Investigation of the hydrophobic sites of DREAM *by Daniel Rapado*

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DREAM (downstream regulatory element antagonist modulator) also known as calsenilin or KChIP-3 is a calcium binding protein that has been associated with memory retention, pain sensing, calcium homeostasis and Alzheimer's disease. It has two EF hands that bind Ca^{2+} and change the conformation of the protein. DREAM has two hydrophobic cavities in both the N- and C- terminus. These hydrophobic sites act as important binding sites with K_v channels, presenilin and other small molecules. Previously our group has showed that hydrophobic molecules such as NS5806 and 1,8-ANS can bind to the hydrophobic cavities in the C-terminus. The aim of this investigation was to characterize interactions of other hydrophobic molecules with DREAM with a long-term goal of finding a potential inhibitor for DREAM interacting with presenilin. *In silico* and *in vitro* approaches were used to determine a mechanism of binding of DREAM with hydrophobic molecules NS5806, NS3623, bezafibrate, trifluoperazine, 5-biphenyl-2-yl-1H-tetrazole, N-[(4-phenylphenyl)methyl]-2H-tetrazol-5-amine and cholesterol. Three binding sites were identified at the C-terminus and N-terminus. The most favored binding site was in the C-terminus in the hydrophobic pocket of the EF-4. All the hydrophobic molecules tested showed strong binding in this region. The major contributing residues were HIS 214, TYR 174, MET 187 and PHE 218. Other binding sites found resided in the hydrophobic pocket in the N-terminus but binding was shown to be weaker with many unfavorable residue interactions. Additional binding site was identified in between EF-3 and EF-4 but had many unfavorable interactions. An inhibitor with a high affinity for DREAM binding to presenilin would be beneficial in the blocking of gamma secretase complex which may lead to a better understanding of the physiology and treatment of Alzheimer disease.