The distribution and targeting of neuronal voltage-gated ion channels

Helen C. Lai and Lily Y. Jan‡*

Abstract | Voltage-gated ion channels have to be at the right place in the right number to endow individual neurons with their specific character. Their biophysical properties together with their spatial distribution define the signalling characteristics of a neuron. Improper channel localization could cause communication defects in a neuronal network. This review covers recent studies of mechanisms for targeting voltage-gated ion channels to axons and dendrites, including trafficking, retention and endocytosis pathways for the preferential localization of particular ion channels. We also discuss how the spatial localization of these channels might contribute to the electrical excitability of neurons, and consider the need for future work in this emerging field.

Axon initial segment
(AIS). The area of the axon near the soma that contains a high density of voltage-gated sodium channels, which are responsible for the initial depolarization that leads to the initiation of the action potential.

Saltatory conduction
The way an action potential 'jumps' between nodes of a myelinated axon, for fast conduction.

Back-propagation
The propagation of action potentials 'backward' up the dendrites.

**Center for Basic Neuroscience, University of Texas Southwestern Medical Center, Dallas, Texas 75390, USA.*
‡Howard Hughes Medical Institute, University of California, San Francisco, 1550 4th Street, the Rock Hall San Francisco, California 94158, USA.
Correspondence to L.J.
e-mail: lily.jan@ucsf.edu
doi:10.1038/nrn1938

Voltage-gated ion channels were among the first ion channels to be identified when voltage-clamp recordings were first undertaken over half a century ago. After the landmark studies by Hodgkin and Huxley[1], which established the crucial roles of voltage-gated sodium and potassium channels in the generation and propagation of action potentials in the squid giant axon, the development of patch-clamp recording has allowed electrophysiological analyses of different subcellular compartments of neurons, revealing a rich and varied consortium of voltage-gated ion channels on dendrites and axons. Molecular studies of voltage-gated ion channels over the past quarter of a century further unveiled the remarkably refined and mosaic-like patterns of channel distribution. Only recently have we begun to appreciate just how the different channel isoforms are targeted to different parts of the neuron to carry out specific functions. This review focuses primarily on recent findings concerning the distribution and targeting of voltage-gated ion channels with a focus on sodium, potassium, and hyperpolarization-activated cation channels. We begin with a summary of the nomenclature and membrane topology of various voltage-gated ion channels to set the framework for understanding the structural motifs involved in targeting these channels.

We will consider a model neuron that is receiving multiple excitatory and inhibitory inputs (excitatory and inhibitory postsynaptic potentials — EPSPs and IPSPs) in the somatodendritic region that summate and bring about membrane potential changes at the axon initial segment (AIS). It is in this region that voltage-gated sodium (Nav) and certain voltage-gated potassium (Kv) channels such as the KCNQ channel determine the threshold for firing an action potential, thereby causing action potential generation (FIG. 1)[2–5]. Action potentials then propagate along the axon and, in the case of myelinated axons, 'jump' between the nodes of Ranvier through saltatory conduction to reach the nerve terminals, where activation of voltage-gated calcium (Cav) channels causes calcium influx and neurotransmitter release. Kv channels and hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channels on dendrites further control action potential back-propagation, and the time course and extent of the passive spread of synaptic potentials. Back-propagating action potentials might signal the occurrence of recent neuronal excitation and influence synaptic plasticity[6,7], leading to long-term potentiation (LTP) or long-term depression (LTD) depending on the timing of the back-propagating action potential relative to the synaptic input[8,9]. Action potentials might also be generated locally in the dendrites[10–14], modulating the processing and integration of synaptic inputs of specific dendritic branches or segments. Synaptic integration and the resultant pattern of action potential firing depend on the spatial distribution of various channels with different electrophysiological properties — a crucial aspect of neuronal differentiation that has recently emerged as a fascinating topic for investigation.

The precise distribution of voltage-gated ion channels with specific biophysical properties that allow for the different electrophysiological properties of axonal and somatodendritic regions raises many questions. How do voltage-gated ion channels move to where they need to be? In how many ways can this feat be achieved in

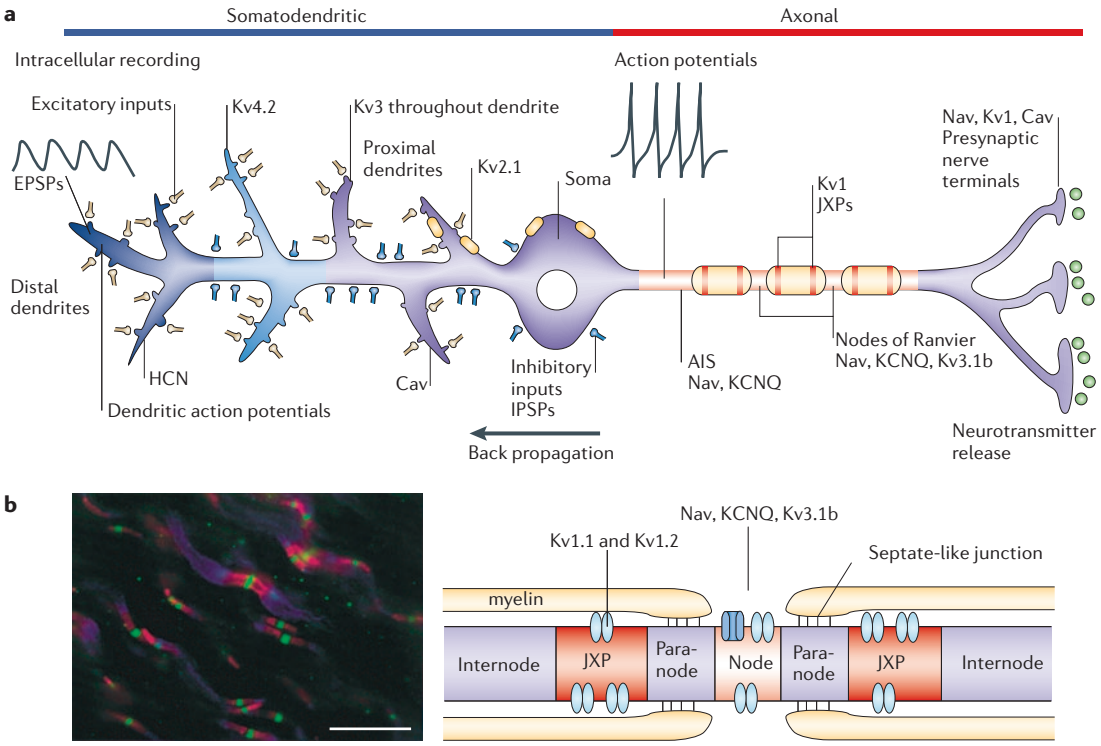


Figure 1 | **General localization of voltage-gated ion channels in a model neuron. a** | In general, Nav channels are found in the axon initial segment (AIS), nodes of Ranvier and presynaptic terminals. Voltage-gated potassium Kv1 channels are found at the juxtaparanodes (JXPs) in adult myelinated axons and presynaptic terminals. The Kv channel KCNQ is found at the AIS and nodes of Ranvier, and Kv3.1b channels are also found at the nodes of Ranvier. Canonically, excitatory and inhibitory inputs (EPSPs and IPSPs — excitatory and inhibitory postsynaptic potentials; yellow and blue presynaptic nerve terminals, respectively) from the somatodendritic region spread passively to the AIS where action potentials are generated by depolarization, and travel by saltatory conduction to the presynaptic nerve terminals to activate voltage-gated calcium (Cav) channels that increase intracellular calcium levels, thereby triggering neurotransmitter release. Hyperpolarization-activated cyclic-nucleotide-gated (HCN) channels have a gradient distribution that increases in density from the soma to the distal dendrites (dark blue shading). Kv2.1 channels are found in clusters on the soma and proximal dendrites (light yellow ovals). Kv3 channels are found throughout the dendrite. Kv4.2 channels are located more prominently on distal dendrites (light blue shading). Kv channels in the dendrites contribute to controlling back propagation. Strong enough inputs in the dendritic region can generate dendritic action potentials. Dendritic Cav channels increase in density toward the proximal dendrites and the soma. **b** | The left panel shows an example of defined channel localization around the nodal region in the myelinated rat optic nerve: Nav channels in green at the nodes; Caspr, a cell-recognition molecule, in red at the paranodes; and Kv1.2 channels in blue at the juxtaparanodes (horizontal scale bar, 10μm). The right panel depicts the channel composition surrounding a myelinated axon with Nav, KCNQ, and Kv3.1b channels at the nodes, no channels at the paranodes underlying the paranodal loops that form septate-like junctions, and Kv1.1 and Kv1.2 channels at the JXPs under the compact myelin. Panel **b** (left) reproduced, with permission, from REF. 207 © (2000) Blackwell Publishing.

Long-term potentiation
(LTP).The prolonged strengthening of synaptic communication, which is induced by patterned input and is thought to be involved in learning and memory formation.

Long-term depression
(LTD). An enduring weakening of synaptic strength that is thought to interact with long-term potentiation (LTP) in the cellular mechanisms of learning and memory in structures such as the hippocampus and cerebellum. Unlike LTP, which is produced by brief high-frequency stimulation, LTD can be produced by long-term, low-frequency stimulation.

Juxtaparanode
A region of the axon that is adjacent to the paranodes, which are adjacent to the nodes of Ranvier and are located underneath the myelin sheath.

different cell types? How do the various channel types coordinate their activities for neuronal signalling? How does channel localization change during development and for what purposes? These are the kinds of questions that researchers have been trying to tackle as they work on different channel isoforms, in different model systems, and use different techniques to reach for some mechanistic insight. The determination of spatial mechanisms is intertwined with temporal considerations, as channels can occupy different locations not only during development, but also in the mature nervous system. It will take some time to determine what global mechanisms exist. Here we review our current knowledge of the distribution, targeting mechanisms and motifs for several voltage-gated ion channels.

Structure of voltage-gated ion channels

Voltage-gated ion channels contain sequence motifs that are necessary for their targeting, presumably because these sequences mediate interactions with proteins that are directly or indirectly involved with channel targeting. Voltage-gated ion channels are formed by either one α-subunit that is a contiguous polypeptide that contains four repeats (domains I–IV), as in the case of Nav and Cav channels; or four α-subunits, each with a single domain, as in the case of Kv and HCN channels (FIG. 2). A single domain contains six α-helical transmembrane segments. The fourth transmembrane segment contains multiple arginines that are mainly responsible for sensing changes in membrane potential. Between the fifth and sixth transmembrane segments is a re-entrant pore

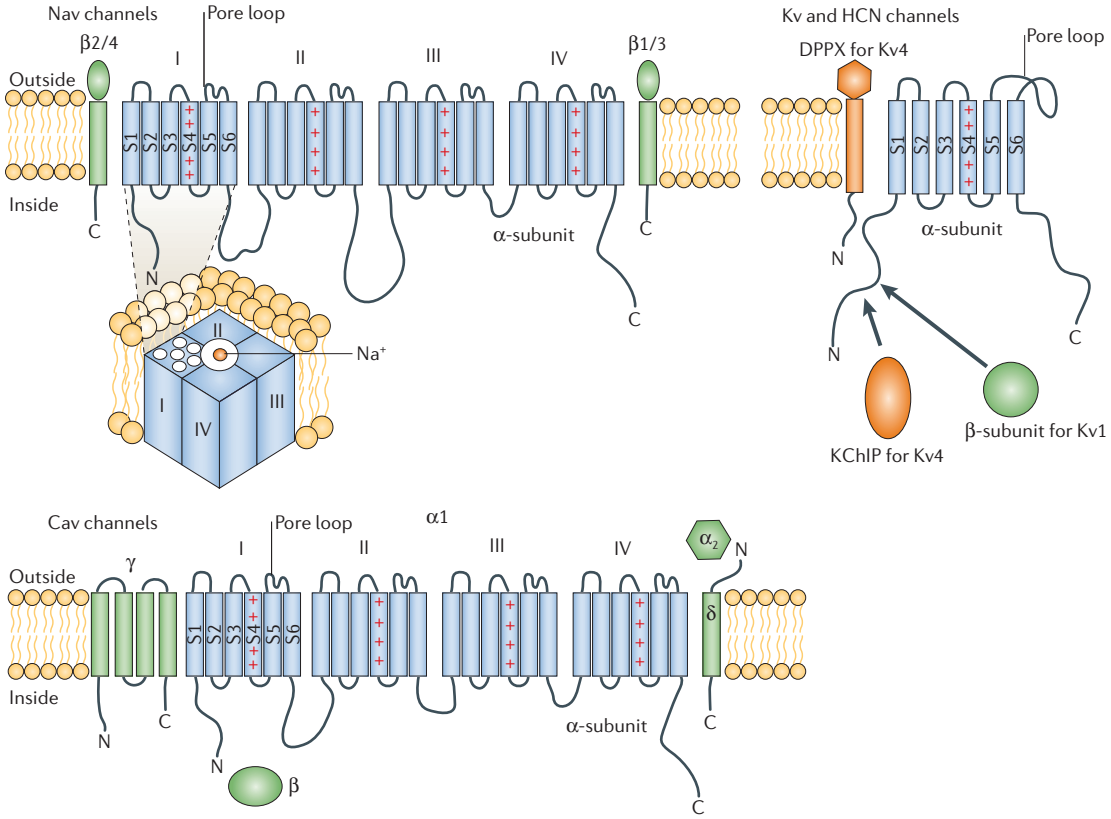


Figure 2 | **General structural topology of voltage-gated ion channels.** Voltage-gated sodium (Nav) channels are formed from a single polypeptide that consists of four domains (I–IV), each of which has six transmembrane segments (S1–S6). The fourth transmembrane segment of each domain contains positively charged arginines that are primarily responsible for voltage sensing, as well as the S5-pore loop-S6 region, which forms the pore domain through which sodium ions flow. The β-subunits, β1/3 and β2/4, are single transmembrane proteins that have an immunoglobulin-like extracellular domain that co-assembles with the Nav α-subunit. Voltage-gated potassium (Kv) channels and hyperpolarization-activated cyclic-nucleotide-gated (HCN) cation channels have four similar or identical α-subunits, each with a single domain. Kv1 channels have cytoplasmic β-subunits that interact with the N-terminal T1 domains. Kv4 channels have two closely associated proteins; the intracellular protein KChIP, and the single-span membrane protein DPPX. Voltage-gated calcium (Cav) channels have a similar topology to Nav channels in their α-subunits. Cav channels can have up to four associated auxiliary subunits: a disulphide-linked $\alpha_2\delta$-complex, an intracellular β-subunit, and an occasional γ-subunit with four transmembrane segments.

loop, which forms the narrowest part of the pore. The interaction of these α-subunits with auxiliary subunits (α2, β, γ or δ) as well as other proteins can modulate channel function and selectively target some channels (such as Nav, Kv1 and KCNQ) to the axon, other channels (such as HCN, Kv2 and Kv4) to somatodendritic regions, and Kv3 and various Cav isoforms to axons and dendrites.

