High-conductance potassium channels of the SLO family

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Abstract | High-conductance, 'big' potassium (BK) channels encoded by the *Slo* gene family are among the largest and most complex of the extended family of potassium channels. The family of SLO channels apparently evolved from voltage-dependent potassium channels, but acquired a large conserved carboxyl extension, which allows channel gating to be altered in response to the direct sensing of several different intracellular ions, and by other second-messenger systems, such as those activated following neurotransmitter binding to G-protein-coupled receptors (GPCRs). This versatility has been exploited to serve many cellular roles, both within and outside the nervous system.

Delayed rectifier voltage-gated K^+ channels
Slowly activating and either non-inactivating or very slowly inactivating voltage-sensitive K^+-selective channels.

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Ion channels are the 'transistors of the brain', selectively gating the flow of each of the ionic species that are present in organic tissue. Nature has produced subfamilies of these channels for each of the principal species of ion in living tissues, including K^+, Na^+, Ca^{2+} and Cl^-. In each of these subfamilies, there are many differences in functional properties, such as voltage-dependence, the kinetics of opening and closing (gating) and modulation by many intracellular factors, such as calmodulin and calcium. Another important property is the single-channel conductance of the channel, which is a measurement of the current that can pass through a single open channel at a given membrane potential. This property differs between channels by at least two orders of magnitude.

K^+ channels are the only ion-selective cation channels that have an equilibrium potential near the typical cellular resting potential. This property makes them crucial in determining the resting potential of most cells. In neurons and excitable tissues, they also have an important role in determining the shape and duration of action potentials, the firing rates of cells and the overall excitability of cells. This review highlights a particular subfamily of K^+ channels that are distinguished by their unusually high single-channel conductance. These channels were originally termed 'big' potassium (BK) channels, but are also called maxi-K channels or SLO family channels, a name derived from the conserved gene that encodes this channel, which was first cloned in *Drosophila melanogaster*.

In some respects, SLO family channels are similar to classical delayed rectifier voltage-gated K^+ channels, but are more versatile in that their voltage range of activation is modifiable by factors including Ca^{2+}, Na^+ or Cl^-, pH and phosphorylation. These properties, together with their very large single-channel conductances, make SLO family channels functionally distinct from voltage-dependent K^+ channels. Recently, the sequencing of all the members of the *Slo* multigene family[1–6] has produced new insights into how molecular evolution of these channels has proceeded along a modular design, essentially coupling a module resembling a voltage-dependent channel to domains that respond to a host of intracellular and extracellular factors (FIG. 1). This versatile design allows the membrane's electrical properties to be modulated in response to a large variety of cellular events. In this article, we review the discovery of SLO family channels, their distinctive properties and regulation, their structure–function relationships and their physiological roles.

Identification of the *Slo* gene family

Now that the genomes of various animals have been sequenced, we know that there are four genes encoding SLO family channels in the mammalian genome: *Slo1*; two highly similar *Slo2* paralogues, *Slo2.1* (also known as *Slick*) and *Slo2.2* (also known as *Slack*); and *Slo3*. All four of these genes encode α-subunits that seem to be capable of forming homotetramer channels that gate a K^+-selective ion current, but which differ markedly in their gating properties (TABLE 1), as will be described below. The identification of the *Slo* gene family was a classic example of the convergence of two independent lines of investigation: the fledgling field of fruitfly (*Drosophila*) neurogenetics, and the ongoing electrophysiological studies of cellular membrane ion currents (BOX 1).

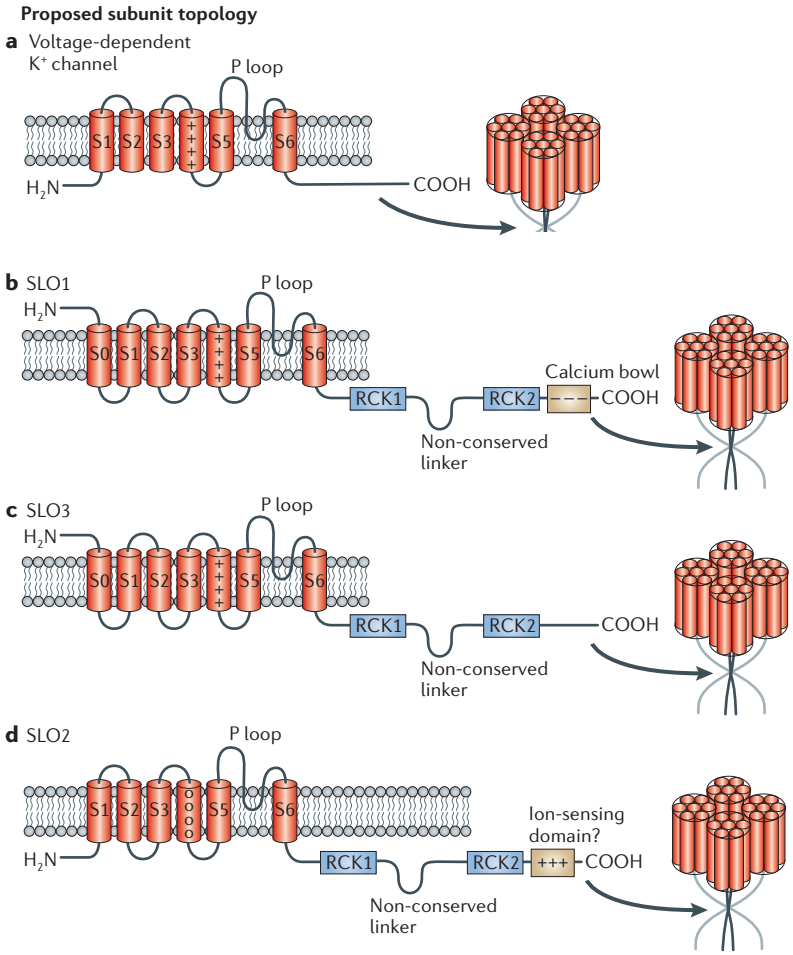

Figure 1 | **Schematic representation of SLO α-subunits.** The structural properties of SLO1–3 are compared to the α-subunit of a voltage-dependent channel (**a**). All channel subunits depicted have membrane-spanning domains S1–S6 surrounding an ion-selective pore. SLO1 and SLO3 subunits each have an additional S0 membrane-spanning domain. SLO α-subunits also include an extensive cytosolic carboxy-terminal extension containing sites that sense cytosolic factors, which modify gating, such as the calcium bowl in SLO1 (**b**), which is absent in SLO3 (**c**) and greatly modified in SLO2 subunits in which some positive charges seem to have replaced negative charges present in SLO1 (**d**). SLO2 is also distinctive in having its amino terminus inside the cell and in its absence of positive charges in S4. Note that four α-subunits group together to form the pore of all channels depicted. RCK, regulators of conductance of K^+ domain. Modified, with permission, from REF. 29 © (2003) Elsevier Science.

