Voltage-gated sodium channels (VGSCs) are key mediators of intrinsic neuronal and muscle excitability. Abnormal VGSC activity is central to the pathophysiology of epileptic seizures, and many of the most widely used antiepileptic drugs, including phenytoin, carbamazepine, and lamotrigine, are inhibitors of VGSC function. These antiepileptic drugs might also be efficacious in the treatment of other nervous system disorders, such as migraine, multiple sclerosis, neurodegenerative diseases, and neuropathic pain. In this Review, we summarise the structure and function of VGSCs and their involvement in the pathophysiology of several neurological disorders. We also describe the biophysical and molecular bases for the mechanisms of action of antiepileptic VGSC blockers and discuss the efficacy of these drugs in the treatment of epileptic and non-epileptic disorders. Overall, clinical and experimental data indicate that these drugs are efficacious for a range of diseases, and that the development of drugs with enhanced selectivity for specific VGSC isoforms might be an effective and novel approach for the treatment of several neurological diseases.

**Introduction**

Many of the most common neurological disorders, such as epilepsy, migraine, neurodegenerative diseases, and neuropathic pain, involve abnormalities of neuronal excitability. There is a growing body of data that implicates abnormal expression and function of voltage-gated sodium channels (VGSCs) in these disorders. Pharmacological inhibitors of VGSCs have been used for decades to treat epileptic seizures, the most common disease of neuronal excitability, and it is becoming increasingly evident that these antiepileptic VGSC blockers might also be efficacious against a broad range of neurological disorders. In this Review, we summarise the emerging evidence for a central role of VGSCs in the pathophysiology of epilepsy, migraine, neurodegeneration, and neuropathic pain, and examine the efficacy of antiepileptic VGSC blockers in the treatment of these neurological diseases. We also outline future developments that might extend the therapeutic use of compounds that target VGSCs.

**Biophysical and molecular properties of VGSCs**

Most neuroscientists and neurologists are familiar with the textbook description of VGSC function (figure 1A). VGSCs are closed at resting membrane potentials characteristic of quiescent neurons. In response to membrane depolarisation, they open within a few hundred microseconds (a process termed activation), resulting in an inward sodium ion (Na+) current, and then convert within a few milliseconds to a non-conducting inactivated state through a process called fast inactivation. Transient Na+ influx through thousands of rapidly opening and inactivating VGSCs results in the familiar transient macroscopic Na+ current detected in whole-cell voltage clamp studies (figure 1B). This transient current gives rise to the depolarising phase of the action potential in neurons and other excitable cells.

In many neurons, inactivation of Na+ current is incomplete, resulting in a small slowly-inactivating current, with kinetics of inactivation in the order of tens of seconds, which is referred to as persistent Na+ current ($I_{NaP}$; figure 1C). In recordings from brain neurons, $I_{NaP}$ amounts for typically less than 1% of the maximal transient current (eg, compare panels B and C in figure 1); nevertheless, this current has important effects on neuronal function, including amplification of synaptic potentials, generation of subthreshold oscillations, facilitation of repetitive firing, and maintenance of prolonged depolarised plateau potentials. Therefore, even small modifications of $I_{NaP}$ amplitude can substantially alter neuronal properties. $I_{NaP}$ undergoes modulation by intracellular factors, which is likely to be important for fine-tuning neuronal excitability. Of particular importance, neurological disorders such as epilepsy and neuropathic pain are associated with $I_{NaP}$ amplitudes several times larger than those typically observed under normal physiological conditions. These relatively large persistent currents are thought to contribute to the pathophysiological hyperexcitability and cytoplasmic Na+ loading that are associated with these disorders as we explain below.

Brain VGSCs comprise a central α-subunit of 260 kDa and two auxiliary β-subunits of about 35 kDa (β1–β4) that modulate the properties of the α-subunit and are implicated in its subcellular targeting (figure 2). The α-subunit, which forms the ion-conducting pore and the channel gate for activation and inactivation, consists of four domains, designated I–IV (or D1–D4), each with six α-helical transmembrane segments, referred to as S1–S6. Pore loops between S5 and S6 in each of the four domains form the selectivity filter of the channel. Each pore loop contributes a single amino acid (aspartate from domain I, glutamate from domain II, lysine from domain III, and alanine from domain IV), which together form a narrow ring that is mainly responsible for conferring Na+ selectivity. The four S6 segments form the cytoplasmic end of the pore, which binds various types of therapeutically important pore-blocking compounds, including local anaesthetics, antirhythmic drugs, and antiepileptic drugs (AEDs). The
S4 segments in each of the four domains contain regularly spaced, positively charged amino acid residues and serve as voltage-sensors, coupling membrane depolarisation to channel activation. The intracellular loop between domains III and IV forms the fast-inactivation gate that occludes the cytoplasmic end of the pore when the channel inactivates (figure 1A). The C-terminal cytoplasmic domain is important for setting some of the properties of fast inactivation and contains binding sites for interacting proteins. In addition to fast inactivation, a distinct process called slow inactivation develops during prolonged depolarising plateaus and during high frequency repetitive firing. The kinetics of onset and recovery of slow inactivation are about four orders of magnitude slower than those of fast inactivation. Slow inactivation does not depend on the fast inactivation gate formed by the intracellular loop, but instead mainly involves rearrangements of the pore of the channel.

