

Mechanisms of action of antiepileptic drugs

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Introduction

The serendipitous discovery of the anticonvulsant properties of phenobarbital in 1912 marked the foundation of the modern pharmacotherapy of epilepsy. The subsequent 70 years saw the introduction of phenytoin, ethosuximide, carbamazepine, sodium valproate and a range of benzodiazepines. Collectively, these compounds have come to be regarded as the 'established' antiepileptic drugs (AEDs). A concerted period of development of drugs for epilepsy throughout the 1980s and 1990s has resulted (to date) in 16 new agents being licensed as add-on treatment for difficult-to-control adult and/or paediatric epilepsy, with some becoming available as monotherapy for newly diagnosed patients. Together, these have become known as the 'modern' AEDs. Throughout this period of unprecedented drug development, there have also been considerable advances in our understanding of how antiepileptic agents exert their effects at the cellular level.

AEDs are neither preventive nor curative and are employed solely as a means of controlling symptoms (i.e. suppression of seizures). Recurrent seizure activity is the manifestation of an intermittent and excessive hyperexcitability of the nervous system and, while the pharmacological minutiae of currently marketed AEDs remain to be completely unravelled, these agents essentially redress the balance between neuronal excitation and inhibition. Three major classes of mechanism are recognised: modulation of voltage-gated ion channels; enhancement of gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission; and attenuation of glutamate-mediated excitatory neurotransmission. The principal pharmacological targets of currently available AEDs are highlighted in Table 1 and discussed further below.

Current antiepileptic drug targets

Voltage-gated sodium channels

Voltage-gated sodium channels are responsible for depolarisation of the nerve cell membrane and conduction of action potentials across the surface of neuronal cells. They are expressed throughout the neuronal membrane, on dendrites, soma, axons, and nerve terminals. Density of expression is highest in the axon initial segment (AIS) where action potentials are generated. Sodium channels belong to a super-family of voltage-gated channels that are composed of multiple protein subunits and which form ion-selective pores in the membrane. The native sodium channel comprises a single alpha-subunit protein, which contains the pore-forming region and voltage sensor, associated with one or more accessory beta-subunit proteins which can modify the function of the alpha-subunit but are not essential for basic channel activity. There are four predominant sodium channel alpha-subunit genes expressed in mammalian brain, denoted *SCN1A*, *SCN2A*, *SCN3A* and *SCN8A*, which encode the channels $Na_v1.1$, $Na_v1.2$, $Na_v1.3$ and $Na_v1.6$, respectively. These channels are expressed differentially in the nervous system. $Na_v1.3$ expression is mainly restricted to the early stages of development, while $Na_v1.1$ is the major sodium channel in inhibitory interneurons and $Na_v1.2$ and $Na_v1.6$ are expressed in the AIS of principal excitatory neurons. $Na_v1.2$ appears

Table 1. Summary of molecular targets of current antiepileptic drugs (+++ = principal target, ++ = probable target, + = possible target).

	Voltage-gated Na ⁺ channels	HVA Ca ²⁺ channels	LVA Ca ²⁺ channels	Voltage-gated K ⁺ channels	GABA _A receptors	GABA Turnover	Glutamate receptors	Synaptic vesicle protein 2A	Carbonic anhydrase
Phenobarbital		+			+++		+		
Phenytoin	+++								
Ethosuximide			+++						
Carbamazepine	+++								
Sodium valproate	++		++			++			
Benzodiazepines					+++				
Vigabatrin						+++			
Lamotrigine	+++	++							
Gabapentin	+	++				+			
Felbamate	++	++			++		++		
Topiramate	++	++		+	++		++		+
Tiagabine						+++			
Oxcarbazepine	+++								
Levetiracetam		+			+			+++	
Pregabalin		++							
Zonisamide	+++		++						+
Stiripentol					+++				
Rufinamide	+++								
Lacosamide	+++								+
Eslicarbazepine acetate	+++								
Retigabine				+++					
Perampanel							+++		

to predominate in the immature brain, with $\text{Na}_v1.6$ becoming more prevalent during maturation. $\text{Na}_v1.6$ also carries a significant proportion of the persistent sodium current and may play an important role in burst firing and ictogenesis.

