Calcium Signal Transduction in the Calmodulin/Kv7.1 Channel Complex

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The cardiac I_{Ks} channel (KCNQ1/KCNE1) is a major repolarization current in the heart adequating diastolic filling time in the face of accompanying accelerated heart rate, while the M-current (KCNQ2/KCNQ3) is a key controller of neuronal excitability. Both are under dynamic control by the phospholipase C cascade, which causes reduction on PIP_2 levels and release of Ca^{2+} from IP_3 sensitive intracellular stores. While the action of PIP_2 in gating is thought to be direct on the channel, Ca^{2+} regulation is thought to be mediated by calmodulin (CaM), which binds to an intracellular site of the channel known as helix A + helix B. The current hypothesis regarding Ca^{2+} gating posits that CaM wraps around helix B under resting conditions, and, when CaM becomes loaded with Ca^{2+}, it embraces both A+B helices simultaneously, causing a large structural rearrangement. We have examined this issue by monitoring conformational changes triggered by Ca^{2+} using FRET.
KCNQ1 is well positioned to integrate changes in intracellular Ca^{2+} into an alteration in action potential duration, consistent with our results, showing that Ca^{2+}-responsive of considerable FRET change. In contrast, Ca^{2+} cause minimal FRET changes in KCNQ2 channels when are loaded with Ca^{2+}, according with our NMR results suggest that the AB module behaves as a rigid body around which CaM accommodates, both loaded with and without Ca^{2+}.
Our investigation is focused on determining the regions responsible of Ca^{2+} signal transduction in KCNQ1 and KCNQ2 channels. For this, we have constructed different chimeras between KCNQ1 and KCNQ2 and we are analyzing FRET changes in response to Ca^{2+}. In combination with NMR studies, we expect to obtain a full description trajectory changes at atomistic level which led to gating of potassium channels by Ca^{2+}.