Slo1. The first step towards the identification of the SLO1 channel was the discovery in many tissues of a prominent outward K^+ current with an unusual dual dependence on both membrane depolarization and a prior influx of Ca^{2+} (REFS 7,8). This macroscopic current was subsequently shown to be the result of the action of K^+ channels with unusually large single-channel conductances averaging over 250 pS (REFS 9–11). These high-conductance channels stood in marked contrast to many other types of voltage-dependent K^+ channels that averaged less than a tenth of that conductance.

Subsequently, voltage-clamp recordings of currents in the flight muscles of a *Drosophila* mutant with a severely lethargic phenotype, named *slowpoke*, revealed that the calcium-dependent component of the outward K^+ current was absent, implicating the *slowpoke* (*slo*) gene as the structural locus encoding the channel protein[12]. Cloning and sequence analysis of *slo* revealed a predicted protein with similarity to Shaker, which was the first voltage-dependent K^+ channel α-subunit to be identified, and which was also first cloned from *Drosophila*[13,14]. The mammalian *slo* orthologue *Slo1* was cloned by low-stringency DNA hybridization of a mammalian cDNA library using the *Drosophila slo* cDNA[1,2].

Slo2. Further cellular electrophysiology studies identified some high-conductance single-channel currents that were similar to BK currents, but were activated by Na^+ instead of Ca^{2+} in many systems, including guinea pig cardiomyocytes[15,16] and various neurons[17–24]. Native Na^+-activated K^+ currents have distinctive properties, including sensitivity to intracellular sodium concentration ($[Na^+]_i$), a large single-channel conductance, prominent subconductance states and inward rectification due to a reblock of single-channel currents at positive potentials. These currents might have an important protective role under ischaemic conditions in cardiomyocytes[15,16,25]. Other reports have suggested that the main components of outward currents that are responsible for action potential repolarization and afterhyperpolarization in neurons are dependent on concomitant Na^+ influx[26]. Even *Drosophila* neurons were reported to have a Na^+-dependent K^+ conductance[27]. However, some of these reports were met with scepticism, as Na^+ was thought to be an unlikely signalling molecule and it was considered dubious that a single action potential could alter the intracellular Na^+ concentration sufficiently to act as a specific modulator of K^+ conductance. Nevertheless, many questions regarding a physiological role for Na^+-activated K^+ conductances during normal cellular electrical activity remain to be resolved.

Because their sequence divergence from *Slo1* is extensive, *Slo2* genes do not appear in low-stringency DNA hybridization screens designed to identify genes that are similar to *Slo1* (L.S., unpublished observations). However, genomic sequencing in *Caenorhabditis elegans* revealed a novel gene encoding a channel with an overall similarity and colinearity to SLO1 (REFS 3,28) (FIG. 1). Cloning and expression of this gene revealed a unique K^+ channel that, like SLO1, was dependent on Ca^{2+}, but had an additional synergistic Cl^- dependence[3]. The *C. elegans slo-2* gene is highly expressed and widely distributed in both neurons and muscles. Genome projects in rodents and humans soon identified mammalian orthologues of *slo-2*, revealing the presence of two closely related mammalian *slo-2* paralogues, *Slo2.1* and *Slo2.2*. However, unlike the *C. elegans* SLO-2 channel, the mammalian orthologues are sensitive to Na^+ and Cl^-, rather than Ca^{2+} and Cl^-, and it soon became evident that SLO2 channels were the elusive mammalian Na^+-dependent K^+ channels[29,4]. The difference in ion-dependence of gating between the SLO2 orthologues in *C. elegans* and mammals could reflect a more important role for Ca^{2+} currents in *C. elegans*, as a voltage-gated Na^+ channel is apparently absent in its genome[30].

Low-stringency DNA hybridization
A technique in which a radioactively labelled strand of DNA is used to isolate a similar but non-identical strand of DNA.

Inward rectification
A functional property that is characteristic of some ion channels, preferentially permitting an ion current to flow into, rather than out of, a cell.

Table 1 | **SLO family channels**

Channel	Alternative names	Gene symbol (human)	Chromosomal location	Conductance (in symmetrical K^+)	Blockers	Openers	Auxiliary subunits
SLO1	BK, K_{Ca}, Maxi-K, KCa1.1	*KCNMA1*	10q22	100–270 pS	Iberiotoxin[139], charybdotoxin[139], (+)–tubocurarine[140], kaliotoxin[141], penitrem A[142], TEA[143]	NS004[144], NS1619[145], DHS1[146]	β1 (KCNMB1), β2 (KCNMB2), β3 (KCNMB3), β4 (KCNMB4)
SLO2.1	Slick, K_{Na}, KCa4.2	*KCNT2*	1q31.3	60–140 pS	Intracellular ATP, quinidine, Ba^{2+}		?
SLO2.2	Slack, K_{Na}, KCa4.1	*KCNT1*	9q34.3	100–180 pS			?
SLO3	Potassium large conductance pH-sensitive channel, KCa5.1	*KCNU1*	8p11.2	70–100 pS			?

BK, 'big' potassium channel; DHS1, an agonist of native BK channels; TEA, tetraethylammoniom chloride.

Afterhyperpolarization
The negative voltage that persists for a short period of time immediately following some action potentials.