Nine α-subunit subtypes have been cloned and functionally expressed. These subtypes are designated Nav1.1–Nav1.9 for the proteins and SCN1A–SCN5A and SCN8A–SCN11A for the genes; SCN6A/SCN7A codifies the related protein NaX, which might be involved in Na+ homoeostasis. Expression of the different subtypes is developmentally regulated and is cell specific and tissue specific. The main subtypes expressed in adult brain neurons are Nav1.6, found at axonal initial segments, nodes of Ranvier, somata, and dendrites of projection neurons; Nav1.2, found in unmyelinated axons and in myelinated axons early in development (before being replaced by Nav1.6); and Nav1.1, localised in neuronal somata. In rodents, Nav1.3 is expressed primarily in embryonic neurons; however, expression in the human CNS remains comparatively high into adulthood. The recent identification of the Lys354Gln mutation in Nav1.3 in a patient with epilepsy (see below) is consistent with expression of this subtype in human neurons for an extended period after embryogenesis. Nav1.4 is the main subtype in adult skeletal muscle, whereas Nav1.5 is expressed in cardiac muscle, and it is also expressed in some neurons. Nav1.7, Nav1.8, and Nav1.9, are found in peripheral primary sensory afferents and have important roles in transmission of nociceptive signals from the periphery. VGSC subtypes Nav1.1–Nav1.4, Nav1.6, and Nav1.7 are inhibited by nanomolar concentrations of tetrodotoxin, whereas Nav1.5 requires micromolar concentrations to be blocked and Nav1.8 and Nav1.9 have

Figure 1: Functional states of the voltage-gated Na+ channel
(A) At hyperpolarised membrane potentials, the channel is in a closed state. In response to depolarisation, the channel briefly opens, resulting in an inward Na+ current, and then converts to a non-conducting inactivated state. (B) A whole-cell Na+ transient current, generated by depolarisations from a holding potential of -80 mV to potentials of -60 mV to -5 mV in 5 mV increments. (C) Traces from a different neuron at a higher gain (note the difference in the scale bars between panels B and C), showing the small persistent Na+ currents (I_{NaP}) remaining at the end of membrane depolarisations, after fast inactivation is complete. Panels B and C are reprinted from Magistretti and colleagues, with permission from the Society for Neuroscience. α-α subunit. β-β subunit.
half maximal effective concentrations for tetrodotoxin in the 40–60 mM range.

VGSCs are also found in microglia, where they might contribute to phagocytic activity, and in oligodendrocytes and astrocytes, where their functional roles are poorly understood, but might include regulation of cytoplasmic Na⁺ homeostasis. Glial cells do not normally generate action potentials; however, action potential-like events have been recorded in glial precursor cells and astrocytes. Káradótter and colleagues described a subset of oligodendrocyte precursor cells, which receive excitatory and inhibitory synaptic inputs from neurons, generate action potentials when depolarised, and are particularly sensitive to excitotoxicity. Substantial up regulation of Na⁺ currents has been reported in astrocytes from human epileptic tissue, suggesting that pathophysiological glial excitability might contribute to the spread of seizures.

VGSCs and epileptic seizures

Epilepsy is a disorder of neuronal excitability, characterised by episodes of excessive synchronised neuronal activity. Electroencephalographic recordings from patients with partial epileptic disorders reveal two types of abnormal activity: interictal events, which are short asymptomatic episodes recurring periodically between seizures, and ictal discharges, which are more prolonged abnormalities in neuronal activity associated with behavioural manifestations. Both ictal and interictal discharges are characterised by sustained firing of Na⁺-dependent action potentials riding on a slow depolarised potential, mainly generated by synaptic ligand-gated cation currents (figure 3A, upper trace).

