In addition, barbiturates act on other ion channel systems, including calcium and sodium channels, and this probably contributes to their therapeutic activity and might also be a factor in side effects[67]. There is evidence that felbamate[105] and topiramate[106,107] might also act, in part, through positive modulation of $GABA_A$ receptors (TABLE 1).

The concentration of GABA in the brain is controlled by two pyridoxal-5′-phosphate-dependent enzymes, glutamate decarboxylase (GAD) and GABA transaminase (GABAT). The AED vigabatrin (γ-vinyl GABA) is a GABA analogue that acts as an IRREVERSIBLE SUICIDE INHIBITOR of GABAT[108]. The drug initially binds reversibly to the pyridoxal-5′-phosphate cofactor and then binds irreversibly to the enzyme. Administration of vigabatrin leads to large elevations in brain GABA levels[109]. The antiepileptic properties of vigabatrin have been attributed to enhanced GABA-mediated inhibition. Paradoxically, vigabatrin does not lead to larger $GABA_A$ receptor-mediated synaptic responses, and it has generally been found to inhibit spontaneous and evoked synaptic GABA currents[110–112]. Rather, the drug probably acts by enhancing tonic GABA-mediated inhibition, owing to an increase in ambient GABA that is attributed either to a reversal of GABA transporters or to a shift in the equilibrium for GABA that favours increased extracellular GABA as a result of the marked elevation in intracellular GABA[113] or of effects on GABA uptake that are unrelated to GABAT[114]. The lack of strong sedation produced by vigabatrin is difficult to reconcile with this mechanism, which would be expected to induce a generalized enhancement of inhibitory tone. In this

IRREVERSIBLE SUICIDE INHIBITOR
An inhibitor that is inactive until acted upon by the enzyme: the inhibitor binds to the enzyme as a substrate and a chemically reactive intermediate is generated that inactivates the enzyme.

regard it is notable that the elevation in extracellular GABA that is produced by vigabatrin might alter the dynamics of inhibitory synaptic function so as to reduce the fading of inhibitory mechanisms during repetitive activation of interneurons[110]. Such fading, which is dependent on $GABA_B$ receptors, is believed to be an important factor that permits focal epileptiform activity to develop into a full-blown seizure. Interference with this process could account for the selective suppression of seizures by vigabatrin. In support of a role for $GABA_B$ receptors in limiting epileptic activity, mice lacking functional $GABA_B$ receptors exhibit spontaneous seizures[115].

The synaptic action of GABA is terminated by rapid reuptake into presynaptic terminals and surrounding glia by high-affinity plasma membrane GABA transporters, including GAT1, the most abundant of the transporters[116]. The AED tiagabine is a potent and selective competitive inhibitor of GAT1 that binds with high affinity to the transporter and prevents GABA uptake without itself being transported[117]. By slowing the reuptake of synaptically released GABA, tiagabine prolongs inhibitory postsynaptic potentials[118–120]. This action can be enhanced with repetitive activation, as is expected to occur during the synchronous discharge of interneurons associated with epileptic activity, so that the behavioural depression that would accompany indiscriminate enhancement of GABA inhibition is minimized.

Glutamate receptors. Ionotropic glutamate receptors are glutamate-gated cation channels that mediate the bulk of fast excitatory neurotransmission in the CNS[121]. Blockade of the NMDA and AMPA subtypes of these receptors protects against seizures in *in vitro* and *in vivo* models[122]; there is emerging evidence that kainate receptors are a potential antiepileptic target[123]. Despite the voluminous preclinical literature, clinical trials with selective NMDA antagonists in the chronic treatment of epilepsy have been disappointing, although there are case reports that ketamine, a channel-blocking NMDA receptor antagonist, might be useful in the treatment of refractory status epilepticus[124–126]. Nevertheless, several marketed AEDs might, at least in part, act through effects on ionotropic glutamate receptors. For example, felbamate, among other actions, inhibits NMDA receptors at clinically relevant concentrations[127,128]. NMDA receptors in mammalian neurons are hetero-oligomers formed by co-assembly of an obligatory NR1 subunit and at least one type of NR2 subunit. Felbamate is modestly more potent as an antagonist of NMDA receptors containing NR2B subunits[129,130]. Unlike the NR2A subunit, which is distributed ubiquitously in the CNS, expression of the NR2B subunit in the adult is largely restricted to the forebrain. NR2B selectivity could in part contribute to felbamate's low neurobehavioural toxicity in relation to other NMDA receptor antagonists, as the drug might target NMDA receptor-mediated synaptic transmission in forebrain areas that are necessary for seizure generation and avoid perturbing non-forebrain structures that could mediate side effects. In addition, NR2B subunits are abundantly expressed in the immature brain and this could also account for felbamate's clinical utility in childhood seizure disorders such as the LENNOX-GASTAUT SYNDROME (TABLE 1).