Slo3. The *Slo3* gene was identified by computer searches identifying an EST (expressed sequence tag) encoding a pattern of amino acids with similarity to the SLO1 channel. The topology of the SLO3 channel (FIG. 1) is highly similar to that of SLO1 but lacks certain features, such as the calcium bowl, which will be described below. It also differs functionally, lacking Ca^{2+}-dependent gating and having instead acquired a dependence on internal pH. Unlike SLO1 channels, which are widely distributed in the brain and in many different organ systems, SLO3 expression is restricted to spermatocytes and mature spermatozoa (L.S., unpublished observations). SLO3 will therefore not be covered in detail in this review.

Structure and function of SLO channels

The structures of the α-subunits of SLO family channels resemble those of voltage-gated K^+ channels in having a symmetrical arrangement of membrane-spanning domains clustered around a water-filled, K^+ ion-selective pore (FIG. 1). However, the α-subunits of SLO1 and SLO3 channels seem to have seven transmembrane domains, whereas SLO2 channels have six, like those of the voltage-dependent K^+ channel extended family. All α-subunits of SLO family channels differ from those of voltage-gated ion channels in having an extensive 'tail' — a carboxyl extension that greatly exceeds the length of the region that encompasses the membrane-spanning domains, and which contains both hydrophobic and hydrophilic domains. It is thought that the tail regions of SLO family channels confer distinctive properties that are not present in the family of voltage-gated ion channels, as will be described below.

Box 1 | **Historical context of SLO channel discovery**

The idea that genetic defects in ion channels might be reflected in mutant behavioural and neurological phenotypes was promoted by one of the founding fathers of neurogenetics, Seymour Benzer, in the 1970s. This insight led not only to the cloning of the SLO1 K^+ channel, but to the earlier identification of the first gene encoding any K^+ channel[131,132] and its cloning and characterization[133]. It also led to the identification of many other ion channels and accessory subunits that are essential to nervous system function[134–136]. Central to the wisdom of Seymour Benzer was the conviction that ion channels and other proteins that are fundamental to behaviour would be highly conserved in all metazoan species[137], a hypothesis that, with the advent of gene cloning, was proven to be true[138] and is now taken for granted by the current generation of neuroscientists.

SLO1. Mammalian SLO1 channels have received a great deal of attention, due to the fact that they are abundant in both the mammalian CNS and in many other mammalian organs, such as the pancreas, hair cells and smooth muscle. In addition, their large single-channel conductance facilitates high-resolution electrophysiological studies. The signature feature of the gating of SLO1 channels is that they can be activated by membrane depolarization alone, intracellular Ca^{2+} alone, or synergistically by depolarization and Ca^{2+} (REF. 31) (FIG. 2). The conserved protein domains of SLO1 seem to reflect separate mechanisms for voltage and Ca^{2+} sensing. The primary sequence consists of two distinct regions. The 'core' region (which includes hydrophobic segments S0–S6) resembles a canonical voltage-gated K^+ channel similar to Shaker[1,13,14], except for the inclusion of the additional S0 segment that places the amino (N) terminus outside the cell[32] and a long carboxyl extension containing additional hydrophobic segments S7–S10 (FIG. 1). The distal part of the carboxyl region (containing S9–S10), termed the tail, includes the region that is most highly conserved among SLO1 proteins from different species, the calcium bowl[33]. The tail is separated from the rest of the channel by a non-conserved linker region (between S8 and S9), which is the only part of the channel that shows significant differences in length between species. Remarkably, the tail domain can be separated from the domain that spans from the core to S8, and, when these two domains are co-expressed as separate peptides in *Xenopus* oocytes, functional channels are formed that are indistinguishable from wild type[28,32].

SLO2. Although the two *Slo2* paralogues, *Slo2.1* and *Slo2.2*, are highly structurally related, they express channels that differ in their modulation by various intracellular factors. Both lack the canonical gating charges in the S4 membrane-spanning segment that are associated with voltage sensing, and both have a low intrinsic voltage dependence[6,29]. Both channels are

synergistically activated by Na^+ and Cl^- (FIG. 2), but SLO2.1 has the added property of being negatively modulated by ATP [6]. This negative regulation by ATP suggests that their physiological function overlaps with that of the inward rectifier ATP-sensitive K^+ (K_{ATP}) channels. Recent experiments have also revealed that the functions of mammalian SLO2 channels might overlap with those of the M-current channels, which are modulated by neurotransmitters. These studies showed that both *Slo2* paralogues are strongly modulated through the activation of G-protein-coupled receptors (GPCRs)[34]. However, they are modulated in opposite ways; SLO2.2 currents increase in size in response to the activation of co-expressed $G\alpha_q$-coupled GPCRs, whereas SLO2.1 currents decrease in size. When heterologously expressed in *Xenopus* oocytes, both SLO2.1 and SLO2.2 modulation can be coupled through at least three different $G\alpha_q$-coupled GPCRs, mGluR1 (glutamate receptor, metabotropic subtype), mAchR1 (acetylcholine receptor, muscarinic subtype), and the angiotensin II receptor[34]. The ramifications of these observations remain speculative. However, the finding that these channels are modulated by metabotrophic neurotransmitters opens up several interesting possibilities. Both SLO2 channels are widely distributed in the brain[34–36]. The low voltage-sensitivity of both SLO2.1 and SLO2.2 permits these channels to be open at a wide range of voltages. The additional fact that they are modulated in an opposite manner by neurotransmitters suggests a possible role for these channels in tuning the resting potentials and basal excitability of neurons, either up or down, in a variety of brain regions.

