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REVIEW

Neurological perspectives on voltage-gated sodium channels

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The activity of voltage-gated sodium channels has long been linked to disorders of neuronal excitability such as epilepsy and chronic pain. Recent genetic studies have now expanded the role of sodium channels in health and disease, to include autism, migraine, multiple sclerosis, cancer as well as muscle and immune system disorders. Transgenic mouse models have proved useful in understanding the physiological role of individual sodium channels, and there has been significant progress in the development of subtype selective inhibitors of sodium channels. This review will outline the functions and roles of specific sodium channels in electrical signalling and disease, focusing on neurological aspects. We also discuss recent advances in the development of selective sodium channel inhibitors.

Keywords: ion channel; genetics; pain; epilepsy; SCN1A
Abbreviations: TTX = tetrodotoxin; VGSC = voltage-gated sodium channel

Sodium channels

Structure and activity

The voltage-gated sodium channel (VGSC) gene family comprises nine homologous members *SCN1A* to *SCN11A*, which encode the sodium selective ion channels $Na_V1.1$ to $Na_V1.9$. Nax (*SCN6A/SCN7A*), though structurally related to VGSCs, is not activated by membrane depolarization, but rather by altered sodium concentrations (Goldin *et al.*, 2000). Each large α-subunit (~260 kDa) contains four homologous domains D*I*–D*IV*, with each domain containing six transmembrane segments. One α-subunit alone is necessary and sufficient to form a functional channel; however α-subunits also associate with β-subunits (*SCN1B* to *SCN4B*), which modulate channel biophysics and trafficking. At resting membrane potentials, VGSCs are closed, requiring depolarization to be activated. Upon activation they contribute to the upstroke of the action potential in excitable cells (Fig. 1A and B). Channel opening

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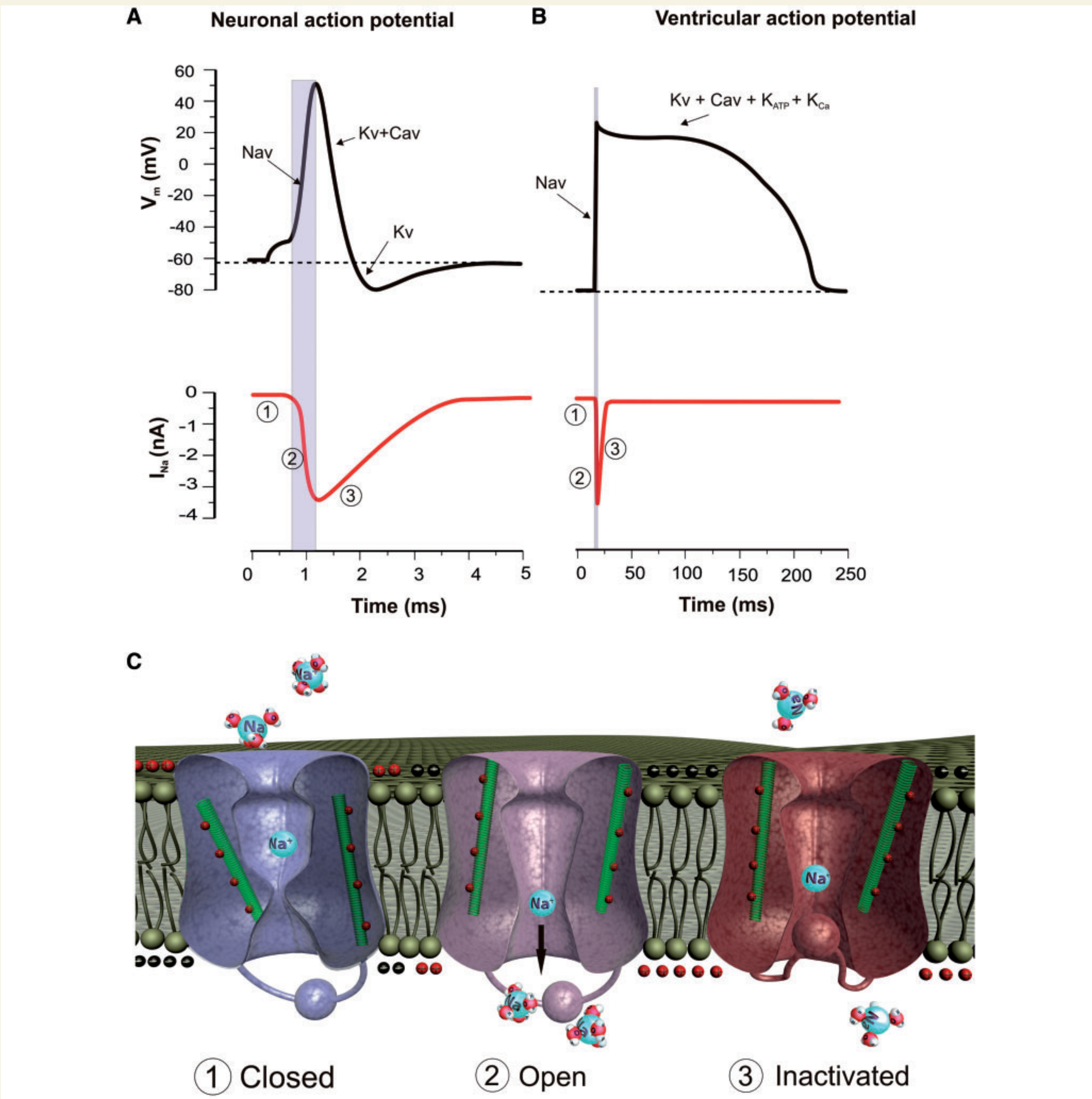


Figure 1 Gating model and contribution of voltage-gated sodium channels to neuronal and cardiac action potential firing. Upper traces depict a cartoon representation of a whole-cell current clamp recording from a typical neuron (**A**) or cardiac myocyte (**B**). Dotted line indicates the resting membrane potential (V_m). Lower trace is temporally aligned to the upper trace and shows the change in sodium current (I_{Na}) during an action potential. Note a downward deflection of the trace reflects an inward movement of sodium ions into the cell. (**1**) At the resting membrane potential VGSCs are closed. A small depolarization of the neuronal membrane potential in response to sensory input or receptor input depolarizes the neuronal membrane potential to the threshold for VGSC activation (~ -50 mV). (**2**) VGSCs activate rapidly ($\sim$1 ms to peak) allowing the influx of sodium and depolarizing the membrane potential further, forming the upstroke of the action potential. Note that the peak sodium current correlates with the peak of the action potential. (**3**) Following activation the sodium channels inactivate resulting in a decrease in sodium current and repolarization of the neuronal membrane potential, contributing to the downstroke of the action potential. Recovery from inactivation allows the channels to participate in the next action potential. (**C**) Mechanism of voltage sensitive gating of VGSCs. The left channel represents a VGSC in a deactivated (closed) state. A small depolarization of the membrane potential causes a movement of the positively charged S4 voltage-sensor domain (green) leading to a conformational change in the protein and opening of the pore (middle channel). Following activation, the pore is rapidly occluded by the inactivation gate, resulting in inactivation of the sodium channel (right channel).

results in a rapid influx of sodium ions into the cell and further depolarization of the membrane potential towards the equilibrium potential for sodium ($\sim +60$ mV in most neurons). VGSCs close within milliseconds of opening, a process called fast inactivation that contributes to the downstroke of the action potential (Fig. 1C). In many neurons, inactivation of VGSCs is incomplete, resulting in a small persistent Na^+ current, which inactivates over a time period of tens of seconds. Functionally, the structure of the VGSCs can be divided into two parts with the transmembrane domains S1–S4 contributing to the voltage sensor and S5–S6 arranging to form the sodium selective pore (Stuhmer *et al*., 1989; Catterall *et al*., 2005). The molecular mechanism by which changes in membrane voltage confer a conformational change on voltage-gated ion channel proteins is through the movement of modular voltage sensors contained within the S4 segment of domains *I–IV* (Fig. 1C) (Alabi *et al*., 2007). The voltage sensors contain repeated motifs of positively charged amino acids followed by hydrophobic residues arranged in an α-helix with a linear array of positively charged residues. Depolarization of the cell alters the electric field across the cell membrane resulting in the rapid movement of the D*I–III* S4 voltage sensors and a conformational change in the protein which opens the ion channel pore. Inactivation follows activation due to the intrinsically slower movement of the D*IV* voltage sensor (Bosmans *et al*., 2008). The VGSC inactivation gate contains a trio of amino acids (IFM) located in a highly conserved intracellular loop connecting domains *III* and *IV* (West *et al*., 1992). Upon inactivation, the inactivation gate moves into the channel pore as shown by the altered accessibility of antibodies targeted to this domain (Vassilev *et al*., 1988, 1989), resulting in occlusion of the pore often depicted as a ball and chain type block (Fig. 1C). The channels remain in a refractory inactivated state until the cell membrane potential repolarizes, normally facilitated by the delayed activation of voltage-gated potassium channels.

Much of what is known about the molecular mechanism of voltage sensing derives from studies on voltage-gated potassium channels for which high-resolution crystal structures have been obtained. Using X-ray crystallography the structure of the S4 voltage sensor in the *Archaea* voltage-dependent potassium channel KvAP was modelled as a paddle (Jiang *et al*., 2003*a*, *b*). However, recent modelling of the bacterial sodium channel NaChBac reveals that the S4 voltage sensor segment is arranged in a 3(10) alpha helical conformation that slides in a linear fashion through a narrow groove formed by the S1, S2 and S3 segments (Yarov-Yarovoy *et al*., 2012). Recently, the crystal structure of a VGSC has been reported (Payandeh *et al*., 2011). Comparison with the previous open potassium channel structures showed that the voltage-sensor domains and the S4–S5 linkers dilate the central pore by pivoting together around a hinge at the base of the pore module (Payandeh *et al*., 2011). This newly described crystal structure of a prokaryotic VGSC shows that the basis of ion channel selectivity for Na^+ is different from potassium channels (Corry and Thomas, 2012).

Persistent sodium currents

All the kinetically fast transient channels ($Na_V1.1$–1.7) appear quite similar in functional properties, but sodium channels sometimes generate much longer openings as a result of incomplete or defective fast inactivation. $Na_V1.9$ gives rise to a low-threshold, persistent tetrodotoxin (TTX)-resistant Na^+ current in sensory neurons (Baker *et al*., 2003). Persistent sodium currents have also been recorded in cells that do not express $Na_V1.9$, including cardiac and skeletal muscle (Patlak and Ortiz, 1986; Bohle and Benndorf, 1995), large diameter dorsal root ganglion neurons (Baker and Bostock, 1997) and cortical pyramidal neurons (Alzheimer *et al*., 1993; Schwindt and Crill, 1995). In some voltage-clamp protocols the amplitude of persistent current is just a few per cent of that of the transient current at the same potentials but is still functionally important. For mammalian primary sensory neurons, persistent currents activate at more negative potentials than the associated transient currents. The hyperpolarized voltage dependence of activation of persistent sodium currents allows these channels to operate as amplifiers of subthreshold depolarization, because their activation kinetics are fast and they operate over a strategic subthreshold membrane potential range with low potassium channel activation. Evidence from muscle fibre recordings indicates that $Na_V1.4$ can generate persistent currents, and $Na_V1.6$ generates such currents in cerebellar Purkinje neurons (Raman *et al*., 1997; Raman and Bean, 1997). The functional importance of persistent currents can be seen from the effects of *SCN8A* mutations that change neuron firing patterns and lead to ataxia in mice (Meisler *et al*., 2002, 2004). In addition, many epileptogenic mutations of *SNC1A*, *SCN2A* and *SCN3A* exhibit increased persistent currents (Meisler and Kearney, 2005). The implication of these findings is that specific blocking of channels with inactivation-defective gating might be a useful way of controlling membrane excitability within the nervous system (Lampl *et al*., 1998). In primary sensory neurons, persistent currents are preferentially targeted by local anaesthetics (Baker, 2000). Local anaesthetics can suppress ectopic firing in damaged sensory neurons without altering action potential properties (Devor *et al*., 1992), probably because the block of persistent currents takes the membrane potential further away from firing threshold.