A growing body of experimental evidence indicates that abnormal expression or function of VGSCs might have a role in the pathophysiology of both acquired and inherited epilepsy. Altered concentrations of mRNA and protein for α-subunits Na₁.1, Na₁.2, Na₁.3, and Na₁.6 and β-subunits have been reported in animals and in human brain tissue in acquired epilepsy. This abnormal channel expression might be involved in the process of epileptogenesis or in the maintenance of the epileptic state. Furthermore, significantly increased I_{NaP} (2–5-fold above control amplitudes) was observed in models of temporal lobe epilepsy and in neurons obtained from the resected temporal lobe of patients with epilepsy. Data from transgenic mice that expressed an incompletely inactivating Nav₁.2 mutant indicated that increased I_{NaP} is sufficient to cause chronic seizures. The most convincing data that support a role for VGSCs in epileptogenesis comprise the identification of several hundred mutations in VGSC genes leading to inherited epileptic syndromes. Epileptic syndromes linked to VGSC mutations range in severity from relatively mild disorders such as benign neonatal-infantile familial seizures, simple febrile seizures, and generalised epilepsy with febrile seizures plus (GEFS+) to the epileptic encephalopathy termed severe myoclonic epilepsy of infancy (SMEI), also known as Dravet’s syndrome. Several other Na⁺ channelopathies fit along this disease spectrum, including borderline SMEI, intractable childhood epilepsy with generalised tonic-clonic seizures, and possibly other epileptic encephalopathies. Although a few epileptogenic VGSC mutations lie within SCN2A (the gene encoding Na₁.2) in SCN1B (encoding the

Figure 2: Membrane topology of voltage-gated Na⁺ channel

(A) Transmembrane segments are shown as cylinders. The main pore-forming and voltage-sensing α-subunit comprises four domains (labelled I–IV), each with six transmembrane segments. The β-subunits have a single transmembrane segment, a short intracellular domain and a single, extracellular immunoglobulin-like loop. β1 and β3 have non-covalent interactions with the α-subunit, whereas β2 and β4 are covalently linked to it with disulfide bridges. Site-directed mutagenesis studies have identified residues (yellow circles) in transmembrane segments IS6, IIIS6, and IVS6, which are important for binding of local anaesthetic and antiepileptic sodium channel blockers. (B) The typical structure of sodium channel blockers consists of a positively charged nitrogen moiety at one end and an aromatic ring at the other end. Molecular modelling of the drug binding site suggests that the positively charged amine interacts strongly with a phenylalanine in domain IV (Phe1579 in the Nav1.4 channel used for the modelling analysis) and, to a lesser extent, with a leucine in domain III (Leu1280 in Nav1.4), whereas the aromatic group interacts with a tyrosine in domain IV (Tyr1586) and an asparagine in domain I (Asn434).
auxiliary β1-subunit),\textsuperscript{32,42–44} and possibly in \textit{SCN9A} (Nav1.7)\textsuperscript{45} and \textit{SCN3A} (Nav1.3),\textsuperscript{18} most are in \textit{SCN1A} (encoding the Nav1.1 α-subtype)\textsuperscript{32–35}.

Nav1.1 mutations that cause GEFS+ are missense mutations, whereas those that give rise to the much more severe disorder SMEI can either be missense ones or result in truncated channels that are predicted to be non-functional. The mutations are distributed throughout the Nav1.1 α-subunit, without any clear hotspots or obvious relations to domains known to give rise to different aspects of channel function (see figure 2 in Harkin et al\textsuperscript{34}). When expressed in heterologous cells, missense Nav1.1 mutants result in loss of function or gain of function, often compromised inactivation, and increased I\textsubscript{NaP}\textsuperscript{46,47} (for an extended review of the heterogeneity of the functional effects, readers are referred to Avanzini and colleagues\textsuperscript{35}). However, several lines of evidence point to a loss of function as the main effect of Nav1.1 mutations. In fact, more than half of the identified SMEI mutants are predicted to be non-functional\textsuperscript{32–35} and a careful review of the data highlights that the effect of most Na\textsubscript{v}1.1 missense mutations, which have been functionally characterised, leads to reduced Na\textsuperscript{+} currents.\textsuperscript{48}

Recent data from transgenic mice have indicated that a GEFS+ mutant characterised by a gain of function in heterologous expression systems induces a loss of function in neurons and, notably, that the functional effects of the mutation depend on the neuronal subtype in which the mutant is expressed.\textsuperscript{49} Some missense mutations cause loss of function because of folding defects, which can be rescued by interactions with accessory proteins or VGSC blockers, and this rescue effect might also be cell-type specific.\textsuperscript{50,51} It is puzzling that loss-of-function mutations in a VGSC lead to epilepsy, a disorder characterised by brain hyperexcitability; however, data from Na\textsubscript{v}1.1 knockout mice\textsuperscript{52,53} and SMEI Na\textsubscript{v}1.1 knock-in mice (Arg1407X mutation)\textsuperscript{54} indicate that Na\textsubscript{v}1.1 is the predominant isoform in at least some types of inhibitory interneurons. Hence, reduced excitability of inhibitory neurons and compromised network inhibition is presumably a major factor in Na\textsubscript{v}1.1-related genetic epilepsies.