Functional domains of SLO channels

Channel gating and conductance. Gating (opening and closing) of ion channels is accomplished through the movement of specialized gating domains, which are physically coupled to the pore and mechanically alter its conformation between non-conducting (closed) and conducting (open) states. Ion channels are often categorized by the types of gating domains that are thought to open the channel. Voltage-dependent channels are gated in response to changes in transmembrane voltage, which pushes, rotates or tilts a charged voltage-sensing domain that is present on each subunit. In ligand-gated channels, the binding of a ligand (such as a neurotransmitter) causes a conformational change of a ligand-binding domain that is physically coupled to the pore of the channel. However, for SLO1 and SLO3 channels this distinction breaks down, because both voltage-gating and ligand-gating domains are present. The gating of SLO1 channels by both voltage and the binding of intracellular Ca^{2+} indicates two independent sensing mechanisms that converge near the gates of the pore[37–39,46]. An analogous arrangement might exist for SLO3 channels, which are gated by both voltage and intracellular pH (FIG. 2). Although the pH-sensing mechanism for SLO3 is not completely characterized, it seems to involve the SLO3 carboxyl tail, perhaps in a manner analogous to the Ca^{2+}-sensing mechanism of SLO1 (REFS 5,40–42).

The gating mechanism of SLO1 channels has been studied more intensely than that of the other SLO channels. Voltage regulation is strongly associated with the core region and arises from mechanisms that are shared with other voltage-gated channels, with S4 having a primary role as the voltage sensor (perhaps acting through the S4–S5 linker to influence the S6 gates)[38,43,44]. Voltage gating is also observed in SLO3, which has a configuration of presumed gating charges in the S4 region that is very similar to that of SLO1. In marked contrast to this, the analogous regions in SLO2 channels lack positive charges in the corresponding positions. Curiously, SLO2 channels have two negative charges in this region, and an apparent deletion of six residues (FIG. 3). Not unexpectedly, SLO2 channels have weak intrinsic voltage sensitivities.

The ligand-gating mechanism might involve specialized structures called RCK (regulators of conductance of K^+) domains, which form an intracellular gating ring. RCK domains are found in many putative prokaryotic K^+ channels that might bind intracellular ligands, and are attached to an intracellular domain extending from the pore-forming core of the channel. It has been proposed that SLO1 channels possess an intracellular gating ring that is composed of four RCK1 and four RCK2 domains, similar to that suggested for the bacterial Ca^{2+}-modulated channel, MthK[45,46]. Binding of Ca^{2+} to the gating ring is proposed to expand the ring, pulling on the linkers between the gating ring and the S6 gates, to open the channel.

A convergence of the gating forces generated by the voltage sensors and the Ca^{2+} sensors at the S6 gates would allow for synergistic action of the two types of sensors on channel gating. Such synergistic action is possible because the conformational changes that occur on opening and closing are separate from the conformational changes that are associated with the activation of the voltage sensors and the Ca^{2+} sensors[37,47–52]. The probability of channel opening is low when neither the Ca^{2+} nor the voltage sensors are activated. Progressively activating more of the Ca^{2+} and/or voltage sensors increases the opening force on the gates, leading to an increased probability of the channel opening. Such a gating mechanism has been represented by a 50-state model, with 25 closed states on the upper tier and 25 open states on the lower tier, reflecting 25 different combinations of 0–4 activated voltage sensors and 0–4 activated Ca^{2+} sensors[31,38,48–52]. However, SLO channels have at least two high-affinity Ca^{2+} binding sites and one low-affinity Ca^{2+}/Mg^{2+} binding site per subunit[33,53–58]. Expanding the model to account for these additional sites could increase the number of states to 250 for two Ca^{2+} sites per subunit and 1,250 for three sites per subunit[51,53,56,59–61].

Multiple Ca^{2+} regulatory domains. It is now well established that there are multiple Ca^{2+}-dependent regulatory domains on the SLO1 α-subunit. These domains have been the subject of extensive site-directed mutagenesis studies[33,40,55–57,62–64]. The calcium bowl is located at the large cytosolic carboxyl (C) terminus and features a string of negative charges that are identical in *C. elegans*,

M current
A K^+ current that is modulated by the activation of muscarinic receptors. It participates in determining the subthreshold excitability of neurons and their responsiveness to synaptic input. The underlying channel is thought to consist of KCNQ K^+ channel subunits.

