

Insight into the calmodulin and DREAM protein complex interaction, mechanism and function

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Abstract ID: 64

Abstract Details

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Abstract

DREAM (Downstream regulatory element antagonistic modulator) is a neuronal calcium sensor which has been shown to modulate gene expression as well as being involved in numerous neuronal processes. In this report, we show that association of calcium bound calmodulin (CaM) with DREAM is mediated by a short amphipathic amino acid sequence located between residues 29 and 44 on DREAM N-termini. The association of CaM with a peptide analogous to DREAM(29-44) or to full length DREAM protein is calcium dependent with the dissociation constant of 136 nM and 3.4 μ M, respectively. Thermodynamic and kinetic studies show that the observed decrease in affinity for the native protein is due to electrostatic interaction between the basic N-terminus and an acidic surface on DREAM. These results are further supported by molecular dynamic simulations, circular dichroism and binding studies. Additionally, in fluorescence anisotropy decay measurements, a rotational correlation time of 10.8 ns for a complex of CaM with a DREAM(29-44) peptide was observed, supporting a wraparound semi-spherical model with 1:1 stoichiometry. Furthermore, the interaction between a IEDANS labeled CaM construct with DREAM is best modeled as a heterotetramer. The CaM:DREAM heterotetramer adopts an elongated conformation with correlation time of 45 ns in the presence of Ca²⁺. We also demonstrate that association of CaM with DREAM eliminates the nonspecific interaction of DREAM with the DRE dsDNA sequence of human prodynorphin gene. The presented work provides an molecular insight into the CaM:DREAM complex and its potential role in modulation of gene expression.

Event Information

Event: FIU Undergraduate Research Conference

Topic: Biochemistry

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