Resurgent sodium currents

Resurgent currents, first observed in cerebellar Purkinje neurons (Raman and Bean, 1997) and present in dorsal root ganglion neurons (Cummins *et al*., 2005), may arise following relief of ultra-fast open-channel block (faster than pore block by the inactivation gate) mediated by yet undetermined proteins. In some neurons, sodium channels transiently open upon recovery from inactivation when the membrane potential is repolarized. This transient opening gives rise to a large inward tail current termed 'resurgent current' (Cannon and Bean, 2010). One possible mechanism for resurgent current involves the blockade of the channel pore by the C-terminus of β4 subunit of sodium channels (Grieco *et al*., 2005; Bant and Raman, 2010). Resurgent currents have recently become an important topic in pain and myopathy research as sodium channel mutations involved in these pathologies were found to increase resurgent currents (Jarecki *et al*., 2010). Mutations in $Na_V1.4$, $Na_V1.5$ and $Na_V1.7$ that lead to paramyotonia congenita, cardiac long QT syndrome/sudden infant death syndrome and paroxysmal extreme pain disorder, respectively, all enhance resurgent currents, thereby affecting the firing properties of the cells. Although resurgent current can be observed with $Na_V1.4$-, $Na_V1.5$-, $Na_V1.6$- and $Na_V1.7$-based sodium channels in expression studies, *in vivo* resurgent currents have only been recorded from neurons and never from cardiac or skeletal muscle.

Many toxins affect sodium channel function by altering the gating of these channels. The wasp venom β-pompilidotoxin (β-PMTX) is able to produce resurgent currents through a molecular mechanism involving the slowing of sodium channel inactivation (Grieco and Raman, 2004). Another toxin, the Cn2 β-scorpion peptide, shifts the activation of $Na_V1.2$ and $Na_V1.6$ towards more hyperpolarized potentials by trapping the D*II* S4 voltage sensor in the inactivated rather than the closed state. A β-scorpion toxin also has the capability of producing resurgent currents by trapping the voltage sensor of human $Na_V1.6$ channels and VGSC in mouse Purkinje cells (Schiavon *et al*., 2006). The data from these two studies strongly suggest that an increased open probability of sodium channels is a key requirement for the generation of resurgent currents. Very recently it has been suggested that the transient, resurgent and persistent phases of the sodium current in cerebellar granule cells are all interlinked through the β4 subunit (Bant and Raman, 2010). These results highlight the critical role that toxins play in unravelling gating mechanisms of sodium channels.

Voltage-gated sodium channel function and disease association

The nine different VGSC α-subunits are differentially expressed (Table 1), and disruption of VGSC function can lead to a broad range of pathologies. The role of VGSCs in epilepsy and pain has been well established; however, there is increasing evidence of a role for VGSCs in other disorders including cancer, multiple sclerosis, muscle and immune disorders, autism, neurodegeneration and cardiovascular complications (Table 1). Human heritable disorders can now be mapped with relative ease. A number of disorders have been ascribed to mutations in genes encoding sodium channels and further genetic insights have been provided by analysis of targeted sodium channel mutations and gene deletion in mice (Table 1). The correlation between the clinical phenotype of patients with channel mutations and channel biophysical properties and observations in mouse models will be discussed later.

$Na_V1.1$ (*SCN1A*)

Broadly expressed in the CNS, $Na_V1.1$ expression may be preferentially expressed in inhibitory gamma-aminobutyric acidergic (GABAergic) neurons (Yu *et al*., 2006). The majority of the >700 associated *SCN1A* mutations are nonsense causing the autosomal dominant disorder Dravet's syndrome. In addition, approximately two dozen *SCN1A* mutations have been identified in families with the milder disorder, generalized epilepsy with febrile seizures plus, which is characterized by short-lasting tonic–clonic seizures accompanied by fever (Meisler *et al*., 2010). Generalized epilepsy with febrile seizures plus mutations change expression and function of $Na_V1.1$ channels due to both gain- and loss-of-function mutations. For example, the D188V mutation leads to impaired slow inactivation (Cossette *et al*., 2003), while the T875M mutation enhances slow inactivation (Spampanato *et al*., 2001). Both mutations lead to the same phenotype. Thus, the relationship between the clinical phenotypes and the functional defects is complex (reviewed in Ragsdale, 2008). Some linkage between specific genetic abnormalities and phenotype has been shown; SCN1A mutations are associated with early onset of febrile seizures/febrile seizures plus while SCN1B mutations are associated with later onset (Sijben *et al*., 2009).

The more detrimental severe myoclonic epilepsy of infancy (or Dravet's syndrome) is associated with haploinsufficiency for *SCN1A* in 50–80% of severe myoclonic epilepsy of infancy patients caused by more deleterious nonsense and frameshift mutations in $Na_V1.1$ (De Jonghe, 2011). In contrast to generalized epilepsy with febrile seizures plus, these mutations prevent channel expression or severely impair channel function. While loss-of-function mutations are common in Dravet's syndrome, a gain-of-function mutation in *SCN1A* (R865G) has also been found (Volkers *et al*., 2011). *SCN1A* duplications and deletions are also found in patients with Dravet's syndrome (Marini *et al*., 2009). More recently, *de novo SCN1A* mutations have been found in patients with the severe early infantile onset syndrome of malignant migrating partial seizures, also a severe epileptic encephalopathy (Carranza *et al*., 2011).

The severity of channel impairment has been suggested to underlie the different efficacies of some anti-epileptic drugs in treating either generalized epilepsy with febrile seizures plus or severe myoclonic epilepsy of infancy, of which many act through inhibiting VGSCs. For example, the sodium channel blocker lamotrigine is very effective for treating generalized epilepsy with febrile seizures plus, while it aggravates symptoms in patients with severe myoclonic epilepsy of infancy (Guerrini *et al*., 1998). The efficacy of some frontline anti-epileptic drugs, which often work through stabilizing channels in the inactive state, has been suggested to be influenced by a polymorphism that modifies splicing of $Na_V1.1$ leading to altered inactivation (Fletcher *et al*., 2011). Studies on $Scn1a^{+/-}$ mice have shown that deletion of $Na_V1.1$ leads to impaired firing of GABAergic inhibitory hippocampal interneurons (Catterall and Kalume, 2010) and cerebellar GABAergic Purkinje neurons (Kalume *et al*., 2007). The impaired functioning of inhibitory GABAergic neurons may contribute to seizures, ataxia, spasticity and failure of motor coordination observed in these mice.

It is interesting to note that targeting $Na_V1.1$ to treat epilepsy is not the only possible therapeutic strategy. Mice with haploinsufficiency for both $Na_V1.1$ and $Na_V1.6$ showed reduced susceptibility to drug-induced seizures compared with $Na_V1.1$ heterozygotes (Martin *et al*., 2007). In contrast with $Na_V1.1$, $Na_V1.6$ is highly expressed in excitatory neurons (Caldwell *et al*., 2000). Thus it seems that the excitatory and inhibitory balance in the brain is restored by $Na_V1.6$ mutations that reduce firing of excitatory neurons. Finally, $Na_V1.1$ mutations are also associated with familial hemiplegic migraine type 3 (Dichgans *et al*., 2005), an autosomal

Table 1 Expression patterns in relation to known effects of human and mouse mutants of VGSCs

Channel	Gene	Major expression	Channel disease association	Phenotype of mouse mutants
Nav1.1	*SCN1A*	CNS (Westenbroek *et al*., 1989), PNS (Black *et al*., 1996)	Epilepsy (Escayg *et al*., 2000), migraine (Dichgans *et al*., 2005), autism (Weiss *et al*., 2003)	(−/−) Ataxia and death at P15 (Yu *et al*., 2006); (+/−) spontaneous seizures and sporadic deaths after P21 (Yu *et al*., 2006)
Nav1.2	*SCN2A*	CNS (Westenbroek *et al*., 1992), PNS (Black *et al*., 1996)	Epilepsy (Sugawara *et al*., 2001; Heron *et al*., 2002; Liao *et al*., 2010) (GOF), autism (Weiss *et al*., 2003), episodic ataxia (GOF) (Liao *et al*., 2010)	(−/−) Perinatal lethal (Planells-Cases *et al*., 2000)
Nav1.3	*SCN3A*	CNS (Whitaker *et al*., 2001; Hains *et al*., 2003), PNS (elevated following nerve injury) (Waxman *et al*., 1994*b*)	Epilepsy (GOF) (Holland *et al*., 2008*b*)	(−/−) and (−/− nociceptor specific) normal acute inflammatory and neuropathic pain (Nassar *et al*., 2006)
Nav1.4	*SCN4A*	Skeletal muscle (Haimovich *et al*., 1987)	Hyperkalaemic periodic paralysis (GOF) (Ptacek *et al*., 1991); paramyotonia congenita (GOF); hypokalaemic periodic paralysis (altered gating pore current) (Sokolov *et al*., 2007)	Unknown
Nav1.5	*SCN5A*	Cardiac muscle (Rogart *et al*., 1989)	Brugada syndrome (Chen *et al*., 1998) (LOF); long QT syndrome 3 (Zimmer and Surber, 2008) (GOF); atrial fibrillation	(−/−) Intrauterine lethality with severe defects in ventricular morphogenesis; (+/−) decreased atrial and atrio-ventricular conduction progressed with age (Papadatos *et al*., 2002). (Δ/+) knockin model of LQT3 resulted in spontaneous ventricular arrhythmias (Nuyens *et al*., 2001)
Nav1.6	*SCN8A*	CNS, PNS (Black *et al*., 2002), smooth muscle (Saleh *et al*., 2005)	Mental retardation, pancerebellar atrophy, ataxia (Trudeau *et al*., 2006); infantile experimental encephalopathy (Veeramah *et al*., 2012)	med mutant (−/−): severe muscle atrophy, progressive paralysis and juvenile death; ataxia, tremor, and impaired coordination (Meisler *et al*., 2004); sleep deficits (Papale *et al*., 2010); Purkinje and granule cells specific (−/−): ataxia (Levin *et al*., 2006) D981V produces paroxysmal tremors and mild deafness (Mackenzie *et al*., 2009)
Nav1.7	*SCN9A*	PNS (Toledo-Aral *et al*., 1997)	Pain free (LOF) (Cox *et al*., 2006, 2010); erythromalalgia (GOF) (Yang *et al*., 2004), paroxysmal extreme pain disorder (reduced fast inactivation) (Fertleman *et al*., 2006), anosmia (Goldberg *et al*., 2007)	(−/−) Perinatal lethal (Nassar *et al*., 2004); (−/− Nociceptor specific deletion) insensitivity to blunt mechanical pressure and lack of inflammatory pain (Nassar *et al*., 2004); (−/− sensory and sympathetic): pain free (Minett *et al*., 2012)
Nav1.8	*SCN10A*	PNS (Akopian *et al*., 1996), heart (Chambers *et al*., 2010)	SNP rs6795970 (G > A) results in prolonged cardiac conduction (Chambers *et al*., 2010)	(−/−) Insensitivity to blunt mechanical pressure; some deficits in inflammatory pain(Akopian *et al*., 1999; Papadatos *et al*., 2002; Abrahamsen *et al*., 2008); prolonged cardiac PR interval (Chambers *et al*., 2010)
Nav1.9	*SCN11A*	PNS (Dib-Hajj *et al*., 1998)	Unknown	(−/−) Reduced cold allodynia in a neuropathic pain model; increased visceral inflammatory pain (Leo *et al*., 2010); reduced thermal but not mechanical hyperalgesia in inflammatory model (Priest *et al*., 2005)
NaX	*SCN7A*	Circumventricular organs (Hiyama *et al*., 2004)	Unknown	Abnormal salt intake under dehydrated conditions (Watanabe *et al*., 2000; Hiyama *et al*., 2004)
β1	*SCN1B*	CNS, cardiac muscle (Isom *et al*., 1992)	Epilepsy (GEFS+) (Scheffer *et al*., 2007), Dravet's syndrome (Patino *et al*., 2009) Brugada syndrome (Watanabe *et al*., 2008) (defective trafficking); atrial fibrillation (LOF) (Watanabe *et al*., 2009)	(−/−) Spontaneous seizures (Patino *et al*., 2009); (+/−) normal seizure susceptibility (Patino *et al*., 2009); (−/−) reduced resurgent sodium current in cebellar neurons (Brackenbury *et al*., 2010); (−/−) hypoglycaemia (Ernst *et al*., 2009); (−/−) long QT interval (Lopez-Santiago *et al*., 2007)
β2	*SCN2B*	PNS (Lopez-Santiago *et al*., 2006)	Atrial fibrillation (LOF) (Watanabe *et al*., 2009)	(−/−) Neuroprotective in model of multiple sclerosis (O'Malley *et al*., 2009); (−/−) increased sensitivity to noxious heat and reduced inflammatory pain (Lopez-Santiago *et al*., 2006)
β3	*SCN3B*	Cardiac muscle, CNS, skeletal muscle (Stevens *et al*., 2001)	Idiopathic ventricular fibrillation (Valdivia *et al*., 2010), atrial fibrillation (DN mutant) (Wang *et al*., 2010a), Brugada syndrome (defective trafficking) (Hu *et al*., 2009), sudden infant death syndrome (Tan *et al*., 2010)	Atrial and ventricular conduction abnormalities (Hakim *et al*., 2008, 2010)
β4	*SCN4B*	CNS, PNS (Yu *et al*., 2003)	Long QT syndrome (Medeiros-Domingo *et al*., 2007), Sudden infant death syndrome (Tan *et al*., 2010)	Unknown

