Pharmacology of A-Type K^+ Channels

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Contents

Abstract

Transient outward potassium currents were first described nearly 60 years ago, since then major strides have been made in understanding their molecular basis and physiological roles. From the large family of voltage-gated potassium channels members of 3 subfamilies can produce such fast-inactivating A-type potassium currents. Each subfamily gives rise to currents with distinct biophysical properties and pharmacological profiles and a simple workflow is provided to aid the identification of channels mediating A-type currents in native cells. Their unique properties and regulation enable A-type K^+ channels to perform varied roles in excitable cells including repolarisation of the cardiac action potential,

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N. Gamper, K. Wang (eds.), *Pharmacology of Potassium Channels*,
Handbook of Experimental Pharmacology 267, https://doi.org/10.1007/164_2021_456

controlling spike and synaptic timing, regulating dendritic integration and long-term potentiation as well as being a locus of neural plasticity.

Keywords

A-type K^+ channel · Kv1.4 · Kv3.4 · Kv4 · Potassium channel · Voltage-clamp

1 Introduction

A-type refers to neuronal K^+ currents generating a transient outward current in response to depolarising voltage-clamp steps. This stereotypical phenotype was first described in neurons from sea slug *Onchidium* (Hagiwara et al. 1961). These early experiments described the now stereotypical hallmarks of A-type currents. They identified a transient outward voltage-gated K^+ current activated by depolarising steps from a hyperpolarised potential (Fig. 1c, d). In current clamp when hyperpolarising steps were used to remove A-current inactivation, they observed an increase in the latency to the first spike in response to depolarising current steps (Fig. 1a, b). Such transient outward currents were later designated as I_A, a term which has persisted (Connor and Stevens 1971). Work over the subsequent decades has described A-type channels in the heart (the corresponding current fraction is called I_{to} in the heart; for more details see chapter "Cardiac K^+ Channels and Channelopathies") where they contribute to the early repolarisation phase (Dixon et al. 1996; Yeola and Snyders 1997) and in many different types of neurons where they contribute to such varied functions as controlling spiking, neurotransmitter release, dendritic integration and long-term potentiation (Molineux et al. 2005; Imai et al. 2019; Watanabe et al. 2002; Frick et al. 2004; Chen et al. 2006; Shevchenko et al. 2004; Kim et al. 2005; Kuo et al. 2017).

The transient nature of A-type currents is due to rapid voltage-dependent inactivation, with inactivation decay time constants typically in the 10s of milliseconds. The subunit composition and presence of accessory subunits or other modulatory factors determine the exact biophysics and pharmacological profile of these currents. Alpha subunits from three subfamilies of voltage-gated K^+ channel generate rapid inactivating K^+ currents when expressed as homomers: Kv1.4, Kv3.3, Kv3.4 and all three Kv4 members, Kv4.1, Kv4.2 & Kv4.3 (Coetzee et al. 1999). The presence of the ß subunit Kvß1 can also confer A-type kinetics to other, normally delayed rectifier subunits from the Kv1 family (Rettig et al. 1994). These different subfamilies have distinct biophysical properties, enabling the subfamily mediating a native A-type current to be narrowed down with simple voltage-clamp protocols and confirmed with their pharmacological profiles (Fig. 1).

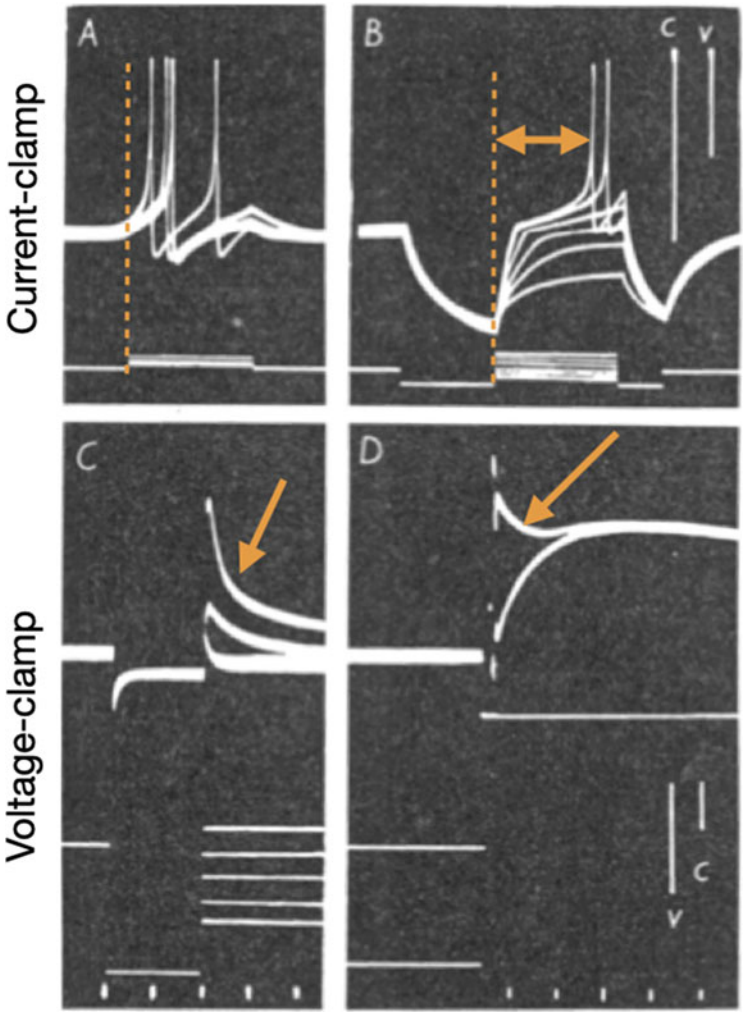

Fig. 1 Initial observations of A-type currents in *Onchidium.* (**a**) Current clamp recording of action potentials evoked from rest with short spike latencies. (**b**) A preceding hyperpolarising step removes steady-state inactivation of the A-type current and results in a lag to the first spike as the A-current inactivates (yellow arrow). (**c**) Voltage-clamp recording showing a fast-inactivating outward current activated at voltage around resting membrane potentials after hyperpolarising steps, yellow arrow. (**d**) The A-current is present at more positive potentials only with a hyperpolarising pre-step, yellow arrow. The delayed rectifier can be isolated by inactivating the A-current. Adapted from Hagiwara et al. (1961) reproduced with permission

2 Identifying Native A-Type Channels

2.1 Biophysics

2.1.1 Activation Range

Canonical A-type K^+ currents have sub-threshold activation ranges, i.e. they begin to activate at voltages more negative than that required to generate an action potential (Fig. 1). A hallmark of the Kv3 subfamily is their supra-threshold activation range, they typically do not begin to activate until voltages greater than −30 mV with half activation voltages around +10 mV (Rudy and McBain 2001). This property restricts their physiological activation window to that of the action potential, in which Kv3 channels act to rapidly repolarise the cell to the resting state (Rudy and McBain 2001; Johnston et al. 2010). A-type K^+ currents mediated by channels containing Kv3.3 and/or Kv3.4 can therefore be distinguished from other A-type subunits by their positively shifted activation curve (Fig. 2b).

