J Physiol 590.11 (2012) pp 2591–2599

The Journal of Physiology

TOPICAL REVIEW

Voltage-gated potassium channels and the diversity of electrical signalling

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Abstract Since Hodgkin and Huxley discovered the potassium current that underlies the falling phase of action potentials in the squid giant axon, the diversity of voltage-gated potassium (Kv) channels has been manifested in multiple ways. The large and extended potassium channel family is evolutionarily conserved molecularly and functionally. Alternative splicing and RNA editing of Kv channel genes diversify the channel property and expression level. The mix-and-match of subunits in a Kv channel that contains four similar or identical pore-forming subunits and additional auxiliary subunits further diversify Kv channels. Moreover, targeting of different Kv channels to specific subcellular compartments and local translation of Kv channel mRNA in neuronal processes diversify axonal and dendritic action potentials and influence how synaptic plasticity may be modulated. As one indication of the evolutionary conservation of Kv1 channel functions, mutations of the *Shaker* potassium channel gene in *Drosophila* and the *KCNA1* gene for its mammalian orthologue, Kv1.1, cause hyperexcitability near axon branch points and nerve terminals, thereby leading to uncontrolled movements and recapitulating the episodic ataxia-1 (EA1) symptoms in human patients.

(Received 6 January 2012; accepted after revision 16 March 2012; first published online 19 March 2012)
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Abbreviations ADP, afterdepolarization; AIS, axon initial segment; EA1, episodic ataxia-1; FMRP, fragile X mental retardation protein; Kv, voltage-gated potassium channel; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; mTOR, mammalian target of rapamycin; LSO, lateral superior olive; PI3 kinase, phosphoinoside 3-kinase; SUDEP, sudden unexplained death in epilepsy; UTR, untranslated region.

Introduction

By tracing the origin of the action potential to sodium current for the rising phase and potassium current for the falling phase of the action potential, Hodgkin & Huxley (1952) led the way for investigating the basis of electrical signalling. In the ensuing six decades it has become abundantly clear that vertebrates and invertebrates share the same basic principles for action potential generation, involving evolutionarily conserved ion channels. Molecular identification of these ion channel families has further revealed a rich variety of

Lily and Yuh Nung Jan switched from physics to biology under the influence of Max Delbrück, then stayed at Caltech for postdoctoral training with Seymour Benzer and began their long-term collaboration, starting with studies of *Shaker* mutant flies and followed with studies of peptide neurotransmission in Steve Kuffler's lab at Harvard Medical School. In 1979 they set up their lab at UCSF. They and their colleagues carried out positional cloning of Shaker and have followed up with expression cloning of IRK1 of the Kir channel family and calcium-activated chloride channels in a novel channel family, to study how these channels work. They also began their work on neural development at UCSF to ask how neurons acquire their specific cell fate and morphology, by identifying *atonal*, a founding member of the proneural genes controlling neuronal cell fates, and *numb*, the first cell fate determinant exhibiting asymmetric localization in dividing neural precursor cells, and the mechanisms for generating diversity in dendritic morphology that contributes to the wiring of the nervous system.

DOI: 10.1113/jphysiol.2011.224212

structurally related sodium and potassium channels with properties tailored to suit the physiological purposes of distinct neuronal types as well as different subcellular compartments of a neuron. Voltage-gated ion channels share a common design of four α subunits, which could be separate proteins that assemble in the endoplasmic reticulum (ER) or strung together in a large polypeptide; each α subunit contains six transmembrane segments, with S1–S4 forming the voltage sensor and S5–S6 forming the pore-lining domain (Yu & Catterall, 2004; Lujan, 2010). This review, which is by no means comprehensive, will focus on Kv1 channels – the first axonal voltage-gated potassium channels characterized electrophysiologically and molecularly – and their close relatives, Kv3.1b, which is also targeted to the axon, and Kv4, which is enriched on neuronal dendrites, as examples to highlight some of the intriguing variations of electrical signalling in the nervous system and to outline the underlying molecular basis with respect to potassium channel diversity.

Molecular diversity of the evolutionarily conserved Kv1 potassium channels

The unveiling of the sodium conductance and potassium conductance with steep voltage dependence by Hodgkin & Huxley (1952) has inspired not only decades of biophysical studies (Hille, 2001), but also attempts for molecular identification of these voltage-gated ion channels. Without the benefit of a rich source of potassium channels for biochemical purification, the finding that treatment of wild-type animals with the potassium channel blocker 4-aminopyridine (4-AP) can mimic the *Shaker* mutant phenotype (Jan *et al.* 1977) raised the prospect of positional cloning that became feasible around that time, owing to the highly invariant banding patterns of the giant polytene salivary gland chromosomes in *Drosophila* (Bridges, 1935). Cloning of the *Drosophila* Shaker potassium channels (Papazian *et al.* 1987; Tempel *et al.* 1987) soon led to cloning of the mammalian orthologue Kv1.1 thanks to the high degree of their sequence conservation (Tempel *et al.* 1988), as well as the realization that the highly conserved N-terminal cytoplasmic domain – the T1 tetramerization domain – is important for the assembly of α subunits belonging to the same subfamily (Covarrubias *et al.* 1991; Li *et al.* 1992). The multiplicity of Kv channel subfamilies, along with the ability of different members of a subfamily to coassemble and form channels with different properties, contributes to the diversity of Kv channels, which is further amplified by alternative splicing and RNA editing mediated by adenosine deaminases that alter the sequence of an RNA from that encoded in the genome (Bass, 2002).

One manifestation of the evolutionary conservation of potassium channel diversification via alternative splicing is the differential expression of splice isoforms of Shaker (Kv1) potassium channels with different channel properties in the fruit fly (Schwarz *et al.* 1990) and the presence of different splice isoforms of the Shaker orthologue in squid axons of different diameters (Rosenthal *et al.* 1997). Whereas the SqKv1A splice isoform is exclusively expressed in the monotypic pool of giant fibre lobe neurons whose axons fuse to form the squid giant axon that innervates the mantle musculature for the all-or-none jet-propelled escape response (Young, 1939), the SqKv1B splice isoform shows a complementary expression pattern in the stellate ganglion, with abundant expression in the neurons that are larger than the giant fibre lobe neurons but give rise to the small axon motor system for graded excitation of the muscle fibres (Rosenthal *et al.* 1997) (Fig. 1).

