

# Voltage Dependent Ca<sup>2+</sup> (Ca<sub>v</sub>) Channels

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In many physiological systems, voltage dependent Ca<sup>2+</sup> (Ca<sub>v</sub>) channels are the molecular link between cellular membrane potential and intracellular Ca<sup>2+</sup> signaling. As such, Ca<sub>v</sub> channels are drug targets for several cardiovascular and neuronal conditions and the role they play in other, non-excitable tissues is beginning to emerge.

## The Importance of the Ca<sup>2+</sup> Ion as a Signaling Molecule

In most cells the intracellular concentration of ionized calcium ([Ca<sup>2+</sup>]<sub>in</sub>) is actively kept very low, at about 100-200 nM, while the plasma Ca<sup>2+</sup> concentration ([Ca<sup>2+</sup>]<sub>out</sub>) is at about 2 mM. This is achieved by several mechanisms. Firstly, the lipid membrane is impermeable to Ca<sup>2+</sup>, unless a Ca<sup>2+</sup> conducting channel in the plasma membrane is open, allowing ion diffusion along its electrochemical gradient. Other mechanisms include fast Ca<sup>2+</sup> buffering either by active transport into organelles such as mitochondria and endoplasmic reticulum (ER) or by binding to cytosolic proteins. Therefore, small and local increases in [Ca<sup>2+</sup>]<sub>in</sub> trigger the cellular signaling cascades which underlie the basis of many physiological systems.<sup>1</sup>

This paper focuses on a set of plasma membrane proteins that respond to membrane potential depolarization by opening a Ca<sup>2+</sup> selective pore: the voltage dependent/gated/operated Ca<sup>2+</sup> (Ca<sub>v</sub>) channels.

## Structure and Naming of Ca<sub>v</sub> Channels

The principal protein (α1 subunit) that forms a Ca<sub>v</sub> channel is a large (~2000 amino acids) protein that spans the membrane 24 times and includes the Ca<sup>2+</sup> selective pore, four voltage sensors and large intracellular loops with different regulatory functions. Such proteins are a single polypeptide analogous to the archetypal K<sub>v</sub> channel tetramer (Ca<sub>v</sub> proteins contain four homologous domains, each resembles a K<sub>v</sub> subunit).<sup>2</sup> Recently, the structures of purified skeletal and cardiac muscle L-type channels was determined by electron microscopy at low resolution.<sup>3-5</sup>

In addition, three other protein families are referred to as Ca<sub>v</sub> auxiliary subunits: a cytoplasmic β subunit, a membrane anchored extracellular α2δ subunit and the integral membrane γ subunit. All the auxiliary subunits affect the activity of all pore forming α1 subunits differently and to different degrees.<sup>6-9</sup> In 2004, the high resolution crystal structures of the core domain of three β subunits as well as of

β subunits complexed with part of the Ca<sub>v</sub> α1 subunit, were published, shedding light on the intersubunit relationship within a Ca<sub>v</sub> complex.<sup>10-12,13</sup>

The ten Ca<sub>v</sub> α1 subunit genes are divided into three subfamilies on both a functional and sequence homology basis (Table). The Ca<sub>v</sub>1 subfamily includes four genes that encode L-type channels and the Ca<sub>v</sub>3 subfamily includes three genes that encode T-type channels. The Ca<sub>v</sub>2 subfamily contains three isoforms encoding P/Q-, N- and R-type channels, with all three contributing to neurotransmitter release in neurons.<sup>14</sup>

## The Role of Voltage Activation

The control of Ca<sup>2+</sup> entry into the cell by selective pathways, which sense the voltage of the plasma membrane, enables fast, localized and brief transduction of electrical signal- into cytosolic Ca<sup>2+</sup>- signal. Hence, the four voltage sensors in each Ca<sub>v</sub> channel detect action potentials (and many other voltage signals) and induce a conformational change which allows Ca<sup>2+</sup> ions