2.1.2 Inactivation Properties

The molecular basis of rapid K^+ channel inactivation has been extensively studied with Kv1.4 used as the prototype. Two forms of inactivation have been demonstrated; fast N-type or "ball and chain" inactivation involves the N-terminal inactivation peptide of the alpha subunit binding within the central cavity to occlude the inner pore (Hoshi et al. 1990; Zhou et al. 2001). The rate of this type of inactivation is directly related to the number of N-terminal peptides, e.g. Kv1.4 homomers, possessing 4 N-terminal peptides, show faster inactivation than Kv1.4/Kv1.1 heteromers, which have 3 of less depending on the stoichiometry (Ruppersberg et al. 1990; MacKinnon et al. 1993). The presence of Kvß1 subunits confers a similar N-terminal inactivation peptide (one per subunit), which further accelerates the inactivation rate of Kv1.4 or can endow Kv1.1 with fast A-type inactivation (Rettig et al. 1994). Kv3.3 and Kv3.4 are thought to inactivate through a similar mechanism showing a similar dose dependency of N-terminal inactivating peptide on inactivation rate (Rudy et al. 1999; Weiser et al. 1994). In addition to the described N-type inactivation, Kv1.4 channels also inactivate by a slower C-type inactivation attributed to partial collapse of the selectivity filter/outer pore. N and C-type inactivation in Kv1.4 are allosterically coupled (Hoshi et al. 1990, 1991; Bett and Rasmusson 2004) and the rate of recovery from inactivation is controlled by the slower C-type inactivation (Rasmusson et al. 1995). As a result Kv1.4 channels recover from inactivation with a time constant of seconds (Bett and Rasmusson 2004; Roeper et al. 1997).

In contrast, the molecular details concerning inactivation of Kv4 channels have not been determined with such precision. Kv4 subunits use neither the N nor C-type inactivation processes identified for Kv1.4, instead inactivation seems to involve the inner vestibule of the pore and readily occurs through the closed state (Jerng et al. 1999; Bähring et al. 2001; Beck and Covarrubias 2001; Shahidullah and Covarrubias 2003). Kv4 channels possess an N-terminal inactivating domain but rather than contributing to inactivation this region is the binding site of the ß-subunits of Kv4

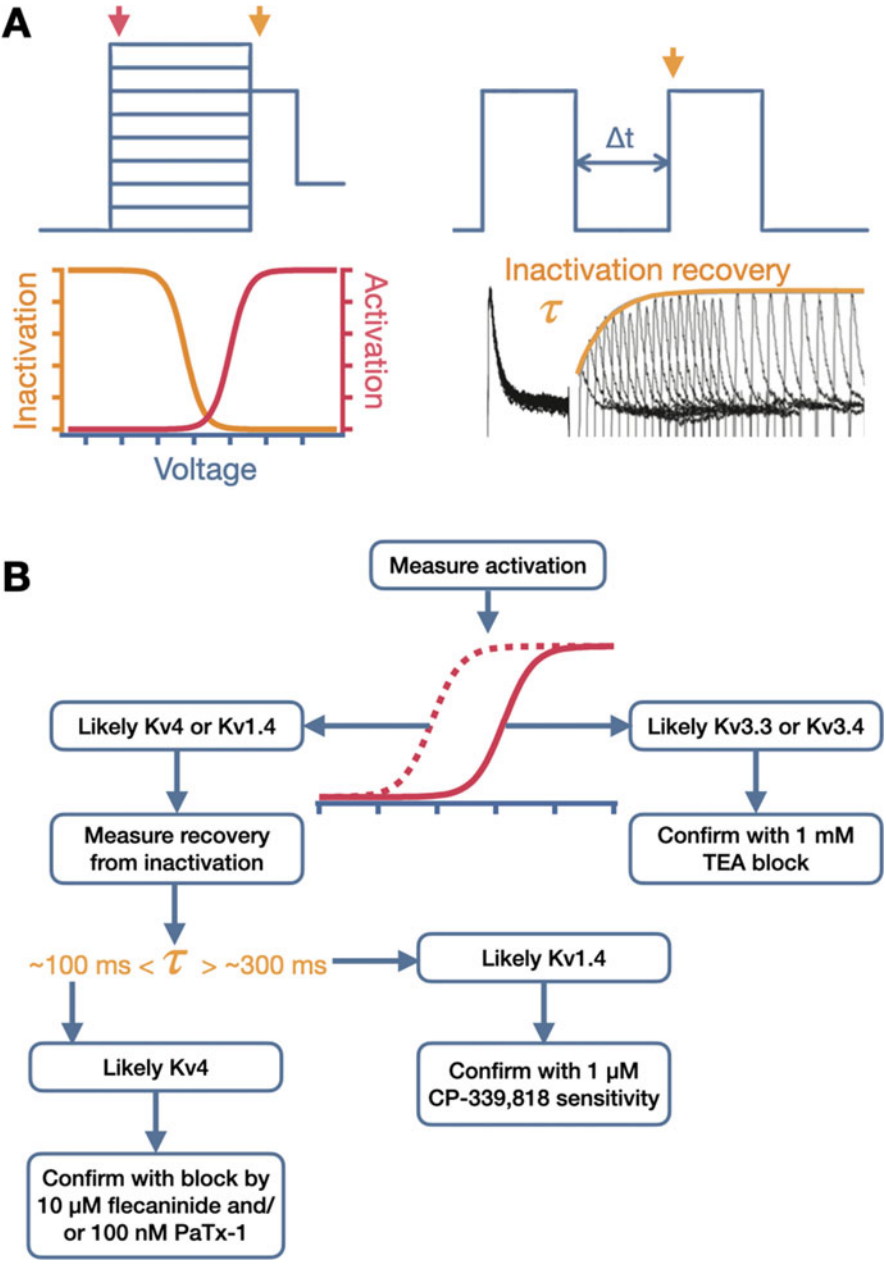

Fig. 2 Biophysical and pharmacological identification of channels mediating native A-type K^+ currents. (**a**) *Left:* Voltage protocol to determine the activation and inactivation curves for A-type channels. The activation curve can be constructed by measuring the peak current soon after the test step (red arrow) and correcting it for the non-linear driving force (see text). The steady-state inactivation curve can be obtained by measuring the current at the yellow arrow as a function of the preceding test step. Note: the duration of the initial hyperpolarising pre-pulse and the test step should be adjusted depending on the kinetics of that current being measured, e.g. the duration