The SqKv1A and SqKv1B channels as encoded by the genomic sequences display indistinguishable properties when expressed in *Xenopus* oocytes (Rosenthal & Gilly, 2003). Given the extensive RNA editing that introduces specific amino acid substitutions in Kv channels of the squid central nervous system (CNS) (Rosenthal & Gilly, 2003), it is intriguing to contemplate the potential diversity and flexibility that may be afforded by RNA editing; the different exons and introns involved in the formation of different splice isoforms may impart different potentials for RNA editing (Bass, 2002). Whereas RNA editing is one conceivable means for channel modifications that may accompany the increase of conduction velocity as axons grow larger during development, a different repertoire of RNA editing may be called for in the unusual design for hastening action potential propagation as the small axons of many giant fibre lobe neurons fuse with one another to form the squid giant axon (Young, 1939).

Besides alternative splicing, another major mechanism for generating potassium channel diversity is RNA editing due to enzymatic conversion of a particular adenosine within a secondary structure involving RNA base-pairing to inosine, which is read as guanidine thereby changing the codon for an amino acid (Bass, 2002). Remarkably, RNA editing of voltage-gated potassium channels is highly conserved among mollusks, arthropods and chordates (Patton *et al.* 1997; Hoopengardner *et al.* 2003; Ryan *et al.* 2008). For example, a valine substitution for isoleucine in the sixth transmembrane segment (S6) of Kv channels – conserved not only in invertebrates like fruit flies (Ryan *et al.* 2008) and squids (Patton *et al.* 1997; Rosenthal & Bezanilla, 2002*b*), but also in mammals such as rodents and humans (Hoopengardner *et al.* 2003) – has the functional consequence of altering channel gating (Patton *et al.* 1997; Rosenthal & Bezanilla, 2002*b*; Ryan *et al.* 2008). There is extensive RNA editing for the N-terminal T1 tetramerization domain as well as the transmembrane domain of squid Kv channels (Rosenthal & Bezanilla, 2002*b*). RNA editing of the T1 domain

could reduce the efficiency of assembly and formation of functional channels by these Kv channel subunits (Rosenthal & Bezanilla, 2002*b*). Whereas some of the editing compromises the ability of the T1 domain to form tetramers, RNA editing of the T1 domain could also alter channel gating (Rosenthal & Bezanilla, 2002*b*; Garrett & Rosenthal, 2012), reminiscent of the impact on channel gating exerted by T1 domain mutations that cause little or no alterations of the crystal structure of the T1 tetramer (Cushman *et al.* 2000; Minor *et al.* 2000).

What might the extensive editing of squid Kv channels be good for? It is interesting to consider the possibility that the variation of RNA editing among different species of squids in different thermal habitats may contribute to the differences in their potassium conductance: When tested at the same temperature (15°C), the action potential of the giant axon is broader for squids inhabiting warmer waters, which may reflect an adaptation to avoid action potential failure at high temperatures (Rosenthal & Bezanilla, 2002*a*). Like squids, octopuses inhabit seawaters as cold as −2°C in the Antarctic or warm waters above 37°C in the tropics and desert lagoons. These poikilotherms appear to have adopted RNA editing to adjust their Kv1 channels in ways appropriate for their habitats; different octopus species from both the arctic and Antarctic employ RNA editing to convert an isoleucine in the S5 segment to valine to destabilize the channel open state, presumably to avoid excessive action potential broadening in frigid waters that would hinder repetitive firing (Garrett & Rosenthal, 2012).

Evolutionary conservation of axonal Kv1 potassium channel functions

Evolutionary conservation of Kv1 channels encompasses not only channel properties and axonal targeting but also their physiological functions in neurons. Episodic ataxia-1 (EA1), an autosomal dominant human neurological disorder manifested by brief episodes of uncontrolled movements induced by physical or emotional stress as well as repetitive discharges of distal musculature known as myokymia, is caused by mutations of human Kv1.1 (*KCNA1*) (Browne *et al.* 1994). The stress-induced ataxia has been recapitulated in a knock-in mutant mouse model carrying the EA1 mutation V408A of the S6 segment, which destabilizes the channel open state (Herson *et al.* 2003). This reduction of Kv1.1-containing potassium channel function reduces the likelihood of action potential propagation failure at axonal branch points (Debanne *et al.* 2011) of the cerebellar basket cell axon plexus, thereby increasing inhibitory synaptic inputs of Purkinje cells and causing motor dysfunction (Herson *et al.* 2003).

Kv1.1 is also important for regulating the action potential waveform (Smart *et al.* 1998). For example, Kv1 channels in the cortical pyramidal neuronal axon collaterals with *en passant* presynaptic terminals (Debanne *et al.* 2011) control action potential duration; inactivation of these axonal Kv1 channels accounts for the ability of neuronal depolarization to broaden axonal action potentials and regulate local synaptic transmission in the brain (Foust *et al.* 2011) (Fig. 2). Thus the axonal Kv1