Some epilepsy mutations of Na\textsubscript{v}1.2 cause a gain of function in transfected cells,\textsuperscript{37,55} and benign neonatal-infantile familial seizure, a Na\textsubscript{v}1.2-related epilepsy, shows spontaneous remission during the infantile period,\textsuperscript{36} consistent with the transient expression of Na\textsubscript{v}1.2 in...
myelinated axons of excitatory neurons early during postnatal development.\textsuperscript{7} Mutations of the β1-subunit induce loss of function of β1, reducing its modulation of α-subunit functions and its interactions with other proteins,\textsuperscript{10,11} although how this effect relates to hyperexcitability is not yet clear.

**VGSCs and other neurological disorders**

**Migraine**

In addition to causing epilepsy, mutations of Na\textsubscript{v}1.1 are also associated with familial hemiplegic migraine type 3,\textsuperscript{8,9} a severe autosomal dominant inherited subtype of migraine with visual aura and hemiparesis during attacks. Data from studies in patients with migraine indicate that the aura coincides with cortical spreading depression (CSD), a wave of neuronal depolarisation that spreads across the cerebral cortex and generates transient intense firing followed by a long-lasting suppression of activity (figure 3A).\textsuperscript{10} CSD is accompanied by increases in potassium ion (K\textsuperscript{+}) concentrations that are several fold larger than those seen during epileptic discharges\textsuperscript{11} (figure 3B). Results from experiments in animals have shown that CSD stimulates trigeminovascular afferents from the meninges, thus activating brain areas involved in the perception of pain.\textsuperscript{12} The headache is probably caused by the activation of this pain pathway.

Familial hemiplegic migraine type 3 mutations of Na\textsubscript{v}1.1 have been studied by heterologous expression in cultured human embryonic cell lines and, similar to epileptogenic mutations, the reported effects vary from gain of function to complete loss of function.\textsuperscript{10,11} The pathogenic mechanisms of familial hemiplegic migraine type 3 are not completely understood, but a current hypothesis states that VGSC mutations cause cortical hyperexcitability, enhanced neurotransmitter release, and accumulation of extracellular K\textsuperscript{+}, leading to CSD and thus to migraine\textsuperscript{10} (figure 3). Some patients with familial hemiplegic migraine type 3 present with seizures,\textsuperscript{10,11} consistent with the view that migraine and epilepsy share a common underlying pathophysiology. Nevertheless, seizures occur independently from migraine attacks, and patients with Na\textsubscript{v}1.1 mutations might have only epilepsy or migraine, indicating that a combination of factors contribute to the disease phenotypes.\textsuperscript{10,11}

**Neurodegeneration**

Neuronal loss can be associated with acute events such as severe seizures, stroke, circulatory arrest, and apnoea. Several lines of experimental evidence indicate that abnormal Na\textsuperscript{+} influx and Na\textsuperscript{+} loading might be involved in the neurodegeneration associated with these events;\textsuperscript{11} hence, VGSC blockers might be effective in preventing neuronal injury caused by decreased oxygen supply. VGSCs are also thought to have a role in the neurodegeneration and inflammation that occur in multiple sclerosis and in other demyelinating diseases, in which degeneration of axons and their cell bodies accompanies the loss of myelin within the CNS white matter.\textsuperscript{12} In these cases, factors such as nitric oxide, inflammation-induced ischaemia, and impairment of mitochondrial function cause reduced energy production, leading to decreased Na\textsuperscript{+}/K\textsuperscript{+}-ATPase pump activity, membrane depolarisation, activation of persistent inward Na\textsuperscript{+} current (probably mediated mainly by Na\textsubscript{v}1.6), and abnormal accumulation of Na\textsuperscript{+} inside the axon. Intracellular Na\textsuperscript{+} overload drives the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger to import calcium ion (Ca\textsuperscript{2+}) into axons, triggering a pathogenic loop that causes further mitochondrial damage and activation of proteases, lipases, and nitric oxide synthase, ultimately leading to axonal injury. Similar Na\textsuperscript{+} overload might be involved in the hypoxia-induced neuronal damage caused by oxygen deprivation in clinical disorders such as stroke and apnoea,\textsuperscript{13} and in degeneration associated with traumatic brain injury.\textsuperscript{14}

In mouse models of amyotrophic lateral sclerosis, I\textsubscript{NaP} is increased in both cortical and spinal motor neurons, resulting in hyperexcitability.\textsuperscript{15} This finding is consistent with the early signs of cortical hyperexcitability observed in patients.\textsuperscript{16} Therefore, in patients with amyotrophic lateral sclerosis, hyperexcitability with consequently increased glutamate release and, alternatively or concomitantly, Na\textsuperscript{+} overload caused by increased I\textsubscript{NaP} might have a major role in neurodegeneration.

