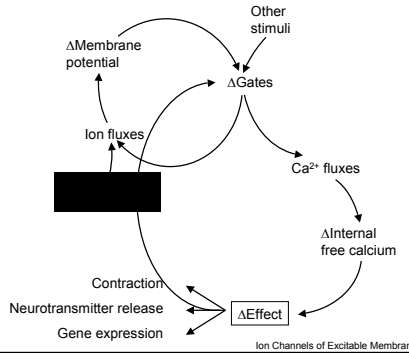
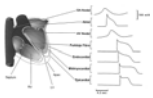
Calcium-dependent gating of Voltage-gated ion channels

Ca^{2+} Ions Transduce Signals

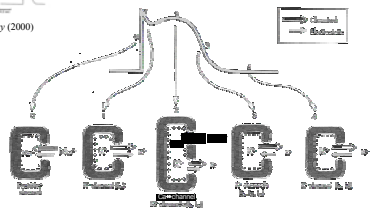


Ion Channels of Excitable Membranes, 3rd Edition, 2001

Ca^{2+} current controls the plateau phase of the cardiac action potential

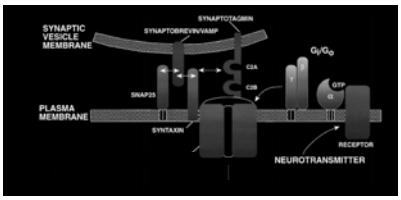


Journal of Physiology (2000) 525.2, pp. 285-298



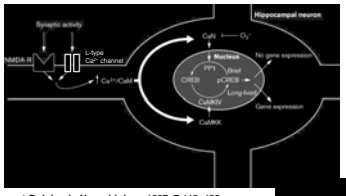
Berne & Levy, Cardiovascular Physiology 6th Edition (1992)

Ca^{2+} channels control neurotransmitter release

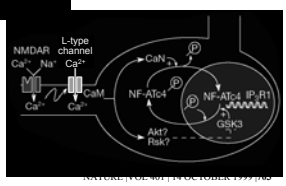


Annu. Rev. Cell Dev. Biol. 2000. 16:521–55

Ca^{2+} channels regulate gene expression in hippocampal neurons



Current Opinion in Neurobiology 1997, **7**:419–429



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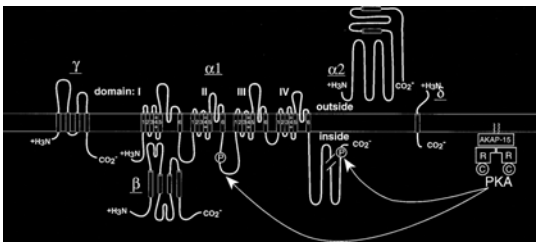
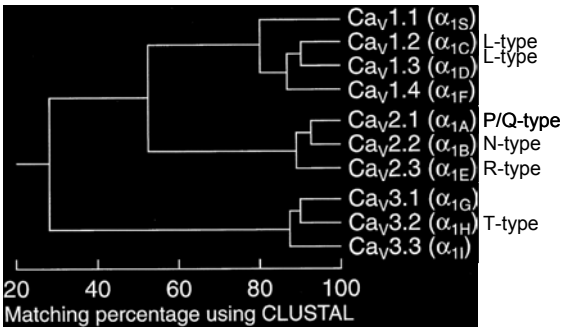
Ca^{2+} channel Structure



Annu. Rev. Cell Dev. Biol. 2000. 16:521–55

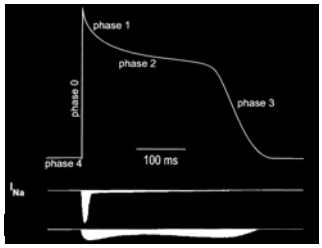
Family of Voltage-Gated Ca^{2+} Channels



Neuron, Vol. 25, 533–535, March, 2000

Ca^{2+}-dependent gating of the L-type Ca^{2+} Channel

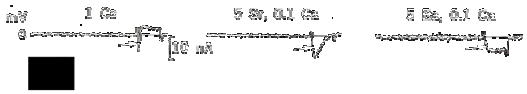
Ca^{2+} channels control the plateau phase of the cardiac action potential



Circ Res. 2001; 89:944-956.