Voltage-gated calcium channels

Voltage-gated calcium channels contribute to the overall electrical excitability of neurones, are closely involved in neuronal burst firing, and are responsible for the control of neurotransmitter release at pre-synaptic nerve terminals. Like sodium channels, voltage-gated calcium channels comprise a single alpha-subunit, of which at least seven are known to be expressed in mammalian brain. There are also accessory proteins, including beta- and alpha₂-delta-subunits, that modulate the function and cell-surface expression of the alpha-subunit but which are not necessarily essential for basic channel functionality. Voltage-gated calcium channels are commonly distinguished on the basis of their biophysical properties and patterns of cellular expression. High-voltage-activated (HVA) channels respond to strong depolarisations and are involved in both pre-synaptic neurotransmitter release (N-, P/Q-, and R-type) and the processing of synaptic inputs at the somatodendritic level (L-type). In contrast, the low-voltage-activated (LVA) channel opens in response to modest depolarisations at or below resting membrane potential and gives rise to transient (T-type) currents which participate in intrinsic oscillatory activity. The T-type channel is highly expressed on the soma and dendrites of thalamic relay and reticular neurones where it has been postulated to underpin the rhythmic 3 Hz spike-wave discharges that are characteristic of absence seizures.

Voltage-gated potassium channels

Voltage-gated potassium channels are primarily responsible for repolarisation of the cell membrane in the aftermath of action potential firing and also regulate the balance between input and output in individual neurones. As a group, they are highly heterogeneous. More than 40 voltage-gated potassium channel alpha-subunits have been identified thus far, each of which is structurally similar to the alpha-subunits of voltage-gated sodium and calcium channels. These are classified into 12 sub-families (K_v1 to K_v12), with individual channels comprising four alpha-subunits from the same sub-family arranged around a central K^+ sensitive pore, typically in a 'two plus two' conformation. Two functional classes of voltage-gated potassium channel are well described in the literature. K_v1 to K_v4 channels are expressed in dendrites, axons and nerve terminals and carry the delayed rectifier current (I_K) that repolarises the neuronal membrane after action potential firing. In contrast, K_v7 channels are expressed in the cell soma and AIS and are responsible for the M-current, which determines the threshold and rate of neuronal firing and modulates the somatic response to dendritic inputs. Mutations in the *KCNA1* gene, which encodes the $\text{K}_v1.1$ subunit, have been implicated in episodic ataxia type 1, while mutations in *KCNQ* genes, which encode K_v7 channels, are responsible for benign familial neonatal convulsions.

Inhibitory neurotransmission

GABA is the predominant inhibitory neurotransmitter in the mammalian central nervous system and is released at up to 40% of all synapses in the brain. GABA is synthesised from glutamate by the action of the enzyme glutamic acid decarboxylase. Following release from GABAergic nerve terminals, it acts on both GABA_A and GABA_B receptors, with a net hyperpolarising or inhibitory effect. The GABA_A receptor is a ligand-gated ion channel, comprising five independent protein subunits arranged around a central anion pore permeable to chloride and bicarbonate. Nineteen GABA_A receptor subunits have been identified to date (alpha1–6, beta1–3, gamma1–3, delta, epsilon, theta, pi, and rho1–3) which come together as heteromeric pentamers to form functional channels. GABA_A receptors mediating transient, rapidly desensitising currents at the synapse (phasic receptors) typically comprise two alpha-, two beta-, and one gamma-subunit, whereas those at extra-synaptic sites and mediating long-lasting, slowly desensitising currents (tonic receptors) preferentially contain alpha4- and

alpha6-subunits and a delta-subunit in place of the gamma-subunit. In contrast, the GABA_B receptor is coupled, via a G-protein, to potassium channels which mediate slow hyperpolarisation of the post-synaptic membrane. This receptor is also found pre-synaptically where it acts as an auto-receptor, with activation limiting further GABA release. GABA is removed from the synaptic cleft into localised nerve terminals and glial cells by a family of transport proteins, denoted GAT-1, GAT-2, GAT-3, and BGT-1. Thereafter, GABA is either recycled to the readily releasable neurotransmitter pool or inactivated by the mitochondrial enzyme GABA-transaminase.