Ten genes encode the α-subunits of Nav channels in mammals; these genes encode Nav1.1 to Nav1.9, plus an atypical sodium channel that is designated Nax and has greater than 50% sequence identity to other Nav proteins in its transmembrane and extracellular regions)[15–17]. There are four known Nav protein β-subunits (β1, β2, β3, β4)[18], each with a single transmembrane segment and an extracellular domain that is structurally homologous to the immunoglobulin G-like domains of L1 cell-adhesion molecules (L1 CAMs)[19,20].

There are approximately 40 mammalian genes for Kv channel α-subunits that are grouped into 12 families known as *Kv1* to *Kv12* (REF. 21). Different genes within a family are denoted with an additional number after the decimal point, such as *Kv1.1* and *Kv1.2*, roughly in order of their molecular characterization. Channel diversity is greatly enhanced by the ability to form homo- or heterotetrameric channels, with the mix and match of members in a subfamily Kv1, Kv3, Kv4, Kv7 (KCNQ) or Kv10. Of the channels described in this review, Kv1 α-subunits associate with the β-subunits Kvβ1.1, Kvβ1.2, Kvβ2 and Kvβ3 through their N-terminal T1 domains, with an $\alpha_4\beta_4$ stoichiometry[22]. Kv4 subunits are associated with KChIPs, calcium-binding proteins that bind to the N-terminus of Kv4 channels[23–25], and DPPX, a single transmembrane-spanning protein in which the extracellular domain resembles a dipeptidyl aminopeptidase, as well as the cell adhesion protein CD26 (REF. 26).

HCN cation channels (HCN1–4) have the same transmembrane topology as Kv channels. However, they are non-selective, pass both Na^+ and K^+ (REF. 3) and are regulated by cyclic nucleotides through a cyclic nucleotide-binding domain in their C-terminus[27].

L1 CAM
A cell adhesion molecule in the nervous system that is important for cell–cell interactions that occur through 6 immunoglobulin G-like protein domains and 3–5 fibronectin type II domains.

KChIPs
β-subunits of Kv4 channels, which have four calcium-binding EF hands with homology to the recoverin/neuronal calcium sensor -1 (NCS1) family.

CD26
A dipeptidyl aminopeptidase and cell adhesion protein.

Cav1–3 channels have an α1 subunit that forms the ion-conduction pore. Cav1 channels give rise to the L-type current, Cav2.1 the P/Q-type current Cav2.2 the N-type current, Cav 2.3 the R-type current, and Cav3 the T-type current[28,29]. Cav channels are associated with several auxiliary subunits *in vivo* that affect channel function and expression: a cytosolic β-subunit, a disulphide-linked $\alpha_2\delta$ complex and an occasional γ-subunit, which create an $\alpha_1\alpha_2\delta\beta\gamma$ native Cav channel[30].

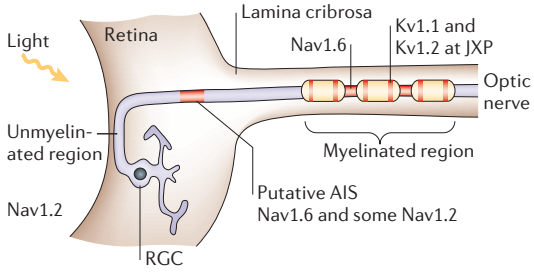
Targeting voltage-gated ion channels to axons

At the nodes of Ranvier, Nav and KCNQ channels allow currents that spread from one node to initiate an action potential at the next node. Kv1 channels at the juxtaparanodal regions increase the fidelity of the action potential at the nodes and reduce excitability during remyelination and development[31,32]. In addition, Kv3 channels reside in the soma, axons and presynaptic terminals of interneurons and other neurons that undergo high frequency firing, and probably contribute to repolarization at the end of an action potential[33–35]. The localization of axonal channels is shown in FIG. 1.

Regarding mechanisms for axonal targeting, studies of proteins such as neuron–glia cell adhesion molecule (NgCAM) and vesicle-associated membrane protein-2 (VAMP2) have elucidated at least three feasible models[36,37]: directed targeting, transcytosis and selective retention. NgCAM, a chick homologue of L1 CAM, might be transported to the axonal membrane by directed targeting or by transcytosis[36,37], which involves insertion of NgCAM into the somatodendritic membrane, followed by its endocytosis and redistribution to the axonal membrane. By contrast, VAMP2, a synaptic vesicle v-SNARE (soluble N-ethylmaleimide-sensitive fusion protein attachment protein (SNAP) receptor), was uniformly inserted into both the somatodendritic and axonal membranes and then endocytosed from the somatodendritic membrane, leaving VAMP2 surface channels along the axon — a mechanism of selective retention (also known as selective endocytosis or elimination) at the axonal membrane[37]. These strategies might be used singly or in combination by axonal ion channels.

Signals such as tyrosine motifs[38] and di-leucine motifs[39], which bind clathrin adaptor proteins and thereby link

Box 1 | Myelin-dependent channel distribution during development



External cues that occur during myelin formation appear to have a role in nodal channel clustering. Retinal ganglion cells (RGCs), with their axons unmyelinated in the retina but myelinated in the optic nerve after they cross the lamina cribrosa (see figure), have voltage-gated sodium (Nav) channel 1.6 localized to a putative axon initial segment (AIS), which is more distal from the soma than previously reported, and nodes of Ranvier, whereas Nav1.2 is located in the unmyelinated region and partially at the AIS[198,199]. During development, Nav1.2 channels appear first at immature nodes of Ranvier, and are eventually replaced by Nav1.6 upon compact myelin formation[199]. Myelination affects channel localization at the nodes of Ranvier but not the AIS[198], and the appearance of Nav1.6 at the AIS correlates well with the appearance of repetitive firing of rat RGCs during development[198,200].

In the *shiverer* mice, which cannot form compact myelin due to a mutation in the myelin basic protein gene, Nav1.6 channels are no longer clustered in the optic nerve[199]. By contrast, in *myelin deficient* rats that have a mutation in the gene that encodes proteolipid protein, which causes oligodendrocytic death[201], Nav channel clusters also become more diffuse in the optic nerve[202]; however, they remain clustered in the spinal cord[106,109]. Moreover, *trembler* mutant mice — which have peripheral nerve hypomyelination, because of mutations in peripheral myelin protein-22 — retain node-like clusters of Nav channels in the sciatic nerve[62,203]. Consistent with these observations, for neurons in culture, myelin is important for initiating clustering but not for maintenance of the clusters[202].

Myelination is required for both initiation and maintenance of voltage-gated potassium channel Kv1.1, Kv1.2 and Kvβ2 clusters at the juxtaparanodal regions in the mouse optic nerve, as their distribution becomes more diffuse in both chronic demyelinating and hypomyelinating mouse models[204]. Kv1 clusters colocalize with postsynaptic density protein-95 (PSD-95), and the appearance of this clustering occurs concurrently with myelination during development in the mouse retina[204]. In a chemically induced rat model of demyelination and remyelination, Kv1.1, Kv1.2 and Kvβ2 are redistributed from their original juxtaparanodal locations in the rat sciatic nerve on demyelination[31]. During remyelination, these subunits cluster first at the nodes of Ranvier, perhaps to reduce excitability, then to paranodal, and finally to juxtaparanodal regions.

As with Nav channels, Kv3.1b channels persist at the nodes in the spinal cord of *myelin deficient* rats[202]. During postnatal development, Kv3.1b channels appear after Nav channels, but before the Kv1.2 channels at the juxtaparanodal regions in the CNS[109].

Both direct contact with myelinating oligodendrocytes and a diffusible secreted factor have been implicated in the clustering of Nav channels[199,202,205,206]. This secreted factor is inactivated by heat and proteases[202], but its identity remains elusive[205]. As with Nav channels, it is unknown what signals are provided by oligodendrocytes or Schwann cells to invoke this clustering in Kv channels[31,204].

The figure is a schematic of a retinal ganglion cell from which axons project into the optic nerve. Portions of the nerve that lie before the lamina cribrosa are unmyelinated and contain Nav1.2 channels, except for the putative AIS, which has Nav1.6 channels. In the myelinated regions (the post-lamina cribrosa and the optic nerve) Nav1.6 channels are at the nodal regions.

Directed targeting
The specific transport of proteins to their proper location (axons or dendrites) after their exit from the ER.

Transcytosis
The targeting of membrane proteins first to one compartment and then, after their endocytosis, to another subcellular compartment.

Selective retention
Interaction with anchor proteins at specific sites causes membrane proteins that are transported to the neuronal membrane uniformly to remain only at those sites (sequestration/retention/stabilizing/anchoring), while being internalized elsewhere.

these proteins to exocytic and endocytic machinery[40–42], target proteins to the basolateral membrane in epithelial cells and might have a role in targeting to dendrites in neurons. However, the signals that target proteins to the apical membrane of epithelial cells do not appear to work for axonal targeting[38]. In light of the identification of novel dendritic targeting signals for transferrin receptors, metabotropic glutamate receptors and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors[43–45], it seems likely that axonal targeting will turn out to involve novel motifs as well.

Nav channels. In axons, Nav channels are responsible for action potential initiation at the AIS and the nodes of Ranvier, action potential propagation along the unmyelinated axon, and action potential back-propagation in dendrites. In addition to their high concentration at the AIS, the biophysical properties of the Nav channels at the AIS might be particularly suited for action potential initiation[46]. The principal Nav channels in the AIS and nodes of Ranvier are Nav1.2 and Nav1.6, and their distribution can change during development in a myelin-dependent manner (BOX 1)[17,30,47,48]. Nav1.1, Nav1.2, Nav1.3 and Nav1.6 are expressed mainly in the CNS, Nav1.4 and Nav1.5 are found in the cardiac and skeletal muscle systems, and Nav1.7, Nav1.8 and Nav1.9 are found in the PNS, although there are exceptions (for example, Nav1.2 and Nav1.6 are found at the nodes of Ranvier in the sciatic nerve[17,30]). The Nav1.1 and Nav1.3 isoforms were found to be somatodendritic for neurons in the brain[30,47], and other distributions have been reported for specific cell types. Here we focus on the channels that are targeted to the axon[30,47,48].

Nav channels associate, or are localized, with a number of molecules that might have a role in anchoring or retaining these channels at the nodes of Ranvier. Nav β-subunits have an extracellular Ig-like domain that is similar to those of Ig-family CAMs[19,20], and these β-subunits colocalize with several CAMs of this family — neuronal cell adhesion molecule (NrCAM), neurofascin-186 (Nf186) and contactin — around the nodes of Ranvier[49,50]. The β1 and β3 subunits interact with Nf186 through their extracellular domains[51], whereas NrCAM and Nf186 bind to ankyrin G through a conserved FIGQY motif in their cytoplasmic C-termini, which connects these CAMs to the actin cytoskeleton through βIV spectrin[52]. Contactin interacts with the Nav β1 subunit and increases the surface expression of Nav1.2, Nav1.3 and Nav1.9 in mammalian cell lines[53–55]. Nav α-subunits also interact with the extracellular matrix proteins tenascin-C, tenascin-R, and phosphacan — probably through the Nav β-subunits[19,56–58]. A summary of protein interactions and motifs is given in FIG. 3.

The precise mechanisms of these CAMs in anchoring or retaining Nav channels at nodes has been probed by assessing their appearance at nodes during development[49,50]. The localization of Nav channels to the AIS and nodes of Ranvier is highly correlated with that of ankyrin G and βIV spectrin[59,60], which appear at the AIS of Purkinje cells early in development, followed by L1 CAMs and Nav channels[61]. This contrasts with the nodes of Ranvier in the rodent sciatic nerve where the L1 CAMs, NrCAM and neurofascin appear before ankyrin G and Nav channels during development[62]. Whether these differences signify differences between axon initial segments and nodes of Ranvier, or between the CNS and PNS, remains to be determined; however, in both cases, ankyrin G and the CAMs are present before the Nav channels, raising the possibility that these proteins might be the first to be targeted to the axon, followed by Nav channels, which are then retained through association.

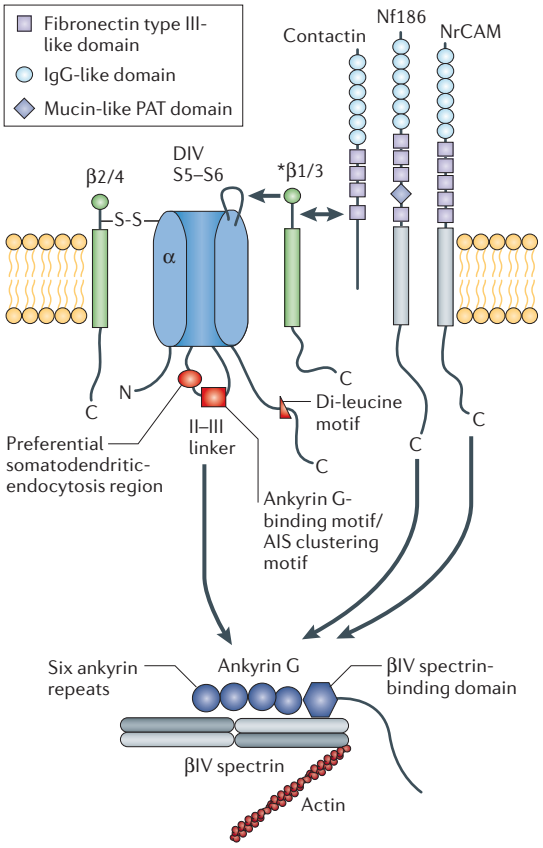


Figure 3 | **Voltage-gated sodium channels.** Contactin, Nf186 (Neurofascin-186), and NrCAM (neuronal cell adhesion molecule) are cell adhesion molecules that interact and/or colocalize with voltage-gated sodium (Nav) channels. The glycosylphosphatidylinositol (GPI)-anchored contactin molecules interact only with the β1 subunit of the Nav channel. Only the β1 subunit (indicated by an asterisk) interacts with the S5–S6 loop in domain IV (DIV) of Nav channels. β2 and β4 subunits are linked by disulphide bonds to Nav channels. A region in the II–III linker is responsible for preferential somatodendritic endocytosis. An ankyrin-G-binding motif that also serves as a clustering motif is also in the II–III linker. Nf186 and NrCAM also interact with ankyrin G, which, through βIV spectrin, connects to the actin cytoskeleton. A di-leucine motif in the C-terminus controls axonal compartmentalization. The N-terminal membrane-binding domain of ankyrin G has four subdomains that consist of six ankyrin repeats that bind other proteins, mainly membrane proteins, followed by a spectrin-binding domain[60]. Actin mostly interacts with the N-terminal region of one β-subunit in the heterotetramer of βIV spectrin[60]. Interactions are indicated by arrows. AIS, axon initial segment, PAT, domain rich in proline, alanine and threonine residues.

