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Review

Clustered K^+ channel complexes in axons

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ABSTRACT

Voltage-gated K^+ (Kv) channels regulate diverse neuronal properties including action potential threshold, amplitude, and duration, frequency of firing, neurotransmitter release, and resting membrane potential. In axons, Kv channels are clustered at a variety of functionally important sites including axon initial segments, juxtaparanodes of myelinated axons, nodes of Ranvier, and cerebellar basket cell terminals. These channels are part of larger protein complexes that include cell adhesion molecules and scaffolding proteins. These interacting proteins play important roles in recruiting K^+ channels to distinct axonal domains. Here, I review the composition, functions, and mechanism of localization of these K^+ channel complexes in axons.

Contents

1. Introduction

Neurons are morphologically complex cells with two major structural and functional domains: the somatodendritic and axonal domains. The somatodendritic domain receives and integrates synaptic input, while the axonal domain is responsible for initiation and propagation of the action potential. The excitable properties of each of these domains depend not only on the kinds of ion channels expressed in the plasma membrane, but also on the location of the channels and receptors distributed throughout the plasma membrane. For example, ligand-gated ion channels are strategically located and enriched in membrane domains opposite the presynaptic terminal where neurotransmitter is released. Among the many different voltage-gated ion channels expressed in the nervous system, the voltage-gated K^+ (Kv) channels have been a favorite of neurobiologists due to their highly restricted locations in axons, their important contributions to neuronal excitability, their diverse mechanisms of clustering, and their experimental tractability as compared to much larger axonal ion channels (e.g. Na^+ and Ca^{2+} channels). Furthermore, the importance of these channels is reflected in the fact that mutations or diseases that disrupt clustering, localization, or composition of axonal Kv channel complexes compromises nervous system function, leading to conduction block, episodic ataxia, and/or epilepsies [11,14,29,31,32].

In axons, four main Kv channel protein complexes have been described. These consist of Kv1 (Kv1.1, Kv1.2, and Kv1.4), Kv2 (Kv2.1 and Kv2.2), Kv3.1b, or Kv7 (Kv7.2 and Kv7.3, but also referred to as KCNQ2 and KCNQ3, respectively (in this review I will refer to

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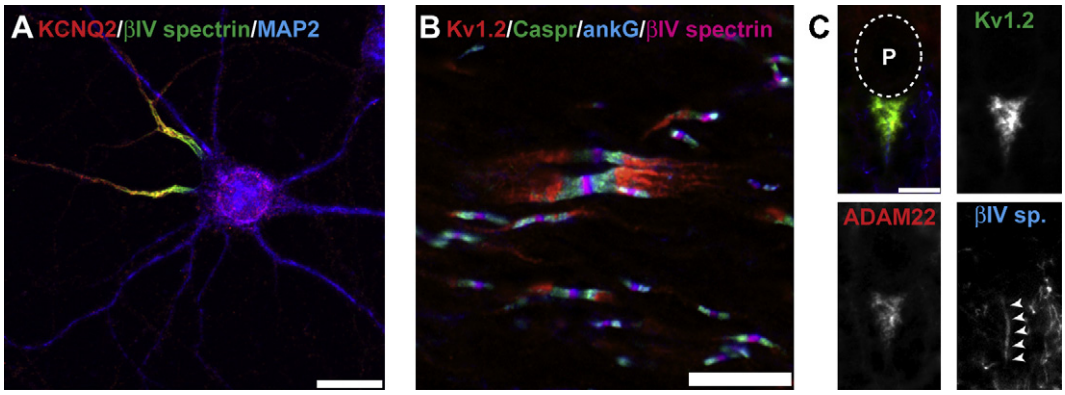

Fig. 1. Kv channels are clustered at many different axonal locations. (A) KCNQ2 K^+ channels (red) are clustered at axon initial segments where they colocalize with the AIS-restricted cytoskeletal scaffolding protein βIV spectrin (green). The microtubule associated protein 2 (MAP2) defines the somatodendritic domain. (B) Kv1 channels (red) are clustered at juxtaparanodes beneath the myelin sheath and on each side of nodes of Ranvier. Kv1 channels are excluded from paranodal regions labeled by Caspr (green), and nodes of Ranvier labeled by ankG (blue) and βIV spectrin (magenta). (C) Basket cell terminals in the cerebellum are highly enriched in Kv1.2 (green) and ADAM22 (red), and envelope the AIS (labeled by βIV spectrin, blue). The location of the Purkinje neuron cell body (P) is indicated by the dotted line. Scale bars: (A) 20 μm; (B, C) 10 μm.

these channels as KCNQ2 and KCNQ3)) channel subunits [52]. Here, I will discuss what we know about the locations, functions, molecular compositions, and mechanisms of clustering for each of these different Kv channel complexes in axons.