Excitatory neurotransmission

Glutamate is the principal excitatory neurotransmitter in the mammalian brain. Following release from glutamatergic nerve terminals, it exerts its effects on three specific subtypes of ionotropic receptor in the postsynaptic membrane, designated according to their agonist specificities; AMPA, kainate and NMDA. These receptors respond to glutamate binding by increasing cation conductance resulting in neuronal depolarisation or excitation. The AMPA and kainate receptor subtypes are permeable to sodium ions and are involved in fast excitatory synaptic transmission. In contrast, the NMDA receptor is permeable to both sodium and calcium ions and, owing to a voltage-dependent blockade by magnesium ions at resting membrane potential, is only activated during periods of prolonged depolarisation, as might be expected during epileptiform discharges. Metabotropic glutamate receptors perform a similar function to GABA_B receptors; they are G-protein coupled and act predominantly as auto-receptors on glutamatergic terminals, limiting glutamate release. Glutamate is removed from the synapse into nerve terminals and glial cells by a family of specific sodium-dependent transport proteins (EAAT1–EAAT5) and is inactivated by the enzymes glutamine synthetase (glial cells only) and glutamate dehydrogenase.

Other putative targets

Countless proteins and processes are involved in the regulation of the neuronal micro-environment and in maintaining the delicate balance between excitation and inhibition in the brain and, theoretically at least, represent additional or secondary targets for AED action. These include the enzyme carbonic anhydrase and components of the synaptic vesicle release pathway, both of which are discussed in more detail below.

Mechanisms of action of existing agents

Sodium channels. Blockade of voltage-gated sodium channels is the most common mechanism of action among currently available AEDs. The established agents phenytoin and carbamazepine are archetypal sodium channel blockers, a mechanism they share with the newer drugs, lamotrigine, felbamate, topiramate, oxcarbazepine, zonisamide, rufinamide, lacosamide, and eslicarbazepine acetate. There is also anecdotal evidence to suggest that sodium valproate and gabapentin have inhibitory effects on neuronal sodium channels. Voltage-gated sodium channels exist in one of three basic conformational states: resting, open, and inactivated. During a single round of depolarisation, channels cycle through these states in turn (resting to open, open to inactivated, inactivated to resting) and are unable to respond to further depolarisations until sufficient numbers have returned from the inactivated state to the resting state. Antiepileptic agents with sodium channel blocking properties have highest affinity for the channel protein in the inactivated state and binding slows the conformational recycling process. As a result, these drugs produce a characteristic voltage- and frequency-dependent reduction in channel conductance, resulting in a limitation of repetitive neuronal firing, with little effect on the generation of single action potentials. Further complexity is added by the existence of multiple inactivation pathways. Although most sodium channel blocking AEDs target the fast inactivation pathway, lacosamide appears to enhance slow inactivation and there is preliminary evidence to suggest that eslicarbazepine acetate may do likewise. The clinical implications of this distinction remain unclear but it has

been proposed that the slow inactivation pathway is more prominent during prolonged depolarisation, as might be expected during epileptiform discharges.

Calcium channels. Voltage-gated calcium channels represent another important target for several antiepileptic agents. The efficacy of ethosuximide and zonisamide in generalised absence epilepsy is believed to be mediated by blockade of the LVA T-type calcium channel in the soma and dendrites of thalamic relay and reticular neurones. There is anecdotal evidence that sodium valproate may have a similar action. Lamotrigine limits neurotransmitter release by blocking both N- and P/Q-types of the HVA calcium channel and levetiracetam exerts a partial blockade of N-type calcium currents, suggesting a selective effect on an as yet unidentified sub-class of this particular channel type. Phenobarbital, felbamate, and topiramate are also believed to influence HVA calcium channel conductance, though their effects are less well characterised in terms of channel subtypes or interaction with specific protein subunits. Finally, gabapentin and pregabalin also exert their effects via HVA calcium channels, but rather than interacting with a traditional channel sub-type such as N- or L-type, they appear to bind to an accessory subunit termed α_2 -delta-1, which can modulate the function of various native channels. This subunit is upregulated in dorsal root ganglion cells of the spinal cord in response to nerve injury, with selective calcium channel blockade via the α_2 -delta-1 subunit explaining the efficacy of gabapentin and pregabalin in the treatment of neuropathic pain.