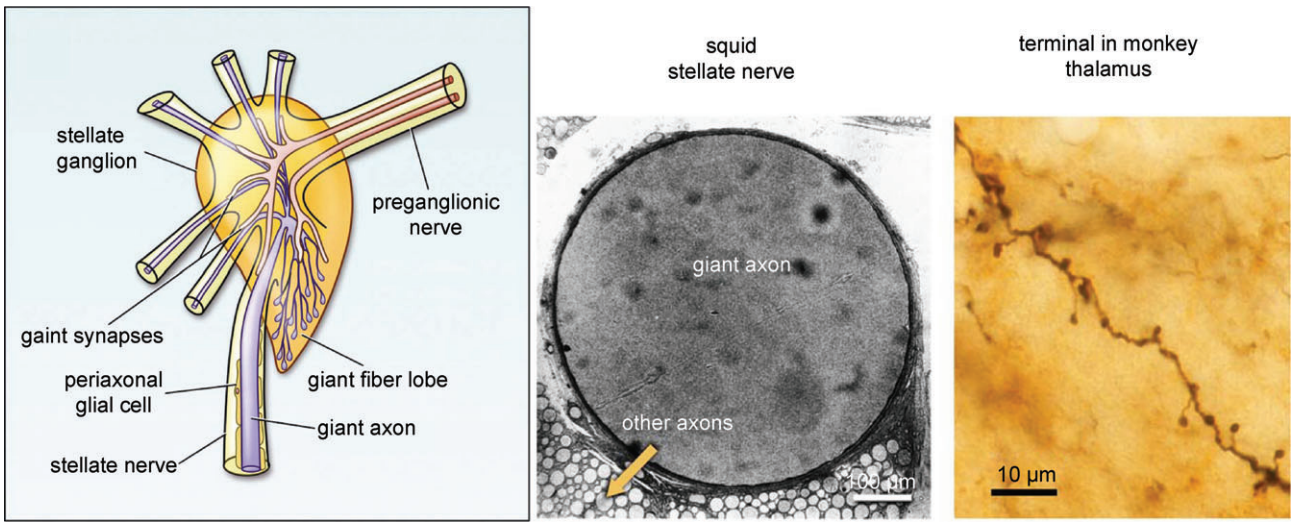

Figure 1. Squid axons and vertebrate axons
Left, a schematic diagram of the squid giant axon emerging from the stellate ganglion. Middle, the squid stellate nerve containing the squid giant axon and other axons of small diameter. Right, the axon of a cortico-thalamic neuron in the macaque monkey. The left panel is from Giuditta *et al.* (2008) with permission of the American Physiological Society, while the middle panel and right panels are from Bucher & Goaillard (2011) with permission of Elsevier.

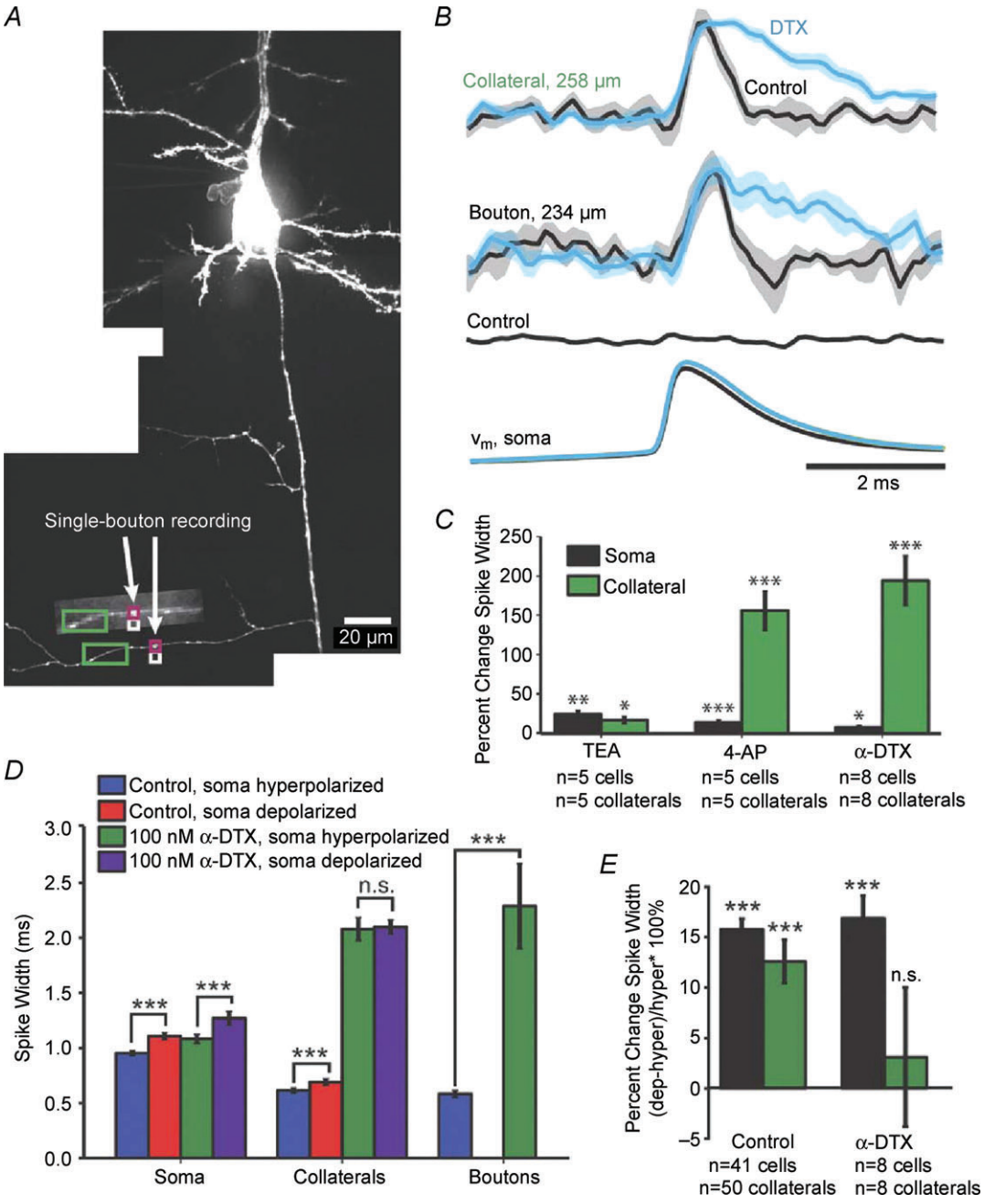

Figure 2. Kv1 channels in the axon collaterals and presynaptic boutons control action potential waveform

A, a pyramidal neuron filled with voltage-sensitive dye in layer 5 of the cortex. *B*, applying the Kv1 channel blocker α-dendrotoxin (DTX) slows the action potential recorded in the axon collaterals and presynaptic boutons in the boxed region in *A*, but causes much less broadening of the action potential recorded from the neuronal soma. The control recording is from a pixel adjacent to the bouton. *C*, the spike width in axon collaterals is sensitive to the Kv1 channel blockers α-DTX and 4-AP. *D*, α-DTX-sensitive Kv1 channels are crucial for somatic membrane potential changes to influence the spike width in axon collaterals and presynaptic boutons. *E*, application of α-DTX to the axon collaterals but not the neuronal soma abolishes the ability of subthreshold depolarization of neuronal soma to cause spike broadening in axon collaterals. From Foust *et al.* (2011) with permission of the Society for Neuroscience.

channel activity may regulate the strength of synaptic transmission by modulating the action potential duration and firing pattern as well as the extent of action potential invasion into axonal branches (Bucher & Goaillard, 2011; Debanne *et al.* 2011).

