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Distinctive role of $K_V1.1$ subunit in the biology and functions of low threshold K^+ channels with implications for neurological disease

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ABSTRACT

The diversity of pore-forming subunits of K_V1 channels ($K_V1.1$–$K_V1.8$) affords their physiological versatility and predicts a range of functional impairments resulting from genetic aberrations. Curiously, identified so far human neurological conditions associated with dysfunctions of K_V1 channels have been linked exclusively to mutations in the *KCNA1* gene encoding for the $K_V1.1$ subunit. The absence of phenotypes related to irregularities in other subunits, including the prevalent $K_V1.2$ subunit of neurons is highly perplexing given that deletion of the corresponding *kcna2* gene in mouse models precipitates symptoms reminiscent to those of $K_V1.1$ knockouts. Herein, we critically evaluate the molecular and biophysical characteristics of the $K_V1.1$ protein in comparison with others and discuss their role in the greater penetrance of *KCNA1* mutations in humans leading to the neurological signs of episodic ataxia type 1 (EA1). Future research and interpretation of emerging data should afford new insights towards a better understanding of the role of $K_V1.1$ in integrative mechanisms of neurons and synaptic functions under normal and disease conditions.

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Abbreviations: AA, amino acid; α-DTX, alpha dendrotoxin; DTX_K, dendrotoxin K; EA-1, episodic ataxia type-1; ER, endoplasmic reticulum; ERR, endoplasmic reticular retention; FTS, forward trafficking signal; HGNC, HUGO Genetic Nomenclature Committee; IS, initial segment; IUPHAR, International Union of Basic and Clinical Pharmacology; JXP, juxta-paranode; *KCNA1*, human gene encoding $K_V1.1$ subunit of potassium channel; *kcna2*, mouse gene encoding $K_V1.2$ subunit of potassium channel; *kcna4*, mouse gene encoding $K_V1.4$ subunit of potassium channel; K_V, voltage-gated potassium channels; $K_V\beta$, beta subunit of voltage-gated potassium channels; MBP, myelin basic protein; N, node of Ranvier; PAUP, phylogenetic analysis using parsimony; S, soma; SD, somato-dendritic; T1, domain; TM, trans-membrane; $V_{1/2}$, half activation voltage.

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1. Introduction

K_V1 voltage-gated potassium channels are integral membrane proteins, which are of major importance in adjusting the bio-electrical activity of neurons. Through an ion conductive pore, they mediate the outflow of K^+ across the lipid bilayer of the surface membrane in response to depolarization, regulating the resting membrane potential and excitability, timing and frequency of action potentials during repetitive spike trains, and the release of neurotransmitters at axon terminals (Hille, 2001; Yellen, 2002; Clark et al., 2009; Kuba et al., 2015). The functional versatility of K_V1 channels arises to a large extent from their molecular diversity and fine regulation. The conductive pore of the channel complex is formed through oligomerization of four α subunits, which are multi-domain proteins composed of six membrane spanning segments (S1–S6) linked via hydrophilic intra- and extra-cellular loops. Since cloning of the first K_V1 channel gene in *Drosophila* affected by *Shaker* mutations (Papazian et al., 1987), eight members of the family ($K_V1.1$–$K_V1.8$) encoded by corresponding *KCNA1-KCNA8* genes have been identified and functionally characterized (Kamb et al., 1988; Pongs et al., 1988; Tempel et al., 1988; Gutman et al., 2005; Jan & Jan, 2012) (Fig. 1). In neurons, typically different K_V1 α subunits co-assemble to form hetero-tetramers, with channels made of four identical subunits (homo-tetramers) also described (Stuhmer et al., 1989; Parcej et al., 1992; Wang et al., 1993; Dolly & Parcej, 1996; Coleman et al., 1999). Studies of K_V1 homo-tetramers in expression systems, in addition to commonalities have revealed differences in the biophysical and pharmacological properties, which in hetero-tetramers equilibrate between contributing subunits (Akhtar et al., 2002; Sokolov et al., 2007; Bagchi et al., 2014). In addition to electrophysiological properties, the molecular composition of K_V1 channels is known to control their mobility and targeting to specific neuronal compartments with surface expression (Manganas & Trimmer, 2000; Manganas et al., 2001b; Heusser & Schwappach, 2005; Vacher et al., 2007b; Vacher et al., 2008).