channels known as K^+ channel interacting proteins (KChIPs). These accessory proteins appear to be obligatory subunits for native channels (Rhodes et al. 2004). KChIPs and DPPX, another group of accessory proteins, dramatically increase the surface expression of Kv4 subunits and alter the kinetics of and recovery from inactivation of Kv4 subunits (Beck et al. 2002; Jerng et al. 2004).

The kinetics of inactivation cannot reliably distinguish between Kv1.4 and Kv4 subunits as their decay time constants can overlap, largely depending on the composition of accessory subunits. However, the recovery from inactivation of Kv4 channels is usually much more rapid, with time constants around 10s of milliseconds (Kim et al. 2005; Beck et al. 2002; Johnston et al. 2008; Amadi et al. 2007), compared to Kv1.4 with recovery rates of 100 s of milliseconds to seconds (Ruppersberg et al. 1990; Rasmusson et al. 1995; Roeper et al. 1997).

Two simple voltage protocols can therefore help to determine the subfamily responsible for native A-type currents. First, the activation curve should be attained with a simple I/V protocol with test steps from ~−100 mV, to ensure removal of inactivation (Fig. 2a). The peak current soon after the test step (red arrow in Fig. 2a) should be corrected for the non-linear driving force of K+ before being normalised and fit with a Boltzmann function (Clay 2000). With the protocol shown in Fig. 2a the steady-state inactivation curve can also be constructed by plotting the current amplitudes measured at the yellow arrow vs the voltage of the preceding test step. The activation curve will distinguish between Kv3 mediated A-type currents with positive shifted activation ranges and Kv4 or Kv1 mediated A-type currents which have more negative sub-threshold activation ranges (Fig. 2b). If necessary, the A-type current can be isolated from other endogenous currents with a subtraction protocol as shown in Johnston et al. (2008). If the A-current has a sub-threshold activation range, the rate of recovery from inactivation can be determined with a protocol similar to that shown in Fig. 2b right; rapid recovery from inactivation, a tau <~100 ms, is indicative of Kv4 subunits whereas currents displaying time constants of several hundreds of milliseconds or longer are likely to be mediated by Kv1.4 subunits.

2.2 Pharmacology

Pharmacology of ion channels can serve multiple purposes as illustrated by the holy grail of pharmacology, a selective antagonist, a molecule that will antagonise one

Fig. 2 (continued) pre-pulse should ensure complete recovery from inactivation. *Right:* The rate of recovery from inactivation can be determined with a pair of test steps of sufficient duration to allow complete inactivation of the A-current and separated by a variable delay (Δt). The time constant of recovery can then be determined by fitting an exponential to the current amplitude of the second step as a function of Δt. Note the current amplitude of the first step should be constant. Adapted from Johnston et al. (2008). (**b**) A biophysical and pharmacological procedure to aid identification of the channel mediating a native A-current (see text for further description)

kind of channel and no other. Such a molecule can be used to unambiguously determine the presence of a channel, its contribution to total current and the role of this channel in normal physiology. There are some striking examples of this with biologically derived toxins, e.g. Dendrotoxin-K is selective for any channel containing Kv1.1 subunits and blocks such channels in the 10 nM range (Wang et al. 1999; Robertson et al. 1996; Dodson et al. 2002). Unfortunately, such molecules are not always available particularly for the large diversity of Kv channels. However, less selective antagonists can still serve a useful role; when combined with other antagonists or biophysical characteristics they can aid identification of the subfamily mediating an A-type current. With these considerations in mind the following discussion largely focuses on molecules that fit these criteria.

2.2.1 Kv3 A-Type Currents

All Kv3 channels are blocked by 1 mM tetraethylammonium (TEA) which is readily washed on and off tissue (Johnston et al. 2010). TEA has an IC50 for Kv3.3 and Kv3.4 in the 100–200 μM range and acts by occluding the pore (De Miera et al. 1992; Rettig et al. 1992). TEA sensitivity in combination with a positive activation range provides a strong indication that a Kv3 subunit mediates an A-type current (Fig. 2b). Block of an A-type current by 1 mM TEA rules out Kv4 subunits which are insensitive to even 100 mM (Johnston et al. 2008, 2010), though the presence of DPPX can increase their sensitivity to TEA somewhat (Colinas et al. 2008). Kv1.4 homomers are also insensitive to TEA (Ruppersberg et al. 1990); however, heteromeric Kv1.1/Kv1.4 channels are endowed with a mix of properties from their homomeric counterparts; they display A-type kinetics with slower inactivation rates and have moderate TEA sensitivity with an IC50 of ~10 mM (Ruppersberg et al. 1990). Although 1 mM TEA can be used to unambiguously identify a high-voltage activated A-type currents, it is of limited use in exploring their functional role as many other non-A-type channels are sensitive to TEA, e.g. some Kv7 subunits and BK channels (Johnston et al. 2010). The sea anemone toxins BD-I and BDS-II were thought to be selective antagonists of Kv3.4 channels which would provide a powerful tool for elucidating the functional role of Kv3.4 A-type currents in physiology (Diochot et al. 1998). However, later detailed investigation of the interaction of BDS toxins with Kv3 subunits revealed them to act as gating modifiers and with little selectivity between Kv3 subunits (Yeung et al. 2005). BDS-I is also highly potent for Nav1.7 channels, slowing inactivation rates with a consequent broadening of action potentials and increased resurgent currents during repolarisation (Liu et al. 2012). Consequently, BDS toxins have limited potential for revealing the physiological role of Kv3 A-type currents. This also highlights a pitfall of using poorly characterised pharmacological tools; it took 14 years after their first characterisation as selective Kv3.4 blockers to realise a more complete pharmacological profile of BDS toxins. To date there are no sufficiently selective antagonists of Kv3.3 or Kv3.4 channels suitable for studying their physiological roles.