DN = dominant negative; GOF = gain-of-function; LOF = loss-of-function; PNS = peripheral nervous system; GEF+ = generalized epilepsy with febrile seizures plus; −/− = homozygous knockout; +/− = heterozygous knockout; med = motor endplate disease.

dominant severe subtype of migraine with aura characterized by hemiparesis during the attacks. Genome-wide linkage analysis revealed three families with the same missense mutation in *SCN1A* (Q1489K). This mutation resulted in complex changes in channel gating including a depolarizing shift in the voltage dependence of inactivation, accelerated recovery from inactivation and increased persistent current (Cestele *et al*., 2008). These biophysical changes could cause either hyper- or hypoexcitability depending on the firing frequency and resting membrane potential of the neuron. More recently, whole exome sequencing has identified candidate genes with *de novo* mutations, including *SCN1A,* in sporadic autism spectrum disorders (O'Roak *et al*., 2011, 2012).

Na_V1.2 (*SCN2A*)

Na_V1.2 is abundantly expressed in the adult CNS, particularly in the cortex and hippocampus (Westenbroek *et al*., 1989), where it is primarily expressed in unmyelinated axons and dendrites (Boiko *et al*., 2001). Early in development, Na_V1.2 is highly expressed in regions destined to become nodes of Ranvier and is replaced during development by Na_V1.6 (Boiko *et al*., 2001; Kaplan *et al*., 2001). Na_V1.2 knockout mice die perinatally from neuronal apoptosis and hypoxia (Planells-Cases *et al*., 2000). In humans, Na_V1.2 mutations are associated with inherited epilepsy, mainly benign familial neonatal-infantile seizures (Heron *et al*., 2002) and less frequently with other forms of epilepsy such as generalized epilepsy with febrile seizures plus (Sugawara *et al*., 2001). Benign familial neonatal-infantile seizure is an autosomal dominant disorder characterized by afebrile seizures with onset within 4 months after birth and spontaneous remission within the first year of life, without residual neurological deficits. Three separate benign familial neonatal-infantile seizures causing mutations in Na_V1.2 resulted in reduced plasma membrane expression while having varied effects on channel activation and inactivation (Misra *et al*., 2008). Although there is little consensus over the pathological mechanisms, studies have demonstrated that either gain- or loss-of-function mutations of Na_V1.2 are associated with disease. A link between Na_V1.2 and autism has been reported at low frequency (1/229 autism families studied), resulting in mutation of the calmodulin binding domain of Na_V1.2 and reduced calmodulin-binding affinity (Weiss *et al*., 2003). *De novo* mutations revealed by whole-exome sequencing including two independent nonsense mutations in *SCN2A*, are strongly associated with autism (Sanders *et al*., 2012).

Na_V1.3 (*SCN3A*)

Na_V1.3 is widely expressed in the human brain and has a predominantly somatodendritic expression pattern (Whitaker *et al*., 2001). In contrast to many of the other VGSC genes, there are as yet no clear monogenic diseases associated with *SCN3A* mutation. However, a small study of patients with cryptogenic paediatric partial epilepsy revealed a mutation in *SCN3A* (K354Q) that led to an increase in persistent current and induced epileptiform hyperexcitability in hippocampal neurons (Holland *et al*., 2008*a*; Estacion *et al*., 2010). Animal studies have focused on a possible role of Na_V1.3 in neuropathic pain. Following axotomy and inflammation in mice, Na_V1.3 transcript levels increase in sensory neurons (Waxman *et al*., 1994*b*; Dib-Hajj *et al*., 1999). Antisense knockdown of Na_V1.3 expression attenuates pain-related behaviour associated with spinal cord injury and chronic constriction injury (Hains *et al*., 2004) but not allodynia in the spared nerve injury model (Lindia *et al*., 2005). However, Na_V1.3 knockout mice, where the gene was deleted globally or selectively in nociceptive neurons, showed normal pain behaviour and normal development of neuropathic pain in the Chung model of neuropathic pain (Nassar *et al*., 2006). Although several lines of investigation have implicated Na_V1.3 as a candidate drug target to treat neuropathic pain, this study does not support an essential role for Na_V1.3 in neuropathic pain.

Na_V1.4 (*SCN4A*)

Na_V1.4 is responsible for the generation and propagation of action potentials that initiate muscle contraction. Currently, five hereditary sodium channelopathies of skeletal muscle involving Na_V1.4 mutations have been identified, such as hyperkalaemic periodic paralysis, hypokalaemic periodic paralysis, paramyotonia congenita, potassium-aggravated myotonia and congenital myasthenic syndrome (Jurkat-Rott *et al*., 2010). Hypokalaemic periodic paralysis and normokalaemic peridodic paralysis causing mutations map to the Na_V1.4 voltage sensor, resulting in ionic leak through the gating pore allowing sustained inward sodium flux at negative membrane potentials (Sokolov *et al*., 2010). In contrast, mutations associated with paramyotonia congenita and hyperkalaemic periodic paralysis are widespread in the Na_V1.4 protein and either enhance activation or impair inactivation resulting in hyperexcitability. Mutations in *KCNA1* and *SCN4A* have been found in a patient with episodic ataxia and paramyotonia congenita. Coexistence of these two ion channelopathies in this patient raises the possibility of a role of sodium channels in episodic ataxias (Rajakulendran *et al*., 2009).

Na_V1.5 (*SCN5A*)

Several syndromes leading to sudden cardiac death have been linked to Na_V1.5. For example, over 80 *SCN5A* mutations have been identified in patients with long QT syndrome type 3 (Zimmer and Surber, 2008). These mutations mostly disrupt fast inactivation, thereby causing persistent sodium currents (Bennett *et al*., 1995). Similarly, Brugada syndrome also leads to sudden cardiac death that may account for up to 50% of all sudden cardiac deaths in young individuals without structural heart disease. *SCN5A* mutations were found in ~20% of patients with Brugada syndrome (Kapplinger *et al*., 2010) resulting in channel loss-of-function through a number of different mechanisms including expression of non-functional Na_V1.5 (Valdivia *et al*., 2004; Hsueh *et al*., 2009), decreased protein expression (Kyndt *et al*., 2001), impaired membrane trafficking (Baroudi *et al*., 2001, 2002) or defective channel inactivation (Hsueh *et al*., 2009). Although Na_V1.5 has been mainly linked to cardiac disease, a more recent report shows a novel *SCN5A* mutation in a patient with idiopathic epilepsy who died in sudden unexpected death in epilepsy (SUDEP) (Aurlien *et al*., 2009)

Interestingly, VGSC upregulation has been associated with several strongly metastatic carcinomas, leading to the hypothesis that VGSC upregulation may 'switch' the cancerous cell to a highly invasive state (Onkal and Djamgoz, 2009). Some cancers express embryonic/neonatal VGSC splice variants, for example, a neonatal isoform of Na_V1.5 (seven amino acid differences) is the predominant (>80%) VGSC in human metastatic breast cancer (Fraser *et al*., 2005) as well as neuroblastoma (Ou *et al*., 2005).

Na_V1.6 (*SCN8A*)

Na_V1.6 is broadly expressed in the nervous system in a variety of cells including Purkinje cells, motor neurons, pyramidal and granule neurons, glial cells and Schwann cells and is enriched at the nodes of Ranvier (Caldwell *et al*., 2000; Kearney *et al*., 2002). Mutation in *SCN8A* is not a common cause of human disease although a patient with a heterozygous mutation in *SCN8A* has been described with mental retardation, pancerebellar atrophy and ataxia (Trudeau *et al*., 2006). This mutation caused a C-terminal truncation of Na_V1.6 resulting in predicted loss of channel function. Naturally occurring med mutant Na_V1.6 knockout mice show a range of movement disorders including tremor, ataxia, dystonia and paralysis (Meisler *et al*., 2002, 2004). Mutant mice are also reported to have disordered sleep patterns with a chronic impairment of REM sleep and enhanced spatial memory (Papale *et al*., 2010). In Purkinje cells of Na_V1.6 knockout mice, resurgent currents are reduced and spontaneous and evoked firing was attenuated (Raman *et al*., 1997). Recently a *de novo* pathogenic *SCN8A* mutation with greatly increased persistent current was identified in a case of SUDEP with infantile epileptic encephalopathy (Veeramah *et al*., 2012). Persistent Na_V1.6 activity can trigger axonal injury within white matter axons during experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (Craner *et al*., 2004). In non-excitable cells such as macrophages, Na_V1.6 is expressed at an intracellular location on podosomes (Carrithers *et al*., 2009*a*). In this study, inhibition of Na_V1.6 with TTX or by genetic ablation was effective at reducing invasion of macrophages into melanoma. Similarly, a non-neuronal role for Na_V1.6 contributing to the invasiveness of cervical carcinomas has been suggested (Hernandez-Plata *et al*., 2012). This suggests that targeting Na_V1.6 in non-neuronal tissue might have therapeutic potential to treat cancer or autoimmune disorders such as multiple sclerosis (Carrithers *et al*., 2009*b*). However, the essential role of Na_V1.6 in many neurological functions may make this a difficult task.

Na_V1.7 (*SCN9A*)

Na_V1.7 is expressed in peripheral sensory neurons innervating the skin, viscera and orofacial region (dorsal root and trigeminal ganglia) as well as sympathetic neurons and olfactory epithelia (Toledo-Aral *et al*., 1997; Weiss *et al*., 2011). A number of human heritable pain disorders map to mutations in *SCN9A*, the gene encoding Na_V1.7 (Dib-Hajj *et al*., 2010). Dominant gain-of-function mutations lead to inherited primary erythromelalgia, which is characterized by bilateral burning pain of the feet/lower legs and hands, elevated skin temperature of affected areas and reddened extremities (Yang *et al*., 2004). Additionally, dominant gain-of-function mutations can cause paroxysmal extreme pain disorder which is characterized by episodic burning pain of the rectum, ocular and mandibular regions (Fertleman *et al*., 2006). Rare recessive loss-of-function conditions can cause an inability to experience pain (Cox *et al*., 2006; Ahmad *et al*., 2007) and anosmia (Weiss *et al*., 2011).