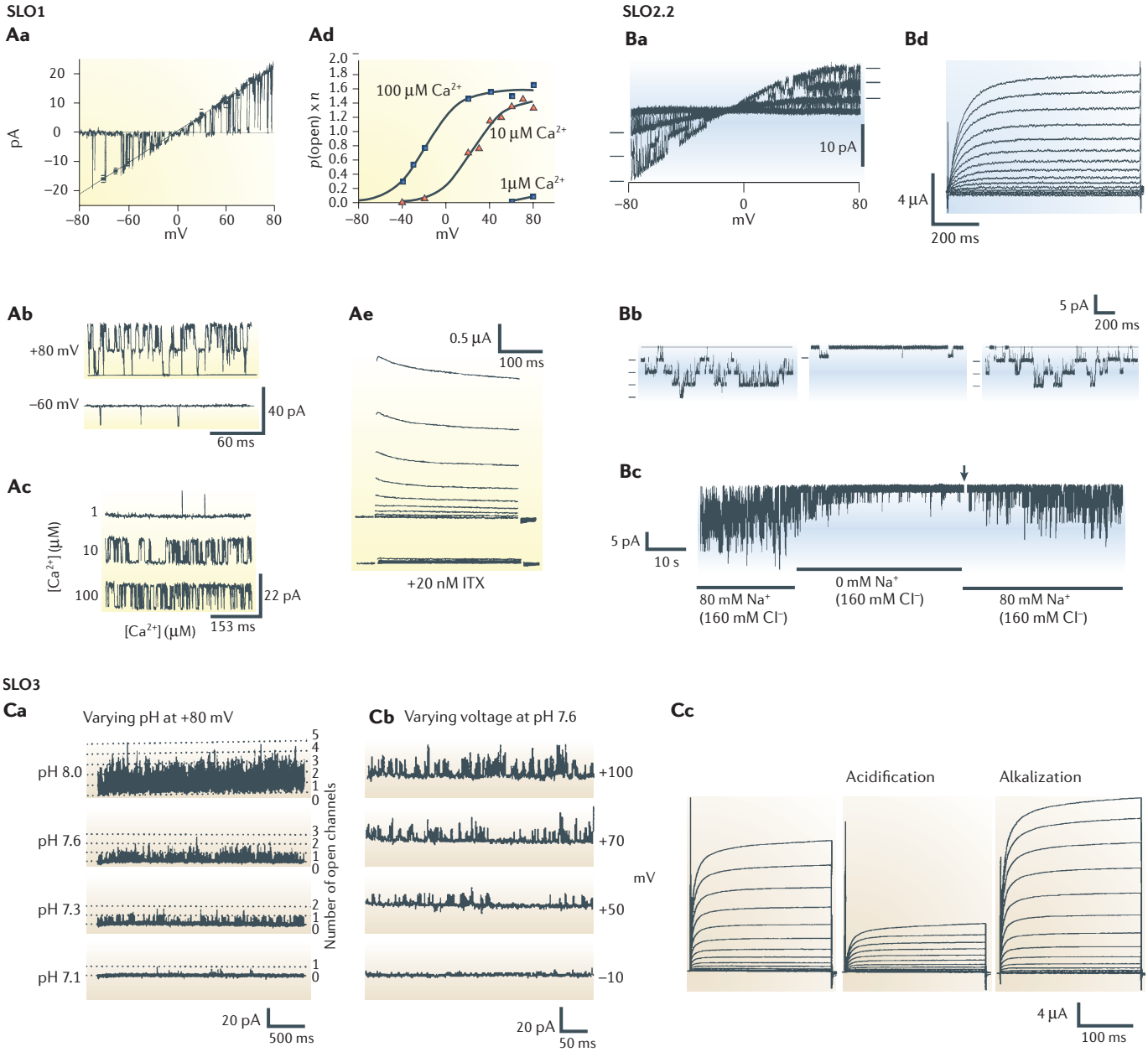

Figure 2 | **Properties of SLO1, SLO2 and SLO3 currents. Aa** | SLO1 single-channel currents generated by a voltage ramp pulse from –80 to +80 mV following heterologous expression in *Xenopus* oocytes. Remarkably, although of high unitary conductance and highly specific for K^+ over Na^+, single-channel conductance is linear over the physiological voltage range. **Ab** | Comparison of channel opening activity at –60 and +80 mV. At any individual Ca^{2+} concentration, the open-channel probability increases at more positive voltages. **Ac,d** | Comparisons of channel opening activity at different concentrations of cytosplasmic Ca^{2+}. Held at a single voltage, the open-channel probability increases as cytoplasmic Ca^{2+} concentration is increased. **Ae** | Whole-cell currents recorded from SLO1 channels heterologously expressed in a *Xenopus* oocyte. Voltage step pulses (not shown) were from –80 to +60 mV at a holding potential of –90 mV. The current is blocked by the scorpion toxin iberiotoxin (ITX; bottom) at a concentration of 20 nM. **Ba** | In contrast to SLO1, SLO2.2 single-channel currents are not linear over a wide voltage range. The apparent single-channel conductance declines at higher voltages. Note the low voltage sensitivity indicated by channel openings at negative voltages. Horizontal bars indicate open channel levels. **Bb,c** | Also in contrast to SLO1, the activity of SLO2.2 currents is increased by the addition of Na^+. The arrow indicates a recording pause. **Bd** | Whole-cell currents resemble a delayed rectifier current in that current activation is slow and there is no apparent inactivation. **Ca** | SLO3 single-channel currents show a dependence on pH. **Cb** | SLO3 currents show marked voltage sensitivity; higher single-channel activity occurs at higher voltages. **Cc** | Whole-cell currents are reduced in amplitude on acidification, and increase in amplitude on alkalization. Panels **Aa–e** modified, with permission, from REF. 1 © (1993) American Association for the Advancement of Science. Panels **Ba–d** modified, with permission, from REF. 29 © (2003) Elsevier Science. Panels **Ca–c** modified, with permission, from REF. 5 © (1998) American Society for Biochemistry and Molecular Biology.

Figure 3 | **The S4 region aligned for SLO1, SLO3 and SLO2.** Greater similarity is seen between SLO1 and SLO3. SLO1 and SLO3 channels have three positively charged residues in the canonical pattern that is seen in all voltage-dependent K^+ channels (+oo+oo+), whereas SLO2 has no residues arranged in this pattern. The absence of these charges might underlie the fact that SLO2 channels have the lowest intrinsic voltage sensitivity. Indeed, the SLO2 sequence is conspicuously shorter in this region, suggesting that the overall conformation of the S4 region is distinct in SLO2 channels. Blue, negatively charged residues; red, positively charged residues; yellow, uncharged residues common to two or more channels.

Drosophila and mammals[33]. The calcium bowl might not be part of an RCK domain, but instead lies just distal to the second RCK domain and interacts with it (FIG. 1). Mutations that affect the calcium bowl alter the high-affinity sensing of Ca^{2+} (REFS 33,40). Further evidence for the role of this region as a Ca^{2+} sensor comes from experiments involving the construction of a chimeric subunit that resulted in the expression of a totally Ca^{2+}-insensitive BK channel[40]. The chimera was composed of the tail of SLO3 attached to the core of SLO1. Adding back the calcium bowl to the SLO3 tail region of this chimera reintroduced Ca^{2+} sensitivity[40]. Additional evidence supporting the role of the calcium bowl as a Ca^{2+} sensor was provided by showing direct binding of Ca^{2+} to this region[61,62,64].

A second region of the C terminus, the first RCK domain, contains at least two other sites that are involved in additional regulatory effects of divalent cations. One of these sites is highly selective for Ca^{2+} and, together with the calcium bowl, probably accounts for most of the regulation of BK channels by Ca^{2+} within the normal physiological range. The other site is sensitive to regulation by millimolar concentrations of divalent cations, and might mediate regulation of SLO1 by cytosolic Mg^{2+} within its normal physiological range[55,57,65]. An additional, non-overlapping site is indicated by a single amino-acid substitution, which specifically reduces channel activation within the 10–100 μm range for $[Ca^{2+}]_i$, suggesting further regulatory complexity[62]. Independent regulation by these multiple binding sites, each of which has a different affinity for Ca^{2+}, explains the large concentration range over which SLO1 channels are regulated by Ca^{2+}.