VGSCs (in particular Nav1.1, Nav1.5, and Nav1.6) are upregulated in activated microglia and macrophages in models of autoimmune and inflammatory disorders and epilepsy, and contribute to phagocytic functions and migration of these cells.\textsuperscript{17,18} Blockade of VGSCs (by selective blockers or genetic mutations) in microglia activated in vitro or in animal models of multiple sclerosis, decreases migration of microglia, ameliorates the inflammatory cell infiltrate, reduces phagocytic functions, and attenuates the release of pro-inflammatory cytokines.\textsuperscript{19,20} Thus, blockade of VGSCs might ameliorate neuroinflammatory disorders not only through inhibition of Na\textsuperscript{+} overload, but also via anti-inflammatory mechanisms.

**Neuropathic pain**

Adult dorsal root ganglion neurons express at least five VGSC subtypes (Na\textsubscript{v}1.1 and Na\textsubscript{v}1.6–Na\textsubscript{v}1.9).\textsuperscript{21} Na\textsubscript{v}1.7 has recently received intense interest in the pain field. Gain-of-function mutations in this subtype cause two different episodic pain syndromes: inherited erythromelalgia\textsuperscript{22,23} and paroxysmal extreme pain disorder.\textsuperscript{24} Loss of Na\textsubscript{v}1.7 function results in congenital indifference to pain,\textsuperscript{25} a disorder in which affected individuals feel no pain, despite otherwise normal sensory, motor, and cognitive function.

Other VGSC subtypes are involved in neuropathic pain resulting from chronic injury to sensory neurons. Among the changes observed in nociceptive sensory neurons after injury are upregulation of the embryonic subtype Na\textsubscript{v}1.3 in the somata, redistribution of tetrodotoxin-re-
sistant sensory neuron-specific subtypes Na,1.8 and Na,1.9 from the somata to the peripheral axon at the site of the lesion, and upregulation of the accessory subunits β2 and β3. These modifications contribute to the spontaneous firing of nociceptive neurons, often at pathologically high frequency and from ectopic sites. In central neuropathic pain, nociceptive neurons in the spinal cord and thalamus also show hyperexcitability caused partly by Na,1.3 upregulation. Na,1.7–Na,1.9 are also upregulated in dorsal root ganglion neurons in models of inflammatory pain, thus contributing to the development and maintenance of chronic inflammatory pain.

**VGSC blockers as AEDs**

The widely used AEDs phenytoin and carbamazepine inhibit VGSCs at therapeutic concentrations, and this attenuation of Na+ current is thought to be the main mechanism of their therapeutic efficacy. These drugs are effective in the maximal electroshock seizure test, a model of tonic-clonic seizures that assesses the ability of AEDs to suppress hindlimb flexion/extension induced in normal rodents by electrical stimuli delivered through corneal electrodes. In contrast, these drugs are ineffective in pentetrazol-treated rodents, a model used to identify drugs that are efficacious for absence seizures. Consistent with these observations, phenytoin and carbamazepine show efficacy for the treatment of partial and generalised tonic-clonic seizures in human beings, but they are not effective against absence seizures. Several other AEDs inhibit VGSCs to varying degrees, but also act on additional molecular targets in the brain. Compared with phenytoin and carbamazepine, these drugs are clinically effective against different types of seizures. In the next sections, we describe the mechanism of action of phenytoin and carbamazepine and discuss other AEDs that have complex mechanisms of action.

**Phenytoin and carbamazepine**

Phenytoin, the prototypic VGSC-specific AED, was used to suppress epileptic activity without substantially interfering with normal cognitive function—a crucial advance in anti-seizure pharmacotherapy. Phenytoin is a weak blocker of VGSCs at hyperpolarised membrane potentials (figure 4A, left traces) and low rates of channel activation, but its inhibitory action is greatly enhanced by sustained membrane depolarisation (figure 4A, right traces) and during high frequency channel activity (figure 4B). Voltage-dependent and frequency-dependent inhibition is currently explained by a modulated receptor model, first developed to describe the action of local anaesthetic drugs (figure 4C). According to this model, closed VGSCs, which predominate at hyperpolarised membrane potentials, have a low affinity for phenytoin (dissociation constant >>100 μM, the solubility limit of phenytoin), whereas inactivated channel states, which are prevalent at depolarised holding potentials and during high frequency channel activation, bind phenytoin with much higher affinity (in the low micromolar range).

Voltage-dependent and frequency-dependent inhibition suggests a basis for the ability of phenytoin to suppress seizures while having minimum effects on cognition. According to this hypothesis, phenytoin only weakly suppresses Na+ currents during the periods between seizures, in which neurons depolarise only transiently and fire single or short bursts of action potentials. Conversely, during seizures, neurons have prolonged discharges of action potentials riding on sustained depolarising episodes (figure 3A), the optimum condition for phenytoin inhibition of VGSC activity. Therefore, phenytoin is thought to selectively inhibit abnormal epileptiform activity while having minimum effects on physiological function.