2.2.2 Kv1.4 A-Type Currents

Kv1.4 channels are relatively insensitive to TEA (Ruppersberg et al. 1990) and have a lower sensitivity (IC50 ~ 12.5 mM) to the broad spectrum K^+ channel blocker 4-AP (Stühmer et al. 1989). In fact, there is a paucity of pharmacological tools available for Kv1.4 channels, they are somewhat unique in their resistance to biological toxins which are very potent against many of the other Kv1.x members. At 1 μM the small molecule CP-339,818 shows comparative selectivity for Kv1.4 and Kv1.3 over other Kv channels, including Kv3 and Kv4 subfamilies (Nguyen et al. 1996). CP-339,818 preferentially binds to the C-type inactivated state and therefore shows a use dependent block. At concentrations greater than 1 μM off-target effects become a problem with many other channels being inhibited, e.g. Kv2.1, HCN1, Kv3.2 (Lee et al. 2008; Nguyen et al. 1996; Sforna et al. 2015). Another small molecule inhibitor, UK-78,282, has a very similar pharmacological profile to CP-339,818 (Hanson et al. 1999). To date there are no well-established selective antagonists of Kv1.4 channels suitable for studying its physiological roles, though if a contribution from Kv1.3 can be ruled out, CP-339,818 may serve this purpose.

2.2.3 Kv4 A-Type Currents

The anti-arrhythmic drug, flecainide, at 10 μM inhibits Kv4.2 & Kv4.3 leaving Kv1.4 unaffected and has been used to determine the contribution of these channels to the cardiac I_{to} current (Dixon et al. 1996; Yeola and Snyders 1997). Although flecainide can be used to distinguish between A-type currents mediated by Kv1.4 and Kv4 subunits, it also inhibits a number of other channels including the cardiac Nav1.7 channel (Ramos and O'leary 2004), ether-a-go-go related gene (ERG) K^+ channels (Paul et al. 2002) and ryanodine receptors (Mehra et al. 2014). The spider toxins, phrixotoxin 1 & 2, are potent and selective inhibitors of Kv4.2 and Kv4.3 with IC50s between 5–70 nM (Diochot et al. 1999), these toxins are gating modifiers stabilising the closed state (Chagot et al. 2004) which shifts the activation curve to more positive potentials (Diochot et al. 1999).

Kv4.2 and Kv4.3 show strong expression in many areas of the brain and heart (Serodio et al. 1996) and consequently have received the most attention. The first member of this family to be cloned, Kv4.1, shows much weaker expression in both heart and brain (Serodio et al. 1996) and as a result the pharmacological profiles of many molecules have mostly omitted this subunit. However, Kv4.1 is expressed in the suprachiasmatic nucleus (Hermanstyne et al. 2017), striatum (Song et al. 1998), basolateral amygdala (Dabrowska and Rainnie 2010) and nociceptive neurons in the dorsal root ganglion (Phuket and Covarrubias 2009). The spider toxin Heteroscodra maculata 1 (HmTx-1) is reported to inhibit all 3 Kv4 members but also inhibits Kv2.1 (Escoubas et al. 2002). Phrixotoxin-1, although only initially tested on Kv4.2 and Kv4.3, also inhibits Kv4.1 but with 3 times lower affinity; this block seems to be voltage-independent (Yunoki et al. 2014). At present phrioxtoxin-1 provides a useful tool for identifying the presence of Kv4 currents and exploring their physiological roles, without being able to distinguish between different Kv4 subunits.

3 Physiological Roles of A Currents

3.1 Neural Excitability and Spike Properties

A-type channels are rapidly activated upon depolarisation and therefore contribute to action potential repolarisation (Kim et al. 2005; Carrasquillo et al. 2012; Rudy and McBain 2001), including in the heart (Dixon et al. 1996; Yeola and Snyders 1997). Kv4 subunits are predominantly located in the somato-dendritic compartments of neurons (Trimmer 2015), which regulates back-propagation of action potentials into the dendritic tree (Fig. 3b). The sub-threshold activation range of Kv4 and Kv1.4 channels enables them to regulate intrinsic firing/bursting of neurons in many areas including the: suprachiasmatic nucleus (Hermanstyne et al. 2017), hypothalamus (Mendonça et al. 2018; Imai et al. 2019), dorsal root ganglion (Zemel et al. 2018), hippocampus (Bourdeau et al. 2007), substantia nigra (Liss et al. 2001) and cortex (Carrasquillo et al. 2012). A key factor determining the ability of A-type channels to exert influence is the availability of channels in their non-inactivated state, for example fast spiking will result in more inactivated A-type channels and consequent spike broadening (Kim et al. 2005). The steady-state inactivation curve (Fig. 2a yellow) describes the proportion of channels available at resting membrane potentials. This property is influenced by the presence of accessory subunits (Jerng et al. 1999) and can be dynamically regulated by phosphorylation (Rosenkranz et al. 2009) and Ca^{2+} (Anderson et al. 2010a). Cav3 T-type channels which are also activated at sub-threshold potentials form complexes with Kv4 channels and provide a source of Ca^{2+} that shifts the inactivation curve of Kv4 channels to more positive potentials (Anderson et al. 2010a, b), increasing their availability. The presence of Cav3 channels can therefore alter the contribution that A-type channels make to neural excitability (Heath et al. 2014) (Fig. 3).

Due to the lack of specific inhibitors of Kv1.4, Kv3.3 and Kv3.4 there are few concrete demonstrations of their physiological roles. Throughout the brain Kv1.4 is often found in axons and presynaptic terminals (Veh et al. 1995; Cooper et al. 1998) and may therefore play a role in regulating transmitter release. Kv1.4's slow recovery from inactivation means that with repetitive firing the repolarisation rate of presynaptic action potentials will reduce as Kv1.4 accumulates in its inactivated state. Slower repolarisation of the action potential causes larger presynaptic Ca^{2+} influx and an increase in release probability (Yang and Wang 2006), suggesting that Kv1.4 may play a role in short-term synaptic plasticity. Consistent with this idea, knockdown of Kv1.4 in the hippocampus reduced paired pulse facilitation (Meiri et al. 1998), a form of presynaptic short-term plasticity. Ca^{2+} can also regulate the rate of recovery from inactivation of Kv1.4 in a CamKinase II dependent manner (Roeper et al. 1997), providing scope for regulation of such short-term plasticity. Kv3.3 and Kv3.4 are also located in axons and synaptic terminals (Laube et al. 1996; Ishikawa et al. 2003; Trimmer 2015) and could have similar roles.