Contactin
A glycosylphosphatidylinositol (GPI) anchored glycoprotein with structural homology to the L1 CAM extracellular domain. It has six IgG-like protein domains followed by four fibronectin type III domains.

Ankyrin G
One of three types of ankyrin adaptor proteins that link integral membrane proteins to the spectrin/actin membrane cytoskeleton. Known as "G" for giant or general, it has two main alternative splice forms that generate proteins of 270 kDa and 480 kDa.

βIV spectrin
A splice form of the β-subunit of spectrin, which is a tetramer with two α- and two β-subunits that form two antiparallel heterodimers.

The effect of ankyrin G and βIV spectrin on the distribution of Nav channels has been studied in knockout mice. In mice lacking the cerebellum-specific form of ankyrin G, Nav channels, neurofascin and βIV spectrin are no longer concentrated at the AIS; and their Purkinje cells showed a decreased ability to initiate action potentials and maintain repetitive firing[63,64]. Moreover, βIV spectrin knockout mice have aberrant ankyrin G and Nav localization[64]. It therefore appears that βIV spectrin and ankyrin G act together to stabilize Nav channels at the AIS and nodes of Ranvier.

Even though Nav channels are associated with CAMs that can interact with ankyrin G, Nav channels themselves interact with ankyrin G through a highly conserved nine amino acid motif — residues 1105 to 1113 in Nav1.2 — in the II–III loop[65–67]. Chimeric fusion proteins that are composed of the entire Nav1.2 II–III linker and proteins not normally localized to the AIS are targeted to the AIS in hippocampal cultured neurons[66], while replacing E1111 with alanine causes a uniform distribution of CD4–Nav1.2 II–III chimaeras to the axons, somas and dendrites[68]. An additional motif in the II–III linker — residues 1010 to 1030 in Nav1.2 — is responsible for selective endocytosis from somatodendritic domains in hippocampal cultured neurons[68]. This suggests that Nav channels are uniformly inserted into the membrane but are retained at the AIS through tethering to ankyrin G, while the non-tethered channels in the somatodendritic domains are preferentially endocytosed[68].

The motifs in the II–III linker of Nav1.2 might further work together with a di-leucine-based motif in the C-terminus for channel targeting to the axon. A chimaera of CD4 and the C-terminus of Nav1.2 localizes to the axon in cultured hippocampal neurons, even though it does not contain the ankyrin G-binding region for sequestration in the AIS[69]. This chimaera is selectively endocytosed at dendritic sites, which suggests a mechanism of selective elimination for axonal localization similar to the mechanism proposed for VAMP2 that is described above[37]. Indeed, the C-terminus of Nav1.2 is recognized by components of the clathrin endocytosis pathway. Axonal localization and endocytosis are compromised when the di-leucine motif within a nine amino acid region is mutated to di-alanine. The C-terminus of Nav1.6 apparently lacks this motif, and its fusion to CD4 results in a somatodendritic or non-polarized distribution of the fusion protein. In this case, perhaps the motifs in the II–III linker, which are conserved in Nav1.6, are sufficient for localization of this channel to the axon.

Kv1 channels. In the mammalian nervous system, Kv1 channels are found in the axons and synaptic terminals of CNS neurons and at juxtaparanodal regions of myelinated axons in both the CNS and PNS[30,31,70–72], where they help to control action potential propagation[73] and neurotransmitter release[74]. Kv1 channels are also present in the somatodendritic regions of some CNS neurons — for example, Kv1.2 on mitral cells in the mouse olfactory bulb — but here we focus on the axonal targeting of Kv1 channels[31,71,75]. Kv1.1 knockout mice have hyperexcitability in the hippocampus and epilepsy, which is consistent with a role for Kv1.1 channels in limiting action potential generation[76]. Kv1 subunits associate or colocalize with other proteins[49,50], including members of the exocytic machinery in presynaptic terminals[77,78], and a contactin-associated protein-2 (CASPR2)–TAG1–4.1B complex at the juxtaparanodal regions[49,50,79]. While a precise targeting mechanism for Kv channels has yet to be elucidated, the interacting proteins and motifs that are involved in axonal targeting, channel trafficking and the clustering of these channels have been explored as detailed below.

The N-terminal T1 domain that initiates tetramerization of Kv1 α-subunits is also essential for axonal targeting, which probably involves mechanisms other than preferential endocytosis from dendrites[80,81]; directed targeting is possibly involved, but this might be specific to neuronal type[81]. The T1 domain can mediate the interaction of Kvβ1 and Kvβ2 subunits with Kv1.1, Kv1.2 and Kv1.4, the most abundant α-subunits in the brain[22,30,82,83]. Kvβ subunits, which resemble aldo-keto reductase enzymes in their protein fold or structure and in their ability to bind the $NADP^+$ moiety[84], have been implicated in promoting the surface expression and axonal targeting of Kv1 channels[85,86]. Axonal targeting is affected by mutations that disrupt the $NADP^+$ binding site, but not by mutations in the putative catalytic active site[85], raising the intriguing question of whether the redox potential of the cell could regulate Kv1 axonal targeting. T1 mutations that disrupt axonal targeting do not necessarily disrupt Kvβ binding, which indicates that subtle structural differences in the T1–Kvβ interaction can affect axonal targeting[80]. A summary of protein interactions and motifs can be found in FIG. 4.

A combination of endoplasmic reticulum (ER) export or retention motifs in the Kv1 channel might regulate surface expression. A putative ER export signal in the C-terminus of Kv1.4, VXXSL[87], allows robust surface expression in mammalian cell lines in a process that is apparently independent of the action of Kvβ. Kv1.1 does not contain this signal and is mainly ER retained, whereas Kv1.2, which contains a VXXSN motif, has both ER and surface distribution in mammalian cell lines[87,88]. The pore region has also been implicated[89]; mutations in this region can switch Kv1.1 from a mostly ER-retained channel to one that is surface expressed, and Kv1.4 from a mostly surface-expressed channel to one that is ER retained. It remains to be determined whether these mutations affect tetramer assembly, binding of an as-yet-unidentified protein that regulates trafficking, or the activity of the channel in the ER, which might affect channel trafficking. Finally, a premature stop codon that causes truncation of the Kv1.1 C-terminus in patients with episodic ataxia type 1 leads to intracellular aggregation of Kv1.1 in COS1 cells[90], underscoring the recurring theme that disease-causing mutations might affect channel folding or trafficking.

An endocytic motif, YXXϕ, in the C-terminus of Kv1.2 regulates the surface expression but not the axonal targeting of Kv1.2[80]. Tyrosine (Y)458 in this motif has been implicated in the binding of cortactin, a filamentous (F) actin binding protein that binds Arp2/3, which nucleates actin filamentation[91]. Cortactin binding is reduced by the

Chimeric fusion protein
A polypeptide that is created by fusing an amino acid sequence of interest to a reporter protein.

CD4
A single-span transmembrane protein that tends to yield a uniform distribution in axons and dendrites when it is expressed in neurons.

ER export or retention motifs
Amino acid sequences that have been identified in a number of proteins to be responsible for either exit from, or retention in, the ER (for example, RXR).

Endocytic motif
A common amino acid sequence (for example, YXXϕ) that signals clathrin-mediated endocytosis.

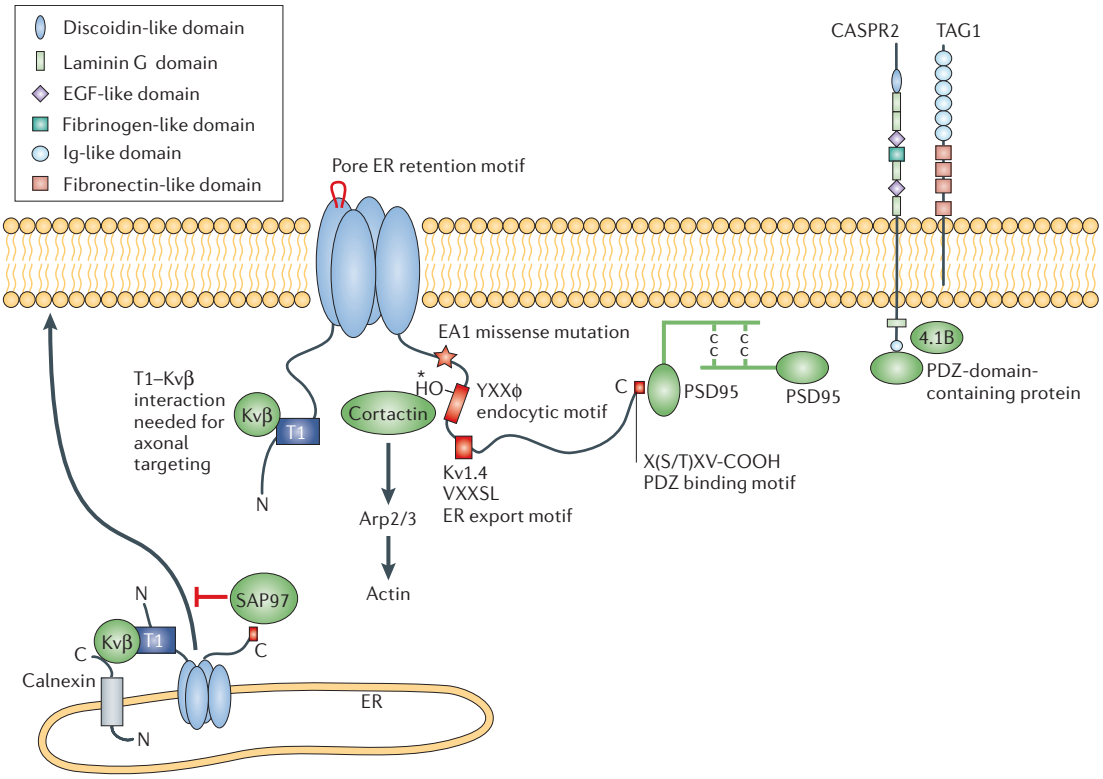


Figure 4 | **Voltage-gated potassium Kv1 channels.** Tetrameric channels are shown as four ovals, in which one oval represents each subunit. Each subunit has an N- and a C-terminus; however, for simplicity, only one N- and one C- terminus are shown here. Proteins and motifs that are involved in the targeting, trafficking, and retention of voltage-gated potassium Kv1 channels are shown. The interaction between the T1 tetramerization domain in the N-terminus of the channel with Kvβ is necessary for axonal targeting. An extreme C-terminal PDZ binding motif (consensus sequence indicated) that binds postsynaptic density protein-95 (PSD-95) might be important for the clustering and possibly anchoring of these channels. Multimerization of PSD-95 might occur through two cysteine residues (C) in its N-terminus that either form a disulphide bridge to another PSD-95 molecule or are palmitoylated. Various motifs regulate the surface expression of Kv1 channels: an endoplasmic reticulum (ER) retention motif in the pore region, an ER export motif in Kv1.4 (VXXSL), and an endocytic motif (YXXϕ). Phosphorylation of a tyrosine (-OH, *) in this endocytic motif can regulate binding to cortactin, a filamentous (F)-actin-binding protein that binds Arp2/3, which nucleates actin polymerization. An EA1 missense mutation causes a truncation of the C-terminus leading to intracellular aggregation of the channel. Kv1 channels are associated with a complex of contactin-associated protein-2 (CASPR2), transient axonal glycoprotein (TAG 1), and 4.1B at the juxtaparanodal regions of myelinated axons that might have a role in clustering. CASPR2 might associate with Kv1 channels through an unidentified PDZ domain-containing protein. At the level of the ER, the ER chaperone, calnexin, promotes forward trafficking while synapse-associated protein-97 (SAP97), a membrane-associated guanylate kinase (MAGUK), inhibits trafficking through binding the same PDZ binding motif as PSD-95. Interacting proteins are in green and sequence motifs or mutations are in red. EA, episodic ataxia type 1; EGF, epidermal growth factor, Ig, immunoglobulin.

phosphorylation of Y458 through activation of the M1 muscarinic acetylcholine receptor in a mammalian cell line, thereby reducing the Kv1.2 ionic current. It will be interesting to explore whether cortactin binding blocks the endocytic motif and thereby allows surface expression, and whether phosphorylation that is regulated by neurotransmitters decreases surface density.

Other binding proteins that are implicated in the trafficking of Kv1 channels include calnexin and synapse-associated protein-97 (SAP97). Calnexin is an ER chaperone that is involved in the folding and assembly of membrane proteins[92]. It promotes the surface expression of Kv1.2, but not that of Kv1.1 or Kv1.6, apparently through the same forward-trafficking pathway that is facilitated by Kvβ. SAP97, a membrane-associated guanylate kinase (MAGUK), appears to retain Kv1 α-subunits in ER-derived vesicular structures by binding to the same C-terminal PDZ binding motif as postsynaptic density protein-95 (PSD-95), thereby inhibiting the trafficking of Kv1.1, Kv1.2 and Kv1.4 (REF. 93).

Clustering of Kv1 channels at the membrane might occur through the interactions of PSD-95 with a PDZ binding motif (X(S/T)XV-COOH) that lies at the C-terminus of Kv1 channels[93,94]. This motif binds to the first or second PDZ domain of PSD-95, which multimerizes, thereby inhibiting internalization and causing clustering of Kv1.4 channels in heterologous cells[95]. Multimerization of PSD-95 occurs through two cysteine residues, Cys3 and Cys5, in its N-terminus[96], possibly involving either disulphide bridging of these cysteines or their palmitoylation[93,94,96–99]. PSD-95 colocalizes with Kv1.2 in presynaptic terminals in the cerebellum[94] and

ER chaperone
A protein that is located in the ER and that helps other proteins to fold.

PDZ binding motif
A PDZ domain binding motif of approximately five amino acids, which is typically located at the extreme C-terminus of a protein.

seems to be necessary, but not sufficient, for the axonal targeting of Kv1.4 in transfected slices of rat cortex[100]. PSD-95 interactions might also be involved in channel anchoring, as discussed in other reviews[49,50,101].

However, although PSD-95 is found colocalized with Kv1 channels at the juxtaparanodal regions, it might not be responsible for the clustering of Kv1 channels. This is because these channels were still correctly clustered, and associated with CASPR2 at the juxtaparanodal regions of the optic nerve in mutant mice that expressed a truncated form of PSD-95 (REF. 102). Interestingly, Kv1.2 and CASPR2 remain clustered in these mutant mice, despite the inability to detect any known MAGUK at the juxtaparanodal region, which suggests that clustering is independent of these scaffolding proteins[102]. Both CASPR2 and Kv1.2 have C-terminal PDZ motifs that might interact with an as-yet-unidentified PDZ-containing protein[49,79,102]. Further studies, possibly using a complete or conditional PSD-95 knockout mouse, might address its role at the juxtaparanodes more clearly.