Carbamazepine, similar to phenytoin, inhibits VGSCs in a voltage-dependent and frequency-dependent manner at clinically relevant concentrations and is effective against partial and generalised tonic-clonic seizures but not against absence seizures. Compared with phenytoin, carbamazepine has 3-fold lower affinity for depolarised channels but binds to them at a 5-fold faster rate. Hence, this drug might be more effective than phenytoin in inhibiting seizures characterised by relatively brief depolarising shifts; this could explain why some patients respond better to phenytoin but others are more effectively treated with carbamazepine.

**AEDs that act on Na+ channels and other molecular targets**

The AEDs reviewed in this section inhibit VGSCs, but also act on other molecular targets in the brain. Compared with phenytoin and carbamazepine, these drugs have different or broader therapeutic profiles. For example, valproate, an AED introduced in the 1970s, has an exceptionally broad range of anticonvulsant efficacy both in animals and in clinical practice. This drug is effective against partial and generalised tonic-clonic seizures, absence seizures, and myoclonic seizures. The molecular basis of valproate action remain unclear, but its wide scope of clinical usefulness suggests that it might act on several brain targets. Although increased GABA turnover might be of particular importance in valproate’s ability to control seizures, experimental evidence suggests that inhibition of VGSCs is a possible additional explanation for its action.

Lamotrigine is another effective treatment not only for partial and generalised tonic-clonic seizures, but also for the management of Lennox-Gastaut syndrome and for absence attacks in primary generalised epilepsies. As with phenytoin, the well established action of lamotrigine is voltage-dependent and frequency-dependent blockade of VGSCs. However, its effectiveness cannot be accounted for solely by VGSC inhibition, as the VGSC blockers phenytoin and carbamazepine are not effective against absence seizures. Indeed, lamotrigine has an effect on the excitability of pyramidal neuron dendrites through a
direct action on the hyperpolarisation-activated cation current. Additionally, this drug inhibits N-type and P-type high-voltage-activated Ca²⁺ channels and enhances K⁺ repolarising currents.

Topiramate and lamotrigine were introduced in clinical practice during the 1990s. Topiramate is effective in patients presenting with partial seizures and has been considered for the treatment of primary generalised seizures.

Figure 4: Voltage-dependent and frequency-dependent inhibition of voltage-gated Na⁺ channels by Na⁺ channel blockers
(A) Inhibition of Na⁺ currents by phenytoin is dependent on membrane holding potential. The top traces show currents evoked by depolarisation to 0 mV, with control (a standard physiological saline solution) and with 50 μM phenytoin. In each of the four pairs of current traces, the larger trace is the control. The traces on the left were elicited from a holding potential of −130 mV, whereas the traces on the right were from a holding potential of −65 mV. The control current at −65 mV is smaller, due to greater inactivation induced by the more depolarised holding potential. Moreover, phenytoin is a much more effective blocker at the more depolarised holding potential. This is more evident in the bottom traces, in which the amplitudes have been scaled so that the control currents are the same size. (B) Phenytoin block builds up during repetitive channel activation. The graph shows normalised current amplitudes of whole-cell Na⁺ currents over the course of depolarising pulses to 0 mV, from a holding potential of −85 mV, applied at 2 Hz. Red dots indicate discrete measurements. Dashed line indicates a baseline to monitor decline in amplitude. (C) Voltage-dependent and frequency-dependent inhibition of Na⁺ channels by phenytoin and other antiepileptic or local anaesthetic drugs with a similar mode of action (green diamond) are qualitatively explained by a modulated receptor model. In this model, the drug binds with higher affinity to inactivated channel states than to resting channel states. Biophysical and molecular data suggest that the modulated receptor site is within the inner vestibule of the ion-conducting pore. Panels A and B are reprinted from Ragsdale et al, with permission from the American Society for Pharmacology and Experimental Therapeutics.
tonic-clonic seizures. Topiramate is characterised by a phenytoin-like profile in maximal electroshock seizure and pentetrazol tests, and it presumably acts on VGSCs, thus depressing sustained repetitive firing and voltage-gated Na+ currents. However, topiramate antiepileptic effects presumably rely on additional mechanisms, including the interaction with excitatory amino acid receptor-mediated transmission.

Inhibition of VGSCs might also be a mechanism of action for ethosuximide, the AED of first choice for patients with absence seizures but not for patients with other types of generalised epilepsies. Absence attacks are characterised by 3 Hz spike-and-wave activity associated with high frequency (200–500 Hz) bursts of action potentials in thalamocortical neurons evoked by the activation of T-type low-threshold Ca2+ current, \( I_{\text{Na}} \). Data from early studies have indicated that therapeutic concentrations of ethosuximide reduce \( I_{\text{Na}} \) in thalamic cells maintained in vitro. However, this evidence was later challenged by Lerescu and colleagues, who reported that ethosuximide reduced \( I_{\text{Na}} \) and Ca2+-activated K+ currents without affecting transient Na+ currents or low-threshold and high-threshold Ca2+ currents in rat and cat thalamic neurons.