Biophysical characterization of the Na_V1.7 mutations present in patients with erythromelalgia shows a significant hyperpolarizing shift in voltage dependence of activation (Cummins *et al*., 2007), resulting in gain-of-function. The Na_V1.7 mutations underlying paroxysmal extreme pain disorder, where mechanical stimulation evokes excruciating pain (Fertleman *et al*., 2006), attenuate the fast inactivation of Na_V1.7 resulting in persistent sodium currents. Such a deficit in inactivation is predicted to produce prolonged bursts of action potentials leading to increased nociceptive signalling. In mouse studies, selective knockout of Na_V1.7 expression in Na_V1.8-positive nociceptors lead to a loss of acute noxious mechanosensation and inflammatory pain (Nassar *et al*., 2004), while deletion of Na_V1.7 in all sensory neurons leads to additional loss of noxious thermosensation (Minett *et al*., 2012). These data suggest that Na_V1.7 expressed within Na_V1.8-positive sensory neurons are important for acute noxious mechanosensation, whilst Na_V1.7 expressed within Na_V1.8 negative dorsal root ganglion neurons are essential for acute noxious thermosensation. Furthermore, no effect on neuropathic pain behaviour was observed in mice that lack expression of Na_V1.7 in Na_V1.8-positive sensory neurons (Nassar *et al*., 2005). This is also true for mice in which Na_V1.7 has been deleted from all dorsal root ganglion neurons. In contrast, mice in which Na_V1.7 is deleted from all sensory neurons as well as sympathetic neurons show a dramatic reduction in mechanical hypersensitivity following a surgical model of neuropathic pain, demonstrating an important role for Na_V1.7 in sympathetic neurons in the development of neuropathic pain (Minett *et al*., 2012). Overall, the role of Na_V1.7 in human as well as animal pain perception highlights Na_V1.7 as an important analgesic drug target.

Na_V1.7 is not only implicated in pain perception. Weiss *et al*. (2011) demonstrated that Na_V1.7 is an essential requirement for odour perception in both mice and humans. Surprisingly, Na_V1.7 is required for synaptic signalling from the primary olfactory neurons to mitral cells, and the release of substance P from nociceptive neurons has also been shown to be Na_V1.7-dependent (Weiss *et al*., 2011; Minett *et al*., 2012).

Na_V1.8 (*SCN10A*)

Na_V1.8 is a TTX-resistant sodium channel subtype that is expressed in nociceptive sensory neurons (Akopian *et al*., 1999) and acts as a major contributor to the upstroke of action potentials (Renganathan *et al*., 2001). Na_V1.8 is essential in maintaining the excitability of nociceptors at low temperatures (Zimmermann *et al*., 2007), becoming the sole electrical impulse generator at temperatures $<10^\circ$C. This is caused by enhanced slow inactivation of TTX-sensitive channels in response to cooling, whereas inactivation of Na_V1.8 is cold resistant. Behavioural studies of mice in which Na_V1.8 expressing sensory neurons are ablated show loss of response to noxious cold and noxious mechanical stimuli (Abrahamsen *et al*., 2008). Antisense studies have shown an important role for Na_V1.8 channels in inflammatory pain (Khasar *et al*., 1998). Antisense oligonucleotides attenuate the development and maintenance of neuropathic pain in rats (Lai *et al*., 2002; Joshi *et al*., 2006) while small interfering RNA selective knockdown of Na_V1.8 reverses mechanical allodynia (Dong *et al*., 2007). However, Na_V1.8 knockout mice as well as Na_V1.7/1.8 double knockout mice show normal neuropathic pain behaviour (Kerr *et al*., 2001; Nassar *et al*., 2005). However, selective blockers of Na_V1.8 such as A-803467 (Jarvis *et al*., 2007) and ambroxol (Gaida *et al*., 2005) successfully suppress various pain symptoms and neuropathic pain in rats. A recent genome wide association study has identified a single nucleotide polymorphism in Na_V1.8 which was associated with prolonged cardiac conduction (Chambers *et al*., 2010) (longer P-wave duration, PR interval and QRS duration), thereby providing evidence that Na_V1.8 has a functional role in the heart, probably through effects on innervation rather than cardiac muscle.

Na_V1.9 (*SCN11A*)

Na_V1.9 is the most recently discovered VGSC subtype (Dib-Hajj *et al*., 1998). It is a marker of primary nociceptors (Fang *et al*., 2002) and is also expressed in the enteric nervous system (Rugiero *et al*., 2003). Na_V1.9 is a biophysically unique sodium channel which generates TTX-resistant currents that have very slow gating kinetics (Dib-Hajj *et al*., 2002). The current generated by Na_V1.9 is 'persistent' and can be activated at potentials close to resting membrane potential (~ -60 mV). Although the activation kinetics are too slow to contribute to the up-stroke of an action potential, the channel acts as a modulator of membrane excitability by contributing regenerative inward currents over a strategic membrane potential range both negative to, and overlapping with the voltage-threshold for other transient sodium channels.

While a selective blocker of Na_V1.9 does not exist at present, *SCN11A* knockout mice exhibit a clear analgesic phenotype (Priest *et al*., 2005; Amaya *et al*., 2006), confirming Na_V1.9 is an important player in generating hyperalgesia in inflammatory pain states. This appears to be explicable by changes in the properties of distal primary afferents. The response to inflammatory mediators is suppressed in Na_V1.9 knockout mice consistent with the immunocytochemical localization of the channel at unmyelinated nerve endings (Black and Waxman, 2002; Padilla *et al*., 2007), and the remarkable functional plasticity of the current, known to be under G-protein pathway control via protein kinase C (Baker *et al*., 2003; Baker, 2005). Overall, therapeutically targeting Na_V1.9 may help regulate pain thresholds following inflammation or injury.

β-Subunits of voltage-gated sodium channels

β-Subunits of VGSCs belong to the immunoglobulin superfamily of cell adhesion molecules and associate with α-subunits in two ways: covalently in the case of β2 and β4 subunits and non-covalently for β1 and β3 subunits (Patino and Isom, 2010). VGSC β-subunit expression is widespread both in excitable and non-excitable tissues (Patino and Isom, 2010). Although reported effect sizes vary, β-subunits shift the voltage-dependent gating of VGSC in heterologous expression systems (Zhao *et al*., 2011). In humans, mutations in β-subunits have been linked to numerous cardiac and epilepsy related diseases (Table 1). Heterozygous β1 mutations have been identified in seven families with generalized epilepsy with febrile seizures plus (Scheffer *et al*., 2007), (4–6% of generalized epilepsy with febrile seizures plus patients) with the most common mutation being C121W, which leads to impaired trafficking of VGSC to the axon initial segment (Wimmer *et al*., 2010). A human SCN1B epilepsy-related mutation (G257R) unique to a splice variant of β1BA has been proposed to contribute to epilepsy through a mechanism that includes intracellular retention β1 resulting in aberrant neuronal path-finding (Patino *et al*., 2011). Mice heterozygous for β1 (C121W) displayed behavioural arrest at elevated core temperatures and enhanced axon initial segment excitability, which is proposed to be due to a hyperpolarized shift in the voltage dependence of activation of VGSC expressed at the axon initial segment (Wimmer *et al*., 2010). Mutations in all four β-subunits have been linked to cardiac pathologies including Brugada syndrome (β1 and β3), atrial fibrillation (β1, β2 and β3), ventricular fibrillation (β3) and long QT syndrome (β4) (Table 1). Mutations in β3 and β4 have also been linked to sudden infant death syndrome (found in 1% of cases) due to reduced peak sodium current through Na_V1.5 and enhanced 'late sodium current' (Tan *et al*., 2010).

Expression levels of VGSC β-subunits vary in different pathological conditions (nerve injury, pain, Huntington's disease) and knockout models of VGSC β-subunits display pain, epilepsy and ataxia phenotypes (Patino and Isom, 2010), suggesting that the range of VGSC β-subunit roles in pathological conditions may be wider than known. Interestingly, recent reports also show that the affinity and efficacy of VGSC inhibitors can be dramatically altered by changing β-subunit expression levels (Uebachs *et al*., 2010; Wilson *et al*., 2011) and that β-subunit expression levels change during diseases such as Huntington's disease (mouse model) (Oyama *et al*., 2006) and after nerve injury (Pertin *et al*., 2005). It remains to be seen whether this altered pharmacology of α-β complexes can be utilized to produce VGSC blockers with higher selectivity and efficacy *in vivo*.

VGSC β-subunits also interact with the extracellular matrix as well as the cytoskeleton and intracellular signalling molecules (Isom, 2002; Brackenbury and Isom, 2011). Enzymatic cleavage leads to production of a soluble ectodomain and membrane bound C-terminal fragment, which have been implicated in the regulation of cell–cell contact and neurite outgrowth (Wong *et al*., 2005). The β4-subunit was recently identified as a novel substrate of the β-secretase, BACE1, an enzyme implicated in the pathogenesis of Alzheimer's disease (Huth *et al*., 2011). In BACE1 knockout mice, the decay of the resurgent sodium current recorded from Purkinje cells was found to be slowed and could be modelled as a decrease in open pore block consistent with proteolytic modification of β4.

Sodium channel trafficking and disease

The pivotal role of sodium channels in electrical signalling requires targeting of VGSCs to the correct cellular location. High channel densities of VGSCs can be found at the axon initial segment and nodes of Ranvier as part of complex protein aggregates (Hedstrom and Rasband, 2006). Cytoplasmatic proteins regulate expression and function of VGSCs through binding to the intracellular domain of VGSCs, that are, in contrast to the extracellular domain, relatively divergent (Wood *et al*., 2004). To date, several studies have focused on identifying VGSC-associated proteins of which some are involved in trafficking (Diss *et al*., 2004; Shao *et al*., 2009; Leterrier *et al*., 2010). For example $Na_V1.8$ requires the expression of the annexin p11 subunit, which binds to the N-terminal region of the channel to facilitate cell-surface expression of the channel (Okuse *et al*., 2002). Nerve growth factor upregulation of functional $Na_V1.8$ expression, important in inflammatory pain appears to be indirectly mediated through enhanced p11 expression and trafficking (Okuse *et al*., 2002; Poon *et al*., 2004). In addition, the interaction of the N-terminus of $Na_V1.6$ with microtubule-associated protein Map1b facilitates trafficking of $Na_V1.6$ to neuronal surfaces (O'Brien *et al*., 2012).

A variety of protein kinases have been shown to regulate the trafficking of VGSCs to the cell membrane or to specialized membrane domains, such as lipid rafts (reviewed in Shao *et al*., 2009). Stimulation of the β2-adrenergic receptor leads to localization of cardiac $Na_V1.5$ to caveolin-enriched membrane domains resulting in increased function and thereby possibly promoting cardiac arrhythmias (Yarbrough *et al*., 2002). Moreover, trafficking of intracellular pools of the sensory neuron-specific VGSCs $Na_V1.8$ and $Na_V1.9$ has been implicated in enhanced pain sensitivity (Dib-Hajj *et al*., 2010).

The co-factors required for $Na_V1.9$ expression have not been defined, but this channel can only be functionally expressed in dorsal root ganglion neurons where it rescues the expression of persistent current in $Na_V1.9$ knockout neurons (Ostman *et al*., 2008).