K_v7 channels. Retigabine was licensed for the add-on treatment of refractory focal epilepsy in the UK in 2011 and has been shown to exert its antiepileptic effects by activation of the K_v7 class of voltage-gated potassium channels. It is specific for channels containing K_v7.2 to K_v7.5 subunits, with particular affinity for channel assemblies containing dimers of K_v7.2/7.3 and K_v7.3/7.5 subunits. These channels underlie the M-current in seizure-prone regions of the brain, such as cerebral cortex and hippocampus. Retigabine enhances the M-current, increasing rate at which it is activated by depolarisation and decreasing the rate at which it is subsequently de-activated. It also enhances the M-current at resting membrane potential, hyperpolarising the cell membrane and reducing overall excitability of neurones. This effect of retigabine is mediated by binding of the drug within the pore of the channel. A single amino acid (Trp236) located in the activation gate of the K_v7 alpha-subunit protein is essential and all four subunits in the channel assembly must contain a tryptophan residue at position 236 for retigabine sensitivity.

GABA_A receptors. Activation of the ionotropic GABA_A receptor resulting in an enhanced response to synaptically released GABA is a major AED mechanism. Barbiturates (e.g. phenobarbital, primidone) and benzodiazepines (e.g. diazepam, clobazam, clonazepam) share this effect, but they bind to distinct sites on the receptor complex and differentially influence the opening of the chloride ion pore. All GABA_A receptors containing at least one alpha- and one beta-subunit appear susceptible to activation by barbiturates, with only minor differences in relative sensitivity. In contrast, benzodiazepines display a much more distinct pattern of selectivity. Benzodiazepine-sensitive GABA_A receptors are typically composed of two alpha-subunits (alpha1, alpha2, alpha3 or alpha5), two beta-subunits (beta2 or beta3), and a gamma2 subunit, whereas the delta-containing GABA_A receptor which mediates tonic inhibition is entirely insensitive to benzodiazepines, as are those containing alpha4- and alpha6-subunits. Functionally, barbiturates increase the duration of chloride channel opening, while benzodiazepines increase the frequency of opening. Barbiturates are also capable of direct activation of the GABA_A receptor in the absence of GABA, an effect which is believed to underlie their sedative properties. Several other antiepileptic agents can modulate GABA responses at the GABA_A receptor. These include felbamate and topiramate (whose binding sites and subunit specificities remain unclear), stiripentol, which has recently been reported to have greatest selectivity for alpha3-beta3-gamma2 containing receptors, and levetiracetam,

which indirectly influences receptor function by blocking its negative allosteric modulation by beta-carbolines and zinc.

GABA turnover. Vigabatrin and tiagabine are modern antiepileptic agents that exert their actions by selective neurochemical effects at the inhibitory synapse, resulting in altered GABA turnover. Vigabatrin is an irreversible inhibitor of the mitochondrial enzyme GABA-transaminase which is responsible for the catabolism of GABA, whereas tiagabine prevents the removal of GABA from the synaptic cleft by blockade of GABA transport. These distinct mechanisms result in the global elevation of brain GABA concentrations and the temporarily prolonged presence of neuronally released GABA in the synapse, respectively. Although these drugs target both neurones and glial cells, vigabatrin has marginally higher affinity for neuronal GABA-transaminase, whereas tiagabine is slightly more effective in reducing glial GABA uptake. Furthermore, tiagabine is selective for the GAT-1 GABA transporter and its pharmacological effects mirror the regional distribution of this protein, with a more pronounced action in hippocampus and neocortex. Other antiepileptic agents, including sodium valproate, gabapentin and topiramate have also been reported to influence GABA turnover by increasing neurotransmitter synthesis and/or release.

Glutamate receptors. Perampanel is the only current AED with selective effects at glutamate receptors. It is a non-competitive AMPA receptor antagonist, which binds to a site on the extracellular domain of the channel protein distinct from the glutamate recognition site. Binding of perampanel induces a conformational change in AMPA receptor subunits that limits their ability to translate agonist (i.e. glutamate) binding into channel opening. The effect is to reduce fast excitatory neurotransmission and thereby limit the ability of seizure discharges to spread. Several other antiepileptic agents exert their effects, in part, by an action on glutamatergic neurotransmission. Blockade of the NMDA subtype of glutamate receptor is believed to contribute to the pharmacological profile of felbamate, topiramate has an inhibitory action on kainate receptors, and phenobarbital has been reported to block AMPA receptors, albeit at concentrations towards the upper end of its clinical range. Although the literature contains reports that several AEDs, most notably lamotrigine, can selectively reduce glutamate release, this phenomenon is more likely related to an inhibitory action on pre-synaptic sodium and calcium channels than any direct effect on the glutamate system.