## Summary of Nomenclature, Pharmacology and Tissue Distribution of Ca<sub>v</sub> Channels

Channel Type	Channel name	Previous name	Pharmacology	Main tissue distribution
L-type	Ca <sub>v</sub> 1.1	α1S	TaiCatoxin, Calciseptine, Calcicludine, FS-2, DHP	Skeletal muscle
	Ca <sub>v</sub> 1.2	α1C		Ubiquitous
	Ca <sub>v</sub> 1.3	α1D		Ubiquitous
	Ca <sub>v</sub> 1.4	α1F		Retina
P/Q-type	Ca <sub>v</sub> 2.1	α1A	ω-Agatoxin IVA, ω-Agatoxin TK, ω-Conotoxin MVIIC	CNS
N-type	Ca <sub>v</sub> 2.2	α1B	ω-Conotoxin GVIA, ω-Conotoxin MVIIA, ω-Conotoxin MVIIC, ω-Grammotoxin SIA	CNS/PNS
R-type	Ca <sub>v</sub> 2.3	α1E	SNX-482	CNS/PNS
T-type	Ca <sub>v</sub> 3.1	α1G	Kurtotoxin	CNS, Heart
	Ca <sub>v</sub> 3.2	α1H		CNS/PNS
	Ca <sub>v</sub> 3.3	α1I		CNS

to permeate into the cell resulting in a brief  $Ca^{2+}$  influx. This elevation of the  $Ca^{2+}$  concentration near the channel might activate any  $Ca^{2+}$  dependent enzyme or processes, which senses it. Two examples which illustrate such very localized signaling are synaptic transmission and calmodulin modulation of channel function. The process of neurotransmitter release from neuronal nerve terminals is triggered by action potential invasion of the terminal leading to opening of  $Ca_v$  channels.  $Ca_v2$  subfamily channels are localized in nerve terminals in the vicinity of docked synaptic vesicles which contain the neurotransmitter. Upon fusion of the vesicles

with the plasma membrane the neurotransmitter is released. The “fusion machinery” consists of a number of SNARE proteins (on both the plasma and vesicle membranes), among them  $Ca^{2+}$  dependent proteins. These are activated directly by  $Ca^{2+}$  entering via  $Ca_v$  channels, which are already complexed with parts of the “machinery” such as syntaxin.<sup>15,16</sup> Such a process highlights the critical role played by  $Ca_v$  channels in the transformation of an electrical signal in one cell (or cell population) into a chemical signal affecting neighboring cells (synaptic transmission) and remote cells or organs (hormone secretion).

Several  $Ca_v$  channels were shown to have an inactive ( $Ca^{2+}$  free) calmodulin tethered to a cytoplasmic C-terminus of the protein. Once the channel opens in response to membrane potential depolarization, the tethered calmodulin binds the entering  $Ca^{2+}$ , is activated, and in many cases enforces channel closure ( $Ca^{2+}$  dependent inactivation), forming a negative feedback loop on the  $Ca^{2+}$  entry activity.<sup>17</sup>

## Tissue Distribution

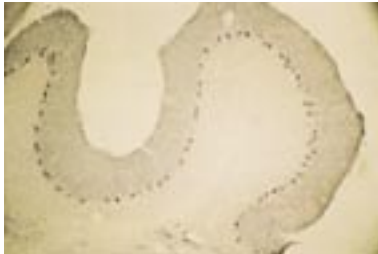
Although all  $Ca_v$  channels are mostly studied in excitable tissues, i.e. nerve and muscle, their presence and roles in other tissues (such as hormonal glands,<sup>18,19</sup> immune system cells,<sup>20</sup> kidney,<sup>21</sup> tumors<sup>22</sup> etc.) are important in a physiological and pathological context.  $Ca_v$  channels control key points in the  $Ca^{2+}$  activation of processes such as neurotransmitter release, skeletal, cardiac and smooth muscle contraction, gene expression, apoptosis and proliferation. Some  $Ca_v$  specific isoforms or splice variants are to a large extent cell type specific. For example,  $Ca_v1.1$  is expressed almost specifically in skeletal muscle and the protein functions as the main L-type channel in these cells, while the  $Ca_v1.4$  isoform is expressed mainly in the retina<sup>23</sup> and T-lymphocytes<sup>20</sup> and underlies their L-type currents. In contrast,  $Ca_v1.2$  is widely expressed, and this gene product underlies L-type currents in both cardiac and smooth muscle myocytes, in many neurons and pancreatic  $\beta$  cells. However, different gene products (splice variants) of the  $Ca_v1.2$  gene might be selectively expressed in one tissue compared to another.<sup>24,25</sup>  $Ca_v1.3$  is also expressed in several different tissues and knockout mice are affected with hearing loss and cardiac arrhythmia<sup>26</sup> as well as with impaired glucose metabolism.<sup>27</sup>