AMPA receptors are key mediators of seizure spread and could have a role in seizure-induced brain damage[122]. They are therefore potentially important AED targets. Selective AMPA receptor antagonists are under investigation, but no currently marketed AED acts predominantly through this target. Like AMPA and NMDA receptors, kainate receptors are responsible for a portion of glutamate-mediated excitation at some synapses, including those in limbic regions that are relevant to epilepsy[131]. As well as contributing to postsynaptic excitation, kainate receptors on presynaptic axon terminals modulate glutamate release from excitatory afferents and they also have the unique property of suppressing GABA release from inhibitory interneurons[132]. The combination of postsynaptic excitation and suppression of inhibition endow kainate receptors with a unique potential to induce epileptic activity[123]. Moreover, selective kainate receptor antagonists can protect against seizures in brain slice and animal models[133]. So, kainate receptors are potential AED targets. Among its complex actions, topiramate selectively inhibits kainate receptors and, to a lesser extent, AMPA receptors[134,135].

Perspective

The modern AED era — spanning a period of 150 years from the first use of bromide to the present day — has seen the introduction into clinical practice of a diverse group of effective and safe drugs that have provided immeasurable benefits for those afflicted with seizure disorders of all kinds. With only a few exceptions, these drugs were discovered by screening in animal models, and the underlying mechanisms are only now coming into clear focus. Remarkably, the set of molecular targets (TABLE 1) overlaps the rapidly enlarging roster of 'epilepsy genes' that have been identified by molecular genetics approaches (TABLE 2). Moreover, the way AEDs act to modulate the activity of these brain targets is often opposite to the functional defect in a genetic epilepsy syndrome. So, AEDs often act on ion channels to subtly reduce excitability whereas the mutations often cause correspondingly subtle gains-of-function in the same ion channels. This illustrates the pivotal importance of ion channels in epilepsy and indicates that inevitable additions to the rapidly enlarging list of ion channel epilepsy genes might provide promising new targets for the rational development of AEDs.

In the end, AEDs are only a step on the way to the ultimate goal of epilepsy medicine, which is to provide treatments that prevent epilepsy or reverse it. ANTIEPILEPTOGENIC strategies are under development using various animal models of chronic epilepsy[136,137]. By targeting plasticity mechanisms that underlie the enhanced seizure susceptibility that often follows brain insults such as head trauma, status epilepticus or neonatal hypoxia, antiepileptogenic drugs of the future would prevent, or reverse, progressive worsening of the epileptic process.

LENNOX-GASTAUT SYNDROME
A devastating paediatric epilepsy syndrome usually beginning between ages 1 to 8 years. It is characterized by multiple seizure types including tonic, atonic, atypical absence and myoclonic seizures. There is often impaired intellectual functioning and behavioural disturbances.

ANTIEPILEPTOGENIC
Protection against the development of epilepsy, a state characterized by recurrent seizures.

It is likely that antiepileptogenic drugs will have mechanisms of action that are distinct from traditional AEDs, as the molecular mechanisms that underlie epileptogenesis and ictogenesis probably differ. As in the case of symptomatic epilepsy therapies that have found enormous utility for indications other than epilepsy[1], it can be expected that such antiepileptogenic approaches will be applied to the prevention of various progressive neurological disorders, such as neuropathic pain, and perhaps important psychiatric disorders as well.

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Competing interests statement
The authors declare that they have no competing financial interests.

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