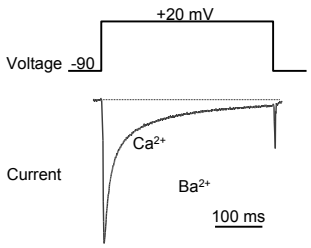
The permeating ion affects Ca^{2+} channel inactivation:
Calcium Dependent Inactivation (CDI)

Calcium Entry Leads to Inactivation of Calcium Channel in *Paramecium*



SCIENCE, VOL. 202, 15 DECEMBER 1978

CDI: accelerated inactivation with Ca^{2+}

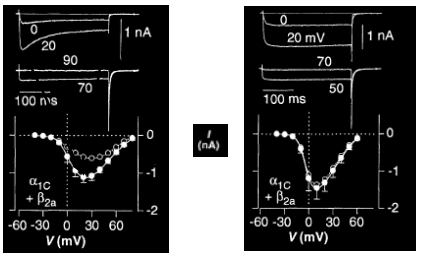


Calcium Dependent Inactivation:
A Ca^{2+}-regulated feedback mechanism

- Ca^{2+} entering through channel
- Requires no cytoplasmic components
  - Ca^{2+} sensor is near channel pore
- Develops rapidly

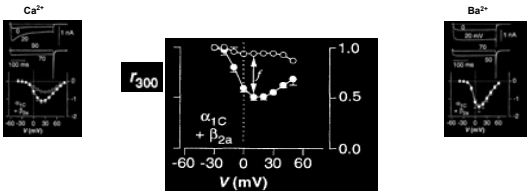
CDI is greatest at membrane potentials eliciting peak inward Ca^{2+} current

Ca^{2+}



SCIENCE • VOL. 270 • 1502

CDI is greatest at membrane potentials eliciting peak inward Ca^{2+} current



SCIENCE • VOL. 270 • 1502

Conditional Open Probability Analysis (COPA)

No inactivation

+10

-90

Inactivation

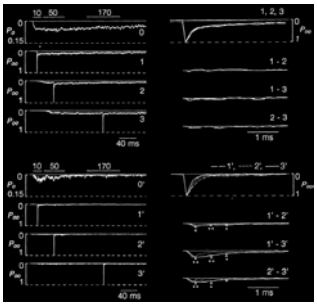
+10

-90

Conditional open probability analysis (COPA):
Ca^{2+} entry enhances inactivation

Ba^{2+}

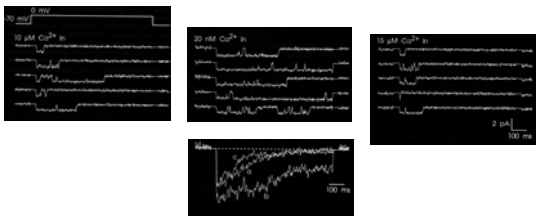
Ca^{2+}



SCIENCE, VOL. 250, 21 DECEMBER 1990

CDI in L-type channels reconstituted in bilayers

Requires no cytoplasmic components



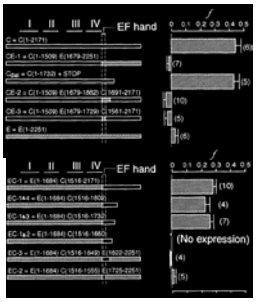
100 mM Ba^{2+} out

Biophysical Journal Volume 66 April 1994 1051-1060

Ca^{2+} sensing apparatus resides within or near $Ca_V1.2$ (α_{1C}) pore

- Rapid effects (< 5 msec)
- CDI in bilayers
- Minimal effects of Ca^{2+} chelators

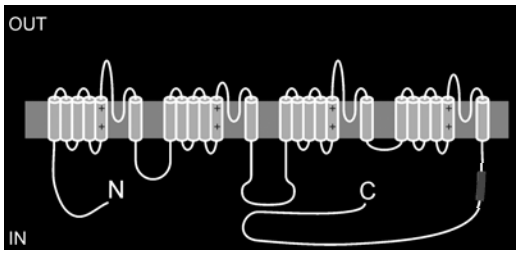
A region of α_{1C} is necessary and sufficient



CE

EC

Does Ca^{2+} bind directly to the α_{1C} subunit?



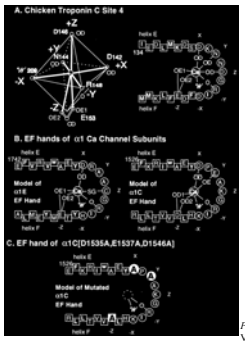
Does Ca^{2+} bind directly to the α_{1C} subunit?