KCNQ channels. The Kv7 (KCNQ) channels are slow delayed rectifiers that activate at sub-threshold levels to maintain the resting potential and reduce excitability[2]. KCNQ2 is localized to the AIS and nodes of Ranvier in the CNS and PNS and is colocalized with KCNQ3 at only some of these locations[2]. KCNQ2/3 channels underlie the M-current (I_M), which is activated at sub-threshold potentials and modulated by G-proteins[2,103]. Mutations in these channels cause myokymia and benign familial neonatal convulsions (BFNCs)[104,105], underscoring their importance in controlling excitability. Moreover, electrophysiological studies show that KCNQ channels in premyelinated fibres of the optic nerve control excitability, a role similar to that of Kv1 channels at the nodes of the sciatic nerve during development[2,5,31] (BOX 1).

KCNQ2 channels, which contain an ankyrin G-binding motif similar to the one found in the II–III linker of Nav channels, colocalize with ankyrin G and Nav channels at the AIS and nodes of Ranvier[2]. KCNQ2 and Nav channels also share a similar developmental pattern in *myelin deficient* rats, suggesting similar spatial and temporal regulation for their targeting and clustering[2,61,106]. The targeting of KCNQ2/3 and Nav to the AIS is affected in ankyrin G-knockout mice, reinforcing the idea that both Nav and KCNQ2/3 rely on ankyrin G for their clustering[107]. It is important to note that, whereas Nav channels and KCNQ channels both localize to the AIS and nodes of Ranvier due to their interactions with ankyrin G, these channels also localize to other axonal compartments, particularly in unmyelinated axons, by mechanisms that are likely to involve other axonal targeting signals[108]. In addition to the ankyrin G-binding motif, other sequences in the KCNQ2 C-terminal domain have been implicated in its surface expression in unmyelinated hippocampal axons beyond the AIS[108].

Kv3 channels. There are four Kv3 genes, *Kv3.1* to *Kv3.4*, which have multiple splice forms. Kv3.1 and Kv3.2 display delayed rectifier currents, whereas Kv3.3 and Kv3.4 give rise to A-type currents. Typically found in fast-spiking central neurons, Kv3 channels might comprise different combinations of Kv3-family members, and are important for action potential repolarization and sustaining high-frequency firing[34,35]. Little is known about the targeting of Kv3 channels, for which various subtypes are found distributed throughout the neuron. Kv3.1b is found at some of the nodes of Ranvier in the CNS, but not at the AIS[109]. It interacts with ankyrin G; however, the Kv3 channel does not appear to be responsible for the 4-AP-sensitive current that is detected in the mouse optic nerve. Kv3.1/Kv3.2 channels at the nerve terminals of fast-spiking interneurons in the cortex and parallel fibres in the cerebellum might regulate action potential duration, and hence transmitter release[110,111]. Kv3 channels have also been found in the soma and dendrites of CNS neurons and the mechanisms involved in their targeting to somatodendritic regions are discussed below.

Targeting voltage-gated ion channels to dendrites

The presence of voltage-gated sodium, calcium and potassium channels on dendritic membranes[30,112–118] helps control the back-propagation of action potentials into dendrites, local action potentials and the spread of synaptic potentials (FIG. 1). Several types of Kv channels might regulate excitability and contribute to neuronal signalling processing in dendrites[119]. Besides voltage-gated ion channels that activate on depolarization, HCN channels are present with an interesting steep density gradient along the dendrite[120–122] (FIG. 1) and might be up- or down-regulated by synaptic plasticity[123,124]. By altering the resting potential and the input resistance[27,125], these channels regulate dendritic excitability[126,127], the size and time course of synaptic potentials[128–130], and therefore the extent of temporal summation and dendritic integration of synaptic inputs[123,131]. In addition, Kv and HCN channel properties and densities might also be regulated by neuronal activity[6,128,132–135].

The targeting of dendritic channels might occur by directed targeting, as with axonal channels; however, it remains possible that the dendritic localization of some ion channels involves selective endocytosis or transcytosis. Work has been focused on the relationship between the distribution of dendritic channels and neuronal activity and proteins localized or interacting with the channels.

Hyperpolarization-activated cyclic nucleotide-gated channels. HCN1 resides primarily in the neocortex, hippocampus and cerebellum, while HCN3 and HCN4 are concentrated in subcortical regions[120]. HCN2 is widely distributed in the brain and accounts for the HCN current in thalamic relay neurons. *HCN2*-null mice display absence seizures, probably due to action potential bursts and oscillatory activities in their thalamocortical neurons[136]. The physiological importance of HCN channels in controlling neuronal excitability is further underscored by the finding that HCN channel expression is altered following seizures in humans and in animal models[137–139].

HCN1 and HCN2 colocalize in the distal dendrites of cortical and hippocampal pyramidal

M current
(I_M). A slow, sub-threshold non-inactivating potassium current that is carried by KCNQ2/3 heteromeric channels and is named for its inhibition by muscarinic agonists.

A-type currents
A rapidly inactivating voltage-dependent potassium current.

4-AP
4-Aminopyridine, a blocker of certain voltage-gated potassium channels.

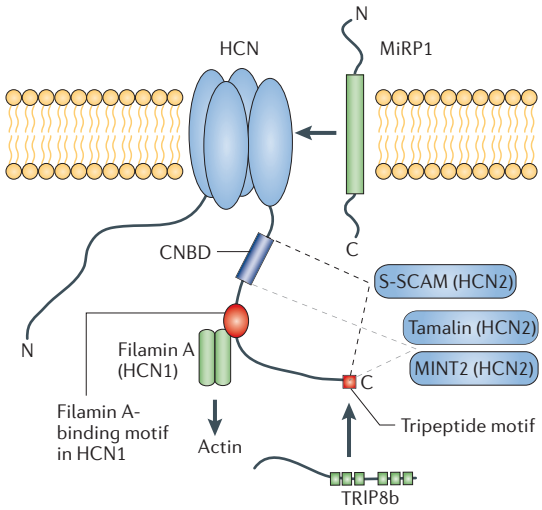


Figure 5 | **Hyperpolarization-activated cyclic nucleotide-gated channels.** The tetrameric channel is shown as four ovals, in which one oval represents each subunit; only one N- and one C- terminus are shown. Proteins and motifs involved in the trafficking and/or retention of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are shown. minK-related peptide-1 (MiRP1) interacts with the transmembrane segments of HCN channels. The cyclic nucleotide-binding domain (CNBD) is involved in promoting exit from the ER. Tetratricopeptide repeat (TPR)-containing Rab8b-interacting protein (TRIP8b), which contains six tetratricopeptide repeats that are involved in protein–protein interactions, interacts with the extreme C-terminal tripeptide motif. HCN1 channels contain a sequence in the C-terminus that interacts with filamin A and connects it to the actin cytoskeleton. The scaffold proteins tamalin and MINT2 interact with the region that is the C-terminal of the CNBD in HCN2, and synaptic scaffolding molecule (S-SCAM) interacts with the C-terminal region including the CNBD. Interactions are indicated by arrows.

neurons[120], and HCN1 and HCN2 expressed in *Xenopus laevis* oocytes seem to form heteromeric channels with properties similar to the native I_h in hippocampal CA1 pyramidal neurons[140]. Indeed, HCN currents in the hippocampal neurons of *HCN2*-null mice are reduced in size, and show characteristics of homomeric HCN1 channels[136]. HCN1–HCN2 heteromeric channel formation in hippocampal and cortical neurons is supported by their co-immunoprecipitation, and HCN1–HCN2 co-assembly can be enhanced by developmental seizures[139]. Both the N- and C-terminal domains of HCN1 and HCN2 seem to be involved in subunit interactions[141–143], and the C-terminal cyclic nucleotide-binding domain (CNBD) appears to be necessary for channel exit from the ER[141,144]. A summary of protein interactions and motifs can be found in FIG. 5.

Pyramidal neurons have a steep gradient of HCN current density, as measured by cell-attached patch-clamp along the dendrite[125,131,140,145]. This has the effect of maintaining temporal resolution in the synaptic potentials[121,131,140,145]. This uneven HCN current distribution probably results from a steep increase of HCN1 and HCN2 proteins in apical dendrites of hippocampal and cortical neurons[114,115,120,121]. It will be interesting to see whether immunostaining of HCN1 and HCN2 will correlate with this increasing HCN current density towards the distal dendrites.

HCN channels are important for regulating the dendritic integration of synaptic potentials[146]. While *HCN1*-null mice have serious motor, learning and memory defects[147], a forebrain-restricted knockout of *HCN1* actually increases hippocampal-dependent learning and memory, and LTP[146]. These intriguing findings have stimulated investigations into HCN channel trafficking and the search for scaffold proteins that might anchor HCN channels in the dendrites.

The MinK-related protein MiRP1 (also known as voltage-gated potassium channel protein KCNE1) assembles with several Kv channel-α subunits, and also forms a complex with HCN2 to modulate HCN2 channel gating kinetics in cardiac ventricular myocytes[148]. MiRP1 overexpression causes enhancement of HCN2 current density[148]. Whether the gradient of HCN channel density along the dendrites of pyramidal neurons involves an uneven distribution of MiRP1 is not yet known.

The C-terminal domains of HCN family members interact with a number of scaffold proteins[149–151]. HCN1–4 interact with the tetratricopeptide repeat (TPR)-containing Rab8b-interacting protein (TRIP8b) through a tripeptide motif in the C-terminus[149]. TRIP8b colocalizes with HCN1 on the apical dendrites of cortical layer V pyramidal neurons, but loses its apical dendrite localization in *HCN1*-null mutant mice, whereas its apical dendritic distribution in hippocampal CA1 neurons is not dependent on HCN1 expression[149]. Expression of TRIP8b in cultured hippocampal neurons and other cell types causes reduction of HCN channel surface expression, probably by promoting channel internalization[149]. So, modulation of HCN channel density could conceivably involve the regulation of TRIP8b interactions with the channel.

HCN1 is the only member of the HCN family that interacts with filamin A, a putative scaffold protein that binds actin[150]. Filamin A causes HCN1 channel clustering and reduces HCN current density in a filamin-deficient human malignant melanoma cell line, or this same cell line stably expressing filamin[150], but how this interaction might affect HCN channel distribution along dendrites is uncertain.

HCN2, but not other HCN family members, interacts with tamalin (also known as GRP1-associated scaffold protein), mostly through a PDZ-like-binding domain at the C-terminus[151]. In addition, HCN2 associates with other scaffold proteins, such as synaptic scaffolding molecule (S-SCAM) and MINT2 through various regions of its C-terminus[151]. In COS7 cells, HCN2 protein levels are increased by its interaction with MINT2, the *Caenorhabditis elegans* homologue of which (LIN-10) has been implicated in targeting glutamate receptors to postsynaptic sites[151]. How these scaffold proteins contribute to the HCN channel distribution in CNS neurons awaits future studies.

I_h
A hyperpolarization-activated cation current that has been identified in cardiac pacemaker and Purkinje fibres for rhythmic and burst firing.

Filamin A
A dimeric scaffold-like protein that connects membrane proteins to the actin cytoskeleton.

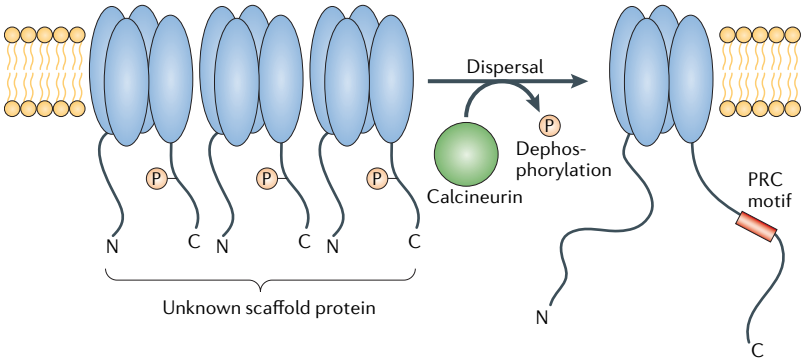


Figure 6 | **Voltage-gated potassium Kv2.1 channels.** Tetrameric channels are shown as four ovals, in which one oval represents each subunit; only one N- and one C- terminus are shown. Proteins and motifs involved in the clustering of the Kv2.1 channel are shown. Dephosphorylation of Kv2.1 channels by a calcineurin-dependent pathway leads to the dispersal of Kv2.1 clusters in proximal dendrites. A proximal restriction and clustering sequence (PRC) motif in the C-terminus is necessary for clustering.

Kv2 channels. Kv2.1 channels underlying the somatodendritic delayed rectifier current I_K form large clusters[152,153] in a process that is dependent on channel phosphorylation[154–156]. Neurotransmitters and neuronal stress trigger dephosphorylation of Kv2.1 in a calcineurin-dependent manner, which disperses Kv2.1 clusters and changes the channel-gating properties[154]. A novel proximal restriction and clustering sequence (PRC) in the C-terminus of Kv2.1 seems to be necessary and sufficient for clustering[157]. Because these channels open and close slowly, they reduce repetitive spiking and could contribute to homeostatic plasticity[154,158]. A summary of protein interactions and motifs is shown in FIG. 6.

Kv3 channels. Kv3 channels are located to somatodendritic regions as well as axons. For example, in the weakly electric fish *Apteronotus leptorhynchus*, Kv3.1 is located in the soma and proximal dendrites of the electrosensory lateral line lobe (ELL), and Kv3.3 is located throughout the dendrites. The targeting of Kv3.3 to the distal dendrite is dependent on the *Apt*Kv3.3 C-terminus containing a putative PDZ-interaction domain[177]. In the mammalian nervous system, Kv3.3 and Kv3.4 reside on the dendrites of Purkinje cells, where they cause dampening of back-propagation from the soma[178]. However, Kv3.1 and Kv3.2 reside in the soma and dendrites of retinal starburst amacrine cells, with Kv3.1b forming a gradient that culminates at high levels in proximal dendrites — a distribution that could account for the preference for centrifugal signal flow along electrically isolated dendrites that are responsible for a direction-selective response to moving objects[179,180]. In the avian auditory nervous system, which is specialized for time coding, there is a developmental shift from the Kv3.1a to the Kv3.1b splice variant with different subcellular expression patterns, resulting in dendritic-channel proteins forming a gradient along the tonotopic axis in the brainstem[181].

