ERG3 potassium channel-mediated suppression of neuronal intrinsic excitability and prevention of seizure generation in mice

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The input-output relationship of neuronal networks depends heavily on the intrinsic properties of their neuronal elements. Profound changes in intrinsic properties have been observed in various physiological and pathological processes, such as learning, memory and epilepsy. However, the cellular and molecular mechanisms underlying acquired changes in intrinsic excitability are still not fully understood. Here, we demonstrate that ERG3 channels are critically involved in the regulation of intrinsic excitability in hippocampal CA1 pyramidal neurons and DG granule cells. Knock-down of ERG3 channels significantly increases neuronal intrinsic excitability, which is mainly caused by decreased fast afterhyperpolarization (AHP), delayed time to the generation of an action potential (AP) and enhanced summation of somatic excitatory post-synaptic potentials (EPSPs). Interestingly, the expression level of ERG3 protein is significantly reduced in human and mouse brain tissues with temporal lobe epilepsy. Moreover, ERG3 channel knock-down in hippocampus significantly enhanced seizure susceptibility, while mice treated with ERG3 channel activator NS1643 were less prone to epileptogenesis. Taken together, our results suggest ERG3 channels play an important role in determining the excitability of hippocampal neurons and dysregulation of these channels may be involved in the generation of epilepsy. ERG3 channels may thus be a novel therapeutic target for the prevention of epilepsy.