EF-hand

Ca^{2+}-binding in the EF-hand is ***not*** necessary

CDI: X

CDI: √

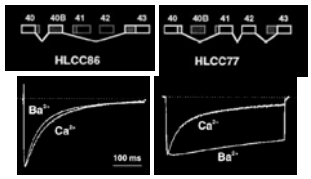


CDI: √

CDI: X

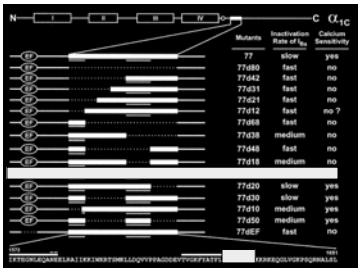
Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 2301–2305, March 1997

Identification of critical region(s) in the C-terminus



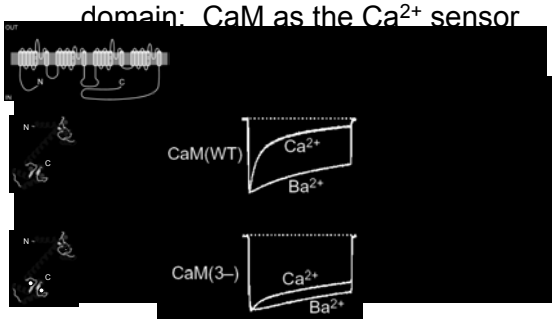
THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 272, No. 6, Issue of February 7, pp. 3560–3566, 1997

Identification of critical region(s) in the C-terminus

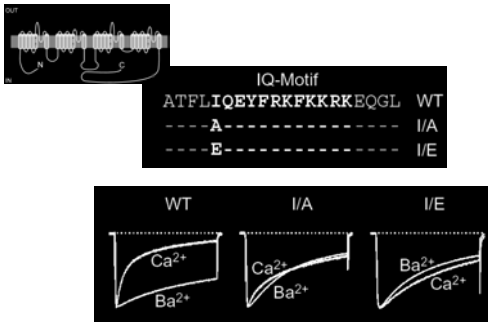


Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 3287–3294, March 1998

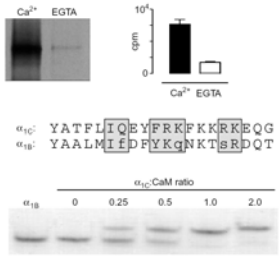
IQ motif / calmodulin (CaM) binding domain; CaM as the Ca^{2+} sensor



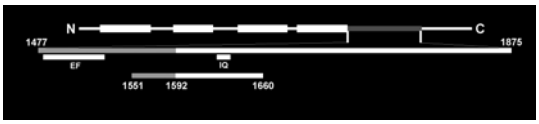
IQ motif is the CaM effector site

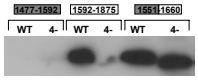


CaM binds to the IQ motif in the C-tail



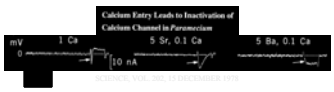
CaM is constitutively bound to α_{1C}





THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 276, No. 33, Issue of August 17, pp. 30794–30802, 2001

CDI correlates with the affinity of the divalent ion for CaM



Comparison of cation binding affinities of Calmodulin EF hands
EC_{50} values (μM)

	Ca^{2+}	Sr^{2+}	Ba^{2+}
Effective ionic radius (Å)	1.06	1.21	1.38
Phosphodiesterase activity via CaM*	~2.5	~25	>1000

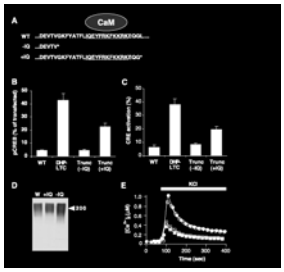
Mol Pharmacol 26:75-82, 1984

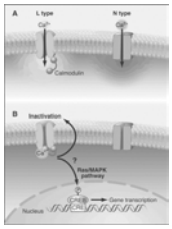
*PDE is one well-studied example of a Ca^{2+}/CaM regulated enzyme, allowing the testing of the ionic dependence of CaM activation; PDE has nothing to do with CDI.

Calcium Dependent Inactivation of L-type Ca^{2+} Channels

- Calmodulin is the Ca^{2+} sensor
- CaM is pre-associated with α_{1C}
- The IQ motif is the effector domain in α_{1C}
- The EF-hand is a structural, non Ca^{2+}-sensing domain

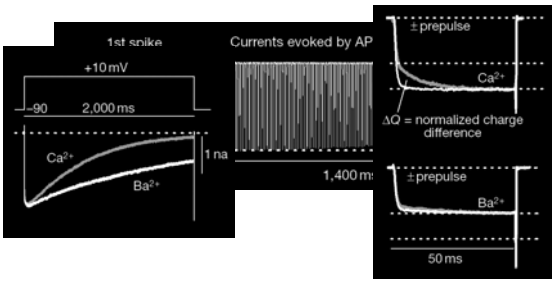
Gene expression in hippocampal neurons: LTCs and CaM



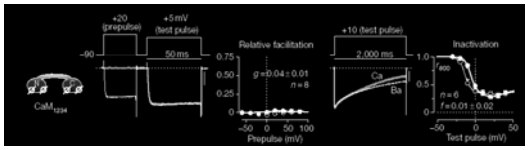


Ca^{2+}-dependent gating of P/Q-type Ca^{2+} Channels

CDI and CDF in P/Q channels



CaM is the Ca^{2+} sensor?