Kv4 channels. In contrast to the restriction of Kv2.1 to proximal dendrites and the soma, Kv4.2 and the β-subunits KChIP2 and KChIP4 are concentrated in more distal regions of pyramidal neurons, whereas Kv4.3 and KChIP1 reside on somatodendritic regions of interneurons of the hippocampus and cortex[159] (FIG. 1). KChIPs bind to the N-terminus of Kv4 channels, thereby reconstituting the native A-type currents[23,25,160] that control the shape of action potential waveforms, repetitive spiking, and back-propagation[161–163]. Neurons that express a dominant-negative Kv4.2 construct also have a reduced threshold, not only for action potentials, but also for dendritically initiated plateau potentials, thereby causing these regenerative events to spread to neighbouring dendritic branches and to trigger action potentials[162,163]. The finding that Kv4.2 is localized near synapses[117,118,164] is intriguing, given that the dendritic targeting of Kv4.2 in cerebellar granule neurons requires glutamate receptor activation[165]. Localizing Kv channels near the synapse might allow neurons to mould their intrinsic excitability in the vicinity of active synapses; for example, NMDA (*N*-methyl-D-aspartate) receptor activation through synaptic inputs to hippocampal CA1 neurons causes a local increase of dendritic excitability, because of modulation of A-type Kv channels that probably contain Kv4.2 (REF. 166).

In cerebellar sections and hippocampal cultured neurons, Kv4.2 colocalizes with the actin-binding protein filamin near synapses[167]. Filamin A and C interact with the C-terminus of Kv4.2, and four amino acids (PTPP) in the Kv4.2 C-terminus were found to be crucial for its interaction with filamin C. A di-leucine-containing motif of 16 amino acids that is found in the C-terminal domain of Kv4 channels mediates dendritic targeting in cultured slices of cortical neurons[168]. The di-leucine motif does not appear to affect the rate of endocytosis in COS7 cells, and another portion of the Kv4.2 C-terminal domain mediates Kv4.2 association with the KIF17 kinesin, which has been implicated in the transport of Kv4.2 to dendrites[169]. A summary of protein interactions and motifs is shown in FIG. 7.

Neuronal Kv4 channels probably contain not only the β-subunit KChIP[159,160], but also CD26-related dipeptidyl aminopeptidase-like proteins such as DPPX and DPP10 (REFS 26,170–173). Both types of β-subunit facilitate Kv4 channel trafficking[172,174–176]. Interestingly, the myristoylated KChIP1 requires calcium binding to promote Kv4.2 forward trafficking, apparently involving novel post-ER transport compartments[176]. When expressed in cultured hippocampal neurons, KChIP1 is closely associated with Golgi in the soma as well as Golgi outposts along the dendrites[176]. It remains to be determined whether these trafficking regulators contribute to dendritic Kv4 targeting and modulation.

The distribution of Cav channels

Studies on Cav channels have delineated the localization of specific channel types. Cav channels are expressed in the neuronal soma, dendrites and nerve terminals. Cav1 channels are mainly found in cardiac tissue; however, some isoforms are found in the proximal dendrites and soma of neurons[182]. Cav2.1, Cav2.2 and Cav2.3 channels are found in presynaptic terminals, dendrites and somas where they are involved in controlling neurotransmitter

Delayed rectifier current
(I_K). Current that is mediated by voltage-gated potassium channels, which activate with a delay after the onset of depolarization.

Calcineurin
A calcium–calmodulin-dependent protein phosphatase.

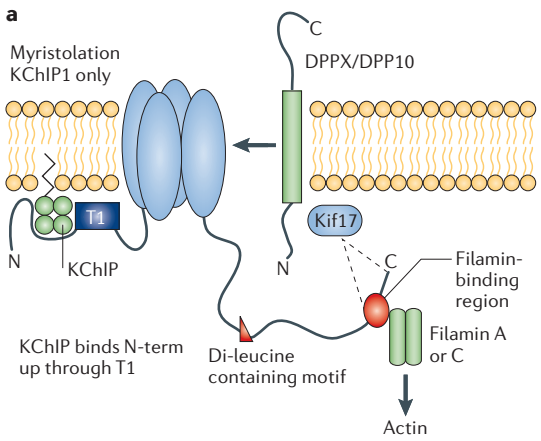


Figure 7 | **Voltage-gated potassium Kv4.2 channels.** The tetrameric channel is shown as four ovals, in which one oval represents each subunit; only one N- and one C- terminus are shown. Proteins and motifs involved in the trafficking and targeting of the Kv4.2 channel are shown. DPPX and DPP10 interact with the transmembrane segments of Kv4.2. KChIPs interact with the N-terminus including the T1 tetramerization domain. KChIP1 is myristoylated and involved in the forward trafficking of Kv4.2 channels. A filamin-binding region in the C-terminus connects Kv4.2 channels to the actin cytoskeleton. A di-leucine motif in the C-terminus mediates dendritic targeting. The last 30 amino acids of Kv4.2 are implicated in kinesin-family member-17 (KIF17) association.

release and also contribute to the induction of LTP at mossy fibre synapses[29,183–185]. In addition, Cav2.3 channels are found in the dendritic spines of CA1 neurons and contribute to synaptic plasticity[186]. Some Cav3 isoforms are localized to dendrites and influence thalamic bursting[29]. Interestingly, a gradient of Cav channels occurs along the dendrite with a higher density located in the soma and proximal dendrites that might have implications for the integration of electrical and calcium signalling[114,187].

Recent studies have begun to identify the components and signalling pathways for the regulation of Cav-channel movement. An ER retention signal in the domain I–II loop (α-interaction domain) of the Cav2.1 α-subunit might be masked by β-subunit binding, thereby allowing forward trafficking out of the ER[188]. The interaction between the α-interaction domain and Cavβ1b or Cavβ2a is essential for the ability of these Cavβ-subunits to promote Cav channel surface expression[189], and this could be sufficiently mediated by the SH3–guanylate-kinase domains in Cavβ[190]. Further regulation of Cav-channel trafficking might involve the phosphatidylinositol 3-kinase–Akt/protein kinase B (PKB) pathway, and the phosphorylation of serine 574 of Cavβ2a[191]. Other cytoplasmic domains of Cav2.1 might also harbour trafficking motifs for ER retention[192]. In addition, the protein kinase A (PKA) anchoring protein AKAP79 regulates surface expression of Cav1 channels independently of PKA, in an interaction that involves a polyproline sequence within the domain II–III loop[193].

Finally, trafficking of Cavα1 channels depends on the metal-ion-dependent adhesion site (MIDAS) of the extracellular Von Willebrand factor-A (VWA) domain of the $\alpha_2\delta$-subunit. Mutation of this presumed Mg^{2+}-binding motif does not affect the trafficking of the $\alpha_2\delta$-subunit when it is expressed alone, but it suppresses surface expression of the $\alpha_2\delta$-subunit and Cavα1 resulting in their co-localization within the cell. This suggests that the conformation of these two subunits in a complex is monitored in the regulation of their forward trafficking[194].

Future perspectives

Proper neuronal signalling depends crucially on the placement of appropriate ion channels at strategic locations on the dendrites or axons. For example, precise sound localization requires the low-threshold Kv1 channels to keep the excitatory synaptic potentials brief, with little or no chance for temporal summation, whereas the high-threshold Kv3 channels have the essential role of enabling fast spiking[195]. The remarkable molecular diversity of voltage-gated ion channels has been suitably exploited to endow neurons with the intricate, finely grained mosaic patterns of these ion channels that underlie neuronal excitability and signalling. This review is by no means comprehensive, leaving out considerations of voltage-gated chloride (ClC) channels and antiporters[196], for example, which might function in intracellular membranous compartments as well as the cell membrane[197]. Ultimately, for these and many other channel types, we would like to understand how the subcellular compartmentalization of channels underlies the electrophysiological activities that are necessary for signal processing and computation in various neuronal circuits.

Molecular and cellular biological studies have begun to explore potential axon-targeting mechanisms and to approach the intriguing question of the spatial and temporal control of channel density along the dendrites. These pioneering studies will surely be followed with more mechanistic analyses of the targeting machineries, their interactions with the polarized cytoskeleton and their regulation by neuronal activity. A summary of sequence motifs that have been identified in recent studies is shown in TABLE 1. Interestingly, endocytic elimination from dendritic membranes acts in a concerted manner, with retention at the AIS for Nav channel localization[66,68], and similar retention through ankyrin G possibly also accounting for the KCNQ channel localization to the AIS[107]. It is also intriguing that axonal channels seem to be bound to the actin cytoskeleton through βIV spectrin while dendritic channels seem to use filamin as the adaptor protein. Future studies will probably further highlight such recurrent themes and elucidate their possible significance.

At this time, global mechanisms for channel targeting remain elusive. A mechanism of selective endocytosis that has been proposed for Nav channels is the closest evidence so far that gives any mechanistic insight. By necessity, the initial investigations identify trafficking motifs and potential interacting proteins; their involvement in ion channel trafficking and targeting probably varies with developmental stages and experience, and depends on

Table 1 | **Summary of the motifs involved in trafficking, targeting and clustering of voltage-gated ion channels**

Channel	Localization	Motif Location	Motif	Motif Description	References
Nav	Axons	II–III linker	n/d	Preferential somatodendritic endocytosis	68
		II–III linker	(V/A)P(I/L)AXXE(S/D)D	Ankyrin G-binding motif/AIS clustering motif	65,66
		C-terminus	Di-leucine	Axonal localization and preferential somatodendritic endocytosis (Nav1.2 only)	69
Kv1	Axons	C-terminus	n/a	Kv1.1 EA1 missense mutation, C-terminal truncation causes intracellular aggregation	90
		C-terminus	YXXϕ	Endocytic motif in Kv1.2 regulates surface expression	80
		C-terminus	VXXSL	ER export motif (Kv1.4 only)	87
		Extreme C-terminus	X(S/T)XV-COOH	PDZ binding motif, channel retention and clustering at the membrane	93,94
		T1	n/d	Axonal targeting	80,81
		Pore region	n/d	ER retention	89
KCNQ	Axons	C-terminus	(I/L)AXGE(S/T)DX(E/D)	Ankyrin G-binding motif	2,107
Cav2.1	Dendrites	I–II linker	n/d	ER retention signal in AID	188
HCN	Dendrites	Extreme C-terminus	Tripeptide motif	TRIP8b binding reduces surface expression	149
		C-terminus: CNBD	n/d	ER exit signal	
		C-terminus: after CNBD	n/d	Filamin A-binding motif (HCN1 only); cytoskeletal interactions	150
		C-terminus: after CNBD	n/d	Tamalin and MINT2 interaction sites (HCN2 only); scaffold interactions	151
		C-terminus: including CNBD	n/d	S-SCAM interaction site (HCN2 only); scaffold interactions	151
Kv2.1	Dendrites	C-terminus	PRC motif	Clustering motif at proximal dendrites	157
		C-terminus	n/d	Phosphorylation-dependent clustering	154,155
Kv4.2	Dendrites	C-terminus	Di-leucine	Dendritic targeting	168
		C-terminus	PTPP for filamin C	Filamin-binding region; cytoskeletal interactions	167
		Extreme C-terminus	n/d	KIF17 association, transport to dendrites	169

AID, α-interaction domain; AIS, axon initial segment; Cav, voltage-gated calcium channel; CNBD, cyclic nucleotide-binding domain; ER, endoplasmic reticulum; HCN, hyperpolarization-activated cyclic nucleotide-gated cation channel; KCNQ, Kv7; KIF17, kinesin family member-17; Kv, voltage-gated potassium channel; n/a, not applicable; Nav, voltage-gated sodium channel; n/d, not determined; PDZ, PSD-95, *Drosophila* disks large protein, ZO-1; PRC, proximal restriction and clustering sequence; S-SCAM, synaptic scaffolding molecule; TRIP8B, tetratricopeptide (TPR)-containing Rab8b-interacting protein.

the potentially dynamic arrangement of microdomains within a neuron. So, the molecular characterization of possible neuronal components is only one of the crucial early steps towards understanding how different neurons transport various ion channels to the proper locations for their physiological functions. It will be important to test their roles in channel trafficking and targeting in different neuronal types — not an easy task given the possibility of functional redundancy and mutual dependence of proteins of macromolecular complexes.

The current shortage of knowledge is the motivation for intensive work in this field. There are many important questions to be addressed. What are the cell-biological mechanisms of channel targeting to polarized regions of the neuron? How might this be differentially modulated in various neuronal cell types? And what are the implications for electrical signalling and neurotransmitter release? These questions are difficult to answer due to the heterogeneity of channel subtypes, localization and neuronal cell types. Key technical challenges include how to distinguish directed targeting from pan-targeting and selective retention or endocytosis, how to determine whether a molecule initiates clustering or merely binds as a scaffold once the channels are correctly targeted, and how all the various motifs coordinate their activities to determine the final location of a channel. Careful experiments combining genetic, molecular, cellular and electrophysiological techniques will be needed to advance this field — for example, live single-cell microscopy to track channel targeting, coupled with electrophysiological recordings to assess functional channel density, as well as studies involving conditional knockout mice for more precise temporal control of gene activity.

Notwithstanding the technical challenges, it will be exciting to learn from future studies how ion channels that control neuronal excitability are positioned in a such a way as to enable the integration of synaptic inputs that are confined to individual dendritic branches, to regulate the extent of spatial and temporal summation of synaptic inputs, to control the extent of dendritic action potential initiation and back-propagation of action potentials that are initiated at the AIS, to dictate the waveform and firing pattern of action potentials, and to control the extent of action potential invasion of axonal branches and nerve terminals.