These regulatory domains can function independently[59]. However, recent results show that the presence of an RCK1 sensor and a calcium bowl on the same subunit confers greater additive sensitivity to Ca^{2+} than when they are on different subunits, indicating positive intra-subunit cooperativity. This complicated system of cooperativity, involving several Ca^{2+}-sensing sites both on the same subunit and on different subunits, might underlie the responsiveness of SLO1 channels to such a broad range of Ca^{2+} concentrations[66]. Indeed, this arrangement of Ca^{2+} sensors might be what allows SLO1 channels to be so useful and versatile, performing a wide variety of physiological roles in different cell types and cellular microdomains, where Ca^{2+} concentrations can vary extensively.

Site-directed mutagenesis
The generation of a mutation at a predetermined position in a DNA sequence by various genetic engineering methods.

Cellular microdomains
Subcellular areas or compartments that have distinctive structural features, such as a clustering of protein complexes.

Symmetrical KCl
Equimolar concentration of KCl on both sides of the membrane.

Selectivity filter
Molecular features in the pore of an ion channel that aid in discriminating between different ion types.

The current understanding of Ca^{2+} sensing by the calcium bowl and the RCK1 domain was challenged by a controversial study by Piskorowski and Aldrich[67], who reported nearly unaltered Ca^{2+} and voltage dependence in a SLO1 channel construct in which the entire cytoplasmic C-terminal region was deleted. These results indicate that functional SLO1 Ca^{2+}-binding sites are actually located in the S0–S6 core membrane-spanning domain. It remains to be seen, however, whether these results can be replicated in other laboratories.

Mechanisms of high single-channel conductance. SLO1 channels have the largest single-channel conductance of all K^+ selective channels: 250–300 pS in symmetrical KCl (150 mM). This means that a single open channel will carry 25–30 pA of current when the driving force on K^+ is 100 mV. By contrast, some potassium channels have a single-channel conductance that is only ~2% of this. SLO1 channels share a selectivity filter sequence (GYG) that is identical to that of most other K^+ channels with lower single-channel conductances. So, the question arises as to why the conductance of SLO1 channels is so large. Several studies have indicated at least two salient structural mechanisms. K^+ flux in SLO1 channels is influenced by a ring of negative charges in the inner and outer pore of the channel's ionic conduction pathway. Charged residues that are located in the vestibules of ion channels can have important roles in controlling measured single-channel conductances, through an electrostatic mechanism. Such rings of fixed charge in SLO channels might locally increase the concentration of permeant ions in the vestibules of the channels, leading to an increased availability of ions to transit across the selectivity filter. This resultant increased flux could explain the unusually high single-channel conductance that is observed in SLO1 channels, and perhaps other SLO channels[68,69]. Site-directed mutagenesis studies of these charged residues located at the base of S6 systematically altered single-channel conductance, which decreased in a stepwise fashion as the net charge of the ring was changed from −8 to +8. This simple electrostatic mechanism was found to double the conductance of BK channels for outward currents (the direction of K^+ current flow under normal physiological conditions)[68,70]. Similarly, the inward flow of K^+ through SLO1 channels is greatly influenced by a ring of negative charges that are located near the extracellular outer pore. These fixed negative charges near the outer vestibule electrostatically raise the local K^+ concentration close to the selectivity filter, thereby increasing the entry rate of ions into the pore[71].

In addition to its unique electrostatic profile, the size of the SLO1 inner pore region might be larger than that of other K^+ channels. A series of quaternary ammonium compounds differing in size were applied to the cytoplasmic pore of SLO1 channels to estimate the size of the inner pore region. These studies showed that molecules as large as decyltriethylammonium and tetrabutylammonium have much faster blocking and unblocking rates in SLO1 channels, compared with several other K^+ channels. Additionally, on repolarization, large quaternary ammonium molecules were found to be trapped inside blocked

SLO1 channels, without slowing observed deactivation rates. Based on these findings, SLO1 channels might differ from other K^+ channels in the geometry of the inner vestibule, with an enlarged cavity and inner pore that could provide greater access to cytoplasmic ions, and thereby a larger single-channel conductance[71,73].

Functional diversity of SLO1

There is significant diversity in the functional characteristics of SLO1 BK currents in native tissues. For example, in smooth muscle, hair cells and some neurons the sensitivity to Ca^{2+} concentration is higher than in other neuronal cell types[79,85,139,140,146]. Another example of diversity is the inactivation properties of these channels. In rat chromaffin cells, BK currents show rapid inactivation, which is in marked contrast to the behaviour of SLO1 channels in smooth muscle and many neurons, in which they lack inactivation[78]. Several pre- and post-translational mechanisms account for the variability of SLO1 currents in native tissues, and underlie the diverse physiological roles that BK channels have in different cell types.

Alternative splicing. A large number of splice variants of the SLO1 α-subunit have been identified[1,13,14,79,81,82], some of which produce channels with significantly different Ca^{2+} sensitivities and kinetics, which could have physiological relevance[80–82]. Indeed, *Slo1* splice variants can provide a mechanism for cochlear hair-cell frequency tuning, in which a gradient of SLO1 K^+ currents across the basilar membrane could modulate the frequency of voltage oscillations in cochlear hair cells[81–85]. The kinetic properties of each SLO1-α/β variant, in combination with voltage-gated Ca^{2+} channels, largely determines the resonant electrical frequency at which each hair cell is tuned to respond. It has also been suggested that the expression of different splice variants might be under hormonal regulation, and might be involved in modulating the long-term excitability of cells that are involved in stress-related responses[86–90].

Modulation by kinases. The intrinsic gating properties of many ion channels are dynamically modulated by a shifting balance between cellular kinase and phosphatase activities, which act to reversibly modify accessible phosphorylation sites on the channel protein. A substantial body of evidence has demonstrated that SLO1 channels are an important substrate for direct regulation by various common serine/theonine kinases, including cyclic AMP-dependent protein kinase A (PKA), cyclic GMP-dependent protein kinase G (PKG) and diacylgycerol/Ca^{2+}-dependent protein kinase C (PKC)[87–93]. Through these kinases, SLO1 channel activity can be coupled to multiple, diverse signalling cascades to allow alternative means of control over basal excitability or contractility. Specific kinases can either increase or decrease SLO1 channel activity, often in complex conditional combinations, and this variation seems to be highly tissue-dependent.