A number of VGSC mutants found in several human diseases have been found to be trafficking-deficient and may give insights into key protein regions/domains important for the regulation of VGSC trafficking (Table 1). Trafficking defects may arise due to improper protein folding or altered binding to essential chaperones within the endoplasmic reticulum, ultimately leading to endoplasmic reticulum retention and/or protein degradation. Alternatively, VGSC domains that are crucial for binding to associated proteins regulating VGSCs localization/functioning may be affected. An important family of scaffolding proteins, ankyrins, is responsible for the localization of structurally diverse membrane-associated and cytosolic protein, including VGSCs. Ankyrin-G is important in clustering $Na_V1.2$ and $Na_V1.6$ into nodes of Ranvier and axon initial segments (Jenkins and Bennett, 2001; Garrido *et al*., 2003). A nine-residue motif has been characterized in the D*II–III* loop that is critical for ankyrin-G binding. This sequence is highly conserved within all VGSC isoforms and is almost identical between $Na_V1.2$, $Na_V1.5$ and $Na_V1.6$ (Lemaillet *et al*., 2003). Mutation of the ankyrin-G binding site of $Na_V1.6$ prevents clustering at the axon initial segments (Gasser *et al*., 2012). A mutation associated with Brugada syndrome has been found within this ankyrin-G-binding motif of $Na_V1.5$. This mutation (E1053K) abolished ankyrin-G binding resulting in a loss of membrane expression in cardiac myocytes (Mohler *et al*., 2004). Other Brugada syndrome mutations in $Na_V1.5$ have been shown to be associated with defective trafficking/surface localization emphasizing the importance of correct targeting of this protein for cardiac function (Baroudi *et al*., 2001, 2002; Kyndt *et al*., 2001; Valdivia *et al*., 2002; Bezzina *et al*., 2003; Herfst *et al*., 2003; Ruan *et al*., 2010).

In patients with long QT syndrome, mutations in $Na_V1.5$-associated genes have been found, such as ankyrin-B and *SCN4B* (Saenen and Vrints, 2008). β-Subunits regulate the surface density and the biophysical properties of the channel complex (Shao *et al*., 2009) and knockout mice lacking β2 subunit show reduced VGSC surface expression (Chen *et al*., 2002). Moreover, a recent report showed that a loss-of-function mutation of the *SCN3B*-encoded channel β3 subunit (Navb3–V54G) is associated with a case of idiopathic ventricular fibrillation. This mutation caused a trafficking defect of $Na_V1.5$ to the plasma membrane (Valdivia *et al*., 2010). Conversely, β-subunits have also been shown to rescue a trafficking-defective $Na_V1.1$ mutant (Rusconi *et al*., 2007).

Four mutations in the *SCN1B* gene have been described that lead to an inherited generalized epilepsy with febrile seizures plus. Both mutations occur in a domain of the β1 subunit that is important for the regulation of the subcellular localization of VGSCs within neurons (Wimmer *et al*., 2010). An epilepsy causing *SCN1A* loss-of-function mutation within the region of the C-terminal cytoplasmatic domain (M1841T) that is involved in interactions with accessory subunits has been identified as trafficking defective. Importantly, trafficking of this mutant could be rescued by modulatory proteins, such as β-subunits, calmodulin or G protein $\beta 2\gamma 3$ and the anti-epileptic drug phenytoin (Rusconi *et al*., 2007). However, phenytoin cannot be used therapeutically as it also blocks channel function.

The broadly expressed 20 amino acid IQ motif also found in VGSCs binds to the ubiquitously expressed Ca^{2+}-sensing protein calmodulin. Mutation of the $Na_V1.4$ calmodulin-binding IQ motif showed that this domain is indispensable for normal channel expression and functioning (Biswas *et al*., 2008). A mutation of *SCN2A* that reduced affinity for calcium-bound calmodulin was observed in a patient with autism (Weiss *et al*., 2003). Finally, a recent study has identified two novel non-truncating missense mutations in families with congenital insensitivity to pain that were mapped within the pore domain of *SCN9A*. These mutations cause complete loss-of-function as well as membrane expression of the channel (Cox *et al*., 2010).

There are no effective drugs in use that target trafficking of VGSC. However, some reports have shown that mexiletine, a drug used to inhibit persistent sodium current and to shorten QT interval, rescues trafficking in defective *SCN5A* mutants (Valdivia *et al*., 2002; Ruan *et al*., 2010). The rescue of trafficking of these mutants, however, counteracts the effectiveness of the drug as the increased trafficking may exacerbate the QT prolongation due to increased expression of the mutant protein. In contrast, phenytoin not only rescues a trafficking-defective *SCN1A* mutant but also blocks the channel (Rusconi *et al*., 2007). Thus, drugs that can act as folding chaperones to rescue mutant protein, but do not block channel function, are required.

Although effective drugs have yet to be designed to modulate VGSC expression by interfering with the trafficking pathway, some promising results have been obtained with the anti-epileptic and anti-nociceptive drug gabapentin and its derivatives. These drugs exert their effect primarily via inhibition of trafficking of the voltage-gated $\alpha 2\delta 2$ calcium channel subunit (Heblich *et al*., 2008; Hendrich *et al*., 2008) indicating that drugs targeting trafficking may be useful in VGSC-related pathologies.

Toxins as useful tools to understand voltage-gated sodium channel function and pharmacology

Toxins have been useful in understanding the structural and molecular determinants of VGSC gating through their modifying actions on the gating of VGSCs (Catterall *et al*., 2007). At least six toxin-binding sites (sites 1–6) for toxins have been localized to specific regions of sodium channels. The site of interaction of a number of more recently characterized toxins, including the inhibitory μO-conotoxins and spider toxins, remains to be fully characterized. Binding to these sites affects channel ion conduction or gating, and sequence differences in the residues involved contribute to subtype specificity (Catterall, 2000). Site 1 toxins such as TTX and the μO-conotoxins inhibit current, while most site 2–6 toxins enhance sodium current through effects on channel gating. While channel enhancers have helped to characterize gating and inactivation mechanisms of sodium channels, and the allosteric interactions between toxin binding sites, these classes of toxins invariably produce toxic effects at all doses.

The usefulness of toxins as clinically relevant drugs is limited in part by their high molecular weights and lack of subtype specificity. However, a peptide derived from tarantula venom, peptide ProTx-II is two orders of magnitude more selective for $Na_V1.7$ compared with other heterologously expressed VGSCs and blocked action potential propagation in nociceptors (Schmalhofer *et al*., 2008*a*). Moreover, a μO-conotoxin selectively blocks $Na_V1.8$ currents and chronic pain behaviour in animal models (Ekberg *et al*., 2006).

Mechanisms of drug binding to voltage-gated sodium channels

VGSCs, like other voltage-gated ion channels, can be differentially modulated by compounds that bind selectively to distinct conformational states of the channels. Upon changes in membrane potential, VGSCs undergo voltage-dependent gating that consists of a succession of conformational transitions: non-conducting closed states upon depolarization adopt an activated conducting open state followed by open-state inactivation in which the flow of ions through the channel pore is blocked by the movement of a molecular 'ball' into the cytoplasmic side of the newly opened pore (Armstrong and Hille, 1998) (Fig. 1). Repolarization of the membrane leads to another conformational transition, the deactivation gate (Kuo and Bean, 1994), which consists in a brief opening of the channel before reaching the closed states again. Other conformational states of VGSCs include closed-state inactivation (Armstrong, 2006), slow inactivation and for some VGSCs the 'resurgent current' gate. Closed-state inactivation is engaged upon small depolarizations (these allow the movement of the S4 voltage sensors in domains III and IV only, which is enough for the inactivation particle to move into the pore before the channel opens). Slow inactivation is reached during prolonged depolarizations.

Extensive mutagenesis studies of VGSCs have identified the local anaesthetic binding site as the intracellular surface of the S6 helices (Ragsdale *et al*., 1994, 1996), binding to which causes occlusion of the pore. The modulated receptor hypothesis (Hille, 1977) first predicted that the local anaesthetic binding site could be accessed via two distinct mechanisms: a hydrophilic pathway requiring binding of the drug from the intracellular side during channel opening and a hydrophobic pathway whereby local anaesthetics can access the water filled pore directly. Indeed, the recent crystal structure of the *Arcobacter butzleri* VGSC NavAb confirmed the existence of hydrophobic fenestrations within the protein lipid interface composed of fatty acyl chains (Payandeh *et al*., 2011, 2012). These observations suggest a molecular mechanism for closed state and use/frequency-dependent inhibition of VGSCs. Highly hydrophilic local anaesthetics have limited access to the hydrophobic pathway and instead require opening of VGSCs, allowing access of local anaesthetics to the pore and promoting binding of local anaesthetics in the inactivated state. In this case cumulative block occurs with high-frequency opening when dissociation from the local anaesthetic binding site occurs with a time constant slower than the association rate. This results in accumulation of inhibition and makes potency dependent on opening frequency. By contrast, neutral or hydrophobic local anaesthetics can access the local anaesthetic binding site through both the hydrophobic pathway when the channel is in the closed state and the hydrophilic pathway during channel opening, resulting in a combination of tonic and use-dependent blocking properties. In addition, quaternary amines such as QX-222 or QX-314 may have restricted access to the local anaesthetic binding site in accordance with the guarded receptor hypothesis (Starmer and Hollett, 1985), which may also contribute to use-dependent block. Many neurological pathological conditions result from neurons firing action potentials at higher frequencies than normal, which lead to these cells displaying a tonically depolarized membrane potential. Therefore, voltage-dependent compounds that exhibit frequency-dependent inhibition of VGSCs are desirable as they will tend to only target VGSCs in affected areas, leaving healthy tissues safe. The voltage dependence of VGSC ligands along with their pharmacokinetic properties (on and off rates) is critical in determining the mode of action of these compounds. Chemical entities with affinity for the resting state of VGSCs, like TTX, simply bind to the extracellular regions of VGSCs, block the passage of ions and cannot be removed by either changing the membrane voltage or the gating of the channel. On the contrary, compounds with affinity for the open-inactivated state need channel opening, and therefore membrane depolarization, to bind to the inner pore of VGSCs. The pharmacokinetic properties of these ligands determine the optimal frequency at which blockade is strongest: slow dissociation rates promote use-dependent block at low frequencies, whereas fast off rates favour block at high frequencies. In other words, voltage-dependent drugs that dissociate quickly from VGSCs when the membrane potential is returned to resting values upon action potential repolarization, such as anti-epileptic VGSC blockers, are best at affecting high-frequency firing as observed in epileptic conditions. On the contrary, voltage-dependent compounds that dissociate more slowly, such as anti-arrhythmic and local anaesthetic VGSC blockers, tend to be more effective in blocking low-frequency firing.

Sodium channel targeted drugs

Voltage-gated sodium channel blockers as local anaesthetics

Cocaine was one of the first topical anaesthetics used by humans. Although cocaine is well known as a serotonin–norepinephrine–dopamine reuptake inhibitor, it also has VGSC blocking properties (Ruetsch *et al*., 2001). Over the years, novel VGSC blockers that can be used as local anaesthetics have been synthesized that target VGSC more specifically, have higher efficacy and have fewer side-effects. Currently, many different VGSC blockers are used as local anaesthetics such as lidocaine, bupivacaine and ropivacaine (Ruetsch *et al*., 2001). Local anaesthetics are weak bases that require to be injected as hydrochloride salts in acid solution to be dissolved. At the site of injection, where the pH is higher, local anaesthetics dissociate according to their pKa and release a free base. The free base is able to cross the nerve cell membrane and once inside the nerve, it becomes re-ionized due to the lower cytoplasmic pH and is unable to diffuse out of the cell (ion trapping).

The most common systemically applied local anaesthetics are lidocaine and mexiletine, which have been demonstrated to be effective drugs in treating neuropathic pain in controlled clinical studies (Challapalli *et al*., 2005). These anti-nociceptive effects of local anaesthetics can be observed even at plasma concentrations that would be too low to physiologically block nerve conduction. However, these low concentrations of local anaesthetics are still sufficient to block/attenuate impulse generation/ectopic discharges that cause pain while nerve conduction is unaffected (Mao and Chen, 2000). Importantly, the anti-inflammatory as well as anti-nociceptive effects of local anaesthetics cannot be explained solely by their action on VGSCs (Hollmann and Durieux, 2000; Mao and Chen, 2000). For example, systemic lidocaine enhances spinal inhibitory glycinergic neurotransmission independent of VGSC inhibition (Muth-Selbach *et al*., 2009).