1. Hodgkin, A. L. & Huxley, A. F. Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. *J. Physiol.* **116**, 449–472 (1952).
2. Devaux, J. J., Kleopa, K. A., Cooper, E. C. & Scherer, S. S. KCNQ2 is a nodal K^+ channel. *J. Neurosci.* **24**, 1236–1244 (2004).
First report that KCNQ is at the AIS and nodes of Ranvier, supported by both co-localization with markers and electrophysiological recordings.
3. Hille, B. *Ion Channels of Excitable Membranes* (Sinauer, Sunderland, Massachusetts, USA, 2001).
4. Shepherd, G. M. *The Synaptic Organization of the Brain* (Oxford University, New York, 2004).
5. Schwarz, J. R. *et al.* KCNQ channels mediate I_{Ks}, a slow K^+ current regulating excitability in the rat node of Ranvier. *J. Physiol.* **573**, 17–34 (2006).
6. Magee, J. C. & Johnston, D. Plasticity of dendritic function. *Curr. Opin. Neurobiol.* **15**, 334–342 (2005).
7. Magee, J. C. & Johnston, D. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* **275**, 209–213 (1997).
8. Sjostrom, P. J. & Nelson, S. B. Spike timing, calcium signals and synaptic plasticity. *Curr. Opin. Neurobiol.* **12**, 305–314 (2002).
9. Dan, Y. & Poo, M. M. Spike timing-dependent plasticity of neural circuits. *Neuron* **44**, 23–30 (2004).
10. Helmchen, F., Svoboda, K., Denk, W. & Tank, D. W. *In vivo* dendritic calcium dynamics in deep-layer cortical pyramidal neurons. *Nature Neurosci.* **2**, 989–996 (1999).
11. Larkum, M. E. & Zhu, J. J. Signaling of layer 1 and whisker-evoked Ca2$^+$ and Na^+ action potentials in distal and terminal dendrites of rat neocortical pyramidal neurons *in vitro* and *in vivo*. *J. Neurosci.* **22**, 6991–7005 (2002).
12. Schiller, J., Schiller, Y., Stuart, G. & Sakmann, B. Calcium action potentials restricted to distal apical dendrites of rat neocortical pyramidal neurons. *J. Physiol.* **505**, 605–616 (1997).
13. Svoboda, K., Helmchen, F., Denk, W. & Tank, D. W. Spread of dendritic excitation in layer 2/3 pyramidal neurons in rat barrel cortex *in vivo*. *Nature Neurosci.* **2**, 65–73 (1999).
14. Oakley, J. C., Schwindt, P. C. & Crill, W. E. Initiation and propagation of regenerative Ca^{2+}-dependent potentials in dendrites of layer 5 pyramidal neurons. *J. Neurophysiol.* **86**, 503–513 (2001).
15. Catterall, W. A., Goldin, A. L. & Waxman, S. G. International union of pharmacology. XLVII. Nomenclature and structure–function relationships of voltage-gated sodium channels. *Pharmacol. Rev.* **57**, 397–409 (2005).
16. Goldin, A. L. *et al.* Nomenclature of voltage-gated sodium channels. *Neuron* **28**, 365–368 (2000).
17. Goldin, A. L. Resurgence of sodium channel research. *Annu. Rev. Physiol.* **63**, 871–894 (2001).
18. Yu, F. H., Yarov-Yarovoy, V., Gutman, G. A. & Catterall, W. A. Overview of molecular relationships in the voltage-gated ion channel superfamily. *Pharmacol. Rev.* **57**, 387–395 (2005).
19. Catterall, W. A. From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron* **26**, 13–25 (2000).
20. Vaughn, D. E. & Bjorkman, P. J. The (Greek) key to structures of neural adhesion molecules. *Neuron* **16**, 261–273 (1996).
21. Gutman, G. A. *et al.* International union of pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacol. Rev.* **57**, 473–508 (2005).
22. Gulbis, J. M., Zhou, M., Mann, S. & MacKinnon, R. Structure of the cytoplasmic β subunit–T1 assembly of voltage-dependent K^+ channels. *Science* **289**, 123–127 (2000).
23. Scannevin, R. H. *et al.* Two N-terminal domains of Kv4 K^+ channels regulate binding to and modulation by KChIP1. *Neuron* **41**, 587–598 (2004).
24. Kim, L. A. *et al.* Three-dimensional structure of I_{to}: Kv4.2–KChIP2 ion channels by electron microscopy at 21 Å resolution. *Neuron* **41**, 513–519 (2004).
25. Zhou, W., Qian, Y., Kunjilwar, K., Pfaffinger, P. J. & Choe, S. Structural insights into the functional interaction of KChIP1 with Shal-type K^+ channels. *Neuron* **41**, 573–586 (2004).
26. Nadal, M. S. *et al.* The CD26-related dipeptidyl aminopeptidase-like protein DPPX is a critical component of neuronal A-type K^+ channels. *Neuron* **37**, 449–461 (2003).
27. Robinson, R. B. & Siegelbaum, S. A. Hyperpolarization-activated cation currents: from molecules to physiological function. *Annu. Rev. Physiol.* **65**, 453–480 (2003).
28. Catterall, W. A. Structure and regulation of voltage-gated Ca^{2+} channels. *Annu. Rev. Cell Dev. Biol.* **16**, 521–555 (2000).
29. Catterall, W. A., Perez-Reyes, E., Snutch, T. P. & Striessnig, J. International union of pharmacology. XLVIII. Nomenclature and structure–function relationships of voltage-gated calcium channels. *Pharmacol. Rev.* **57**, 411–425 (2005).
30. Trimmer, J. S. & Rhodes, K. J. Localization of voltage-gated ion channels in mammalian brain. *Annu. Rev. Physiol.* **66**, 477–519 (2004).
31. Rasband, M. N. *et al.* Potassium channel distribution, clustering, and function in remyelinating rat axons. *J. Neurosci.* **18**, 36–47 (1998).
32. Chiu, S. Y. & Ritchie, J. M. Evidence for the presence of potassium channels in the paranodal region of acutely demyelinated mammalian single nerve fibres. *J. Physiol.* **313**, 415–437 (1981).
33. Rudy, B. *et al.* Contributions of Kv3 channels to neuronal excitability. *Ann. NY Acad. Sci.* **868**, 304–343 (1999).
34. Baranauskas, G., Tkatch, T., Nagata, K., Yeh, J. Z. & Surmeier, D. J. Kv3.4 subunits enhance the repolarizing efficiency of Kv3.1 channels in fast-spiking neurons. *Nature Neurosci.* **6**, 258–266 (2003).
35. Lien, C. C. & Jonas, P. Kv3 potassium conductance is necessary and kinetically optimized for high-frequency action potential generation in hippocampal interneurons. *J. Neurosci.* **23**, 2058–2068 (2003).
36. Wisco, D. *et al.* Uncovering multiple axonal targeting pathways in hippocampal neurons. *J. Cell Biol.* **162**, 1317–1328 (2003).
Proposes mechanisms of directed targeting or transcytosis for the axonal cell adhesion molecule, NgCAM.
37. Sampo, B., Kaech, S., Kunz, S. & Banker, G. Two distinct mechanisms target membrane proteins to the axonal surface. *Neuron* **37**, 611–624 (2003).
Proposes a selective endocytosis mechanism for the axonal protein, VAMP2.
38. Jareb, M. & Banker, G. The polarized sorting of membrane proteins expressed in cultured hippocampal neurons using viral vectors. *Neuron* **20**, 855–867 (1998).
39. Poyatos, I. *et al.* Polarized distribution of glycine transporter isoforms in epithelial and neuronal cells. *Mol. Cell. Neurosci.* **15**, 99–111 (2000).
40. Ohno, H. *et al.* Interaction of tyrosine-based sorting signals with clathrin-associated proteins. *Science* **269**, 1872–1875 (1995).
41. Owen, D. J. & Evans, P. R. A structural explanation for the recognition of tyrosine-based endocytotic signals. *Science* **282**, 1327–1332 (1998).
42. Rapoport, I., Chen, Y. C., Cupers, P., Shoelson, S. E. & Kirchhausen, T. Dileucine-based sorting signals bind to the β chain of AP-1 at a site distinct and regulated differently from the tyrosine-based motif-binding site. *EMBO J.* **17**, 2148–2155 (1998).
43. West, A. E., Neve, R. L. & Buckley, K. M. Identification of a somatodendritic targeting signal in the cytoplasmic domain of the transferrin receptor. *J. Neurosci.* **17**, 6038–6047 (1997).
44. Stowell, J. N. & Craig, A. M. Axon/dendrite targeting of metabotropic glutamate receptors by their cytoplasmic carboxy-terminal domains. *Neuron* **22**, 525–536 (1999).
45. Ruberti, F. & Dotti, C. G. Involvement of the proximal C terminus of the AMPA receptor subunit GluR1 in dendritic sorting. *J. Neurosci.* **20**, RC78 (2000).
46. Colbert, C. M. & Pan, E. Ion channel properties underlying axonal action potential initiation in pyramidal neurons. *Nature Neurosci.* **5**, 533–538 (2002).
47. Westenbroek, R. E., Merrick, D. K. & Catterall, W. A. Differential subcellular localization of the RI and RII Na^+ channel subtypes in central neurons. *Neuron* **3**, 695–704 (1989).
48. Caldwell, J. H., Schaller, K. L., Lasher, R. S., Peles, E. & Levinson, S. R. Sodium channel $Na_v1.6$ is localized at nodes of ranvier, dendrites, and synapses. *Proc. Natl Acad. Sci. USA* **97**, 5616–5620 (2000).
49. Salzer, J. L. Polarized domains of myelinated axons. *Neuron* **40**, 297–318 (2003).
50. Poliak, S. & Peles, E. The local differentiation of myelinated axons at nodes of Ranvier. *Nature Rev. Neurosci.* **4**, 968–980 (2003).
51. Ratcliffe, C. F., Westenbroek, R. E., Curtis, R. & Catterall, W. A. Sodium channel β1 and β3 subunits associate with neurofascin through their extracellular immunoglobulin-like domain. *J. Cell Biol.* **154**, 427–434 (2001).
52. Garver, T. D., Ren, Q., Tuvia, S. & Bennett, V. Tyrosine phosphorylation at a site highly conserved in the L1 family of cell adhesion molecules abolishes ankyrin binding and increases lateral mobility of neurofascin. *J. Cell Biol.* **137**, 703–714 (1997).
53. Liu, C. J. *et al.* Direct interaction with contactin targets voltage-gated sodium channel $Na_v1.9$/NaN to the cell membrane. *J. Biol. Chem.* **276**, 46553–46561 (2001).
54. Kazarinova-Noyes, K. *et al.* Contactin associates with Na^+ channels and increases their functional expression. *J. Neurosci.* **21**, 7517–7525 (2001).
55. Shah, B. S. *et al.* Contactin associates with sodium channel Nav1.3 in native tissues and increases channel density at the cell surface. *J. Neurosci.* **24**, 7387–7399 (2004).
56. Srinivasan, J., Schachner, M. & Catterall, W. A. Interaction of voltage-gated sodium channels with the extracellular matrix molecules tenascin-C and tenascin-R. *Proc. Natl Acad. Sci. USA* **95**, 15753–15757 (1998).
57. Xiao, Z. C. *et al.* Tenascin-R is a functional modulator of sodium channel β subunits. *J. Biol. Chem.* **274**, 26511–26517 (1999).
58. Ratcliffe, C. F. *et al.* A sodium channel signaling complex: modulation by associated receptor protein tyrosine phosphatase β. *Nature Neurosci.* **3**, 437–444 (2000).
59. Kordeli, E., Lambert, S. & Bennett, V. $Ankyrin_G$. A new ankyrin gene with neural-specific isoforms localized at the axonal initial segment and node of Ranvier. *J. Biol. Chem.* **270**, 2352–2359 (1995).
60. Bennett, V. & Baines, A. J. Spectrin and ankyrin-based pathways: metazoan inventions for integrating cells into tissues. *Physiol. Rev.* **81**, 1353–1392 (2001).
61. Jenkins, S. M. & Bennett, V. Ankyrin-G coordinates assembly of the spectrin-based membrane skeleton, voltage-gated sodium channels, and L1 CAMs at Purkinje neuron initial segments. *J. Cell Biol.* **155**, 739–746 (2001).
62. Lambert, S., Davis, J. Q. & Bennett, V. Morphogenesis of the node of Ranvier: co-clusters of ankyrin and ankyrin-binding integral proteins define early developmental intermediates. *J. Neurosci.* **17**, 7025–7036 (1997).
63. Zhou, D. *et al.* AnkyrinG is required for clustering of voltage-gated Na channels at axon initial segments and for normal action potential firing. *J. Cell Biol.* **143**, 1295–1304 (1998).
64. Komada, M. & Soriano, P. βIV-spectrin regulates sodium channel clustering through ankyrin-G at axon initial segments and nodes of Ranvier. *J. Cell Biol.* **156**, 337–348 (2002).
65. Lemaillet, G., Walker, B. & Lambert, S. Identification of a conserved ankyrin-binding motif in the family of sodium channel α subunits. *J. Biol. Chem.* **278**, 27333–27339 (2003).
66. Garrido, J. J. *et al.* A targeting motif involved in sodium channel clustering at the axonal initial segment. *Science* **300**, 2091–2094 (2003).
Reports the identification of a motif in the II–III loop of Nav1.2 channels that is necessary and sufficient to target these channels to the AIS.
67. Srinivasan, Y., Elmer, L., Davis, J., Bennett, V. & Angelides, K. Ankyrin and spectrin associate with voltage-dependent sodium channels in brain. *Nature* **333**, 177–180 (1988).
68. Fache, M. P. *et al.* Endocytotic elimination and domain-selective tethering constitute a potential mechanism of protein segregation at the axonal initial segment. *J. Cell Biol.* **166**, 571–578 (2004).
69. Garrido, J. J. *et al.* Identification of an axonal determinant in the C-terminus of the sodium channel $Na_v1.2$. *EMBO J.* **20**, 5950–5961 (2001).
First suggestion that Nav1.2 axonal targeting is by selective elimination in the dendrites through a di-leucine motif in the C-terminus that is associated with the clathrin endocytic pathway.
70. Monaghan, M. M., Trimmer, J. S. & Rhodes, K. J. Experimental localization of Kv1 family voltage-gated K^+ channel α and β subunits in rat hippocampal formation. *J. Neurosci.* **21**, 5973–5983 (2001).
71. Wang, H., Kunkel, D. D., Martin, T. M., Schwartzkroin, P. A. & Tempel, B. L. Heteromultimeric K^+ channels in terminal and juxtaparanodal regions of neurons. *Nature* **365**, 75–79 (1993).
72. Sheng, M., Liao, Y. J., Jan, Y. N. & Jan, L. Y. Presynaptic A-current based on heteromultimeric K^+ channels detected *in vivo*. *Nature* **365**, 72–75 (1993).
73. Debanne, D., Guerineau, N. C., Gahwiler, B. H. & Thompson, S. M. Action-potential propagation gated by an axonal I_A-like K^+ conductance in hippocampus. *Nature* **389**, 286–289 (1997).