Although in heterologous systems all combinations of K_V1 subunits yield K^+ currents, native channels from crude forebrain extracts and synaptosomes have revealed a predominance of certain subunits and their combinations over others (Koch et al., 1997; Shamotienko et al., 1997; Coleman et al., 1999; Wang et al., 1999). These data suggests that the assembly of K_V1 channels within intact neurons is not promiscuous but is tightly regulated, and predict a greater role for molecular aberrations in prevalent subunits in the generation of neurological phenotypes associated with *KCNA* mutations. Surprisingly and notwithstanding of the similar distribution with comparable expression levels of $K_V1.2$, $K_V1.4$, $K_V1.6$ and $K_V1.1$ throughout the mammalian nervous system, linkage studies of human K_V1 channelopathies, which are characterized by bouts of cerebellar ataxia with motor deficits, vertigo and occasions of sporadic seizures (fits of epilepsy), and defined clinically as episodic ataxia type 1 (EA1) have mapped all related mutations to the *KCNA1* gene (12p13) encoding for $K_V1.1$ subunit (Kullmann et al., 2001; Kullmann, 2002; Imbrici et al., 2006; Rajakulendran et al., 2007). The absence of $K_V1.1$ homo-tetramers in the mammalian brain along with distinct neurological signs in *kcna2* and *kcna4* null mice (London et al., 1998; Smart et al., 1998; Brew et al., 2003; Brew et al., 2007) raises the possibility of special traits of $K_V1.1$ subunit, which afford the greater penetrance of *KCNA1* mutations. Because EA1 is a dominantly inherited disease and $K_V1.1$ co-assembles with others to produce channels, it is expected that a defective $K_V1.1$ will interfere with the functions of K_V1 channels to which they contribute. Reports from expression systems showed that co-expression of mutant $K_V1.1$ with wild type yield currents with intermediate biophysical characteristics (Zerr et al., 1998b; D'Adamo et al., 1999; Spauschus et al., 1999; Zuberi et al., 1999; Eunson et al., 2000), an observation which confirms not only the ability of the faulty $K_V1.1$ to form channels but also yield anomalous integral membrane currents. Below, we overview the molecular and biophysical properties of the $K_V1.1$ subunit in comparison with others, and the possible mechanistic grounds for the disruptive effects of EA1 mutations on K_V1 channel functions and integrative mechanisms of the brain.

2. Molecular partners of the $K_V1.1$ subunit in native K^+ channels

In neurons, K_V1 channels are produced by oligomerization of four pore-forming α and an equal amount of cytoplasmic $K_V\beta$ ($K_V\beta1$, β2 and β3) subunits. Although in expression systems K_V1 α subunits co-assemble randomly to yield K^+ currents, native channels from mammalian brain tissue are known to prefer certain combinations of α subunits over others (Isacoff et al., 1990; Ruppersberg et al., 1990; Rettig et al., 1994; Koch et al., 1997; Rhodes et al., 1997; Shamotienko et al., 1997). Analysis of native K_V1 channels isolated from total cerebral extracts as

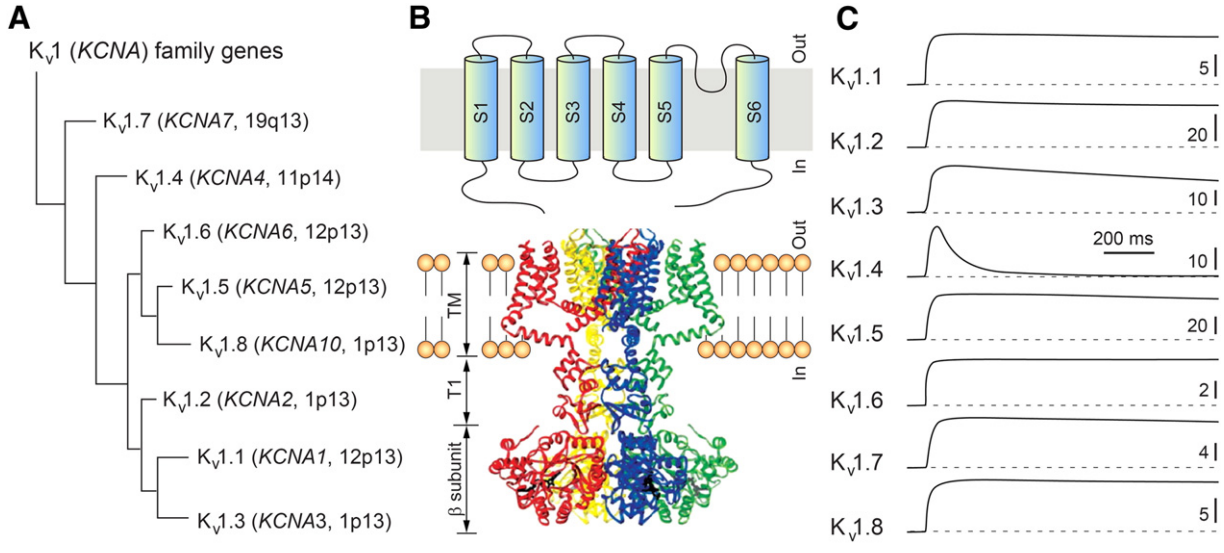

Fig. 1. Family of *Shaker*-related K_V1 channels: an overview. **(A)** Phylogenetic tree of the gene family of K_V1 channel subunits: amino acid sequence alignment of the human K_V1 channel proteins were generated using CLUSTALW and analyzed by maximum parsimony with PAUP. The IUPHAR and HGNC names are shown together with the genes chromosomal localization. **(B)** Schematic illustration of the structure of the K_V1 α subunit (top) with crystal structure of $K_V1.2$–β_2 subunit complex: stereo-view of a ribbon representation from the side (bottom). Four K_V1 α subunits assembled into the channel pore (including the T-domain (T1)) and four associated cytoplasmic β_2 subunits are presented in different color. TM corresponds to the integral membrane component of the complex (adapted with permission from Long et al., 2005). **(C)** Representative recordings of K_V1 currents mediated via $K_V1.1$ – $K_V1.8$ subunits expressed in heterologous expression systems; adapted with permission from (Heinemann et al., 1996; Tian et al., 2002; Finol-Urdaneta et al., 2006). Current amplitude units—μA.