Nature Reviews Neuroscience **5**, 758 -770 (2004); doi:10.1038/nrn1516

CA2+-ACTIVATED K+ CHANNELS: MOLECULAR DETERMINANTS AND FUNCTION OF THE SK FAMILY

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Abstract

Ca^{2+}-activated K^+ (K_{Ca}) channels of small (SK) and intermediate (IK) conductance are present in a wide range of excitable and non-excitable cells. On activation by low concentrations of Ca^{2+}, they open, which results in hyperpolarization of the membrane potential and changes in cellular excitability. K_{Ca}-channel activation also counteracts further increases in intracellular Ca^{2+}, thereby regulating the concentration of this ubiquitous intracellular messenger in space and time. K_{Ca} channels have various functions, including the regulation of neuronal firing properties, blood flow and cell proliferation. The cloning of SK and IK channels has prompted investigations into their gating, pharmacology and organization into calcium-signalling domains, and has provided a framework that can be used to correlate molecularly identified K_{Ca} channels with their native currents.

Summary

- Ca^{2+}-activated K^+ (K_{Ca}) channels have evolved to use Ca^{2+} to regulate their opening and closing (gating), and to support the ability of the cell to finely regulate the amount of Ca^{2+} that is able to enter. This review describes the molecular and functional properties of K_{Ca} channels of small and intermediate conductance (SK and IK channels, respectively).
- The genes that encode the three SK channels $K_{Ca}2.1$, $K_{Ca}2.2$ and $K_{Ca}2.3$ belong to the *KCNN* gene family. The closely related family member $K_{Ca}3.1$ was named IK on the basis of its intermediate single-channel conductance. The structures of the SK-channel genes are complex, and there is evidence of alternative splicing.
- SK channels have a similar topology to members of the voltage-gated (Kv) K^+ channel superfamily, which consist of six transmembrane segments with the pore located between segments 5 and 6. The S4 segment, which confers voltage sensitivity to the Kv channel, contains a reduced number of positively charged amino acids in SK channels, which might explain their observed voltage independence.
- $K_{Ca}2.1$, $K_{Ca}2.2$, and $K_{Ca}2.3$ channels are predominantly expressed in the nervous system, whereas the $K_{Ca}3.1$ channel is mainly expressed in blood and epithelial cells, and in some peripheral neurons. The expression patterns in the brain indicate that specific SK-channel subunits contribute to neuronal excitability and function in different regions, and possibly in different neuronal compartments.

- Ca^{2+} sensitivity seems to be conferred on the $K_{Ca}2.2$ channel by the intimate interaction of calmodulin (CaM) with each of the four subunits, and it is generally accepted that CaM has a role in the gating of all $K_{Ca}2$ and $K_{Ca}3$ channels. CaM is also essential for the assembly and trafficking of SK-channel subunits.
- In central neurons, SK channels mediate an apamin-sensitive K^+ current that is known as I_{AHP}, which contributes to the generation of an afterhyperpolarization of medium duration (mAHP) that follows single, or bursts of, action potentials. Depending on the neuronal subtype and its contingent of ion channels, the I_{AHP} might contribute to the instantaneous firing rate, set the tonic firing frequency or regulate burst firing and rhythmic oscillatory activity.
- SK channels are functionally coupled to Ca^{2+} sources: apamin-sensitive currents are coupled to the activation of different subtypes of voltage-gated Ca^{2+} channels in a cell-type-specific manner, and there is also evidence for SK-channel activation by Ca^{2+} that is released from intracellular stores.
- The SK-channel blocker apamin has been used in behavioural studies to investigate the role of the SK channels in cognitive functions. SK-channel blockade improves performance on hippocampus-dependent learning tasks, and it seems to facilitate the induction of long-term potentiation in the hippocampal formation by increasing postsynaptic neuronal excitability.
- Questions that remain to be answered concern the molecular make-up of native SK channels in different brain regions, their localization in specific neuronal compartments and their functional coupling and interplay with Ca^{2+} sources. A better understanding of SK-channel physiology might also clarify their hypothesized role in various pathological conditions.