74. Lambe, E. K. & Aghajanian, G. K. The role of Kv1.2-containing potassium channels in serotonin-induced glutamate release from thalamocortical terminals in rat frontal cortex. *J. Neurosci.* **21**, 9955–9963 (2001).
75. Wang, H., Kunkel, D. D., Schwartzkroin, P. A. & Tempel, B. L. Localization of Kv1.1 and Kv1.2, two K channel proteins, to synaptic terminals, somata, and dendrites in the mouse brain. *J. Neurosci.* **14**, 4588–4599 (1994).
76. Smart, S. L. *et al.* Deletion of the $K_v1.1$ potassium channel causes epilepsy in mice. *Neuron* **20**, 809–819 (1998).
77. Fili, O. *et al.* Direct interaction of a brain voltage-gated K^+ channel with syntaxin 1A: functional impact on channel gating. *J. Neurosci.* **21**, 1964–1974 (2001).
78. Michaelevski, I. *et al.* Modulation of a brain voltage-gated K^+ channel by syntaxin 1A requires the physical interaction of Gβγ with the channel. *J. Biol. Chem.* **277**, 34909–34917 (2002).
79. Poliak, S. *et al.* Juxtaparanodal clustering of Shaker-like K^+ channels in myelinated axons depends on Caspr2 and TAG-1. *J. Cell Biol.* **162**, 1149–1160 (2003).
80. Gu, C., Jan, Y. N. & Jan, L. Y. A conserved domain in axonal targeting of Kv1 (Shaker) voltage-gated potassium channels. *Science* **301**, 646–649 (2003). **Reports that the T1 domain of Kv1 channels is necessary and sufficient to target to the axons that depend on proper association with Kvβ.**
81. Rivera, J. F., Chu, P. J. & Arnold, D. B. The T1 domain of Kv1.3 mediates intracellular targeting to axons. *Eur. J. Neurosci.* **22**, 1853–1862 (2005).
82. Pongs, O. *et al.* Functional and molecular aspects of voltage-gated K^+ channel β subunits. *Ann. NY Acad. Sci.* **868**, 344–355 (1999).
83. Rhodes, K. J. *et al.* Association and colocalization of the Kvβ1 and Kvβ2 β-subunits with Kv1 α-subunits in mammalian brain K^+ channel complexes. *J. Neurosci.* **17**, 8246–8258 (1997).
84. Gulbis, J. M., Mann, S. & MacKinnon, R. Structure of a voltage-dependent K^+ channel β subunit. *Cell* **97**, 943–952 (1999).
85. Campomanes, C. R. *et al.* Kv β subunit oxidoreductase activity and Kv1 potassium channel trafficking. *J. Biol. Chem.* **277**, 8298–8305 (2002).
86. Shi, G. *et al.* β subunits promote K^+ channel surface expression through effects early in biosynthesis. *Neuron* **16**, 843–852 (1996).
87. Li, D., Takimoto, K. & Levitan, E. S. Surface expression of Kv1 channels is governed by a C-terminal motif. *J. Biol. Chem.* **275**, 11597–11602 (2000).
88. Manganas, L. N. & Trimmer, J. S. Subunit composition determines Kv1 potassium channel surface expression. *J. Biol. Chem.* **275**, 29685–29693 (2000).
89. Manganas, L. N. *et al.* Identification of a trafficking determinant localized to the Kv1 potassium channel pore. *Proc. Natl Acad. Sci. USA* **98**, 14055–14059 (2001).
90. Manganas, L. N. *et al.* Episodic ataxia type-1 mutations in the Kv1.1 potassium channel display distinct folding and intracellular trafficking properties. *J. Biol. Chem.* **276**, 49427–49434 (2001).
91. Hattan, D., Nesti, E., Cachero, T. G. & Morielli, A. D. Tyrosine phosphorylation of Kv1.2 modulates its interaction with the actin-binding protein cortactin. *J. Biol. Chem.* **277**, 38596–38606 (2002).
92. Manganas, L. N. & Trimmer, J. S. Calnexin regulates mammalian Kv1 channel trafficking. *Biochem. Biophys. Res. Commun.* **322**, 577–584 (2004).
93. Tiffany, A. M. *et al.* PSD-95 and SAP97 exhibit distinct mechanisms for regulating K^+ channel surface expression and clustering. *J. Cell Biol.* **148**, 147–158 (2000).
94. Kim, E., Niethammer, M., Rothschild, A., Jan, Y. N. & Sheng, M. Clustering of Shaker-type K^+ channels by interaction with a family of membrane-associated guanylate kinases. *Nature* **378**, 85–88 (1995).
95. Jugloff, D. G., Khanna, R., Schlichter, L. C. & Jones, O. T. Internalization of the Kv1.4 potassium channel is suppressed by clustering interactions with PSD-95. *J. Biol. Chem.* **275**, 1357–1364 (2000).
96. Hsueh, Y. P., Kim, E. & Sheng, M. Disulfide-linked head-to-head multimerization in the mechanism of ion channel clustering by PSD-95. *Neuron* **18**, 803–814 (1997).
97. Hsueh, Y. P. & Sheng, M. Requirement of N-terminal cysteines of PSD-95 for PSD-95 multimerization and ternary complex formation, but not for binding to potassium channel Kv1.4. *J. Biol. Chem.* **274**, 532–536 (1999).
98. Topinka, J. R. & Bredt, D. S. N-terminal palmitoylation of PSD-95 regulates association with cell membranes and interaction with K^+ channel Kv1.4. *Neuron* **20**, 125–134 (1998).
99. Kim, E. & Sheng, M. Differential K^+ channel clustering activity of PSD-95 and SAP97, two related membrane-associated putative guanylate kinases. *Neuropharmacology* **35**, 993–1000 (1996).
100. Arnold, D. B. & Clapham, D. E. Molecular determinants for subcellular localization of PSD-95 with an interacting K^+ channel. *Neuron* **23**, 149–157 (1999).
101. Kim, E. & Sheng, M. PDZ domain proteins of synapses. *Nature Rev. Neurosci.* **5**, 771–781 (2004).
102. Rasband, M. N. *et al.* Clustering of neuronal potassium channels is independent of their interaction with PSD-95. *J. Cell Biol.* **159**, 663–672 (2002).
103. Wang, H. S. *et al.* KCNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel. *Science* **282**, 1890–1893 (1998).
104. Castaldo, P. *et al.* Benign familial neonatal convulsions caused by altered gating of KCNQ2/KCNQ3 potassium channels. *J. Neurosci.* **22**, RC199 (2002).
105. Dedek, K. *et al.* Myokymia and neonatal epilepsy caused by a mutation in the voltage sensor of the KCNQ2 K^+ channel. *Proc. Natl Acad. Sci. USA* **98**, 12272–12277 (2001).
106. Arroyo, E. J. *et al.* Genetic dysmyelination alters the molecular architecture of the nodal region. *J. Neurosci.* **22**, 1726–1737 (2002).
107. Pan, Z. *et al.* A common ankyrin-G-based mechanism retains KCNQ and Nav channels at electrically active domains of the axon. *J. Neurosci.* **26**, 2599–2603 (2006).
108. Chung, H. J., Jan, Y. N. & Jan, L. Y. Polarized axonal surface expression of neuronal KCNQ channels is mediated by multiple signals in the KCNQ2 and KCNQ3 C-terminal domains. *Proc. Natl Acad. Sci. USA* 30 May 2006 (doi: 10.1073/pnas.0603376103).
109. Devaux, J. *et al.* Kv3.1b is a novel component of CNS nodes. *J. Neurosci.* **23**, 4509–4518 (2003). **First report that Kv3.1b is at the nodes of Ranvier.**
110. Goldberg, E. M. *et al.* Specific functions of synaptically localized potassium channels in synaptic transmission at the neocortical GABAergic fast-spiking cell synapse. *J. Neurosci.* **25**, 5230–5235 (2005).
111. Matsukawa, H., Wolf, A. M., Matsushita, S., Joho, R. H. & Knopfel, T. Motor dysfunction and altered synaptic transmission at the parallel fiber–Purkinje cell synapse in mice lacking potassium channels Kv3.1 and Kv3.3. *J. Neurosci.* **23**, 7677–7684 (2003).
112. Magee, J. C. & Johnston, D. Characterization of single voltage-gated Na^+ and Ca^{2+} channels in apical dendrites of rat CA1 pyramidal neurons. *J. Physiol.* **487**, 67–90 (1995).
113. Johnston, D., Magee, J. C., Colbert, C. M. & Cristie, B. R. Active properties of neuronal dendrites. *Annu. Rev. Neurosci.* **19**, 165–186 (1996).
114. Magee, J., Hoffman, D., Colbert, C. & Johnston, D. Electrical and calcium signaling in dendrites of hippocampal pyramidal neurons. *Annu. Rev. Physiol.* **60**, 327–346 (1998).
115. Hoffman, D. A., Magee, J. C., Colbert, C. M. & Johnston, D. K^+ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. *Nature* **387**, 869–875 (1997).
116. Johnston, D. *et al.* Dendritic potassium channels in hippocampal pyramidal neurons. *J. Physiol.* **525**, 75–81 (2000).
117. Jinno, S., Jeromin, A. & Kosaka, T. Postsynaptic and extrasynaptic localization of Kv4.2 channels in the mouse hippocampal region, with special reference to targeted clustering at gabaergic synapses. *Neuroscience* **134**, 483–494 (2005).
118. Strassle, B. W., Menegola, M., Rhodes, K. J. & Trimmer, J. S. Light and electron microscopic analysis of KChIP and Kv4 localization in rat cerebellar granule cells. *J. Comp. Neurol.* **484**, 144–155 (2005).
119. Chen, X. & Johnston, D. Properties of single voltage-dependent K^+ channels in dendrites of CA1 pyramidal neurones of rat hippocampus. *J. Physiol.* **559**, 187–203 (2004).
120. Notomi, T. & Shigemoto, R. Immunohistochemical localization of Ih channel subunits, HCN1–4, in the rat brain. *J. Comp. Neurol.* **471**, 241–276 (2004).
121. Lorincz, A., Notomi, T., Tamas, G., Shigemoto, R. & Nusser, Z. Polarized and compartment-dependent distribution of HCN1 in pyramidal cell dendrites. *Nature Neurosci.* **5**, 1185–1193 (2002).
122. Kole, M. H., Hallermann, S. & Stuart, G. J. Single Ih channels in pyramidal neuron dendrites: properties, distribution, and impact on action potential output. *J. Neurosci.* **26**, 1677–1687 (2006).
123. Wang, Z., Xu, N. L., Wu, C. P., Duan, S. & Poo, M. M. Bidirectional changes in spatial dendritic integration accompanying long-term synaptic modifications. *Neuron* **37**, 463–472 (2003).
124. Fan, Y. *et al.* Activity-dependent decrease of excitability in rat hippocampal neurons through increases in I_h. *Nature Neurosci.* **8**, 1542–1551 (2005).
125. Pape, H. C. Queer current and pacemaker: the hyperpolarization-activated cation current in neurons. *Annu. Rev. Physiol.* **58**, 299–327 (1996).
126. Poolos, N. P., Migliore, M. & Johnston, D. Pharmacological upregulation of h-channels reduces the excitability of pyramidal neuron dendrites. *Nature Neurosci.* **5**, 767–774 (2002).
127. Berger, T., Senn, W. & Luscher, H. R. Hyperpolarization-activated current Ih disconnects somatic and dendritic spike initiation zones in layer V pyramidal neurons. *J. Neurophysiol.* **90**, 2428–2437 (2003).
128. Williams, S. R. & Stuart, G. J. Role of dendritic synapse location in the control of action potential output. *Trends Neurosci.* **26**, 147–154 (2003).
129. Williams, S. R. & Stuart, G. J. Voltage- and site-dependent control of the somatic impact of dendritic IPSPs. *J. Neurosci.* **23**, 7358–7367 (2003).
130. Williams, S. R. & Stuart, G. J. Site independence of EPSP time course is mediated by dendritic I_h in neocortical pyramidal neurons. *J. Neurophysiol.* **83**, 3177–3182 (2000).
131. Magee, J. C. Dendritic I_h normalizes temporal summation in hippocampal CA1 neurons. *Nature Neurosci.* **2**, 848 (1999). **Reports that the HCN current density gradient maintains temporal resolution of synaptic potentials.**
132. Migliore, M. & Shepherd, G. M. Emerging rules for the distributions of active dendritic conductances. *Nature Rev. Neurosci.* **3**, 362–370 (2002).
133. Zhang, W. & Linden, D. J. The other side of the engram: experience-driven changes in neuronal intrinsic excitability. *Nature Rev. Neurosci.* **4**, 885–900 (2003).
134. Frick, A. & Johnston, D. Plasticity of dendritic excitability. *J. Neurobiol.* **64**, 100–115 (2005).
135. Bernard, C. *et al.* Acquired dendritic channelopathy in temporal lobe epilepsy. *Science* **305**, 532–535 (2004).
136. Ludwig, A. *et al.* Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2. *EMBO J.* **22**, 216–224 (2003).
137. Shah, M. M., Anderson, A. E., Leung, V., Lin, X. & Johnston, D. Seizure-induced plasticity of h channels in entorhinal cortical layer III pyramidal neurons. *Neuron* **44**, 495–508 (2004).
138. Chen, K., Aradi, I., Santhakumar, V. & Soltesz, I. H-channels in epilepsy: new targets for seizure control? *Trends Pharmacol. Sci.* **23**, 552–557 (2002).
139. Brewster, A. L., Bernard, J. A., Gall, C. M. & Baram, T. Z. Formation of heteromeric hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in the hippocampus is regulated by developmental seizures. *Neurobiol. Dis.* **19**, 200–207 (2005).
140. Chen, S., Wang, J. & Siegelbaum, S. A. Properties of hyperpolarization-activated pacemaker current defined by coassembly of HCN1 and HCN2 subunits and basal modulation by cyclic nucleotide. *J. Gen. Physiol.* **117**, 491–504 (2001).
141. Proenza, C. *et al.* Different roles for the cyclic nucleotide binding domain and amino terminus in assembly and expression of hyperpolarization-activated, cyclic nucleotide-gated channels. *J. Biol. Chem.* **277**, 29634–29642 (2002).
142. Tran, N. *et al.* A conserved domain in the NH_2 terminus important for assembly and functional expression of pacemaker channels. *J. Biol. Chem.* **277**, 43588–43592 (2002).
143. Zagotta, W. N. *et al.* Structural basis for modulation and agonist specificity of HCN pacemaker channels. *Nature* **425**, 200–205 (2003).
144. Akhavan, A. *et al.* Identification of the cyclic-nucleotide-binding domain as a conserved determinant of ion-channel cell-surface localization. *J. Cell Sci.* **118**, 2803–2812 (2005).
145. Magee, J. C. Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons. *J. Neurosci.* **18**, 7613–7624 (1998). **Reports an increase in current density of I_h using cell-attached patch from the soma to the dendrites in hippocampal CA1 pyramidal neurons.**
146. Nolan, M. F. *et al.* A behavioral role for dendritic integration: HCN1 channels constrain spatial memory and plasticity at inputs to distal dendrites of CA1 pyramidal neurons. *Cell* **119**, 719–732 (2004).
147. Nolan, M. F. *et al.* The hyperpolarization-activated HCN1 channel is important for motor learning and neuronal integration by cerebellar Purkinje cells. *Cell* **115**, 551–564 (2003).