The hyperexcitability of mammalian motor axons due to compromised Kv1.1 function (Fig. 3) most likely arises from reflections of action potentials from the nerve endings (Zhou *et al.* 1998), similar to the *Shaker* mutant phenotype (Fig. 4) that enabled positional cloning of the founding members of voltage-gated potassium channels (Jan *et al.* 1977; Papazian *et al.* 1987; Tempel *et al.* 1987; Jan & Jan, 1997). These mutant phenotypes support the notion that, to counterbalance the requirement for a substantial sodium channel density to ensure action potential invasion of nerve terminals, Kv1.1-containing channels are strategically positioned to prevent reentrant action potentials (Zhou *et al.* 1998); removing the safeguard provided by these Kv1 channels in CNS neurons and motor neurons would cause uncontrolled movements of organisms ranging from flies to man.

Heteromeric axonal Kv1 channels in normal and pathological conditions

Axonal Kv1 channels in the mammalian CNS tend to be heteromeric. Whereas Kv1.1 is likely to associate with Kv1.4 in striatal efferents in globus pallidus and pars reticulata of substantia nigra, Kv1.1 probably forms heterotetramers with Kv1.2 in cerebellar basket cell terminals and the juxtaparanodal membrane adjacent to nodes of Ranvier; ultrastructural studies place these channels in preterminal axonal membranes (Trimmer & Rhodes, 2004), consistent with the channel function in regulating excitability and transmitter release (Foust *et al.* 2011).

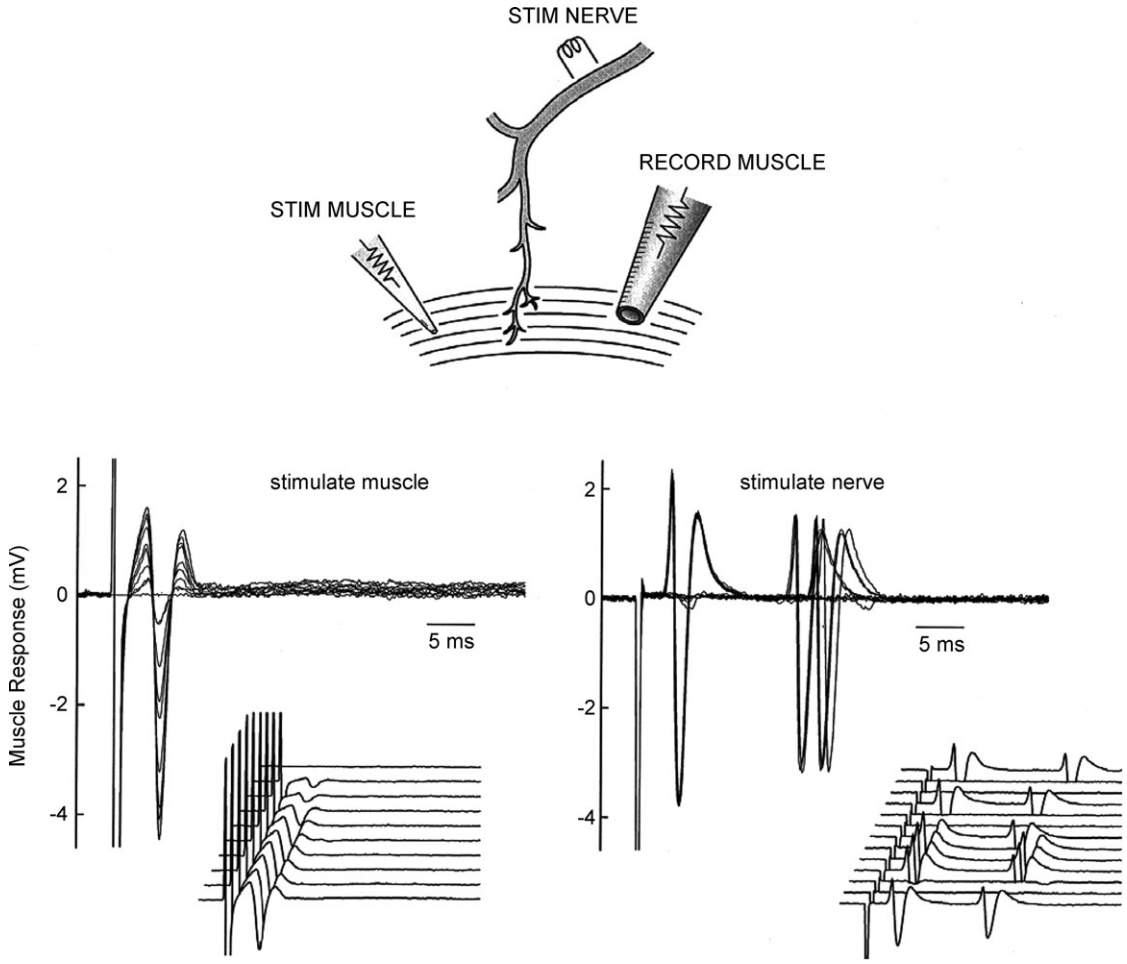

Figure 3. Loss of Kv1.1 function causes reentrant action potentials of mouse motor axons
Top, the experimental scheme for extracellular recording of the muscle compound action potential with a surface electrode in the phrenic nerve–diaphragm preparation of a P18 null mutant mice lacking Kv1.1. The action potentials are evoked either by stimulating the nerve (bottom right) or by directly stimulating the muscle (bottom left). In the absence of Kv1.1-containing channels, action potentials may 'reflect' from the nerve terminals and result in 'backfiring' along the motor axon. From Zhou *et al.* (1998) with permission of the Society for Neuroscience.