SLO1 modulation by PKA phosphorylation is perhaps the best understood example of SLO1 modulation by a specific kinase[87,88,90,91]. The mammalian SLO1 subunit contains a conserved PKA site found in all splice variants (RQPS*IT; asterisk indicates that phosphorylation is on the preceding amino acid; phosphorylation occurs at S899 in murine mSLO1), which is located near to the C-terminal edge of the calcium-bowl sequence. Phosphorylation of this site on all four subunits of a homomeric SLO1 channel is required to augment basal channel activity by ~60%. Additional PKA modulation occurs in SLO1 splice variants that include the alternative STREX exon[86]. In native tissues, β-adrenergic receptor activation of PKA through adenylate cyclase stimulation leads to the activation of SLO1 channels in many smooth muscles[88] and neurons[89], whereas in other cell types, such as neuroendocrine cells, SLO1 channels are inhibited[92]. Analogous studies with PKG have provided a complex and, so far, less complete model of SLO1 regulation, although PKG might couple SLO1 channels to a signalling pathway of major physiological significance[93]. Direct modulation of basal SLO1 currents by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) has also been reported[94].

Heteromultimer formation. The formation of heteromultimers between SLO1 α-subunits and the α-subunits of other SLO family members might contribute to functional diversity. The tissue expression pattern of SLO1 overlaps extensively with that of the other members of the *Slo* gene family, and it has been suggested that heteromultimerization between SLO1 and SLO2 α-subunits might occur[4], although direct evidence is lacking. We are currently exploring the possibility that SLO2.1 and SLO2.2 form heteromultimers with novel properties.

Regulation by auxiliary β-subunits. In some but not all tissues, auxiliary β-subunits interact with SLO1 α-subunits to provide yet more functional diversity. β-subunits were first isolated by biochemical purification from bovine tracheal and aortic smooth muscle by Knaus *et al.*[95,96]. The first of these auxiliary β-subunits to be discovered, the β1 protein, was identified as a glycosylated 31 kDa peptide of 191 amino acids. When combined with SLO1 α-subunits, this protein formed a non-covalent channel complex that bound the BK channel blocker charybdotoxin and formed functional channels when reconstituted into planar lipid bilayers. It was later established that the β-subunit of smooth muscle was only one of a family of auxiliary β-subunits from mammals (β1–β4). β1 is expressed primarily in smooth muscle, hair cells and some neurons (for a review, see REF. 97). Several studies have shown that the β1 subunit affects both the gating and the apparent Ca^{2+} sensitivity of the α-subunit[72,74–77,98]. Estradiol binding to the β1 subunit also offers another mode of regulating BK channels[99]. It has also been proposed that the β1 subunit might be responsible for the high sensitivity to intracellular Ca^{2+} that native BK channels show in hair cells[85]. Structurally, it has been determined that the β1 subunit has two membrane-spanning segments, with its N and C termini located on the intracellular side of the channel. β1 subunits interact with the S0 transmembrane segment of the SLO1 α-subunit[100].

Splice variants
Alternative forms of a protein derived from alternative processing of its mRNA.

The discovery of the β1 subunit and its effect on the α-subunit seems to explain some of the differences in gating that have been reported in different native tissues. The four distinct mammalian β-subunits contribute to differences in functional properties of the SLO1 channels in different tissues. The β2 subunit shares sequence similarities with β1 (REF. 101) but, unlike β1, it promotes a fast inactivation mechanism in SLO1 channels[78,100,101]. Charybdotoxin binding is not enhanced by the presence of the β2 subunit. Cloning and expression was achieved for the β3 and β4 subunits almost simultaneously[102–104]. β3 is structurally similar to β1 and β2, whereas β4 is an outlier[97]. β3 is found in the testis, pancreas and spleen[105], and has several splice variants in its N-terminal region[78,97]. Three of these splice variants confer fast inactivation, but apparently none alters the apparent Ca^{2+} sensitivity of SLO1 channels[104–106]. Of the four β-subunits, β4 seems to be most highly expressed in the brain. The complex that is composed of the β4 and SLO1 α-subunits produces BK channels that are uniquely resistant to charybdotoxin and iberiotoxin[106,107].

Currently, little is known about β-subunits that might interact with the other SLO family channels. Indeed, even for SLO1 channels it is likely that the story regarding β-subunits and other interacting subunits is incomplete, as suggested by the intriguing finding in *Drosophila* that a slowpoke binding protein (SLOB) interacts with the carboxyl tail region of SLO1 and modifies its channel properties[107].

Physiological roles of SLO1 channels

Far more is known about the physiological roles of SLO1 channels than those of SLO2 or SLO3 channels, which are more speculative. The sensitivity of SLO1 to Ca^{2+} makes it an important negative-feedback system for Ca^{2+} entry in many cell types. Other members of the SLO family of K^+ channels have evolved the ability to couple gating to a wide variety of changes in other intracellular conditions. SLO1 channels are expressed throughout most tissues of the body. Particularly well understood are the diverse roles of these channels in neurons, smooth muscles, secretory endocrine cells and specialized sensory receptors. These diverse roles all take advantage of the unique properties of these channels, in particular their sensitivity to intracellular Ca^{2+} and their large single-channel conductances, often in combination with closely tethered Ca^{2+} channels[108].