Synaptic vesicle protein 2A. Levetiracetam was developed for the treatment of epilepsy with no clear indication of how it worked at the cellular level. The identification of a specific binding site for the drug in mammalian brain and its later classification as synaptic vesicle protein 2A (SV2A) has resulted in claims that levetiracetam represents the first in a new class of antiepileptic agents. To some extent, this remains a speculative assertion. Despite intense investigation, the precise physiological role of SV2A is still unclear and important details of the interaction between drug and protein remain to be defined. Indeed, there is still no convincing evidence to suggest whether the interaction is facilitatory or inhibitory or if it results in altered packaging, trafficking, membrane fusion or recycling of synaptic vesicles within the nerve terminal. There is, however, credible evidence to support selective binding of levetiracetam to SV2A, with little or no affinity for other members of the same protein family, and an impressive correlation between SV2A binding affinity and the anticonvulsant efficacy of a series of levetiracetam analogues in audiogenic seizure sensitive mice.

Carbonic anhydrase. The acid-base balance and maintenance of local pH is critical to normal functioning of the nervous system. Various isoenzymes of carbonic anhydrase play an important role in this regard. They are responsible for catalysing the bi-directional conversion of carbon dioxide and water to bicarbonate and hydrogen ions ($\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{HCO}_3^- + \text{H}^+$). The forward reaction is rapid, whereas the rate of the reverse reaction is more modest. As a result, inhibition of carbonic anhydrase influences the latter more significantly, producing a localised acidosis and increased bicarbonate ion concentration. This, in turn, attenuates

excitatory neurotransmission by reducing NMDA receptor activity and enhances inhibitory neurotransmission by facilitating the responsiveness of GABA_A receptors. Acetazolamide is a classical carbonic anhydrase inhibitor which has been employed as an antiepileptic agent with some success. Topiramate and zonisamide are known to share this mechanism but are significantly less potent and have greater selectivity for individual isoenzymes (topiramate inhibits CA-II and CA-IV). Recent evidence suggests that lacosamide may also inhibit carbonic anhydrase, but this finding requires independent verification. Thus, carbonic anhydrase inhibition can be considered as an AED mechanism of action but the extent to which it contributes to the clinical activity of individual compounds remains to be determined.

Implications of mechanisms of action

Efficacy

One of the more surprising aspects of AED pharmacology is the apparent lack of a direct relationship between mode of action and efficacy. It is, however, possible to make the following broad generalisations regarding spectrum of activity. Selective sodium channel blockers (i.e. carbamazepine, phenytoin, oxcarbazepine, eslicarbazepine acetate) and selective HVA calcium channel blockers (i.e. gabapentin, pregabalin) tend to have efficacy against partial and primary generalised tonic-clonic seizures alone and are generally inactive against or can exacerbate most other generalised epilepsies. This characteristic is shared with selective GABA turnover drugs (i.e. vigabatrin, tiagabine) but interestingly not with selective GABA_A receptor drugs (i.e. phenobarbital, benzodiazepines) which are active in several generalised epilepsy syndromes. Any compound that exerts its effects by blockade of T-type LVA calcium channels, either wholly (i.e. ethosuximide) or in part (i.e. zonisamide), is likely to be effective against absence seizures and drugs with multiple mechanisms of action (i.e. sodium valproate, topiramate, levetiracetam, zonisamide) tend to be broad spectrum with efficacy against a wide range of seizure types and in multiple syndromes. The spectrum of efficacy associated with newer AED mechanisms, such as potassium channel activation and AMPA receptor blockade, remains to be fully explored but is likely to be similar to that observed with sodium channel blockers.

