

IMPLICATING A-CURRENT IN A HEREDITARY PARTIAL EPILEPSY

The Epilepsy-Linked Lgi1 Protein Assembles into Presynaptic Kv1 Channels and Inhibits Inactivation by Kv β 1

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The voltage-gated potassium (Kv) channel subunit Kv1.1 is a major constituent of presynaptic A-type channels that modulate synaptic transmission in CNS neurons. Here, we show that Kv1.1-containing channels are complexed with Lgi1, the functionally unassigned product of the *leucine-rich glioma inactivated gene 1* (LGI1), which is causative for an autosomal dominant form of lateral temporal lobe epilepsy (ADLTE). In the hippocampal formation, both Kv1.1 and Lgi1 are coassembled with Kv1.4 and Kv β 1 in

axonal terminals. In A-type channels composed of these subunits, Lgi1 selectively prevents N-type inactivation mediated by the Kv β 1 subunit. In contrast, defective Lgi1 molecules identified in ADLTE patients fail to exert this effect resulting in channels with rapid inactivation kinetics. The results establish Lgi1 as a novel subunit of Kv1.1-associated protein complexes and suggest that changes in inactivation gating of presynaptic A-type channels may promote epileptic activity.

COMMENTARY

Adding to a growing list of channelopathies associated with epilepsy syndromes, autosomal dominant lateral temporal lobe epilepsy (ADLTLE) now has been linked to altered ion channel function. It has been known since 2002 that ADLTLE is linked to chromosome 10q22–q24, and several mutations in the *leucine-rich glioma inactivated gene 1* (LGI1) were found in families with the disorder (1). The disorder is characterized by the occurrence of simple partial seizures with auditory or sensory hallucinations and ictal aphasia, but many afflicted individuals have complex partial and/or secondarily generalized seizures. The protein product of the gene, Lgi1, contains leucine-rich repeat sequences, which are important in protein–protein interactions, and seven copies of another repeat sequence. The gene initially was thought to function as a tumor suppressor since Lgi1 is downregulated in some malignant gliomas, but so far there is no evidence of increased risk of cancer in ADLTLE families.

In this study, proteomic analysis identified Lgi1 as a component of membrane protein complexes containing the voltage-

gated potassium (Kv) channel subunit Kv1.1, which is expressed abundantly in the brain and is targeted to axons and axon terminals. Kv1.1 α subunits assemble in tetramers to form channels with the properties of delayed rectifiers: noninactivating channels that participate in the repolarization and undershoot of the action potential. Coexpression of Kv1.1 with Kv1.4 α subunits or accessory Kv β subunits, which are localized together on many axon terminals (2), confers the characteristic properties of A-type potassium channels: rapid activation in the subthreshold range, rapid inactivation, and the requirement for membrane hyperpolarization (deinactivation) before reactivation can occur. As a result of their subcellular localization and biophysical properties, A-type channels accelerate repolarization and force a delay between successive action potentials, thereby shortening the action potential duration and limiting firing rate. However, during high frequency trains of action potentials, the A-type channel's effects are overcome, since they do not have time to recover from inactivation between spikes. As a result, the presynaptic action potentials widen, allowing more calcium influx per spike and potentiating neurotransmitter release (3). Despite their recognized importance in regulating neuronal excitability, alterations in A-type channels had not previously been associated with human epilepsy, unlike the related M-type potassium channels in which mutations are associated with benign familial neonatal convulsions (4).