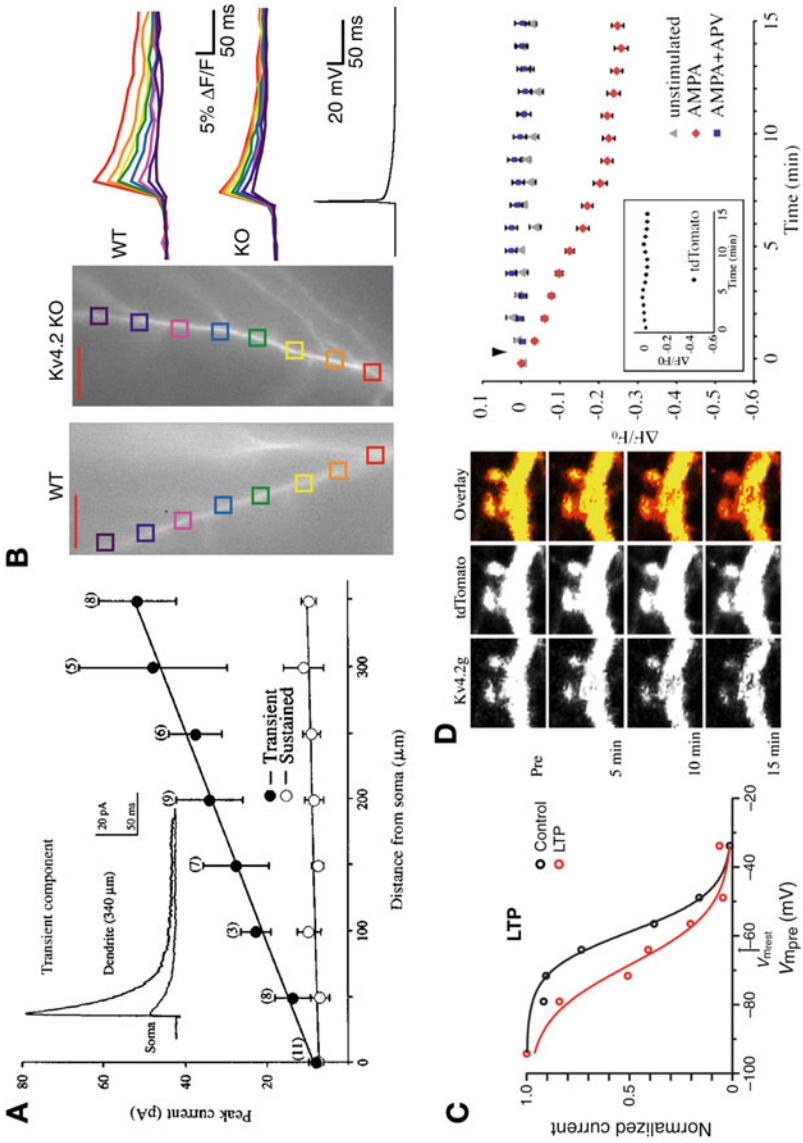

Fig. 3 Dendritic Kv4 A-type channels regulate and are a locus of plasticity in hippocampal CA1 neurons. (**a**) Dendritic recordings of Kv4 A-type K^+ currents demonstrate a gradient of current that increases with distance from soma adapted from Hoffman et al. (1997) with permission. (**b**) Imaging of fura-2 loaded CA1

neurons reveal attenuation of back-propagating action potential evoked Ca^{2+} transients. This attenuation is dramatically reduced when Kv4.2 is absent, adapted from Chen et al. (2006, Copyright 2006, Society for Neuroscience) with permission. (**c**) The steady-state inactivation curve of dendritically located Kv4 channels is shifted to more hyperpolarised potentials after induction of LTP with theta burst stimuli. Note that this decreases the available Kv4 current at resting membrane potentials by ~50%, adapted from Frick et al. (2004) with permission. (**d**) Fluorescently tagged A-type channels (Kv4.2 g) are trafficked from the membrane following activation of synaptic receptors, adapted from Kim et al. (2007) with permission

3.2 Dendritic Integration and LTP

In hippocampal pyramidal neurons the density of Kv4 channels increases from the soma towards the distal dendrites (Fig. 3a), this gradient depends on expression of the accessory subunit DPP6 (Sun et al. 2011). The gradient of Kv4 channels controls the ability of action potentials to back-propagate and invade the dendritic tree (Hoffman et al. 1997; Johnston et al. 2000) (Fig. 3b), a phenomenon required for induction of synaptic plasticity in these cells (Magee and Johnston 1997; Buchanan and Mellor 2007). Consistent with this idea, action potentials more readily back-propagate into the dendritic tree when Kv4.2 channels are knocked down (Fig. 3b) and consequently the threshold for LTP induction is lowered (Chen et al. 2006). Kv4 channels are also a locus of plasticity in CA1 dendrites being targeted by mitogen-activated protein kinase (Rosenkranz et al. 2009). Induction of LTP results in a shift in the steady-state inactivation of Kv4 channels to more negative-potentials (Fig. 3c) (Frick et al. 2004) and internalisation of channels (Fig. 3d) (Kim et al. 2007), effects which are localised to the site of synaptic input. Both of these changes reduce the available A-type current and consequently increase dendritic excitability and therefore the likelihood of further plasticity.

A similar attenuation of back-propagating action potentials by A-type currents is observed in the lateral dendrites of mitral cells of the olfactory bulb (Margrie et al. 2001; Christie and Westbrook 2003), this influences the extent of lateral dendrodendritic interactions with inhibitory granule cells. A-type K^+ channels also influence the inhibitory side of the reciprocal synapse between granule and mitral cell dendrites. Granule cells receive excitation from mitral cell dendrites via AMPA and NMDA receptors and provide GABAergic feedback inhibition. The A-type current in granule cells attenuates excitation for the fast AMPA component; spiking and feedback inhibition then occur with a delay, following the time course of the NMDA component (Schoppa and Westbrook 1999).

The varied biophysics, sub-cellular distributions and dynamic modulation of A-type K^+ channels enable them to perform a multitude of roles in regulating cellular excitability. Large strides have been made in the 60 years since their discovery but much still remains to be elucidated.