Subtype selective blockers to treat pain

$Na_V1.7$ and $Na_V1.8$ have expression patterns restricted predominantly to the PNS and are both essential for normal pain transmission. Selective antagonists (Table 2) of these channels therefore make attractive targets for the treatment of pain due to the reduced chance of CNS or cardiac side-effects (although $Na_V1.8$ may play a role in cardiac conduction). A-803467 is a $Na_V1.8$ selective small molecule showing selective block of both recombinant and native $Na_V1.8$ currents (Jarvis *et al*., 2007). *In vitro* studies performed on isolated small-diameter dorsal root ganglion neurons have demonstrated that A-803467 blocks $Na_V1.8$ currents in a voltage-dependent manner and inhibits action potential firing. A-803467 shows efficacy in alleviating acute mechanical pain, inflammatory thermal hyperalgesia and neuropathic pain in rodents (Jarvis *et al*., 2007). These behavioural data are consistent with data showing systemic injection of A-803467 decreases both mechanically evoked and spontaneous firing of spinal neurons in nerve-injured rats (McGaraughty *et al*., 2008). The identification of this compound provides an important proof of concept that it is possible to develop isoform-specific blockers of sodium channels that are analgesic. Following the development of the $Na_V1.8$ selective blocker A-830467, Abbott Labs have succeeded in developing an orally active preparations based on a modified structure of A-830467 that is effective in rodent models of neuropathic pain (Drizin *et al*., 2008). These compounds generally inhibited $Na_V1.8$ with IC50s in the sub-micromolar range and had some selectivity for $Na_V1.8$ over other Nav isoforms with the best compound displaying a 5-fold and 20-fold greater potency for $Na_V1.8$ over $Na_V1.2$ and $Na_V1.5$, respectively. Importantly, this class of drugs shows improved effects after oral application and better safety profiles than currently clinically used sodium channel blockers such as mexiletine and lamotrigine (Drizin *et al*., 2008).

$Na_V1.7$ blockers have also been developed, but the benzazepinone structures have equipotent actions on Nav 1.2 and 1.5, suggesting that side-effects may be an issue (Williams *et al*., 2007).

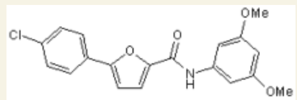
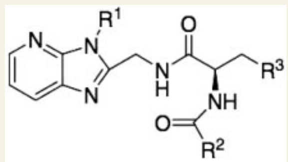
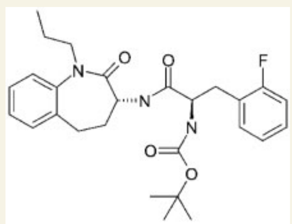
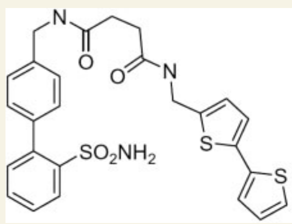
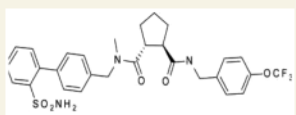
Currently, specific $Na_V1.7$ blockers are being tested by a number of companies in human trials. For example, Convergence Pharmaceuticals are evaluating a $Na_V1.7$ inhibitor in phase II trials of trigeminal neuralgia.

A selective small molecule $Na_V1.7$ blocker (BZP) is an example of an approach to facilitate inhibition of peripherally expressed VGSCs by designing compounds that poorly penetrate the CNS (McGowan *et al*., 2009). BZP was demonstrated to have anti-nociceptive effects in animal models of inflammatory and neuropathic pain after oral administration, while inducing fewer CNS-related side-effects compared to mexiletine.

State-dependent acting agents to treat pain

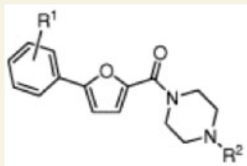
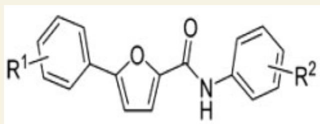
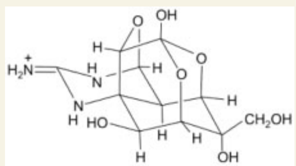
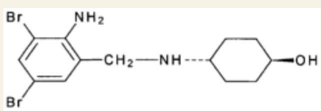
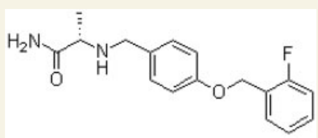
Biophysical characterization of rare gain-of-function mutations affecting pain signalling has provided us with invaluable insight into the way various sodium channel blocking drugs differentially modulate the transition between the states of VGSCs. $Na_V1.7$ mutations in primary erythromelalgia and paroxysmal extreme

Table 2 Isoform-selective compounds

Compound	Structure	IC_{50}	Mode of action	*In vivo* effects	References
A-803467		Nav1.8: 8 nM Nav1.2, $Na_v1.3$, Nav1.5, and Nav1.7: ⩾1 μM	Voltage-dependent block; hyperpolarizing shift in steady-state inactivation; no frequency-dependent block observed	Attenuates neuropathic and inflammatory pain in rats	(Jarvis *et al*., 2007; McGaraughty *et al*., 2008)
Imidazopyridines class		Compound 4: hNav1.7: 80 nM hNav1.8: 270 nM	State-dependent (inactive) channel block	Reversal of neuropathic pain as well as inflammatory pain in rats	(London *et al*., 2008)
1-Benzazepin-2-one class		(Compounds 1–9):hNav1.5: 200–5000 nM hNav1.7: 270–510 nM hNav1.8: 130–>10000 nM	State-dependent (inactive) channel block	Oral efficacy in rat model of neuropathic pain	(Hoyt *et al*., 2007; Williams *et al*., 2007)
Succinamide derivative BPBTS		Nav1.2: 140 nM Nav1.5: 80 nM Nav1.7: 150 nM	Preferential binding to open and inactivated states; voltage- and use-dependent block; concentration-dependent hyperpolarizing shift in steady-state inactivation	Attenuates nociceptive behaviour in formalin test	(Priest *et al*., 2004)
Cyclopentane dicarboxamide class		Compound 54 (CDA54):hNav 1.2: 430 nM hNav 1.5: 150 nM hNav 1.7: 250 nM hNav 1.8: 180 nM	Hyperpolarizing shift of steady-state inactivation; use-dependent block	Inhibition of peripheral nerve injury-induced spontaneous neuronal firing. Attenuates neuropathic pain in rats	(Shao *et al*., 2005; Brochu *et al*., 2006)

(continued)

Table 2 Continued

Compound	Structure	IC_{50}	Mode of action	*In vivo* effects	References
Furan piperazines		hNav1.8: 30–300 nM hNav1.2: 100–1100 nM hNav1.5: 100–4600 nM	Voltage-dependent block and hyperpolarizing shifts in steady-state inactivation curve; no frequency-dependent block observed	Analgesic effect in a rat model of neuropathic pain No adverse effects on CNS cardiovascular system	(Drizin *et al.*, 2008)
5-Aryl-2-furfuramides		hNav1.8: 8 nM hNav1.3: >3000 nM	Voltage- and state-dependent (preferential affinity for the inactivated states)	Dose-dependent reduction of pain-related behaviour in rat models of neuro-pathic and inflammatory pain	(Kort *et al.*, 2008)
TTX metabolite4,9-anhydro-TTX		Nav1.2: 1.26 μmol Nav1.3: 341 nmol Nav1.4: 988 nmol Nav1.5: 78.5 μmol Nav1.6: 7.8 nmol Nav1.7: 1270 nmol Nav1.8: >300 μmol	Hyperpolarizing shift in the voltage-dependence of steady-state inactivation	Not tested	(Rosker *et al.*, 2007)
Ambroxol		TTXr: 35.2 μM tonic block TTXr: 22.5 μM phasic block TTXs: 111.5 μM tonic block TTXs: 57.6 μM phasic block	Use-dependence of block; no frequency-dependent block observed; hyperpolarizing shift in the voltage dependence of steady-state inactivation	Relieves pain associated with sore throat	(Fischer *et al.*, 2002; Weiser and Wilson, 2002)
Ralfinamide		TTXr: 10 μM TTXs: 22 μM	Voltage- and state dependent; use- and frequency-dependent block; hyperpo-larizing shift in the steady-state inactivation	Anti-allodynic in rat models of neuropathic (chronic constriction injury) and inflammatory (complete Freund adjuvant and for-malin) pain	(Veneroni *et al.*, 2003; Stummann *et al.*, 2005)

This table summarizes examples of VGSC isoform-selective compounds that have been investigated in an approach to identify potentially therapeutically useful drugs. TTXr = TTX-resistant; TTXs = TTX-sensitive.

pain disorder exhibit gain-of-function. Interestingly, patients with paroxysmal extreme pain disorder respond favourably to carbamazepine treatment, while carbamazepine is generally ineffective in patients with inherited primary erythromelalgia (Dib-Hajj *et al*., 2007; Fertleman *et al*., 2007). Paroxysmal extreme pain disorder mutations enhance recovery from inactivation and mutant channels can give rise to persistent and enhanced resurgent currents (Dib-Hajj *et al*., 2008; Jarecki *et al*., 2008; Theile *et al*., 2011). Carbamazepine specifically targets these deficits by shifting the voltage dependence of fast inactivation towards more hyperpolarized potentials and targets persistent currents while leaving normal currents relatively unaffected. In contrast, in most patients with inherited primary erythromelalgia, negative shifts in the voltage dependence of activation are observed. These altered properties of the channel are not affected by carbamazepine. In addition, sodium channel inhibitors such as riluzole that effectively target persistent currents and accelerate the rate of inactivation display enhanced efficacy towards inhibiting Navβ4-peptide-mediated resurgent currents and also paroxysmal extreme pain disorder mutant currents (Theile *et al*., 2011). In agreement with this view, it was recently demonstrated that patients with primary erythromelalgia with a (V400M) mutation in *SCN9A* also display a modified VGSC fast inactivation and can be successfully treated with carbamazepine (Fischer *et al*., 2009).

The local anaesthetics mexiletine and lidocaine are effective in some cases of primary erythromelalgia (Iqbal *et al*., 2009; Kuhnert *et al*., 1999). Importantly, the effectiveness of these drugs can be affected by the causative mutation. For example, a specific primary erythromelalgia causing mutation (V872G) can lead to increased use-dependent block of this mutant channel, indicating some patients might have a favourable response to mexilitine (Choi *et al*., 2009). On the contrary, another primary erythromelalgia mutation (N395K) has been found to cause a loss in lidocaine sensitivity and this was associated with ineffectiveness of treatment with Las (Sheets *et al*., 2007).

Lacosamide is a novel amino acid derivative with anticonvulsant activity that is also effective as an analgesic (Stohr *et al*., 2006) in several animal models of neuropathic pain (Beyreuther *et al*., 2006, 2007*a*) and as a therapy for painful diabetic neuropathy (Doty *et al*., 2007). Lacosamide selectively enhances sodium channel slow inactivation with no effects on fast inactivation (Errington *et al*., 2008) as demonstrated on recombinant $Na_V1.3$, $Na_V1.7$ and neuronal $Na_V1.8$ currents (Sheets *et al*., 2008). Slow inactivation is induced under conditions of sustained depolarization and repeated firing, conditions relevant for the pathophysiology of chronic pain. The difference in affinity of lacosamide for binding inactivated channels rather than channels in the resting state was much higher than that for carbamazepine or lidocaine. Recently, it has been shown that lacosamide mediates some actions on VGSC through binding to collapsin response mediator protein 2 (now known as DPYSL2) and this interaction with collapsin response mediator protein 2 results in lacosamide-induced slowing of inactivation (Wang *et al*., 2010*b*). This novel class of VGSC blockers, which targets VGSC channels in specific conformations associated with certain pathologies, opens a new avenue of drug development that may lead to blockers of 'pathological' VGSCs. Recently, it has been shown that uncoupling of collapsin response mediator protein 2 from N-type voltage-gated calcium channels also suppresses inflammatory and neuropathic pain (Brittain *et al*., 2011). However, the relative importance of lacosamide effects on VGSC and voltage-gated calcium channels is uncertain (Wang and Khanna, 2011).