Axonal Kv1 channel variations have been found in pathological conditions. Whereas sciatic nerve injury reduces a subpopulation of potassium currents accompanied with a reduction of Kv1.2 and Kv2.1 in dorsal root ganglion (DRG) neurons of different sizes (Ishikawa *et al.* 1999), spinal cord injury causes up-regulation of Kv1.1 and Kv1.2 as well as their dispersal from juxtaparanodal regions of the injured axons (Karimi-Abdolrezaee *et al.* 2004). Loss of myelin sheath and remyelination are also associated with alterations in Kv1 channel distribution, which would affect action potential conduction properties (Salzer, 2003).

There are other possible scenarios for Kv1 channelopathy. The Kv1.1 null mutation causes epilepsy (Smart *et al.* 1998) that may further initiate sustained ictal bradycardia and asystole, raising the possibility that the hyperexcitability resulting from the loss of Kv1.1 function may lead to impaired neural control of heartbeat and 'sudden unexplained death in epilepsy' (SUDEP) (Glasscock *et al.* 2010). In addition to Kv1.1 mutations, autoantibodies to Kv1.1 and other Kv1 family members are found in patients with acquired neuromyotonia that is associated with peripheral nerve hyperexcitability and possibly autonomic and central nervous system involvement, perhaps due to a reduction of Kv1 channel expression (Kleopa *et al.* 2006).

Axonal targeting of Kv1 subfamily members and Kv3.1b

Axonal targeting of Kv1 channels is likely to be mediated by evolutionarily conserved mechanisms, since it involves the T1 domain (Gu *et al.* 2003; Rivera *et al.* 2005) due to its association with Kvβ subunits, which are also evolutionarily conserved (Vacher & Trimmer, 2011). The Kvβ2 associated proteins KIF3 (kinesin II) and EB1 (microtubule plus end binding protein) are both required for Kv1 axonal targeting (Gu *et al.* 2006; Gu & Gu, 2010). Colocalized with Kv1 at the axon initial segment (AIS) and juxtaparanodes of myelinated axons are cyclin-dependent kinases that phosphorylate Kvβ2 to modulate its binding to EB1 and regulate the release of Kv1 channel-bearing vesicles from EB1 and the microtubule, possibly for their uploading to the cell membrane (Vacher *et al.* 2011).

It is of interest to note that, despite the indistinguishable biophysical properties of the alternative splice isoforms Kv3.1a and Kv3.1b, their differential propensity for supporting fast spiking can be accounted for by the axonal targeting and AIS localization of Kv3.1b but not Kv3.1a (Gu *et al.* 2011). Thus, notwithstanding the much larger number of potassium channel genes in mammals, alternative splicing of these genes causes further diversification in a variety of channel properties including their targeting to different subcellular compartments.

Gradients of Kv1 channels and Kv3.1b

Voltage-gated potassium channels also reside on the dendrites to modulate dendritic excitability and synaptic plasticity (Sjostrom *et al.* 2008). One elegant example concerns the auditory brainstem neurons with bifurcating dendrites in the medial superior olive (MSO); one dendrite receives synaptic inputs triggered by sounds impinging on one ear and the other dendrite gets synaptic inputs originating from the other ear – a set-up critical for discerning the interaural time difference as the basis for sound localization (Grothe, 2003). A graded distribution of Kv1 channels along these two dendrites of the MSO principal neuron is important to sharpen the excitatory postsynaptic potentials (EPSPs) that provide phase-locked

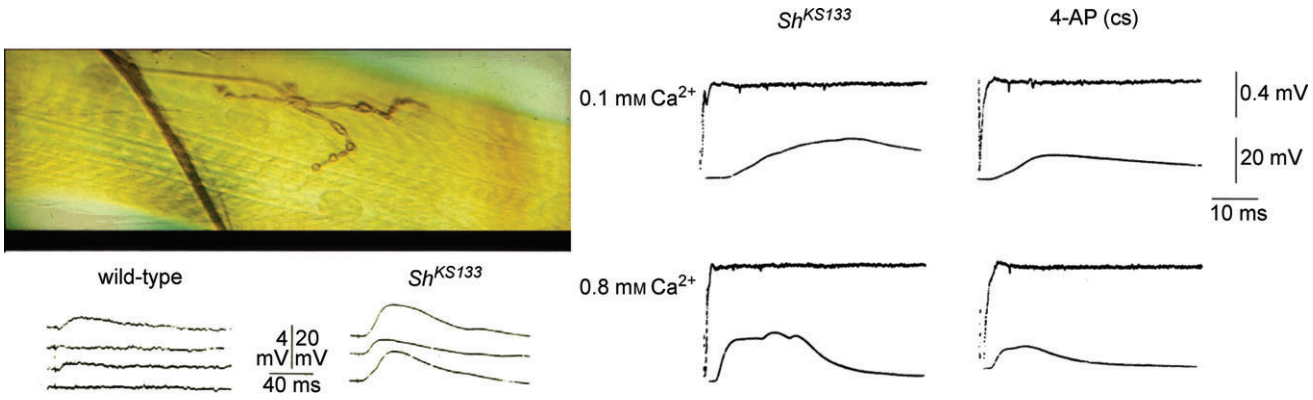

Figure 4. The *Shaker* mutant phenotypes observed at the larval neuromuscular junction
Left top, a *Drosophila* larval muscle innervated by motor axons stained with antibody against horseradish peroxidase (HRP) (Jan & Jan, 1982). Left bottom, *Shaker* mutant (Sh^{KS133}) larvae display much larger synaptic potentials at low (0.1 mM) external calcium concentration as compared to Canton-S (CS) wild-type larvae. From Jan *et al.* (1977) with permission of the Royal Society. Right, simultaneous recordings from the motor nerve (above) and muscle (below) in *Shaker* mutant (Sh^{KS133}) larvae, and in wild-type (CS) larvae treated with 6 mM 4-AP to block potassium channels. Stimulus artifacts are at the left end of the records. From Jan & Jan (1997).

auditory information from the two ears for sound localization (Mathews *et al.* 2010).