References

Amadi CC, Brust RD, Skerritt MR, Campbell DL (2007) Regulation of Kv4.3 closed state inactivation and recovery by extracellular potassium and intracellular KChIP2b. Channels (Austin) 1:305–314

Anderson D, Mehaffey WH, Iftinca M, Rehak R, Engbers JD, Hameed S, Zamponi GW, Turner RW (2010a) Regulation of neuronal activity by Cav3-Kv4 channel signaling complexes. Nat Neurosci 13:333–337

Anderson D, Rehak R, Hameed S, Mehaffey WH, Zamponi GW, Turner RW (2010b) Regulation of the KV4.2 complex by CaV3.1 calcium channels. Channels (Austin) 4:163–167

Bähring R, Boland LM, Varghese A, Gebauer M, Pongs O (2001) Kinetic analysis of open-and closed-state inactivation transitions in human Kv4. 2 A-type potassium channels. J Physiol 535:65

Beck EJ, Covarrubias M (2001) Kv4 channels exhibit modulation of closed-state inactivation in inside-out patches. Biophys J 81:867–883

Beck EJ, Bowlby M, An WF, Rhodes KJ, Covarrubias M (2002) Remodelling inactivation gating of Kv4 channels by KChIP1, a small-molecular-weight calcium-binding protein. J Physiol 538:691–706

Bett GCL, Rasmusson RL (2004) Inactivation and recovery in Kv1.4 K+ channels: lipophilic interactions at the intracellular mouth of the pore. J Physiol Lond 556:109–120

Bourdeau ML, Morin F, Laurent CE, Azzi M, Lacaille JC (2007) Kv4.3-mediated A-type K+ currents underlie rhythmic activity in hippocampal interneurons. J Neurosci 27:1942–1953

Buchanan KA, Mellor JR (2007) The development of synaptic plasticity induction rules and the requirement for postsynaptic spikes in rat hippocampal CA1 pyramidal neurones. J Physiol 585:429–445

Carrasquillo Y, Burkhalter A, Nerbonne JM (2012) A-type K+ channels encoded by Kv4.2, Kv4.3 and Kv1.4 differentially regulate intrinsic excitability of cortical pyramidal neurons. J Physiol 590:3877–3890

Chagot B, Escoubas P, Villegas E, Bernard C, Ferrat G, Corzo G, Lazdunski M, Darbon H (2004) Solution structure of Phrixotoxin 1, a specific peptide inhibitor of Kv4 potassium channels from the venom of the theraphosid spider Phrixotrichus auratus. Protein Sci 13:1197–1208

Chen X, Yuan L-L, 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

Christie JM, Westbrook GL (2003) Regulation of backpropagating action potentials in mitral cell lateral dendrites by A-type potassium currents. J Neurophysiol 89:2466–2472

Clay JR (2000) Determining K+ channel activation curves from K+ channel currents. Eur Biophys J 29:555–557

Coetzee WA, Amarillo Y, Cu JOANNA, Chow ALAN, Lau DAVID, McCormack TOM, Morena HERMAN, Nadal MARCELAS, Ozaita ANDER, Pountney DAVID, Saganich MICHAEL, de Miera ELEAZARVEGA-SAENZ, Rudy BERNARDO (1999) Molecular diversity of K+ channels. Ann N Y Acad Sci 868:233–255

Colinas O, Pérez-Carretero FD, López-López JR, Pérez-García MT (2008) A role for DPPX modulating external TEA sensitivity of Kv4 channels. J Gen Physiol 131:455–471

Connor JA, Stevens CF (1971) Voltage clamp studies of a transient outward membrane current in gastropod neural somata. J Physiol 213:21

Cooper EC, Milroy A, Jan YN et al (1998) Presynaptic localization of Kv1. 4-containing A-type potassium channels near excitatory synapses in the hippocampus. J Neurosci 18:965–974

Dabrowska J, Rainnie DG (2010) Expression and distribution of Kv4 potassium channel subunits and potassium channel interacting proteins in subpopulations of interneurons in the basolateral amygdala. Neuroscience 171:721–733

De Miera EV-S, Moreno H, Fruhling D, Kentros C, Rudy B (1992) Cloning of ShIII (Shaw-like) cDNAs encoding a novel high-voltage-activating, TEA-sensitive, type-A K+ channel. Proc R Soc Lond Ser B Biol Sci 248:9–18

Diochot S, Schweitz H, Béress L, Lazdunski M (1998) Sea anemone peptides with a specific blocking activity against the fast inactivating potassium channel Kv3.4. J Biol Chem 273:6744–6749

Diochot S, Drici M, Moinier D, Fink M, Lazdunski M (1999) Effects of phrixotoxins on the Kv4 family of potassium channels and implications for the role of Ito1 in cardiac electrogenesis. Br J Pharmacol 126:251–263

Dixon JE, Shi W, Wang HS, McDonald C, Yu H, Wymore RS, Cohen IS, McKinnon D (1996) Role of the Kv4.3 K+ channel in ventricular muscle. A molecular correlate for the transient outward current. Circ Res 79:659–668