2. KCNQ2/3 K^+ channels

KCNQ K^+ channels are broadly expressed, and mutations in these channels lead to a variety of channelopathies including epilepsy, deafness, and disrupted cardiac function [23]. In neurons, KCNQ2 and KCNQ3 channels have been reported at axon initial segments (AIS; Fig. 1A) and nodes of Ranvier (Fig. 1B) [8,36]. Physiologically, these channels underlie the so-called M-current, and play essential roles in regulating neuronal and axonal excitability through their actions at nodes and initial segments [3,47]. Mutations in KCNQ2 and KCNQ3 lead to neonatal epilepsies, including benign neonatal familial convulsions (BNFC).

In axons, the only known binding partner for KCNQ2 and KCNQ3 is the large cytoskeletal scaffolding protein ankyrinG (ankG) [36], and KCNQ2/3 colocalizes with ankG at both the AIS and nodes. AnkG is highly enriched at nodes of Ranvier and AIS and plays essential roles in both the initial assembly of the AIS and long-term maintenance of neuronal polarity, i.e. the distinction between axonal and somatodendritic domains. However, the mechanism responsible for clustering ankG at the AIS remains unknown (Fig. 2). AnkG binds directly to a variety of Na^+ channels (including Nav1.1, Nav1.2 and Nav1.6) which underlie the initiation of the action potential, cell adhesion molecules (NrCAM and neurofascin-186), and other cytoskeletal and scaffolding proteins (βIV spectrin) enriched at the AIS [35]. Indeed, experiments to silence expression of ankG demonstrate that its loss results in failure to recruit all other AIS proteins, including KCNQ2 and KCNQ3 [22,36].

The clustering of Na^+ channels at the AIS was shown to depend on an AIS targeting motif found in the II–III linker of Na^+ channels [13,27]. Pan et al. [36], noticed that a similar motif is located near the C-terminus of KCNQ2 and KCNQ3 channels. They then demonstrated that this sequence does in fact mediate the channel's interaction with ankG. In a remarkable follow-up paper, Hill et al. [17], further analyzed this AIS targeting sequence in both Na^+ and KCNQ channels and found that the sequence evolved first in basal chordates to permit Na^+ channel clustering and retention at the AIS. They then demonstrated that it was not until much later in evolution (about the time myelin evolved), that the KCNQ2/3 channels acquired the AIS targeting motif. They were able to show that this sequence evolved independently, providing the first known example of convergent molecular evolution. Furthermore, their results strongly suggested that nodes of Ranvier are evolutionary derivatives of the AIS, and the requirements of Na^+ channel clustering in axons likely drove the evolution of KCNQ2/3 K^+ channel clustering. Mutation of the ankG-interacting motif in KCNQ2 and KCNQ3 blocks the ability of these subunits to become restricted to the AIS [43].

Intriguingly, one recent paper demonstrated that the binding of Nav channels to ankG is strongly facilitated by casein kinase 2 (CK2) – dependent phosphorylation of serine residues within the AIS targeting motif [2] (Fig. 2). Since KCNQ K^+ channels have a similar motif, it will be interesting to determine if localization of these channels can also be regulated by CK2.

At the AIS, the initial events responsible for ankG clustering remain unknown. However, at nodes of Ranvier it appears that two different kinds of neuron–glia interactions can initiate clustering of ankG (Fig. 2B). In the peripheral nervous system, Schwann cells secrete a protein called gliomedin that is incorporated into the extracellular matrix and binds to the axonal cell adhesion molecule neurofascin (NF)-186 [10]. NF-186, in turn, is a binding partner for ankG and functions as a nucleation site for the recruitment of ankG and the subsequent clustering of Na^+ and KCNQ2/3 K^+ channels [4,9]. Intriguingly, experiments also indicate that a second, overlapping mechanism exists to facilitate node of Ranvier assembly, one which depends on interactions between the myelin sheath and the axon at paranodal junctions (Fig. 1B) [12,42,58]. These interactions create a barrier that limits the lateral diffusion of ion channels and other nodal proteins. Although the molecular details for how this happens are lacking, ankG appears to be critical in both situations. However, the importance of ankG for KCNQ2/3 channel clustering at nodes has only been inferred from in vitro experiments examining Na^+ channel clustering; loss of ankG from neurons in myelinating co-cultures blocks the clustering of Na^+ channels [9]. Since the interaction of Na^+ channels and KCNQ2/3 K^+ channels with ankG depends on the same AIS targeting motif, it is likely that nodal localization of KCNQ2/3 channels is also mediated by ankG.

3. Kv3.1b channels

Kv3 channels contribute to the rapid spiking behavior of many neurons [44]. Among the Kv3 channels, Kv3.1b, a unique splice variant of the Kv3.1 gene, has been reported at a subset of CNS and PNS nodes of Ranvier [5] with greater extent of expression in the CNS. Intriguingly, although biochemical analyses showed that it can be co-immunoprecipitated with ankG, Kv3.1b was not detected at the