Tolerability

All AEDs elicit dose-related adverse effects, the majority of which are CNS in origin (i.e. somnolence, dizziness, ataxia, headache). For the most part, these side effects reflect a general dampening of neuronal activity and are unconnected to specific mechanisms of action, although paraesthesia with topiramate and zonisamide is likely to correspond to their inhibition of carbonic anhydrase in the peripheral nervous system, as is their modest propensity to cause renal calculi following prolonged exposure. Many antiepileptic agents are also associated with one or more specific, dose-independent adverse reaction of variable incidence. This category includes skin rash with phenytoin, carbamazepine, lamotrigine and oxcarbazepine, which is unrelated to their common blockade of sodium channels and instead reflects similarities in their chemical structures and the consequent propensity to elicit allergic reactions. At present there is no obvious pharmacological explanation for weight gain with sodium valproate and pregabalin, weight loss with topiramate, or gingival hyperplasia with phenytoin. Other than renal calculi with carbonic anhydrase inhibitors, the only adverse reaction with a convincing link to mechanism is visual field constriction with vigabatrin, believed to be a function of its irreversible inhibition of GABA-transaminase.

Polypharmacology

While many AEDs can be categorised according to a single, principal mechanism of action, it is increasingly recognised that several agents have multiple primary effects at therapeutic concentrations (Table 1). Polypharmacology, or the possession of multiple mechanisms of action within a single molecule, is more common among modern antiepileptic agents than

their traditional counterparts. One exception is sodium valproate, which is assumed to have multiple mechanisms of action on the basis that extensive laboratory investigations have failed to find a single mechanism that would explain its broad spectrum of clinical activity. In the case of modern drugs, such as topiramate, levetiracetam and zonisamide, the evidence for multifactorial pharmacology is compelling. The use of AEDs with multiple mechanisms of action may confer certain advantages when treating patients with multiple seizure types or in whom the diagnosis is initially unclear. Such drugs cover all the pharmacological bases, with limited potential for overload on any given system. This may reduce the likelihood of tolerance and increase the possibility of synergism between mechanisms but has also been suggested to elevate the propensity for adverse effects.

Conclusions

The explosion in licensing of new drugs for epilepsy throughout the 1990s and the early part of this century has been paralleled by remarkable advances in our understanding of how antiepileptic agents exert their effects at the cellular level. Among currently available compounds the predominant mechanisms of action include blockade of voltage-gated sodium and calcium channels, activation of voltage-gated potassium channels, allosteric activation of GABA_A receptors, augmentation of GABA turnover, blockade of glutamate receptors, inhibition of carbonic anhydrase, and modulation of synaptic vesicles. This new-found pharmacological knowledge is tempered to some extent by the apparent absence of an association between mode of action and clinical activity, either in terms of efficacy or tolerability. It is possible to make some general observations, not least of which is the fact that drugs with a single selective mechanism tend to have a narrow spectrum of efficacy, although even here there are exceptions (c.f. benzodiazepines). Knowing how AEDs work has important implications for clinical practice, particularly when selecting an alternative drug to replace for a previously ineffective agent or when adding a new drug to an existing regimen. Why pharmacology fails to predict clinical activity *per se* is unclear but probably reflects an as yet incomplete understanding of both drug and disease mechanisms.

Further reading

- BENARROCH EE. GABA_A receptor heterogeneity, function, and implications for epilepsy. *Neurology* 2007; 68: 612-4.
- BENARROCH EE. Potassium channels: brief overview and implications in epilepsy. *Neurology* 2009; 72: 664-9.
- BIALER M, WHITE HS. Key factors in the discovery and development of new antiepileptic drugs. *Nat Rev Drug Discov* 2010; 9: 68-82.
- BRODIE MJ, COVANIS A, GIL-NAGEL A et al. Antiepileptic drug therapy: does mechanism of action matter? *Epilepsy Behav* 2011; 21: 331-41.
- KÖHLING R. Voltage-gated sodium channels in epilepsy. *Epilepsia* 2002; 43: 1278-95.
- KWAN P, SILLS GJ, BRODIE MJ. The mechanisms of action of commonly used antiepileptic drugs. *Pharmacol Ther* 2001; 90: 21-34.
- MELDRUM BS, ROGAWSKI MA. Molecular targets for antiepileptic drug development. *Neurotherapeutics* 2007; 4: 18-61.
- ROGAWSKI MA. AMPA receptors as a molecular target in epilepsy therapy. *Acta Neurol Scand* 2013; 197 (suppl): 9-18.
- ROGAWSKI MA, LÖSCHER W. The neurobiology of antiepileptic drugs. *Nat Rev Neurosci* 2004; 5: 553-64.