Finally, two molecules, riluzole and lacosamide, might be atypical in our list of AEDs. Riluzole—originally developed as an AED but approved for treatment of patients with amyotrophic lateral sclerosis—is generally thought to be an antiglutamatergic drug; however, this drug has also been characterised as a classic VGSC blocker. Lacosamide—effective in patients with uncontrolled partial seizures and inhibitory of seizure activity in several in vivo and in vitro models of epilepsy—also inhibits VGSCs, at least partly by selectively enhancing channel slow inactivation. Voltage-clamp experiments on cultured cortical cells have also revealed that lacosamide decreases the frequency of inhibitory and excitatory postsynaptic currents without influencing membrane passive properties or several ligand-gated mechanisms. Thus, lacosamide might selectively target VGSCs, but with a different mechanism from that of phenytoin and carbamazepine.

VGSC blockers and treatment of other neurological disorders

VGSC blockers might be clinically effective in several neurological disorders, including migraine, neurodegeneration, and neuropathic pain; their potential uses in the treatment of these disorders is described in the next sections.

Migraine

A wide range of drugs are used to treat migraine, including \( \beta \)-adrenergic receptor antagonists, Ca2+ channel blockers, serotonin antagonists, tricyclic antidepressants, monoamine oxidase inhibitors, and non-steroidal anti-inflammatory drugs. Recent evidence from controlled clinical trials suggests that valproate and topiramate prevent migraine and are a further resource for migraine therapy; clinical data also suggest that lamotrigine and carbamazepine can reduce aura and migraine attacks. The mechanism of action of these AEDs in the treatment of migraine is not fully understood, but it might involve interrupting the pathogenic cycle of migraine by inhibiting the abnormal cortical excitability that leads to CSD or modifying nociceptive signalling in trigeminal fibres and in central pain pathways.

Neurodegenerative disorders and multiple sclerosis

As stated above, abnormal Na+ influx and Na+ loading is involved in neuronal loss induced by severe seizures, stroke, circulatory arrest, and apnoea. Accordingly, administration of tetrodotoxin, a potent and highly selective blocker of VGSCs, before or during anoxia, attenuates neurodegeneration in animal models of hypoxia both in vitro and in vivo, showing that Na+ influx through VGSCs is involved in hypoxia-induced neuronal injury. Tetrodotoxin is not a useful therapeutic compound, because its high affinity for neuronal and skeletal muscle VGSCs makes it extremely toxic; however, several clinically relevant VGSC blockers have shown neuroprotective effects in animal models of epilepsy and in models of anoxia or hypoxia. Phenytoin, carbamazepine, lamotrigine, topiramate, and the antiarrhythmic VGSC blocker flecainide reduce ischaemic damage induced by permanent middle cerebral artery occlusion or global ischaemia in rats or in in vitro models. Valproate or topiramate treatment after chemical or electrical induction of status epilepticus reduced neurodegeneration in the rat hippocampus, although did not prevent the subsequent development of spontaneous seizures. These data are intriguing but whether these drugs provide significant beneficial effects in patients is still not known.

Administration of phenytoin, lamotrigine, or flecainide significantly decreased axon degeneration and improved neurological status in the experimental autoimmune encephalomyelitis rodent model of multiple sclerosis. These data are consistent with the hypothesis that blocking VGSCs prevents neurodegeneration induced by cytoplasmic Na+ overload. These blockers might also act through the inhibition of VGSCs involved in activation and phagocytic functions of microglia, which might contribute to their beneficial effects in animal models of multiple sclerosis. These results have provided the rationale for the initiation of clinical trials with phenytoin, topiramate, lamotrigine, and riluzole in patients with multiple sclerosis. Disappointingly, in a recent phase 2 trial, lamotrigine did not show significant beneficial effects in patients with secondary progressive multiple sclerosis. Furthermore, withdrawal of phenytoin in a mouse experimental autoimmune encephalomyelitis model resulted in increased inflammatory infiltrate, worsening of symptoms, and high incidence of mortality, leading to suspension of one of the clinical trials. Thus, whether VGSC blockers will provide a safe and effective
new strategy for the treatment of multiple sclerosis is not clear at present.

As mentioned above, riluzole is used to delay the progression of motor neuron degeneration in amyotrophic lateral sclerosis. This compound inhibits $I_{\text{NaP}}$ at therapeutic concentrations in slices of rat neocortex, consistent with the upregulation of $I_{\text{NaP}}$ observed in animal models of amyotrophic lateral sclerosis. This evidence suggests that Na+-mediated hyperexcitability and excitotoxicity might have important uses in the pathogenic mechanism of the disease.