Dodson PD, Barker MC, Forsythe ID (2002) Two heteromeric Kv1 potassium channels differentially regulate action potential firing. J Neurosci 22:6953–6961
Escoubas P, Diochot S, Celerier M-L, Nakajima T, Lazdunski M (2002) Novel tarantula toxins for subtypes of voltage-dependent potassium channels in the Kv2 and Kv4 subfamilies. Mol Pharmacol 62:48–57
Frick A, Magee J, Johnston D (2004) LTP is accompanied by an enhanced local excitability of pyramidal neuron dendrites. Nat Neurosci 7:126–135
Hagiwara S, Kusano K, Saito N (1961) Membrane changes of Onchidium nerve cell in potassium-rich media. J Physiol 155:470
Hanson DC, Nguyen A, Mather RJ, Rauer H, Koch K, Burgess LE, Rizzi JP, Donovan CB, Bruns MJ, Canniff PC (1999) UK-78,282, a novel piperidine compound that potently blocks the Kv1. 3 voltage-gated potassium channel and inhibits human T cell activation. Br J Pharmacol 126:1707–1716
Heath NC, Rizwan AP, Engbers JD, Anderson D, Zamponi GW, Turner RW (2014) The expression pattern of a Cav3-Kv4 complex differentially regulates spike output in cerebellar granule cells. J Neurosci 34:8800–8812
Hermanstyne TO, Granados-Fuentes D, Mellor RL, Herzog ED, Nerbonne JM (2017) Acute knockdown of Kv4.1 regulates repetitive firing rates and clock gene expression in the suprachiasmatic nucleus and daily rhythms in locomotor behavior. eNeuro 4
Hoffman DA, Magee JC, Colbert CM, Johnston D (1997) K+ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. Nature 387:869–875
Hoshi T, Zagotta WN, Aldrich RW (1990) Biophysical and molecular mechanisms of shaker potassium channel inactivation. Science 250:533–538
Hoshi T, Zagotta WN, Aldrich RW (1991) Two types of inactivation in shaker K+ channels: effects of alterations in the carboxy-terminal region. Neuron 7:547–556
Imai R, Yokota S, Horita S, Ueta Y, Maejima Y, Shimomura K (2019) Excitability of oxytocin neurons in paraventricular nucleus is regulated by voltage-gated potassium channels Kv4.2 and Kv4.3. Biosci Biotechnol Biochem 83:202–211
Ishikawa T, Nakamura Y, Saitoh N, Li W-B, Iwasaki S, Takahashi T (2003) Distinct roles of Kv1 and Kv3 potassium channels at the Calyx of held presynaptic terminal. J Neurosci 23:10445–10453
Jerng HH, Shahidullah M, Covarrubias M (1999) Inactivation gating of Kv4 potassium channels: molecular interactions involving the inner vestibule of the pore. J Gen Physiol 113:641–660
Jerng HH, Pfaffinger PJ, Covarrubias M (2004) Molecular physiology and modulation of somatodendritic A-type potassium channels. Mol Cell Neurosci 27:343–369
Johnston D, Hoffman DA, Magee JC, Poolos NP, Watanabe S, Colbert CM, Migliore M (2000) Dendritic potassium channels in hippocampal pyramidal neurons. J Physiol 525(Pt 1):75–81
Johnston J, Griffin SJ, Baker C, Forsythe ID (2008) Kv4 (A-type) potassium currents in the mouse medial nucleus of the trapezoid body. Eur J Neurosci 27:1391–1399
Johnston J, Forsythe ID, Kopp-Scheinpflug C (2010) Going native: voltage-gated potassium channels controlling neuronal excitability. J Physiol 588:3187–3200
Kim J, Wei D-S, Hoffman DA (2005) Kv4 potassium channel subunits control action potential repolarization and frequency-dependent broadening in rat hippocampal CA1 pyramidal neurones. J Physiol 569:41–57
Kim J, Jung SC, Clemens AM, Petralia RS, Hoffman DA (2007) Regulation of dendritic excitability by activity-dependent trafficking of the A-type K+ channel subunit Kv4.2 in hippocampal neurons. Neuron 54:933–947
Kuo Y-L, Cheng J-K, Hou W-H, Chang Y-C, Du P-H, Jian J-J, Rau R-H, Yang J-H, Lien C-C, Tsaur M-L (2017) K+ channel modulatory subunits KChIP and DPP participate in Kv4-mediated mechanical pain control. J Neurosci 37:4391–4404
Laube G, Röper J, Pitt JC, Sewing S, Kistner U, Garner CC, Pongs O, Veh RW (1996) Ultrastructural localization of shaker-related potassium channel subunits and synapse-associated protein 90 to septate-like junctions in rat cerebellar Pinceaux. Brain Res Mol Brain Res 42:51–61

Lee YT, Vasilyev DV, Shan QJ, Dunlop J, Mayer S, Bowlby MR (2008) Novel pharmacological activity of loperamide and CP-339,818 on human HCN channels characterized with an automated electrophysiology assay. Eur J Pharmacol 581:97–104

Liss B, Franz O, Sewing S, Bruns R, Neuhoff H, Roeper J (2001) Tuning pacemaker frequency of individual dopaminergic neurons by Kv4.3L and KChip3.1 transcription. EMBO J 20:5715–5724

Liu P, Jo S, Bean BP (2012) Modulation of neuronal sodium channels by the sea anemone peptide BDS-I. J Neurophysiol 107:3155–3167

MacKinnon R, Aldrich RW, Lee AW (1993) Functional stoichiometry of shaker potassium channel inactivation. Science 262:757–759

Magee JC, Johnston D (1997) A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. Science 275:209–213

Margrie TW, Sakmann B, Urban NN (2001) Action potential propagation in mitral cell lateral dendrites is decremental and controls recurrent and lateral inhibition in the mammalian olfactory bulb. Proc Natl Acad Sci U S A 98:319–324

Mehra D, Imtiaz MS, van Helden DF, Knollmann BC, Laver DR (2014) Multiple modes of ryanodine receptor 2 inhibition by flecainide. Mol Pharmacol 86:696–706

Meiri N, Sun MK, Segal Z, Alkon DL (1998) Memory and long-term potentiation (LTP) dissociated: normal spatial memory despite CA1 LTP elimination with Kv1.4 antisense. Proc Natl Acad Sci U S A 95:15037–15042

Mendonça PRF, Kyle V, Yeo SH, Colledge WH, Robinson HPC (2018) Kv4.2 channel activity controls intrinsic firing dynamics of arcuate kisspeptin neurons. J Physiol 596:885–899

Molineux ML, Fernandez FR, Mehaffey WH, Turner RW (2005) A-type and T-type currents interact to produce a novel spike latency-voltage relationship in cerebellar stellate cells. J Neurosci 25:10863–10873

Nguyen A, Kath JC, Hanson DC, Biggers MS, Canniff PC, Donovan CB, Mather RJ, Bruns MJ, Rauer H, Aiyar J, Lepple-Wienhues A, Gutman GA, Grissmer S, Cahalan MD, Chandy KG (1996) Novel nonpeptide agents potently block the C-type inactivated conformation of Kv1.3 and suppress T cell activation. Mol Pharmacol 50:1672–1679

Paul AA, Witchel HJ, Hancox JC (2002) Inhibition of the current of heterologously expressed HERG potassium channels by flecainide and comparison with quinidine, propafenone and lignocaine. Br J Pharmacol 136:717–729

Phuket TR, Covarrubias M (2009) Kv4 channels underlie the subthreshold-operating A-type K-current in nociceptive dorsal root ganglion neurons. Front Mol Neurosci 2:3

Ramos E, O'leary ME (2004) State-dependent trapping of flecainide in the cardiac sodium channel. J Physiol 560:37–49

Rasmusson RL, Morales MJ, Castellino RC, Zhang Y, Campbell DL, Strauss HC (1995) C-type inactivation controls recovery in a fast inactivating cardiac K+ channel (Kv1. 4) expressed in Xenopus oocytes. J Physiol 489:709–721

