Epilepsy Currents
2019, Vol. 19(5) 339-340

DOI: 10.1177/1535759719868185
journals.sagepub.com/home/epi
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Oligodendrocyte $K_{ir}4.1$ Channels Clear Out Congested K^+

Oligodendrocytes Control Potassium Accumulation in White Matter and Seizure Susceptibility.

Larson VA, Mironova Y, Vanderpool KG, Waisman A, Rash JE, Agarwal A, Bergles DE. *Elife*. 2018 Mar 29;7. pii: e34829. doi:10.7554/eLife.34829.

The inwardly rectifying K^+ channel $K_{ir}4.1$ is broadly expressed by central nervous system glia and deficits in $K_{ir}4.1$ lead to seizures and myelin vacuolization. However, the role of oligodendrocyte $K_{ir}4.1$ channels in controlling myelination and K^+ clearance in white matter has not been defined. Here, we show that selective deletion of $K_{ir}4.1$ from oligodendrocyte progenitors or mature oligodendrocytes did not impair their development or disrupt the structure of myelin. However, mice lacking oligodendrocyte $K_{ir}4.1$ channels exhibited profound functional impairments, including slower clearance of extracellular K^+ and delayed recovery of axons from repetitive stimulation in white matter, as well as spontaneous seizures, a lower seizure threshold, and activity-dependent motor deficits. These results indicate that $K_{ir}4.1$ channels in oligodendrocytes play an important role in extracellular K^+ homeostasis in white matter and that selective loss of this channel from oligodendrocytes is sufficient to impair K^+ clearance and promote seizures.

Commentary

Extracellular potassium (K^+) levels in the brain are under exquisite control because of the important role that K^+ plays in setting the resting membrane potential of neurons. The repolarization phase of the action potential moves K^+ out of the cell, and this K^+ can accumulate during periods of increased neuronal activity.[1,2] Excessive neuronal activity produces rising K^+ levels that depolarize surrounding neurons and in turn produce even more action potential firing.[1] This positive feedback loop has been implicated as a mechanism of seizure propagation for decades,[3] and it has generally been accepted that astrocytes, a ubiquitous glial cell type, play the dominant role in regulating extracellular K^{+2}. However, in a new paper from Larson et al, these authors show that oligodendrocytes, the myelinating cells of the central nervous system (CNS), also play a critical role in regulating extracellular K^+ inside white matter tracts. Fascinatingly, they also found that interrupting oligodendrocyte K^+ buffering leads to seizures. This discovery sheds light into a basic mechanism of seizure activity which could inform the development of new therapeutics.

Glial cells buffer extracellular K^+ using a specific class of K^+ channel termed "inwardly-rectifying" potassium channels (K_{ir}).[2] These channels are distinct from the "delayed-rectifier" potassium channels that open in response to membrane depolarization during an action potential and permit the exit of K^+ in order to restore membrane hyperpolarization. Instead, K_{ir} channels allow K^+ to flow into the cell, but not out of it. As a result, this class of channels is well suited to a role in soaking up excess K^+ and preventing runaway depolarization and seizures. One member of this class in particular, $K_{ir}4.1$, is well known to be essential for K^+ buffering in astrocytes, but 2 key observations suggested to Larson et al that there might be more to learn. First, $K_{ir}4.1$ channels are also expressed at high levels in oligodendrocytes although their function was previously unknown.[4] Second, astrocytes have a limited presence within the white matter of the CNS. In their absence, what mechanism could be responsible for buffering the K^+ loads associated with high neuronal activity?[5]

To answer these questions, Larson et al employed a host of genetic tools to precisely eliminate $K_{ir}4.1$ channels only in specific cell types in the brain. Consistent with prior results, they found that eliminating $K_{ir}4.1$ channels in neurons, astrocytes, and oligodendrocytes at the same time led to a severe phenotype featuring ataxia, white matter vacuolation, and high mortality. They then eliminated $K_{ir}4.1$ channels only in oligodendrocytes, expecting that they would recreate at least some aspect of the neurologic deficits of the mice that lack $K_{ir}4.1$ channels in all cell types. Instead, these animals were indistinguishable from wild-type littermates. Even electron microscopy showed no difference in either the oligodendrocytes or the myelin.

