Calcium-dependent gating of Voltage-gated ion channels

Ca\textsuperscript{2+} Ions Transduce Signals

Ca\textsuperscript{2+} current controls the plateau phase of the cardiac action potential
Ca\textsuperscript{2+} channels control neurotransmitter release

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

Ca\textsuperscript{2+} channel Structure
Family of Voltage-Gated Ca$^{2+}$ Channels

- L-type
- T-type
- P/Q-type
- N-type
- R-type
- T-type

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

Ca$^{2+}$ channels control the plateau phase of the cardiac action potential
The permeating ion affects Ca\(^{2+}\) channel inactivation: Calcium Dependent Inactivation (CDI)

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

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\textsuperscript{2+} current.

Conditional Open Probability Analysis (COPA)

- No inactivation
- Inactivation
Conditional open probability analysis (COPA): Ca\(^{2+}\) entry enhances inactivation

![Graph showing conditional open probability analysis (COPA) with Ba\(^{2+}\) and Ca\(^{2+}\) entry enhancements.]

CDI in L-type channels reconstituted in bilayers

- Requires no cytoplasmic components

![Graph showing CDI in bilayers with Ca\(^{2+}\) sensing apparatus within or near Ca\(_{v}1.2\) (\(\alpha_{1C}\)) pore]

Ca\(^{2+}\) sensing apparatus resides within or near Ca\(_{v}1.2\) (\(\alpha_{1C}\)) pore

- Rapid effects (< 5 msec)
- CDI in bilayers
- Minimal effects of Ca\(^{2+}\) chelators
A region of $\alpha_{1C}$ is necessary and sufficient

Does Ca$^{2+}$ bind directly to the $\alpha_{1C}$ subunit?
Ca$^{2+}$-binding in the EF-hand is **not** necessary

Identification of critical region(s) in the C-terminus
IQ motif / calmodulin (CaM) binding domain: CaM as the Ca\textsuperscript{2+} sensor

IQ motif is the CaM effector site

CaM binds to the IQ motif in the C-tail
CaM is constitutively bound to $\alpha_{1C}$

**Comparison of cation binding affinities of Calmodulin EF hands**

<table>
<thead>
<tr>
<th>Cation</th>
<th>$\text{Ca}^{2+}$</th>
<th>$\text{Sr}^{2+}$</th>
<th>$\text{Ba}^{2+}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC$_{50}$ values (µM)</td>
<td>&gt;1000</td>
<td>25</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**CDI correlates with the affinity of the divalent ion for CaM**

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

- Calmodulin is the Ca$^{2+}$ sensor
- CaM is pre-associated with $\alpha_{1C}$
- The IQ motif is the effector domain in $\alpha_{1C}$
- 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?

Different kinetics: different effector site?

Different kinetics: different Ca\(^{2+}\) sensor?
Ionic Dependence of $I_{pCa}$ Inactivation

is it really CaM?

Neuron, Vol. 20, 797–807, April, 1998

$>1000$ ~ $25$ ~ $2.5$
PDE activity via CaM

$\tau$

$88.5 \pm 8.6$

$48.8 \pm 2.9$

$67.5 \pm 5.4$

$57.8 \pm 4.9$

$67.3 \pm 4.6$

$<$ $2.5$

$>25$

$>$ $1000$

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 $\alpha_{1A}$
• 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
Ca\(^{2+}\)-dependent gating of SK channels

CaM is the Ca\(^{2+}\) sensor

CaM is the Ca\(^{2+}\) sensor
Ca²⁺/CaM modulation of CNG channels

Adaptation

Mechanism of Action

Loss of auto-excitatory interaction
Other channels

• NMDA subtype of excitatory glutamate receptors

• BK_{Ca} channels