148. Qu, J. *et al.* MiRP1 modulates HCN2 channel expression and gating in cardiac myocytes. *J. Biol. Chem.* **279**, 43497–43502 (2004).
149. Santoro, B., Wainger, B. J. & Siegelbaum, S. A. Regulation of HCN channel surface expression by a novel C-terminal protein–protein interaction. *J. Neurosci.* **24**, 10750–10762 (2004).
150. Gravante, B. *et al.* Interaction of the pacemaker channel HCN1 with filamin A. *J. Biol. Chem.* **279**, 43847–43853 (2004).
151. Kimura, K., Kitano, J., Nakajima, Y. & Nakanishi, S. Hyperpolarization-activated, cyclic nucleotide-gated HCN2 cation channel forms a protein assembly with multiple neuronal scaffold proteins in distinct modes of protein–protein interaction. *Genes Cells* **9**, 631–640 (2004).
152. Murakoshi, H. & Trimmer, J. S. Identification of the Kv2.1 K^+ channel as a major component of the delayed rectifier K^+ current in rat hippocampal neurons. *J. Neurosci.* **19**, 1728–1735 (1999).
153. Malin, S. A. & Nerbonne, J. M. Delayed rectifier K^+ currents, I_K, are encoded by Kv2 α-subunits and regulate tonic firing in mammalian sympathetic neurons. *J. Neurosci.* **22**, 10094–10105 (2002).
154. Misonou, H. *et al.* Regulation of ion channel localization and phosphorylation by neuronal activity. *Nature Neurosci.* **7**, 711–718 (2004).
Seminal paper describing the activity-dependent phosphorylation of Kv2.1 leading to clustering of these channels at somatodendritic membranes, which thereby changes the current properties of the neuron.
155. Misonou, H., Mohapatra, D. P., Menegola, M. & Trimmer, J. S. Calcium- and metabolic state-dependent modulation of the voltage-dependent Kv2.1 channel regulates neuronal excitability in response to ischemia. *J. Neurosci.* **25**, 11184–11193 (2005).
156. Misonou, H., Mohapatra, D. P. & Trimmer, J. S. Kv2.1: a voltage-gated K^+ channel critical to dynamic control of neuronal excitability. *Neurotoxicology* **26**, 743–752 (2005).
157. Lim, S. T., Antonucci, D. E., Scannevin, R. H. & Trimmer, J. S. A novel targeting signal for proximal clustering of the Kv2.1 K^+ channel in hippocampal neurons. *Neuron* **25**, 385–397 (2000).
158. Du, J., Haak, L. L., Phillips-Tansey, E., Russell, J. T. & McBain, C. J. Frequency-dependent regulation of rat hippocampal somato-dendritic excitability by the K^+ channel subunit Kv2.1. *J. Physiol.* **522**, 19–31 (2000).
159. Rhodes, K. J. *et al.* KChIPs and Kv4 α subunits as integral components of A-type potassium channels in mammalian brain. *J. Neurosci.* **24**, 7903–7915 (2004).
160. An, W. F. *et al.* Modulation of A-type potassium channels by a family of calcium sensors. *Nature* **403**, 553–556 (2000).
161. Johnston, D. *et al.* Active dendrites, potassium channels and synaptic plasticity. *Phil. Trans. R. Soc. Lond. B* **358**, 667–674 (2003).
162. Cai, X. *et al.* Unique roles of SK and Kv4.2 potassium channels in dendritic integration. *Neuron* **44**, 351–364 (2004).
163. Yuan, W., Burkhalter, A. & Nerbonne, J. M. Functional role of the fast transient outward K^+ current IA in pyramidal neurons in (rat) primary visual cortex. *J. Neurosci.* **25**, 9185–9194 (2005).
164. Alonso, G. & Widmer, H. Clustering of KV4.2 potassium channels in postsynaptic membrane of rat supraoptic neurons: an ultrastructural study. *Neuroscience* **77**, 617–621 (1997).
165. Shibasaki, K. *et al.* Mossy fibre contact triggers the targeting of Kv4.2 potassium channels to dendrites and synapses in developing cerebellar granule neurons. *J. Neurochem.* **89**, 897–907 (2004).
166. Frick, A., Magee, J. & Johnston, D. LTP is accompanied by an enhanced local excitability of pyramidal neuron dendrites. *Nature Neurosci.* **7**, 126–135 (2004).
167. Petrecca, K., Miller, D. M. & Shrier, A. Localization and enhanced current density of the Kv4.2 potassium channel by interaction with the actin-binding protein filamin. *J. Neurosci.* **20**, 8736–8744 (2000).
168. Rivera, J. F., Ahmad, S., Quick, M. W., Liman, E. R. & Arnold, D. B. An evolutionarily conserved dileucine motif in Shal K^+ channels mediates dendritic targeting. *Nature Neurosci.* **6**, 243–250 (2003).
Reports a C-terminal di-leucine motif that is necessary and sufficient for dendritic targeting of Kv4.2.
169. Chu, P. J., Rivera, J. F. & Arnold, D. B. A role for Kif17 in transport of Kv4.2. *J. Biol. Chem.* **281**, 365–373 (2006).
170. Ren, X., Hayashi, Y., Yoshimura, N. & Takimoto, K. Transmembrane interaction mediates complex formation between peptidase homologues and Kv4 channels. *Mol. Cell. Neurosci.* **29**, 320–332 (2005).
171. Jerng, H. H., Kunjilwar, K. & Pfaffinger, P. J. Multiprotein assembly of Kv4.2, KChIP3 and DPP10 produces ternary channel complexes with ISA-like properties. *J. Physiol.* **568**, 767–788 (2005).
172. Zagha, E. *et al.* DPP10 modulates Kv4-mediated A-type potassium channels. *J. Biol. Chem.* **280**, 18853–18861 (2005).
173. Strop, P., Bankovich, A. J., Hansen, K. C., Garcia, K. C. & Brunger, A. T. Structure of a human A-type potassium channel interacting protein DPPX, a member of the dipeptidyl aminopeptidase family. *J. Mol. Biol.* **343**, 1055–1065 (2004).
174. Jerng, H. H., Qian, Y. & Pfaffinger, P. J. Modulation of Kv4.2 channel expression and gating by dipeptidyl peptidase 10 (DPP10). *Biophys. J.* **87**, 2380–2396 (2004).
175. Shibata, R. *et al.* A fundamental role for KChIPs in determining the molecular properties and trafficking of Kv4.2 potassium channels. *J. Biol. Chem.* **278**, 36445–36454 (2003).
176. Hasdemir, B., Fitzgerald, D. J., Prior, I. A., Tepikin, A. V. & Burgoyne, R. D. Traffic of Kv4 K^+ channels mediated by KChIP1 is via a novel post-ER vesicular pathway. *J. Cell Biol.* **171**, 459–469 (2005).
Describes that KChIP1 can increase surface expression of Kv4.2 by a pathway that is COPII independent.
177. Deng, Q. *et al.* A C-terminal domain directs Kv3.3 channels to dendrites. *J. Neurosci.* **25**, 11531–11541 (2005).
178. Martina, M., Yao, G. L. & Bean, B. P. Properties and functional role of voltage-dependent potassium channels in dendrites of rat cerebellar Purkinje neurons. *J. Neurosci.* **23**, 5698–5707 (2003).
179. Ozaita, A. *et al.* A unique role for Kv3 voltage-gated potassium channels in starburst amacrine cell signaling in mouse retina. *J. Neurosci.* **24**, 7335–7343 (2004).
180. Euler, T., Detwiler, P. B. & Denk, W. Directionally selective calcium signals in dendrites of starburst amacrine cells. *Nature* **418**, 845–852 (2002).
181. Parameshwaran-Iyer, S., Carr, C. E. & Perney, T. M. Localization of KCNC1 (Kv3.1) potassium channel subunits in the avian auditory nucleus magnocellularis and nucleus laminaris during development. *J. Neurobiol.* **55**, 165–178 (2003).
182. Hell, J. W. *et al.* Identification and differential subcellular localization of the neuronal class C and class D L-type calcium channel α1 subunits. *J. Cell Biol.* **123**, 949–962 (1993).
183. Westenbroek, R. E. *et al.* Biochemical properties and subcellular distribution of an N-type calcium channel α1 subunit. *Neuron* **9**, 1099–1115 (1992).
184. Castillo, P. E., Weisskopf, M. G. & Nicoll, R. A. The role of Ca^{2+} channels in hippocampal mossy fiber synaptic transmission and long-term potentiation. *Neuron* **12**, 261–269 (1994).
185. Dietrich, D. *et al.* Functional specialization of presynaptic Cav2.3 Ca^{2+} channels. *Neuron* **39**, 483–496 (2003).
186. Yasuda, R., Sabatini, B. L. & Svoboda, K. Plasticity of calcium channels in dendritic spines. *Nature Neurosci.* **6**, 948–955 (2003).
187. Magee, J. C., Avery, R. B., Christie, B. R. & Johnston, D. Dihydropyridine-sensitive, voltage-gated Ca^{2+} channels contribute to the resting intracellular Ca^{2+} concentration of hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* **76**, 3460–3470 (1996).
188. Bichet, D. *et al.* The I–II loop of the Ca^{2+} channel α1 subunit contains an endoplasmic reticulum retention signal antagonized by the β subunit. *Neuron* **25**, 177–190 (2000).
189. Leroy, J. *et al.* Interaction via a key tryptophan in the I–II linker of N-type calcium channels is required for β1 but not for palmitoylated β2, implicating an additional binding site in the regulation of channel voltage-dependent properties. *J. Neurosci.* **25**, 6984–6996 (2005).
190. Takahashi, S. X., Miriyala, J., Tay, L. H., Yue, D. T. & Colecraft, H. M. A CaVβ SH3/guanylate kinase domain interaction regulates multiple properties of voltage-gated Ca^{2+} channels. *J. Gen. Physiol.* **126**, 365–377 (2005).
191. Viard, P. *et al.* PI3K promotes voltage-dependent calcium channel trafficking to the plasma membrane. *Nature Neurosci.* **7**, 939–946 (2004).
192. Cornet, V. *et al.* Multiple determinants in voltage-dependent P/Q calcium channels control their retention in the endoplasmic reticulum. *Eur. J. Neurosci.* **16**, 883–895 (2002).
193. Altier, C. *et al.* Trafficking of L-type calcium channels mediated by the postsynaptic scaffolding protein AKAP79. *J. Biol. Chem.* **277**, 33598–33603 (2002).
194. Canti, C. *et al.* The metal-ion-dependent adhesion site in the Von Willebrand factor-A-domain of α2δ subunits is key to trafficking voltage-gated Ca^{2+} channels. *Proc. Natl Acad. Sci. USA* **102**, 11230–11235 (2005).
195. Carr, C. E., Soares, D., Parameshwaran, S. & Perney, T. Evolution and development of time coding systems. *Curr. Opin. Neurobiol.* **11**, 727–733 (2001).
196. Jentsch, T. J., Neagoe, I. & Scheel, O. CLC chloride channels and transporters. *Curr. Opin. Neurobiol.* **15**, 319–325 (2005).
197. Scheel, O., Zdebik, A. A., Lourdel, S. & Jentsch, T. J. Voltage-dependent electrogenic chloride/proton exchange by endosomal CLC proteins. *Nature* **436**, 424–427 (2005).
198. Boiko, T. *et al.* Functional specialization of the axon initial segment by isoform-specific sodium channel targeting. *J. Neurosci.* **23**, 2306–2313 (2003).
Reports the differential expression of Nav1.2 and Nav1.6 during development at the axon initial segment and that the appearance of Nav1.6 coincides with repetitive firing in retinal ganglion cells.
199. Boiko, T. *et al.* Compact myelin dictates the differential targeting of two sodium channel isoforms in the same axon. *Neuron* **30**, 91–104 (2001).
Describes the differential expression of Nav1.2 and Nav1.6 during development at the nodes of Ranvier.
200. Wang, G. Y., Ratto, G., Bisti, S. & Chalupa, L. M. Functional development of intrinsic properties in ganglion cells of the mammalian retina. *J. Neurophysiol.* **78**, 2895–2903 (1997).
201. Grinspan, J. B., Coulalaglou, M., Beesley, J. S., Carpio, D. F. & Scherer, S. S. Maturation-dependent apoptotic cell death of oligodendrocytes in myelin-deficient rats. *J. Neurosci. Res.* **54**, 623–634 (1998).
202. Kaplan, M. R. *et al.* Induction of sodium channel clustering by oligodendrocytes. *Nature* **386**, 724–728 (1997).
203. Henry, E. W. & Sidman, R. L. Long lives for homozygous trembler mutant mice despite virtual absence of peripheral nerve myelin. *Science* **241**, 344–346 (1988).
204. Baba, H. *et al.* Completion of myelin compaction, but not the attachment of oligodendroglial processes triggers K^+ channel clustering. *J. Neurosci. Res.* **58**, 752–764 (1999).
205. Kaplan, M. R. *et al.* Differential control of clustering of the sodium channels $Na_v1.2$ and $Na_v1.6$ at developing CNS nodes of Ranvier. *Neuron* **30**, 105–119 (2001).
Reports the changing distribution of Nav1.2 and Nav1.6 channels in a myelinating culture system.
206. Rasband, M. N., Trimmer, J. S., Peles, E., Levinson, S. R. & Shrager, P. K^+ channel distribution and clustering in developing and hypomyelinated axons of the optic nerve. *J. Neurocytol.* **28**, 319–331 (1999).
207. Rasband, M. N. & Shrager, P. Ion channel sequestration in central nervous system axons. *J. Physiol.* **525**, 63–73 (2000).

Acknowledgements
We would like to thank F. Haass for critical reading of the manuscript. We thank K. Raab-Graham and members of the Jan laboratory for helpful discussions. H.C.L. was supported by an American Heart Association pre-doctoral fellowship, Western States Affiliate. L.Y.J. is a Howard Hughes Medical Institute investigator.

DATABASES
The following terms in this article are linked online to:
Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
Ankyrin G | 4.1B | calnexin | CASPR2 | Cav2.1 | Cav2.2 | Cav2.3 | Cav3 | DPPX | HCN1 | HCN2 | HCN3 | HCN4 | KChiP1 | KChiP2 | KChiP4 | Kv1.1 | Kv1.2 | Kv1.4 | Kvβ1.1 | Kv2.1 | *Kv3.1* | Kv3.2 | Kv3.3 | *Kv3.4* | Kv4.2 | MiRP1 | Nav1.1 | Nav1.2 | Nav1.3 | Nav1.6 | Nav1.7 | Nav1.8 | Nav1.9 | Nax | βIV spectrin | SAP97 | S-SCAM | TRIP8b | VAMP2

FURTHER INFORMATION
Jan's laboratory: http://www.ucsf.edu/jan
Access to this links box is available on line.