CALMODULIN BINDING DOMAIN OF SMALL CALCIUM ACTIVATED POTASSIUM CHANNEL

AIM

- to investigate the structure of the calmodulin binding domain of the SK potassium channel
- to compare different calcium binding domains

SK Channels

- Voltage independent
- Heterotrimeric complexes composed by Pore forming α subunits and Calmodulin
- Activated by submicromolar $[Ca^{2+}]$

They are high affinity (~100 nM) Ca^{2+} sensors: they transduce fluctuation in intracellular $[Ca^{2+}]_i$ into changes in membrane potential.

Calmodulin

Examples of Target molecules:

- **calcium/calmodulin-dependent protein kinase IV**
- **calcineurin**
- **muscle myosin light chain kinase**

Biological roles of Ca

- **Protein Translation**
- **Cell Cycle Progression**
- **LTP**
- **Microtubule assembly**

Small-conductance Ca2+-activated k+K channels family

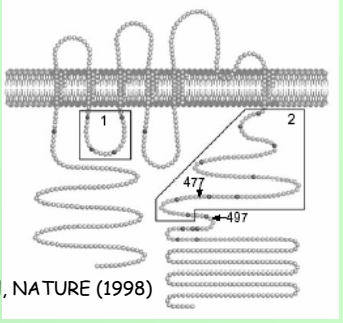
Sequence Homology between the SK K+ channels

	SK1	SK2	SK3
SK1	-	74% Identity	63% Identity
SK2	74% Identity	-	69% Identity
SK3	63% Identity	69% Identity	-

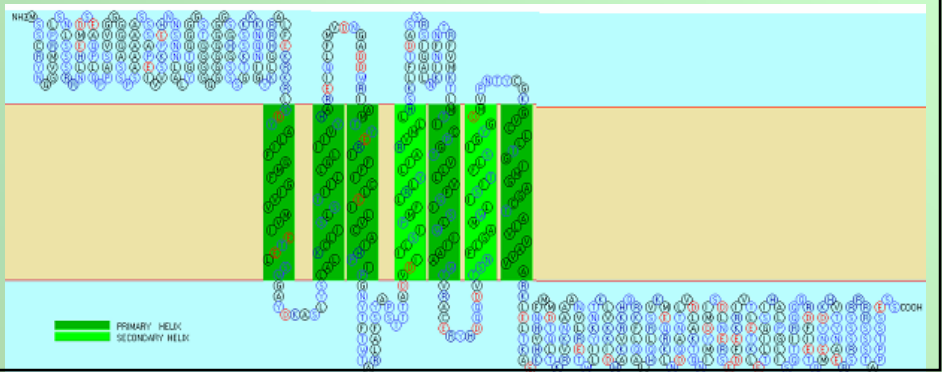
Homology between species

	SK1	SK2	SK3
Mouse	85% Identity	84% Identity	81% Identity
Human	76% Identity	83% Identity	79% Identity

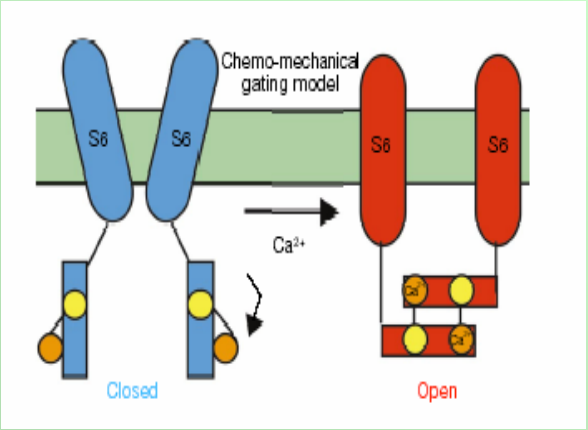
The SK2 subunit. Region two contains the calmodulin binding domain between residues 395-490