Neuropathic pain
Abnormal hyperexcitability in nociceptive pathways is now widely accepted to contribute to various forms of neuropathic pain. VGSC blockers, including the AEDs carbamazepine, phenytoin, and lamotrigine, might be efficacious in the treatment of neuropathic pain associated with painful peripheral neuropathies, such as diabetic neuropathy. As recently reviewed, experiments with lacosamide indicate that this AED is efficacious in animal models of tumour-induced and chemotherapy-induced cancer pain, osteoarthritis pain, painful diabetic neuropathy, and spinal cord or trigeminal nerve injury. Lacosamide was approved by the US Food and Drug Administration in 2008 as an adjunctive treatment for partial seizures; however, this drug is not approved for neuropathic pain at present.

High doses of carbamazepine are also effective in ameliorating symptoms of patients with paroxysmal extreme pain disorder. In contrast, inherited erythromelalgia is unresponsive to carbamazepine or other VGSC blockers. The reason for the different efficacy of carbamazepine in paroxysmal extreme pain disorder versus inherited erythromelalgia might be explained by the fact that paroxysmal extreme pain disorder involves changes in VGSC inactivation, a process that is modulated by VGSC blockers, whereas inherited erythromelalgia involves negative shifts in the voltage dependence of activation, which are not ameliorated by these drugs. Consistent with this hypothesis, in a recent investigation, patients with inherited erythromelalgia in whom the valine at position 400 in Na$_1$7 (SCN9A) is mutated to methionine (Val400Met) also present with a modified fast inactivation of Na$^+$ current and actually their symptoms improve when treated with carbamazepine.

Conclusions and future directions
An emerging theme that unifies many supposedly diverse neurological disorders is altered neuronal excitability, caused by abnormal expression and function of membrane ion channels. VGSCs, as the main determinants of intrinsic neuronal excitability, are implicated in many of these inherited and acquired channelopathies and, thus, they are particularly appealing targets for pharmacological intervention. VGSC blockers, including AEDs and local anaesthetics, have been used for decades to treat epilepsy and some pain syndromes. As highlighted in this Review, these drugs have more recently been used to treat patients with migraine and might also be used in other disorders. However, current VGSC blockers have little discrimination between various VGSC subtypes, and thus the development of selective blockers might increase their clinical usefulness. For example, a drug that selectively inhibits the Na$_1$7 VGSC, which seems to be crucially and specifically involved in nociception, would presumably act as a powerful analgesic, with few side-effects. Moreover a VGSC blocker that selectively targets Na$_1$6 would probably be an effective AED, as indicated by the amelioration of the phenotype of SMEI mouse models and by the resistance to the initiation and development of kindling epileptogenesis obtained by impairing Na$_1$6 function.

Interestingly, so far VGSC openers have been considered only as toxic compounds; however, a selective opener could have clinical applications in some disorders. For example, a VGSC opener selective for Na$_1$1, whose loss of function can cause GEFS+, SMEI, and other genetic epileptic syndromes, might be a particularly effective AED for these syndromes. Similarly, compounds able to selectively increase Na$_1$1 expression levels would probably be even more efficacious in these cases, but little has been done to develop drugs with this mechanism of action. Furthermore, VGSC blockers that selectively target $I_{\text{NaP}}$ could be effective to limit some types of pathological excitability and neurodegeneration. Riluzole has some specificity for $I_{\text{NaP}}$, as does ranolazine, which inhibits the cardiac persistent Na$^+$ current and has been approved for treating angina pectoris, but has not been tested yet in neurological diseases. Additionally, compounds able to target different functional properties of VGSCs might be effective in disorders that do not respond to VGSC blockers (eg, in inherited erythromelalgia, in which mutations modify activation properties).

The range of VGSC pathologies will probably continue to expand, as shown by the identification of a loss-of-function mutation of Na$_1$6 in a patient with cerebellar atrophy, behavioural deficits, and ataxia; thus, novel selective VGSC modulators are likely to be increasingly attractive for personalised treatment of various neurological disorders. The new generation of VGSC

Search strategy and selection criteria
References for this Review were identified through searches of PubMed with the search terms “amyotrophic lateral sclerosis”, “antiepileptic drugs”, “epilepsy”, “inflammation”, “migraine”, “multiple sclerosis”, “mutation”, “neurodegenerative”, “pain”, “sodium channels”, and “stroke” from June, 1963, to October, 2009. Further references were identified from those cited in articles. The final reference list was generated from papers that were relevant to the topics covered in the Review.
modulators might be synthetic compounds or derivatives of naturally occurring toxins, but all could be important new weapons in our arsenal against neurological diseases.

**Contributors**
All authors wrote the initial draft of the paper, which was later extended by MM. MM, DSR, and MA finalised the paper, including the figures.

**Conflicts of interest**
MA has received consultancy fees and/or research grants from Pfizer and UCB Pharma. DSR has received a consultation fee from Pfizer. MM, GC, and GB have no conflicts of interest.

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Review