SLO1 is widely distributed in the CNS, where it is localized to cell somas, dendrites and presynaptic terminals[108,109]. SLO1 channels could provide the main negative-feedback mechanism for timing the bursts of Ca^{2+} action potentials, such as those generated in the dendrites of cerebellar Purkinje cells[111,112]. At the neuronal soma, SLO1 is thought to contribute to the fast phase of the afterhyperpolarization potential observed in pyramidal cells of the hippocampal CA1 region[113–115]. The afterhyperpolarization potential is a chief determinant of the refractory period and therefore the maximum firing rate of a neuron. SLO1 channels that are found at presynaptic terminals might provide a homeostatic mechanism for regulating synaptic transmission by limiting the influx of extracellular Ca^{2+} through presynaptic voltage-gated Ca^{2+} channels[116–120]. More recently, a novel role for the SLO1 channel has been reported in the oxygen-sensing dopaminergic glomus cells of the carotid body, which mediate compensatory respiratory reflexes to hypoxia[121]. In addition, heme has been reported to bind directly to SLO1 channels, raising the possibility that this is the mechanism by which SLO1 channels are directly regulated by oxygen, NO or other gases[122,123].

These physiological roles for SLO1 channels are consistent with genetic studies in model organisms (*Drosophila*, *C. elegans* and mice) and a recently reported human genetic linkage to an epilepsy locus. *slo1* mutants in *Drosophila* have a behavioural phenotype consistent with a generalized neural and muscle defect[12,13]. *C. elegans slo-1*-null mutants display no obvious gross behavioural phenotypes, but do have increased neurotransmitter release at the neuromuscular junction, consistent with a specific presynaptic role for SLO1 channels in the control of quantal content[117]. The *C. elegans* mutants also show reduced intoxication by ethanol, suggesting that SLO1 channels might be an important target in this respect[124]. Mouse *Slo1* knockout strains[125,126] are viable and exhibit a spectrum of subtle abnormal phenotypes including ataxia[125], high-frequency hearing loss[127], vascular hypertension[128], incontinence due to overactive bladder function[126] and erectile dysfunction[129], consistent with defects in brain and smooth muscle excitability. Recently, a human *SLO1* missense mutation was found to be responsible for generalized epilepsy and paroxysmal dyskinesia[130].

Conclusions and future perspectives

Based on structurally conserved features, SLO family channels might have a common evolutionary ancestor that was a member of the voltage-dependent K^+ channel family (FIG. 4). Diversification of that ancestor produced a channel family in which different members retain a common functional architecture that is characterized by a K^+-selective gated pore core, which is similar to that of voltage-dependent channels, linked to a carboxyl tail structure that senses different intracellular factors and appropriately tailors pore gating behaviour. The SLO2 channels are apparently different in this regard, as they retain the core structure but seem to have lost the positive charges that are associated with voltage gating (FIG. 3). In the course of evolution, the ancestral *Slo* gene has given rise to one of the most widely distributed and versatile K^+ channels (SLO1) and to one of the most tissue-restricted channels involved in a specific physiological event (SLO3).

SLO channels are gated by intracellular ions, and therefore might be considered as ligand-gated K^+ channels for which the ligands are intracellular ions. All SLO channels are high-conductance K^+ channels and so have the ability to strongly link changes in K^+ conductance to variations in the intracellular concentrations of the ions that they sense. Although SLO channels share features in common with voltage-sensitive channels, they are able to modulate their voltage range of activity to adapt to different intracellular conditions.

Quantal content
The number of quanta — unitary packets of transmitter — released per action potential.

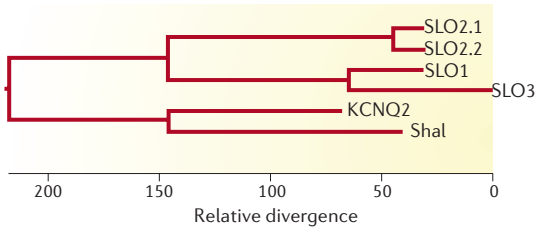

Figure 4 | **Inter-relatedness of SLO family proteins and similarity to two voltage-dependent channels.** The dendrogram shows the relationship of SLO family channel subunits and subunits of two voltage-dependent channels. All sequences are from rodents. Shal refers to Kv4.1, the voltage-dependent K^+ channel that is most highly conserved across species. KCNQ2 refers to Kv7.2, a subunit component of the M current and possibly the voltage-dependent K^+ channel with the greatest similarity to the SLO family. Branch length corresponds to sequence divergence. Clustal V parameters. Multiple alignment parameters: gap penalty, 10; gap length penalty, 10. Pairwise alignment parameters: ktuple, 1; gap penalty, 3; window, 5; diagonals, 5.

SLO1 channels are particularly well studied because they were the first to be identified and characterized, and because they are gated by intracellular Ca^{2+}, which is a common second messenger in many cells of the nervous system. In addition to the roles outlined in this article, other postulated physiological roles of SLO1 channels remain to be explored and documented. The fact that SLO1 channels participate in so many disparate functions is probably the reason that these channels are so highly conserved throughout the animal kingdom. It seems that any major change in SLO1 protein structure will upset the optimization that has been achieved for this many-faceted channel protein. The highly structurally similar SLO3 channel is at the other end of the spectrum, seems to be present only in mammalian spermatocytes, and is evolving rapidly (L.S., unpublished observations).

SLO2 channels are intermediate in their levels of conservation. Orthologues of SLO2 are found in *C. elegans* and *Drosophila*, as well as in mammals, but their functional properties have drifted; SLO2 channels in *C. elegans* are sensitive to Ca^{2+} and Cl^-, whereas mammalian SLO2 channels are sensitive to Na^+ and Cl^-. In addition, SLO2 channels are also linked to signal-transduction mechanisms controlled by neurotransmitters that can bind to $G\alpha_q$-coupled GPCRs. Furthermore, SLO2.1 channels are modulated by intracellular ATP, suggesting that these channels might link K^+ conductance to the metabolic state of cells, as in the case of the inward rectifier K_{ATP} channels. Because they are modulated by neurotransmitters, the function of SLO2 channels might overlap with that of M-current channels, and their presence in the frontal cortex and hippocampus suggests the possibility of involvement in higher brain functions. Intriguing possibilities are presented by the fact that these channels are present near the initial segments of dendrites, where they could modulate the integration of synaptic potentials. However, further speculation must await future studies. It is certainly the case that the entire spectrum of physiological functions undertaken by all SLO family channels is currently only partially understood, and biophysicists, physiologists, biochemists and geneticists have a long road ahead in sorting them all out.

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Competing interests statement
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