To compare and contrast this gradient of Kv1 channels along each dendrite of the MSO principal neuron, we will consider the gradient of Kv3.1b channels along the tonotopic axis of the medial nucleus of the trapezoid body (MNTB), which relays sound inputs from the contralateral ear to the lateral superior olive (LSO) for sound localization based on comparison of the sound intensities detected by the two years. High levels of Kv3.1b expressed in presynaptic as well as postsynaptic regions of MNTB neurons that are responsive to high frequency sounds endow these neurons with the capacity to fire at high frequencies, whereas the lower levels of Kv3.1b expression in MNTB neurons that are responsive to low frequency sounds could increase the fidelity of timing of action potential firing at low frequencies (Kaczmarek *et al.* 2005). As exemplified by the gradient of Kv1 channels along a single dendrite and the gradient of Kv3.1b across an entire nucleus in the auditory brainstem, proper functions of our nervous system rely on a mosaic of Kv channels that not only have their properties finely tuned to the physiological needs, but also have their number and distribution precisely arranged to enable the neuronal computations necessary for adequate perception and response.

Local translation of Kv1.1 and Kv4.2 in hippocampal neuronal dendrites

Though Kv1 channels primarily reside in the axon whereas Kv4 channels mainly localize to the dendrites (Sheng *et al.* 1992), Kv1 channels are also present in hippocampal neuronal dendrites to modulate temporal integration (Storm, 1988) and the action potential aferdepolarization (ADP) and hence burst firing (Metz *et al.* 2007). Not only are Kv1 channels present in dendrites, Kv1.1 mRNA is localized to dendrites where its local translation is under the regulation of glutamate receptors of the NMDA subtype and the downstream cascade of PI3 kinase and mammalian target of rapamycin (mTOR) kinase (Raab-Graham *et al.* 2006).

The molecularly distinct A-type potassium channels in axons and dendrites (Sheng *et al.* 1992) serve a range of physiological functions; whereas Kv1.4-containing channels in mossy fibre terminals are likely to mediate activity-dependent spike broadening that enhances transmitter release (Debanne *et al.* 2011), Kv4.2 is responsible for the regulation of synaptic plasticity in hippocampal neuronal dendrites (Chen *et al.* 2006). A gradient of dendritic Kv4 channels, with channel density increasing distally along the apical dendrite, is set up with the help of the auxiliary subunit DPP6 to restrict action potential back-propagation and calcium spike generation (Sun *et al.* 2011). Like Kv1.1 mRNA, Kv4.2 mRNA is also localized in dendrites so that its local translation is under the modulation of NMDA receptors. The 3′-UTR of Kv4.2 mRNA binds the RNA binding protein fragile X mental retardation protein (FMRP) – an interaction important for FMRP suppression of Kv4.2 expression in dendrites. NMDA receptor activation causes rapid dephosphorylation of the mTOR kinase, the downstream S6 kinase and its substrate FMRP, thereby relieving FMRP suppression and causing Kv4.2 up-regulation (Lee *et al.* 2011). This type of synaptic regulation of local translation of Kv1.1 and Kv4.2 mRNA may allow local adjustments of dendritic excitability according to synaptic activities nearby.

Evolutionary conservation and diversity of local translation

As a form of compartmentalized synthesis of proteins, local translation in dendrites provides one mechanism to achieve specificity in synaptic plasticity (Sutton & Schuman, 2005). Local translation also takes place in axons, including the squid giant axon (Piper & Holt 2004; Giuditta *et al.* 2008; Kaplan *et al.* 2009). A significant fraction of proteins synthesized in axons are nuclear encoded mitochondrial proteins. Moreover, inhibition of local translation in the axons of sympathetic neurons cultured in the Campenot chamber reduces mitochondrial functions in those axons (Kaplan *et al.* 2009).

The evolutionarily conserved local translation in neuronal processes may serve a variety of functions including axon growth (Piper & Holt, 2004) and synaptic regulation of dendrite structure and function (Sutton & Schuman, 2005). For the squid giant axon derived from numerous giant fibre lobe neurons in the stellate ganglion, local translation offers a means to sustain the giant axon without having to coordinate protein production in multiple cell bodies. In contrast, the smallest flying insect Hymenoptera, whose body length is just a fraction of the diameter of the squid giant axon, loses the cell bodies and nuclei of over 95% of its neurons due to massive lysis before emerging from the pupa (Polilov, 2012). Its lifespan of ∼5 days is comparable to the time it takes to exhaust the maternal supply of mRNAs for essential *Drosophila* genes such as *technical knockout* (*tko*) coding for a mitochondrial ribosomal protein (Royden *et al.* 1987), indicating that the reserve of mRNAs left behind in the Hymenoptera neuronal processes can adequately support protein production for days. Thus, the ability of this tiny insect to take flight and go about its business without the burden of thousands of neuronal cell bodies (Polilov, 2012) may be sustained by local translation in neuronal processes.

Synopsis

Pioneered by Hodgkin and Huxley in their delineation of the basis of action potential generation in the squid giant axon (Hodgkin & Huxley, 1952), studies over

the last six decades have elucidated the roles of a rich variety of voltage-gated ion channels in neuronal signalling (Trimmer & Rhodes, 2004; Yu & Catterall, 2004; Bean, 2007; Sjostrom *et al.* 2008; Lujan, 2010; Bucher & Goaillard, 2011; Debanne *et al.* 2011). Diversity of electrical signalling not only derives from the extended ion channel families with numerous family members and the further diversification of channel properties and assembly efficiency via alternative splicing and RNA editing, but also encompasses cell biological variations in the synthesis and trafficking of ion channels, often shedding light on evolutionarily conserved mechanisms that have enabled organisms of vastly different sizes and forms to cope with their environment and thrive.

References

Bass BL (2002). RNA editing by adenosine deaminases that act on RNA. *Annu Rev Biochem* **71**, 817–846.

Bean BP (2007). The action potential in mammalian central neurons. *Nat Rev Neurosci* **8**, 451–465.

Bridges CB (1935). Salivary chromosome maps. *J Heredity* **26**, 60–64.