Alternative modes of action to treat pain

To limit the side-effects of VGSC blockers, one possibility is to develop compounds that target VGSCs to the desired tissue only (Clare, 2010). One example of such a drug is cyclopentane dicarboxamide CDA54, a non-selective VGSC blocker developed by Merck (Shao *et al*., 2005). Oral administration of CDA54 is effective at reducing pain responses in models of inflammatory and neuropathic pain (Shao *et al*., 2005; Brochu *et al*., 2006). Importantly, after oral administration of CDA54 into rats, brain homogenate concentrations were found to be 33-fold lower than plasma concentrations, thus reducing the likelihood of side effects caused by actions within the CNS. In addition, compound 54 showed less cardiotoxicity than mexiletine (Brochu *et al*., 2006).

Transdermal drug application may be an advantageous way of targeting the PNS. The effectiveness of this administration route has been demonstrated by the success of lidocaine patches. Lidocaine patches are approved for the relief of pain associated with post-herpetic neuralgia and have proved efficacious in the treatment of peripheral neuropathies, lower back pain, myofascial pain, osteoarthritis, leg ulceration, erythromelalgia and carpal tunnel syndrome (Nalamachu *et al*., 2006).

One often undesired effect of classic VGSC blockers such as lidocaine and its derivatives is that they block action potential firing not only in nociceptive neurons after perineural injection but also in other neurons, thereby inhibiting tactile and mechanical sensation as well as motor function. Thus, targeting derivates of lidocaine specifically to nociceptive neurons, while leaving tactile and mechanical sensation unaffected, is an attractive strategy to treat pain. One strategy for selectively inhibiting nociceptors is cell-specific targeting of the quaternary lidocaine-derivative QX-314 to nociceptive neurons. QX-314 produces a long-lasting non-selective neuronal block with a slow onset (Lim *et al*., 2007). The slow onset of neuronal block is most probably linked to the low membrane permeability of QX-314 reducing the capacity of QX-314 to reach the intracellular blocking site of VGSCs. However, the transient receptor potential cation channel (TRPV1) agonist capsaicin facilitates the selective cellular entry of QX-314 into nociceptive sensory neurons through TRPV1, which is selectively expressed in nociceptors (Binshtok *et al*., 2007). By combining QX-314 with other TRPV1 agonists such as lidocaine itself or protons (lowering pH), similar effects can be achieved (Binshtok *et al*., 2009; Liu *et al*., 2011; Roberson *et al*., 2011). One report also showed that QX-314 itself acts as a TRPV1 agonist (Rivera-Acevedo *et al*., 2011). Unfortunately, intrathecal application of QX-314 causes serious irritation and death (Schwarz *et al*., 2010) and is twice as toxic as lidocaine when applied systemically in mice (Cheung *et al*., 2011). Activation of TRPV1 results in intense pain and does therefore not appear to be the most appealing route to affect analgesia through the use of sodium channel blockers.

Biologicals as the next generation of analgesics

Over recent years, biological compounds such as peptides and antibodies have begun to feed into drug discovery programmes for many disease indications including pain. These include analgesic peptides based on venom toxins, which interact with VGSC. The perceived advantage of venom peptides over conventional small molecule inhibitors is that the toxins are often highly potent and efficacious (low nanomolar IC_{50}s) and have a greater potential for selectivity due to their larger drug target interface. Subsequent mutagenesis of the wild-type toxin can then further improve potency and strive to improve selectivity for a given VGSC isoform. ProTx-II is a venom toxin from the tarantula *Thrixopelma prurient* and has been reported to block $Na_V1.7$ channels ($IC_{50} = 0.3$ nM) with >100-fold selectivity over other Nav isoforms (Middleton *et al*., 2002; Priest *et al*., 2007; Schmalhofer *et al*., 2008*a*). ProTx-II was effective at reducing C-fibre action potential firing frequency in an isolated skin nerve preparation in which the nerve had been de-sheathed (Schmalhofer *et al*., 2008*b*); however, no effect of ProTx-II was observed with an intact nerve sheath indicating that this peptide cannot access sodium channels in intact tissues. Intravenously applied ProTx-II was also ineffective at reducing complete Freund's adjuvant-induced mechanical hyperalgesia. These data confirm that targeting $Na_V1.7$ with a potent selective inhibitor is sufficient to dampen peripheral nociceptive drive (reduce firing of C fibres); however, due to the low permeability of ProTx-II, it is ineffective as an analgesic. Future toxin-derived analgesics targeted to peripherally expressed proteins must therefore overcome this limitation. Importantly, it is possible to use a herpes viral vector to specifically deliver biologicals to sensory neurons of the dorsal root ganglion (Fink *et al*., 2011).

Monoclonal antibodies targeted to essential pain pathway proteins also have the potential to revolutionize analgesic drug discovery due to their potential for high selectivity, high affinity (femtomolar range), low cardiotoxicity and long half-life (monthly subcutaneous injections are achievable). Monoclonal antibodies targeted against nerve growth factor (e.g. tanezumab, Pfizer) have successfully been used to treat chronic joint pain in osteoarthritic patients (Cattaneo, 2010). Polyclonal antibodies targeted against the second or third extracellular loop of ion channels have been successfully used as isoform selective channel blockers of TRP channels (Klionsky *et al*., 2006; Naylor *et al*., 2008), VGSCs (Chioni *et al*., 2005) and voltage-gated calcium channels (Liao *et al*., 2008). However, to date there are no published records of a therapeutically useful monoclonal antibody with ion channel blocking function, although a patent has been filed (US2011/0135662 A1) which describes a $Na_V1.7$ (E3 loop) targeted rabbit antibody which inhibits $Na_V1.7$ currents in a frequency-dependent manner, indicating that this approach may be valid.

Voltage-gated sodium channel blockers in neurological diseases

Voltage-gated sodium channel blockers as anti-epileptic drugs

Phenytoin and carbamazepine are the most widely used compounds to treat epilepsy. Both these drugs act in a state-dependent manner and slow the recovery from inactivation, thereby reducing the availability of channels for subsequent opening (Rogawski and Loscher, 2004). Phenytoin and carbamazepine are both effective in combating partial and generalized tonic–clonic seizures in humans and in animal models of these conditions (Perucca and Tomson, 2011). However, phenytoin and carbamazepine do not show efficacy against absence seizures (very brief generalized epileptic seizures of sudden onset and termination) both in humans and in the animal models of this condition (Dreifuss, 1983; Mantegazza *et al*., 2010). Phenytoin is most effective at depolarized membrane potentials and high-frequency action potential firing. The state dependence of phenytoin causes minimal effects on cognitive functions (low-frequency firing). Carbamazepine displays the same pharmacological properties as phenytoin (VGSC specificity, voltage and state dependence). However, carbamazepine binds VGSCs less effectively, but with a much faster rate than phenytoin, rendering carbamazepine more effective in blocking high-frequency firing (Mantegazza *et al*., 2010). These differences in properties might explain why some epileptic patients respond better to one or the other drug if they carry different VGSC mutations.

Lamotrigine, like phenytoin and carbamazepine, is effective against partial and generalized tonic–clonic seizures and also shows efficacy for the treatment of absence seizures and Lennox–Gastaut syndrome, a rare and intractable form of childhood epilepsy associated with learning difficulties. The mode of action of lamotrigine on VGSCs is similar to that of phenytoin and carbamazepine (voltage and use dependence). However, lamotrigine also acts on other molecular targets, such as the hyperpolarization-gated cationic current I_h in dendrites of pyramidal neurons (Poolos *et al*., 2002), N- and P-type voltage-gated Ca^{2+} channels in cortical neurons (Stefani *et al*., 1996) and neocortical potassium currents (Zona *et al*., 2002). Therefore, the anti-epileptic action of lamotrigine may have a different biophysical basis to carbamazepine and phenytoin.

Topiramate, a sulphamate derivative of the naturally occurring sugar D-fructose, is another broad-spectrum anti-epileptic drug prescribed in cases of partial and generalized tonic–clonic seizures. It blocks both VGSCs and voltage-gated Ca^{2+} channels and enhances potassium channel activity (Shank and Maryanoff, 2008). Interestingly, the action of topiramate on VGSCs consists of slowing down the opening of the channels and protein kinase C activation limits the effect of topiramate of blocking persistent sodium currents (Curia *et al*., 2004).

Introduced as an anti-epileptic drug in 1962, valproate has an even more extensive range of pharmacological actions, being effective against partial and generalized tonic–clonic seizures, absence seizures, and myoclonic seizures. Valproate is a widely prescribed anti-epileptic drug, in both adults and children, and its success is likely to be due to modes of actions different from blocking VGSCs. However, valproate selectively inhibits persistent sodium currents over transient ones in neocortical and sympathetic neurons (Taverna *et al*., 1998; Lamas *et al*., 2009), although the exact mechanism remains unknown. In part, its therapeutic effects are caused by increases in the turnover of GABA, inhibition of NMDA (*N*-methyl-D-aspartic acid) receptors and reduction in gamma-hydroxybutyrate release (Maitre, 1997).

Riluzole was first developed as an anti-epileptic drug but is now used as the first-in-line drug for treatment of amyotrophic lateral sclerosis. It has neuroprotective effects due to blockade of VGSCs on presynaptic terminals and enhancing glutamate uptake by astrocytes thereby inhibiting glutamatergic transmission. Additionally, riluzole has been demonstrated recently to protect against cardiac ischaemia and reperfusion injury by inhibiting persistent sodium currents and is now being tested as a possible treatment for psychiatric disorders (Pittenger *et al*., 2008; Weiss *et al*., 2010).

Voltage-gated sodium channel blockers for the treatment of migraine

Migraine is thought to originate from the activation of meningeal and blood vessel nociceptive fibres, in conjunction with neurogenic inflammation and a change in central pain modulation (Kalra and Elliott, 2007). In common with epilepsy, migraine is characterized by recurrent episodes of nervous system dysfunction with a return to baseline between attacks. Rare forms of familial migraine are caused by mutation of *SCN1A* (Dichgans *et al*., 2005; Vahedi *et al*., 2009). Migraine is treated with a wide range of drugs, including tryptans that, through their agonist effects on serotonin receptors, block the release of vasoactive neuropeptides such as CGRP. Other treatments include the use of non-steroidal anti-inflammatory drugs, anti-depressants and calcium channel blockers (Bolcskei *et al*., 2009). Epilepsy is a co-morbid condition of migraine. Several anti-epileptic drugs targeting VGSCs have been tested for efficacy in migraine conditions. Anti-epileptic compounds, such as valproate, topiramate and lamotrigine, which act through VGSC, have been shown to be effective at reducing the frequency of migraine attacks. However, these drugs all act on other targets as well and therefore their therapeutic effect may be unrelated to their effect on VGSCs (Calabresi *et al*., 2007). It is important to note that use-dependent selective VGSC blockers, such as phenytoin and carbamazepine, have not been documented to be efficacious against migraine attacks (Rogawski and Loscher, 2004). Finally, intranasal application of the local anaesthetic and anti-arrhythmic compound lidocaine was reported to be an effective treatment for some refractory migraines (Kudrow *et al*., 1995; Bolcskei *et al*., 2009).

Voltage-gated sodium channel blockers in neurodegenerative disorders and neuroinflammation

Multiple sclerosis is a condition that may be linked to an autoimmune reaction. However, drug treatment to suppress immune responses is of limited effectiveness. Neurodegeneration as a consequence of progression of multiple sclerosis also involves the activation of VGSCs (Smith, 2007). In particular, demyelination of axons that occurs in patients with multiple sclerosis leads to ectopic action potential firing that is caused by slow sodium-dependent membrane potential oscillations (Kapoor *et al*., 1997).