At this point, many investigators would have moved on to other projects as there was no obvious deficit in any of the mice where the $K_{ir}4.1$ channel was deleted only in oligodendrocytes. However, Larson et al made an interesting observation that justified additional experimentation. They noted that these mice were dying earlier than their control littermates with about 50% dying by 6 months of age (mice typically live about 2 years). Moreover, the tonic posture of the deceased animals suggested that their death was preceded by a generalized seizure, which led the team to investigate seizure susceptibility. Consistent with their hypothesis, mice lacking $K_{ir}4.1$ channels only in the oligodendrocytes were substantially more susceptible to chemoconvulsant administration. To investigate, they recorded from oligodendrocytes while stimulating white matter pathways. Although wild-type cells rapidly cleared the ensuing buildup of K^+, the oligodendrocytes that lacked $K_{ir}4.1$ channels remained depolarized for longer, indicating a deficit in K^+ buffering.

Larson et al next discovered a role for these channels outside epilepsy as well. During high-intensity activity, such as running on a wheel, mice lacking the $K_{ir}4.1$ channels were not able to keep up with their wild-type peers. The authors attributed this deficit to the buildup of K^+ in white matter pathways preventing the neural activity required to support motor performance. Combined, their results point to a newly discovered role for $K_{ir}4.1$ channels in the trophic support of neurons by oligodendrocytes in health and disease.[4]

$K_{ir}4.1$ channels have been identified by many studies as key regulators of neuronal excitability, and polymorphisms in *KCNJ10* (the gene encoding the channel) are risk factors for epilepsy in humans.[6] Perhaps most dramatically, the rare genetic SeSAME syndrome (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance) which has also been referred to as EAST syndrome (epilepsy, sensorineural deafness, and tubulopathy)[7] is the result of a mutation in *KCNJ10*. However, the data from human patients point to a global role for $K_{ir}4.1$ channels in all cell types, while the data from Larson et al specifically identify a novel pathway whereby $K_{ir}4.1$ channels influence seizure susceptibility. An important limitation of this work is that it was carried out entirely in animal models. Given that basic physiological mechanisms governing ionic conductances and buffering are similar in mouse and human brains, it is reasonable to assume that oligodendrocyte buffering of extracellular K^+ occurs in humans and could similarly influence seizure susceptibility. It nonetheless remains to be seen if the mechanisms are identical.

Larson and colleagues demonstrated that oligodendrocytes in white matter areas play an essential role in buffering extracellular K^+, and in turn, regulating seizure susceptibility could have important ramifications beyond the rare genetic syndromes defined by mutations in $K_{ir}4.1$ channels. The spread of epileptic activity through white matter pathways is likely to play a crucial role in the generalization of ictal activity from a single focus (a hypothesis not tested here), and drugs that act to augment K^+ buffering could in principle limit this generalization. To date, only Retigabine has been approved as a selective potassium channel agonist used to treat epilepsy,[8] although it was subsequently removed from the market for safety concerns. However, it may still be possible to develop a cell-type specific strategy that could safely increase $K_{ir}4.1$ channel function only in glial cells. The tightly regulated subcellular distribution of the channel within glial cells suggests the presence of binding partners that guide the channels to where they need to be.[4,9,10] Rather than trying to find a small molecule to increase $K_{ir}4.1$ channel function wherever it is expressed, increasing its function only in glial cells (ie, by inhibiting a glial-specific protein that limits $K_{ir}4.1$ surface expression) might limit side effects associated with altering channel function in neurons. Future efforts to better understand the role of white matter tracts and K^+ buffering in propagating seizures may lead to new treatments for epilepsy.

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