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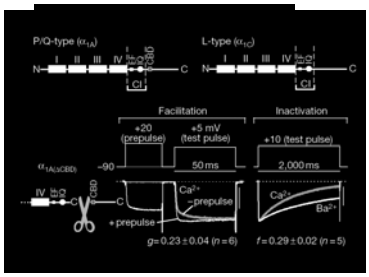
Different kinetics: different effector site?



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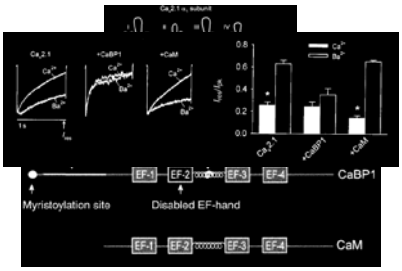
Different kinetics: different Ca^{2+} sensor?



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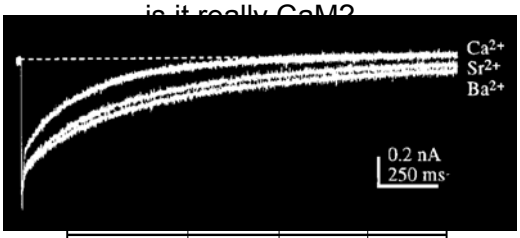
Ionic Dependence of I_{pCa} Inactivation

is it really CaM?



τ Fast (ms)	43.6 ± 6.4	48.8 ± 2.9	88.5 ± 8.6
τ Slow (ms)	477 ± 51	576 ± 49	673 ± 46
PDE activity via CaM	~2.5	~25	>1000

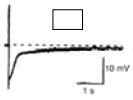
Neuron, Vol. 20, 797–807, April, 1998

Calcium Dependent Gating of P/Q Ca^{2+} Channels

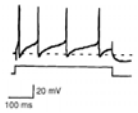
- Kinetics of inactivation and facilitation differ from L-type channel gating
- Calmodulin appears to be the Ca^{2+} sensor and the IQ motif is one effector domain in α_{1A}
- CBD may be another effector domain
- The Ca^{2+}-binding protein CaBP1 regulates inactivation in a Ca^{2+}-independent manner

Ca^{2+}-dependent gating of SK channels

I_{AHP}

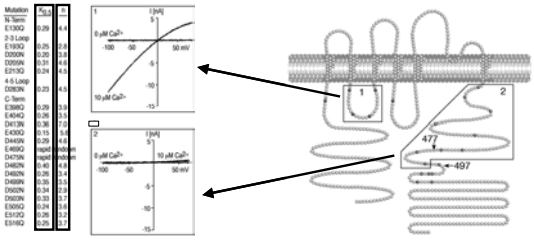


Tonic spiking



TINS Vol. 19, No. 4 1996

Ca^{2+}-dependent gating of SK channels



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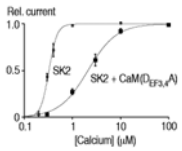
CaM is the Ca^{2+} sensor



NATURE |VOL 395 | 1 OCTOBER 1998

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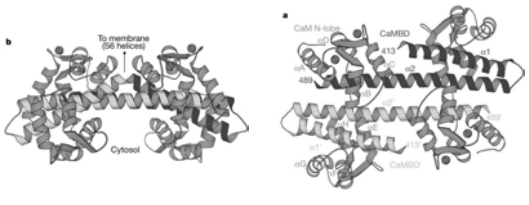

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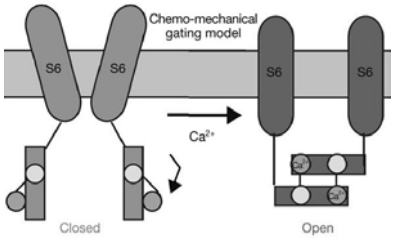
Gating Switch



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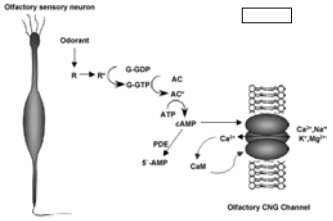
Ca^{2+}/CaM modulation of CNG channels



Adaptation

JBC Papers in Press. Pub. on March 7, 2003

Mechanism of Action

Loss of auto-excitatory interaction

JBC Papers in Press. Pub. on March 7, 2003

Other channels

- NMDA subtype of excitatory glutamate receptors
- BK_{Ca} channels