VGSCs have also been implicated in anoxia/injury-induced neurodegeneration. Energy loss leads in part to persistent sodium currents that cause an increase in axonal intracellular sodium leading to membrane depolarization and further activation of VGSCs. These events promote the reversal of Na^+/Ca^{2+} exchanger and overload of axonal calcium (Stys, 2004).

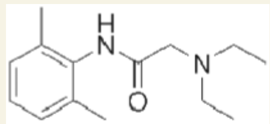
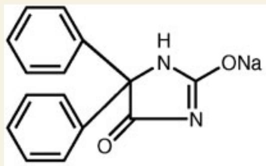
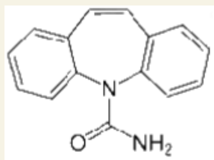
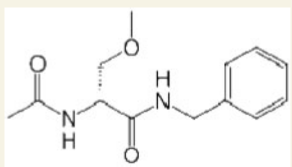
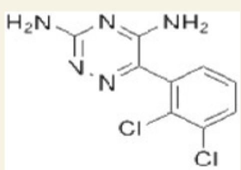
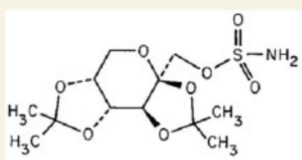
VGSC blockers such as TTX, lidocaine, procaine, mexiletine, phenytoin and carbamazepine protect against white matter axonal damage in multiple sclerosis models (Waxman *et al*., 1994*a*; Carter, 1998; Hewitt *et al*., 2001; Kapoor *et al*., 2003; Black and Waxman, 2008). These protective effects can be observed at concentrations that do not compromise the conduction of action potentials. Lidocaine and flecainide can also protect axons from nitric oxide-triggered degeneration (Kapoor *et al*., 2003). However, withdrawal of phenytoin or carbamazepine in experimental autoimmune encephalomyelitis, a mouse model for multiple sclerosis, resulted in increased inflammatory infiltrate, worsening of symptoms and high incidence of mortality, leading to the suspension of clinical trials (Black and Waxman, 2008). In other trials, lamotrigine did not positively affect clinical outcome measures of patients with secondary progressive multiple sclerosis (Kapoor *et al*., 2010).

Other clinical trials involving a combined therapy with interferon β1a and topiramate, riluzole and lamotrigine, respectively, are still ongoing (Conway and Cohen, 2010). Thus, whether VGSC blockers will ultimately provide an effective new strategy for the treatment of multiple sclerosis is unclear.

Effects of VGSC blockers might also occur through inhibition of phagocytic functions of microglia. Expression of $Na_V1.6$ is upregulated in activated microglia and inhibition of VGSC reduces their phagocytic capacity and reduces inflammatory cells infiltration in brain tissue of mice with experimental autoimmune encephalomyelitis (Craner *et al*., 2005)

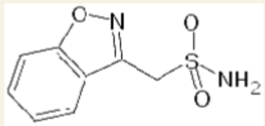
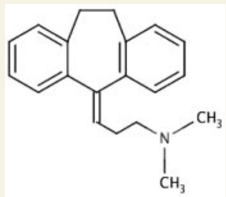
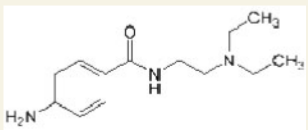
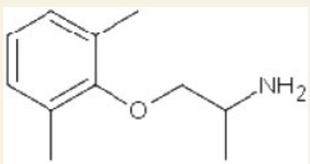
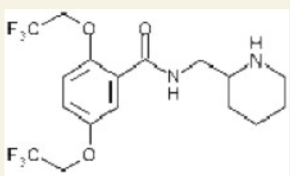
$Na_V1.5$ is present in late endosomes of human macrophages, which play an important role in phagocytosis. $Na_V1.6$ is also expressed in macrophages where it associates with the cytoskeleton, possibly aiding macrophage motility (Carrithers *et al*., 2007). VGSCs were also shown to have a role in T-lymphocyte motility (Fraser *et al*., 2004). However, given the possible side-effects, the value of VGSC blockers to modulate immune responses is unclear (Roselli *et al*., 2006).

Table 3 Most commonly used classic, non-selective VGSC blockers

Compound	Structure	Clinical indications	Mode of action	References
Lidocaine		Widely used local anaesthetic; Class 1b anti-arrhythmic drug; status epilepticus; neuropathic pain	Frequency-dependent, state-dependent and voltage-dependent block; hyperpolarizing shift of half-maximal inactivation	(Durham, 1999; Mao and Chen, 2000; Sheets *et al*., 2008)
Phenytoin		Second/third line therapy of generalized tonic–clonic seizures; Class 1b anti-arrhythmic drug	Slowing of recovery from inactivation; voltage-dependent and frequency-dependent block	(Schwarz and Grigat, 1989)
Carbamazepine		Epilepsy (tonic–clonic and partial seizures); trigeminal neuralgia; neuropathic pain in general and SCN9A-related painful channelopathies in particular	Frequency-dependent and voltage-dependent block; slowing of recovery from inactivation; partial block of persistent sodium currents in a concentration-dependent manner	(Mattson *et al*., 1985; Smith *et al*., 1987; Schwarz and Grigat, 1989; Fertleman *et al*., 2007; Sun *et al*., 2007; Sheets *et al*., 2008; Fischer *et al*., 2009; Wiffen *et al*., 2011)
Lacosamide		Diabetic painful neuropathy; adjunct anti-epileptic therapy	Enhances slow inactivation; no effect on fast inactivation	(Ben-Menachem *et al*., 2007; Rauck *et al*., 2007; Sheets *et al*., 2008)
Lamotrigine		First-line therapy of generalized tonic–clonic, absence, tonic and atonic seizures	Hyperpolarizing shift in voltage-dependency of steady-state inactivation	(Zona *et al*., 2002; French *et al*., 2004)
Topiramate		Generalized tonic–clonic, myoclonic, focal with/without secondary generalization seizures; neuropathic pain	Partial block of persistent sodium currents	(Zona *et al*., 2002; Chong and Libretto, 2003; Khoromi *et al*., 2005)

(continued)

Table 3 Continued

Compound	Structure	Clinical indications	Mode of action	References
Zonisamide		Adjunctive treatment of partial seizures in adults; promising, but not licensed in treatment of refractory neuropathic pain in adults	Hyperpolarizing shift in voltage-dependence of fast inactivation; reduces sustained high-frequency repetitive firing of action potentials	(Hasegawa, 2004; Leppik, 2004; Biton, 2007)
Amitriptyline		First-line treatment for neuropathic pain in the UK	Hyperpolarizing shift in voltage-dependence of fast inactivation	(Graff-Radford *et al*., 2000; Song *et al*., 2000; Cardenas *et al*., 2002; Robinson *et al*., 2004)
Procainamide		Class 1a anti-arrhythmic drug.	Use-dependent block	(Giardina, 1984; Harmer *et al*., 2011)
Mexiletine		Class 1b anti-arrhythmic drug; neuropathic pain in general and SCN9A-related painful channelopathies in particular	Hyperpolarizing shift in voltage-dependent channel inactivation state-dependent and use-dependent block	(Campbell, 1987; Jang *et al*., 2004; Ebell, 2006; Choi *et al*., 2009)
Flecainide		Class 1c anti-arrhythmic agent; Phase II trial data for chronic neuropathic pain	Use-dependent block	(Wang *et al*., 1993; von Gunten *et al*., 2007; Harmer *et al*., 2011)

Although many of these blockers also act through mechanisms other than blocking VGSCs, only VGSC-related indications and mechanisms are reported.

Voltage-gated sodium channel blockers in neuromuscular disorders

Currently, 12 channelopathies affecting skeletal muscle have been described. All five VGSC channelopathies affecting skeletal muscle are found in *SCN4A*/$Na_V1.4$ (Jurkat-Rott *et al*., 2010). These channelopathies, as described earlier, are classified as potassium-aggravated myotonia, paramyotonia congenita, hyperkalaemic periodic paralysis, hypokalaemic periodic paralysis and a form of congenital myasthenic syndrome. Depending on the functional consequence of the mutation (gain- or loss-of-function), treatment options are to either use VSGC blockers to directly block the channel or to reduce the fraction of inactivated channels by restoring the skeletal muscle membrane potential (Jurkat-Rott *et al*., 2010). Pharmacological treatment in myotonia is aimed at decreasing muscle stiffness by mitigating the involuntary action potential bursts without blocking voluntary high-frequency muscle stimulation (Jurkat-Rott *et al*., 2010). VGSC blockers reduce muscle stiffness in potassium-aggravated myotonia and paramyotonia congenita by promoting the inactivated state of $Na_V1.4$ by inducing a hyperpolarized shift in steady-state inactivation and by prolonging recovery time from inactivation. VSGC blockers such as mexiletine, flecainide and other lidocaine analogues can reduce repetitive firing of action potential because of their use-depended properties, a mechanism that leads to a preferential action on channels with pathogenic gain-of-function mutations (Mohammadi *et al*., 2005). Symptoms of muscle weakness are often caused by other pathogenic factors and cannot be treated sufficiently with VGSC blockers. However, influencing potassium concentration or blocking potassium channels have been proven to be beneficial (Jurkat-Rott *et al*., 2010). Burge and Hanna (2012) performed a more detailed analysis of mechanisms and therapeutic options in neuromuscular disorders.

Voltage-gated sodium channel blockers in non-neurological diseases

Voltage-gated sodium channel blockers as anti-arrhythmic drugs

VGSCs are important therapeutic targets in the management of cardiac arrhythmias. According to the Singh Vaughan Williams classification (Walker, 2006), the group of anti-arrhythmic drugs is subdivided into four categories depending on whether they block VGSCs, β-adrenergic receptors, potassium channels or Ca^{2+} channels. Class I anti-arrhythmics are primarily VGSC blockers that are further subdivided into three subclasses (Nattel, 1993), based upon their effect on the length of the action potential. VGSCs blockers as anti-arrhythmic drugs have been discussed extensively previously (Ganjehei *et al*., 2011)

Potential dangers of voltage-gated sodium channel blockers on human development

A missense mutation in the *SCN9A* gene encoding $Na_V1.7$ has been linked to abnormal limb development (Hoeijmakers *et al*., 2012). Some VGSC blockers may have teratogenic effects. Anti-epileptic medication during pregnancy might elevate the risk for congenital malformations, particularly when the treatment involves multiple compounds and/or valproate (Morrow *et al*., 2006). Anti-epileptic treatment with valproate during pregnancy was also linked to significantly lower intelligence in children (Bromley *et al*., 2009). Lacosamide is not used in young children because it was demonstrated to interact with the collapsin response mediator protein 2, which is involved in neuronal differentiation and control of axonal growth (Beyreuther *et al*., 2007*b*; Wang *et al*., 2010*b*).

Conclusions and future directions

Sodium channel blockers originally derived from cocaine, such as lidocaine, have been in clinical use for more than a century. Progress in understanding the molecular basis of channel activity and the mechanisms of action of some analgesic drugs that have been found to act on sodium channels have provided a clear framework in which to pursue medicinal chemistry approaches. Toxins also provide important models for the development of novel analgesic families, based on natural peptides or on organic peptidomimetics. Recent advances in the development of orally active small molecule-specific $Na_V1.8$ blockers will eventually be followed by antagonists of $Na_V1.7$ and $Na_V1.9$. In the meantime the state-dependent blocker lacosamide looks set to join the broad-spectrum sodium channel blockers already in clinical use in Europe. While pain control and epilepsy are still the major focus of interest in terms of sodium channel drug development, it remains possible that indications ranging from autism to immune disorders may be modulated by compounds targeted at sodium channel activity. Manipulation of VGSCs in particular cell types is desirable for many of these indications, as global channel blocking is likely to have deleterious consequences. Topical application, targeted delivery or drugs that lower functional channel expression are all potential future approaches to these problems.

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