Rettig J, Wunder F, Stocker M, Lichtinghagen R, Mastiaux F, Beckh S, Kues W, Pedarzani P, Schröter KH, Ruppersberg JP (1992) Characterization of a Shaw-related potassium channel family in rat brain. EMBO J 11:2473–2486

Rettig J, Heinemann SH, Wunder F, Lorra C, Parcej DN, Dolly JO, Pongs O (1994) Inactivation properties of voltage-gated K+ channels altered by presence of β-subunit. Nature 369:289–294

Rhodes KJ, Carroll KI, Sung MA, Doliveira LC, Monaghan MM, Burke SL, Strassle BW, Buchwalder L, Menegola M, Cao J, An WF, Trimmer JS (2004) KChIPs and Kv4 alpha subunits as integral components of A-type potassium channels in mammalian brain. J Neurosci 24:7903–7915

Robertson B, Owen D, Stow J, Butler C, Newland C (1996) Novel effects of dendrotoxin homologues on subtypes of mammalian Kv1 potassium channels expressed in Xenopus oocytes. FEBS Lett 383:26–30

Roeper J, Lorra C, Pongs O (1997) Frequency-dependent inactivation of mammalian A-type K+ channel KV1.4 regulated by Ca2+/calmodulin-dependent protein kinase. J Neurosci 17:3379–3391

Rosenkranz JA, Frick A, Johnston D (2009) Kinase-dependent modification of dendritic excitability after long-term potentiation. J Physiol 587:115–125

Rudy B, McBain CJ (2001) Kv3 channels: voltage-gated K+ channels designed for high-frequency repetitive firing. Trends Neurosci 24:517–526

Rudy B, Chow A, Lau D, Amarillo Y, Ozaita A, Saganich M, Moreno H, Nadal MS, Hernandez-Pineda RICARDO, Hernandez-Cruz ARTURO (1999) Contributions of Kv3 channels to neuronal excitability. Ann N Y Acad Sci 868:304–343

Ruppersberg JP, Schröter KH, Sakmann B, Stocker M, Sewing S, Pongs O (1990) Heteromultimeric channels formed by rat brain potassium-channel proteins. Nature 345:535–537

Schoppa NE, Westbrook GL (1999) Regulation of synaptic timing in the olfactory bulb by an A-type potassium current. Nat Neurosci 2:1106–1113

Serodio P, Vega-Saenz de Miera E, Rudy B (1996) Cloning of a novel component of A-type K+ channels operating at subthreshold potentials with unique expression in heart and brain. J Neurophysiol 75:2174–2179

Sforna L, D'Adamo MC, Servettini I, Guglielmi L, Pessia M, Franciolini F, Catacuzzeno L (2015) Expression and function of a CP339,818-sensitive K+ current in a subpopulation of putative nociceptive neurons from adult mouse trigeminal ganglia. J Neurophysiol 113:2653–2665

Shahidullah M, Covarrubias M (2003) The link between ion permeation and inactivation gating of Kv4 potassium channels. Biophys J 84:928–941

Shevchenko T, Teruyama R, Armstrong WE (2004) High-threshold, Kv3-like potassium currents in magnocellular neurosecretory neurons and their role in spike repolarization. J Neurophysiol 92:3043–3055

Song W-J, Tkatch T, Baranauskas G, Ichinohe N, Kitai ST, Surmeier DJ (1998) Somatodendritic depolarization-activated potassium currents in rat neostriatal cholinergic interneurons are predominantly of the A type and attributable to coexpression of Kv4. 2 and Kv4. 1 subunits. J Neurosci 18:3124–3137

Stühmer W, Ruppersberg JP, Schröter KH, Sakmann B, Stocker M, Giese KP, Perschke A, Baumann A, Pongs O (1989) Molecular basis of functional diversity of voltage-gated potassium channels in mammalian brain. EMBO J 8:3235–3244

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

Trimmer JS (2015) Subcellular localization of K+ channels in mammalian brain neurons: remarkable precision in the midst of extraordinary complexity. Neuron 85:238–256

Veh RW, Lichtinghagen R, Sewing S, Wunder F, Grumbach IM, Pongs O (1995) Immunohistochemical localization of five members of the Kv1 channel subunits: contrasting subcellular locations and neuron-specific co-localizations in rat brain. Eur J Neurosci 7:2189–2205

Wang FC, Parcej DN, Dolly JO (1999) Subunit compositions of Kv1.1-containing K+channel subtypes fractionated from rat brain using dendrotoxins. Eur J Biochem 263:230–237

Watanabe S, Hoffman DA, Migliore M, Johnston D (2002) Dendritic K+ channels contribute to spike-timing dependent long-term potentiation in hippocampal pyramidal neurons. Proc Natl Acad Sci U S A 99:8366–8371

Weiser M, de Miera EV-S, Kentros C, Moreno H, Franzen L, Hillman D, Baker H, Rudy B (1994) Differential expression of Shaw-related K+ channels in the rat central nervous system. J Neurosci 14:949–972

Yang Y-M, Wang L-Y (2006) Amplitude and kinetics of action potential-evoked Ca2+ current and its efficacy in triggering transmitter release at the developing Calyx of held Synapse. J Neurosci 26:5698–5708. https://doi.org/10.1523/JNEUROSCI.4889-05.2006

Yeola SW, Snyders DJ (1997) Electrophysiological and pharmacological correspondence between Kv4.2 current and rat cardiac transient outward current. Cardiovasc Res 33:540–547

Yeung SY, Thompson D, Wang Z, Fedida D, Robertson B (2005) Modulation of Kv3 subfamily potassium currents by the sea anemone toxin BDS: significance for CNS and biophysical studies. J Neurosci 25:8735–8745

Yunoki T, Takimoto K, Kita K, Funahashi Y, Takahashi R, Matsuyoshi H, Naito S, Yoshimura N (2014) Differential contribution of Kv4-containing channels to A-type, voltage-gated potassium currents in somatic and visceral dorsal root ganglion neurons. J Neurophysiol 112:2492–2504

Zemel BM, Ritter DM, Covarrubias M, Muqeem T (2018) A-type K_V channels in dorsal root ganglion neurons: diversity, function, and dysfunction. Front Mol Neurosci 11:253

Zhou M, Morais-Cabral JH, Mann S, MacKinnon R (2001) Potassium channel receptor site for the inactivation gate and quaternary amine inhibitors. Nature 411:657–661