X.-M. Xia et al, NATURE (1998) 395,503-507

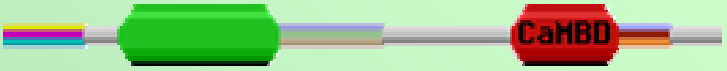


CHEMO-MECHANICAL GATING MODEL



' the CaMBD/CaM complex is monomeric in the absence and dimeric in the presence of Ca^{2+} '

Schumacher et al, NATURE (2001) 410,
1120-1124



MSSRSHNGSV GRPLGSGPGF LGWEPVDPEA GRPRQPTQGP GLQMMAKGQP
AGLSPSGPRG HSQAQEEEEE EEDEDRPGSG KPPTVSHRLG HRRALFEKRK
RLSDYALIFG MFGIVVMVTE TELSWGVYTK ESLCSFALKC LISLSTVILL
GLVILYHARE IQLFLVDNGA DDWRIAMTWE RVSLISLELA VCAIHPVPGH
YRFTWTARLA FSLVPSAAEA DVDVLLSIPM FLRLYLLARV MLLHSRIFTD
ASSRSIGALN RVTFNTRFVT KTLMTICPGT VLLVFSISSW IVAAWTVRVC
ERYHDKQEVT SNFLGAMWLI SITFLSIGYG DMVPHTYCGK **GVCLLTGIMG**
AGCTALVVAV VARKLELTKA EKHVHNFMMD TQLTKRVKNA AANVLRETWL
IYKHTRLVKK PDQSRVRKHQ RKFLQAIHQA QKLRTVKIEQ GKVNDQANTL
ADLAKAQSIA YEVVSELQAQ QEELEARLAA LESRLDVLGA SLQALPSLIA
QAICPLPPPW PGPSHLTTAA QSPQSHWLPT TASDCG

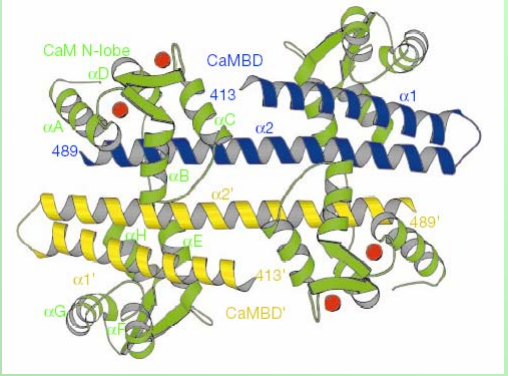
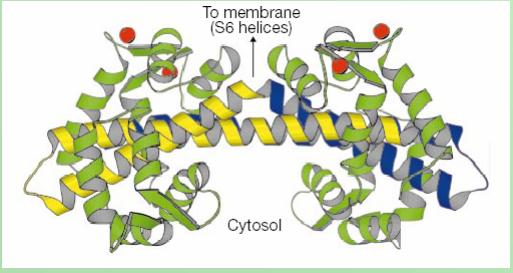


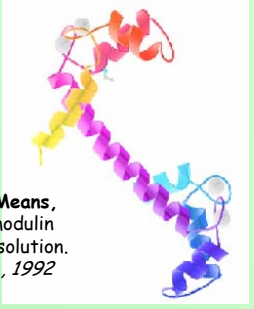
Diagram of the CaMBD/Ca2+/CaM dimeric complex. CaM are shown in green.



The diagram has been rotated 90°, to show the orientation of the complex relative to the membrane

(Schumacher et all, 2001)

Sutton, R.B., Sprang, S.R. Structure of the protein kinase Cbeta phospholipid-binding C2 domain complexed with Ca2+. *Structure v6 pp. 1395 , 1998*



Chatto., Meador, W.E., Means, A.R., Quiocho, F.A. Calmodulin structure refined at 1.7 A resolution. *J.Mol.Biol. v228 pp. 1177 , 1992*

Griffith, J.P. et al X-ray structure of calcineurin inhibited by the immunophilin-immunosuppressant FKBP12-FK506 complex. *Cell* 82 *pp.* 507 (1995)