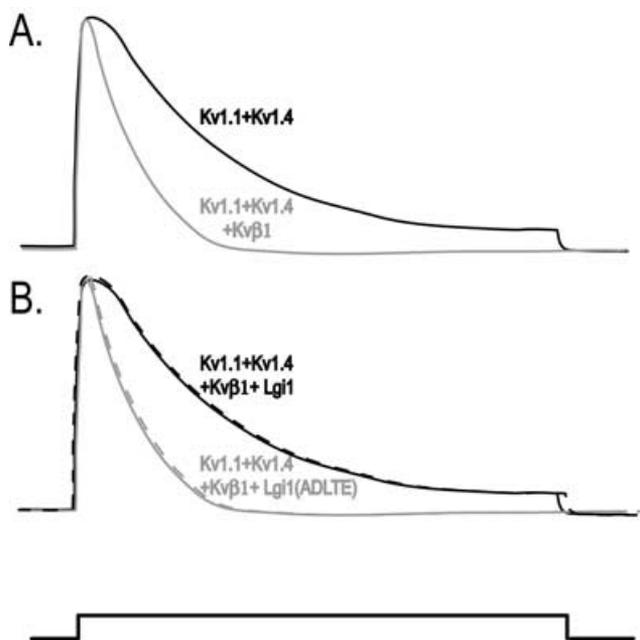


FIGURE 1. Schematic representation of currents obtained from voltage-gated potassium channels formed by coexpression of the subunits noted. The traces depict currents activated under voltage clamp by a step in holding potential from -100 mV to 0 mV (shown at bottom). **A.** The $Kv\beta 1$ subunit confers faster inactivation to channels containing $Kv1.1$ and $Kv1.4$ subunits. **B.** $Lgi1$ reverses the effect of the $Kv\beta 1$ subunit on inactivation (solid black line), but the ADLTE mutant $Lgi1$ does not (solid gray line). For comparison, dashed lines show currents from panel A without $Lgi1$.

$Lgi1$ and $Kv1.1$ have an overlapping, but not identical, pattern of expression in the rat brain, particularly in the cortex (including lateral temporal lobe), the mossy fiber pathway of the hippocampus, and the middle molecular layer of the dentate gyrus (i.e., the entry zone of the perforant path from the entorhinal cortex into the hippocampal formation). The authors show that $Kv1.4$ and $Kv\beta 1$ each contribute additively to the rapid inactivation of channels when coexpressed with $Kv1.1$ in oocytes (Figure 1A). When $Lgi1$ is expressed along with $Kv1.1$, $Kv1.4$, and $Kv\beta 1$, the rate of channel inactivation is slowed in comparison to the intermediate rate observed when $Kv1.1$ and $Kv1.4$ are expressed without the $Kv\beta 1$ subunit (Figure 1B). $Lgi1$ appears to specifically counteract the effect of the accessory β subunit on the rate of channel inactivation. When the mutations known to cause ADLTLE were introduced into $Lgi1$, none of the mutant proteins were able to alter the rate of channel inactivation.

As a result of defective interactions with A-type channels, ADLTLE mutations are expected to result in channels that inactivate more quickly and, therefore, the A-current would be more readily overcome during trains of action potentials. Broadening of the presynaptic action potential during relatively lower

frequency firing would enhance calcium entry at synapses expressing these channels and result in a lowered threshold for potentiation in these excitatory circuits. It is interesting to note that two of the regions showing high expression of both $Lgi1$ and $Kv1.1$ are in mesial temporal excitatory circuits that are already heavily implicated in models of temporal lobe epilepsy.

Almost all currently identified epilepsy gene mutations are located in ion channels or their accessory subunits (5). A major challenge for epilepsy research lies in determining how these mutations produce a particular phenotype. At first glance, it is more intuitive that channelopathies would underlie generalized epilepsy disorders, and this is indeed the case in most observations to date. However, autosomal dominant nocturnal frontal lobe epilepsy and, now, ADLTLE are the first of what is likely to be a larger number of partial epilepsies that are caused by ion channel dysfunction. In the case of ADLTLE, it appears that selective alteration of A-type channel inactivation in the cortical and hippocampal excitatory circuits, where $Lgi1$ is expressed, causes hyperexcitability and seizures. Of course, the involvement of $Lgi1$ in A-type channel regulation in neuronal systems—and particularly in temporal lobe excitatory circuits—remains to be demonstrated. It seems reasonable that additional hereditary partial epilepsies will be found to be associated with proteins that have an expression pattern that is more regionally selective than the ubiquitous ion channel subunits. Finally, three additional LGI-like genes have been identified, and all are expressed in brain (6). Therefore, LGI1 may represent the first of a new family of genes involved in the regulation of neuronal excitability and possibly in epileptogenesis.

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