Browne DL, Gancher ST, Nutt JG, Brunt ER, Smith EA, Kramer P & Litt M (1994). Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. *Nat Genet* **8**, 136–140.

Bucher D & Goaillard JM (2011). Beyond faithful conduction: short-term dynamics, neuromodulation, and long-term regulation of spike propagation in the axon. *Prog Neurobiol* **94**, 307–346.

Chen X, Yuan LL, Zhao C, Birnbaum SG, Frick A, Jung WE, Schwarz TL, Sweatt JD & Johnston D (2006). Deletion of Kv4.2 gene eliminates dendritic A-type K^+ current and enhances induction of long-term potentiation in hippocampal CA1 pyramidal neurons. *J Neurosci* **26**, 12143–12151.

Covarrubias M, Wei AA & Salkoff L (1991). Shaker, Shal, Shab, and Shaw express independent K^+ current systems. *Neuron* **7**, 763–773.

Cushman SJ, Nanao MH, Jahng AW, DeRubeis D, Choe S & Pfaffinger PJ (2000). Voltage dependent activation of potassium channels is coupled to T1 domain structure. *Nat Struct Biol* **7**, 403–407.

Debanne D, Campanac E, Bialowas A, Carlier E & Alcaraz G (2011). Axon physiology. *Physiol Rev* **91**, 555–602.

Foust AJ, Yu Y, Popovic M, Zecevic D & McCormick DA (2011). Somatic membrane potential and Kv1 channels control spike repolarization in cortical axon collaterals and presynaptic boutons. *J Neurosci* **31**, 15490–15498.

Garrett S & Rosenthal JJ (2012). RNA editing underlies temperature adaptation in K^+ channels from polar octopuses. *Science* **335**, 848–851.

Giuditta A, Chun JT, Eyman M, Cefaliello C, Bruno AP & Crispino M (2008). Local gene expression in axons and nerve endings: the glia-neuron unit. *Physiol Rev* **88**, 515–555.

Glasscock E, Yoo JW, Chen TT, Klassen TL & Noebels JL (2010). Kv1.1 potassium channel deficiency reveals brain-driven cardiac dysfunction as a candidate mechanism for sudden unexplained death in epilepsy. *J Neurosci* **30**, 5167–5175.

Grothe B (2003). New roles for synaptic inhibition in sound localization. *Nat Rev Neurosci* **4**, 540–550.

Gu C, Jan YN & Jan LY (2003). A conserved domain in axonal targeting of Kv1 (Shaker) voltage-gated potassium channels. *Science* **301**, 646–649.

Gu C, Zhou W, Puthenveedu MA, Xu M, Jan YN & Jan LY (2006). The microtubule plus-end tracking protein EB1 is required for Kv1 voltage-gated K^+ channel axonal targeting. *Neuron* **52**, 803–816.

Gu Y, Barry J, McDougel R, Terman D & Gu C (2011). Alternative splicing regulates Kv3.1 polarized targeting to adjust the maximal spiking frequency. *J Biol Chem* **287**, 1755–1769.

Gu Y & Gu C (2010). Dynamics of Kv1 channel transport in axons. *PLoS One* **5**, e11 931.

Herson PS, Virk M, Rustay NR, Bond CT, Crabbe JC, Adelman JP & Maylie J (2003). A mouse model of episodic ataxia type-1. *Nat Neurosci* **6**, 378–383.

Hille B (2001). *Ion Channels of Excitable Membranes*, 3rd edn. Sinauer, Sunderland, MA, USA.

Hodgkin AL & Huxley AF (1952). Currents carried by sodium and potassium ions through the membrane of the giant axon of *Loligo*. *J Physiol* **116**, 449–472.

Hoopengardner B, Bhalla T, Staber C & Reenan R (2003). Nervous system targets of RNA editing identified by comparative genomics. *Science* **301**, 832–836.

Ishikawa K, Tanaka M, Black JA & Waxman SG (1999). Changes in expression of voltage-gated potassium channels in dorsal root ganglion neurons following axotomy. *Muscle Nerve* **22**, 502–507.

Jan LY & Jan YN (1982). Antibodies to horseradish peroxidase as specific neuronal markers in *Drosophila* and in grasshopper embryos. *Proc Natl Acad Sci U S A* **79**, 2700–2704.

Jan LY & Jan YN (1997). Voltage-gated and inwardly rectifying potassium channels. *J Physiol* **505**, 267–282.

Jan YN, Jan LY & Dennis MJ (1977). Two mutations of synaptic transmission in *Drosophila*. *Proc R Soc Lond B Biol Sci* **198**, 87–108.

Kaczmarek LK, Bhattacharjee A, Desai R, Gan L, Song P, von Hehn CA, Whim MD & Yang B (2005). Regulation of the timing of MNTB neurons by short-term and long-term modulation of potassium channels. *Hear Res* **206**, 133–145.

Kaplan BB, Gioio AE, Hillefors M & Aschrafi A (2009). Axonal protein synthesis and the regulation of local mitochondrial function. *Results Probl Cell Differ* **48**, 225–242.

Karimi-Abdolrezaee S, Eftekharpour E & Fehlings MG (2004). Temporal and spatial patterns of Kv1.1 and Kv1.2 protein and gene expression in spinal cord white matter after acute and chronic spinal cord injury in rats: implications for axonal pathophysiology after neurotrauma. *Eur J Neurosci* **19**, 577–589.

Kleopa KA, Elman LB, Lang B, Vincent A & Scherer SS (2006). Neuromyotonia and limbic encephalitis sera target mature Shaker-type K^+ channels: subunit specificity correlates with clinical manifestations. *Brain* **129**, 1570–1584.

Lee HY, Ge WP, Huang W, He Y, Wang GX, Rowson-Baldwin A, Smith SJ, Jan YN & Jan LY (2011). Bidirectional regulation of dendritic voltage-gated potassium channels by the fragile x mental retardation protein. *Neuron* **72**, 630–642.

Li M, Jan YN & Jan LY (1992). Specification of subunit assembly by the hydrophilic amino-terminal domain of the Shaker potassium channel. *Science* **257**, 1225–1230.

Lujan R (2010). Organisation of potassium channels on the neuronal surface. *J Chem Neuroanat* **40**, 1–20.

Mathews PJ, Jercog PE, Rinzel J, Scott LL & Golding NL (2010). Control of submillisecond synaptic timing in binaural coincidence detectors by Kv1 channels. *Nat Neurosci* **13**, 601–609.

Metz AE, Spruston N & Martina M (2007). Dendritic D-type potassium currents inhibit the spike afterdepolarization in rat hippocampal CA1 pyramidal neurons. *J Physiol* **581**, 175–187.

Minor DL, Lin YF, Mobley BC, Avelar A, Jan YN, Jan LY & Berger JM (2000). The polar T1 interface is linked to conformational changes that open the voltage-gated potassium channel. *Cell* **102**, 657–670.

Papazian DM, Schwarz TL, Tempel BL, Jan YN & Jan LY (1987). Cloning of genomic and complementary DNA from Shaker, a putative potassium channel gene from *Drosophila*. *Science* **237**, 749–753.

Patton DE, Silva T & Bezanilla F (1997). RNA editing generates a diverse array of transcripts encoding squid Kv2 K^+ channels with altered functional properties. *Neuron* **19**, 711–722.

Piper M & Holt C (2004). RNA translation in axons. *Annu Rev Cell Dev Biol* **20**, 505–523.

Polilov AA (2012). The smallest insects evolve anucleate neurons. *Arthropod Struct Dev* **41**, 29–34.

Raab-Graham KF, Haddick PC, Jan YN & Jan LY (2006). Activity- and mTOR-dependent suppression of Kv1.1 channel mRNA translation in dendrites. *Science* **314**, 144–148.

Rivera JF, Chu PJ & Arnold DB (2005). The T1 domain of Kv1.3 mediates intracellular targeting to axons. *Eur J Neurosci* **22**, 1853–1862.

Rosenthal JJ & Bezanilla F (2002*a*). A comparison of propagated action potentials from tropical and temperate squid axons: different durations and conduction velocities correlate with ionic conductance levels. *J Exp Biol* **205**, 1819–1830.

Rosenthal JJ & Bezanilla F (2002*b*). Extensive editing of mRNAs for the squid delayed rectifier K^+ channel regulates subunit tetramerization. *Neuron* **34**, 743–757.

Rosenthal JJ & Gilly WF (2003). Identified ion channels in the squid nervous system. *Neurosignals* **12**, 126–141.

Rosenthal JJ, Liu TI & Gilly WF (1997). A family of delayed rectifier Kv1 cDNAs showing cell type-specific expression in the squid stellate ganglion/giant fiber lobe complex. *J Neurosci* **17**, 5070–5079.

Royden CS, Pirrotta V & Jan LY (1987). The *tko* locus, site of a behavioral mutation in *D. melanogaster*, codes for a protein homologous to prokaryotic ribosomal protein S12. *Cell* **51**, 165–173.

Ryan MY, Maloney R, Reenan R & Horn R (2008). Characterization of five RNA editing sites in Shab potassium channels. *Channels (Austin)* **2**, 202–209.

Salzer JL (2003). Polarized domains of myelinated axons. *Neuron* **40**, 297–318.

Schwarz TL, Papazian DM, Carretto RC, Jan YN & Jan LY (1990). Immunological characterization of K^+ channel components from the Shaker locus and differential distribution of splicing variants in *Drosophila*. *Neuron* **4**, 119–127.

Sheng M, Tsaur ML, Jan YN & Jan LY (1992). Subcellular segregation of two A-type K^+ channel proteins in rat central neurons. *Neuron* **9**, 271–284.

Sjostrom PJ, Rancz EA, Roth A & Hausser M (2008). Dendritic excitability and synaptic plasticity. *Physiol Rev* **88**, 769–840.

Smart SL, Lopantsev V, Zhang CL, Robbins CA, Wang H, Chiu SY, Schwartzkroin PA, Messing A & Tempel BL (1998). Deletion of the $K_V1.1$ potassium channel causes epilepsy in mice. *Neuron* **20**, 809–819.

Storm JF (1988). Temporal integration by a slowly inactivating K^+ current in hippocampal neurons. *Nature* **336**, 379–381.

Sun W, Maffie JK, Lin L, Petralia RS, Rudy B & Hoffman DA (2011). DPP6 establishes the A-type K^+current gradient critical for the regulation of dendritic excitability in CA1 hippocampal neurons. *Neuron* **71**, 1102–1115.

Sutton MA & Schuman EM (2005). Local translational control in dendrites and its role in long-term synaptic plasticity. *J Neurobiol* **64**, 116–131.

Tempel BL, Jan YN & Jan LY (1988). Cloning of a probable potassium channel gene from mouse brain. *Nature* **332**, 837–839.

Tempel BL, Papazian DM, Schwarz TL, Jan YN & Jan LY (1987). Sequence of a probable potassium channel component encoded at Shaker locus of *Drosophila*. *Science* **237**, 770–775.

Trimmer JS & Rhodes KJ (2004). Localization of voltage-gated ion channels in mammalian brain. *Annu Rev Physiol* **66**, 477–519.

Vacher H & Trimmer JS (2011). Diverse roles for auxiliary subunits in phosphorylation-dependent regulation of mammalian brain voltage-gated potassium channels. *Pflugers Arch* **462**, 631–643.

Vacher H, Yang JW, Cerda O, Autillo-Touati A, Dargent B & Trimmer JS (2011). Cdk-mediated phosphorylation of the Kvβ2 auxiliary subunit regulates Kv1 channel axonal targeting. *J Cell Biol* **192**, 813–824.

Young JZ (1939). Fused neurons and synaptic contacts in the giant nerve fibres of cephalopods. *Phil Trans R Soc Lond B* **229**, 465–503.

Yu FH & Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004**, re15.

Zhou L, Zhang CL, Messing A & Chiu SY (1998). Temperature-sensitive neuromuscular transmission in Kv1.1 null mice: role of potassium channels under the myelin sheath in young nerves. *J Neurosci* **18**, 7200–7215.

Acknowledgements

This work is supported by the NIH grant MH065334. L.Y.J. and Y.N.J. are Howard Hughes Medical Institute investigators.