The  $Ca_v2$  family’s most notable function is in linking membrane potential depolarization to neurotransmitter release in presynaptic nerve terminals. As such, these channels are key regulators of neuronal communication. Within various nerve cell populations,  $Ca_v2$  family members are differentially expressed, sometimes with overlapping patterns.<sup>28</sup> Here as well, splice variants may be specifically expressed. A most interesting example is related to pain control with regard to an N-type channel ( $Ca_v2.2$ ) variant, which is selectively expressed in sensory neurons in DRG.<sup>29</sup>  $Ca_v2$  channels are modulated by G-protein coupled receptors, a cellular pathway that is most important to physiological processes such as hormonal regulation of neuronal activity as well as in clinical interventions such as morphine-induced analgesia.<sup>30</sup>

The three T-type ( $Ca_v3.1-3$ ) channel isoforms are also widely and differentially distributed and for members of this subfamily as well specific expression of splice variants was demonstrated.<sup>31</sup>

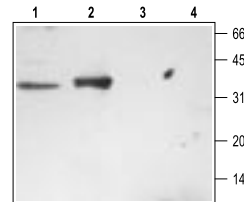
## Exocytotic Machinery Protein Antibodies

### Expression of Syntaxin 2 in Rat Cerebellum



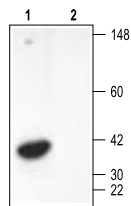
Immunohistochemical staining of Syntaxin 2 with Anti-Syntaxin 2 (#ANR-008) in the rat cerebellum. The soma of Purkinje cells are stained, as well as the upper layers of the cerebellum. Immunoreactive product is black.

### Western Blotting of Rat Brain and Kidney Membranes with Anti-Syntaxin 3



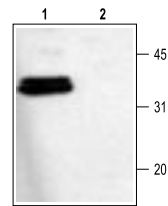
1. Rat brain membranes, Anti-Syntaxin 3 antibody (#ANR-005) (1:200).
2. Rat kidney membranes, Anti-Syntaxin 3 antibody (1:200)
3. Rat brain membranes, Anti-Syntaxin 3 antibody, preincubated with the control peptide antigen.
4. Rat kidney membranes, Anti-Syntaxin 3 antibody, preincubated with the control peptide antigen.

### Western Blotting of Rat Kidney Membranes with Anti-Syntaxin 4



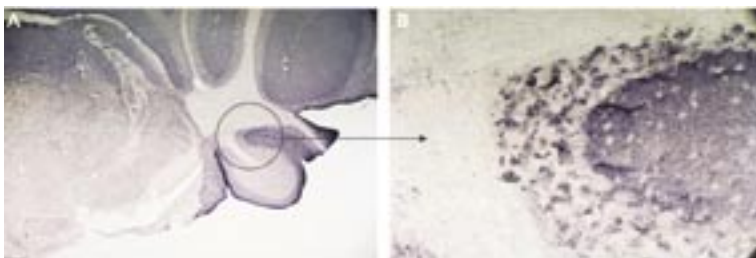
1. Anti-Syntaxin 4 antibody (#ANR-004) (1:600).
2. Anti-Syntaxin 4 antibody, preincubated with the control peptide antigen.

### Western Blotting of Rat Brain Membranes with Anti-Syntaxin 1



1. Anti-Syntaxin 1 antibody (#ANR-002) (1:1000).
2. Anti-Syntaxin 1 antibody, preincubated with the control fusion protein antigen.

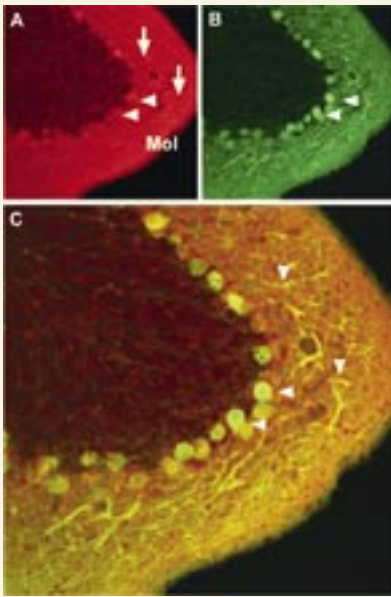
### Expression of VAMP-2 in Mouse Cerebellum



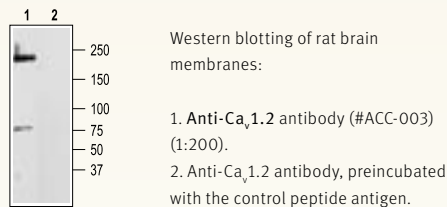
Immunohistochemical staining using Anti-VAMP-2, (#ANR-007) in mouse cerebellum (A). The entire molecular layer and patches of the granule layer were stained. The patchy pattern of staining is demonstrated in the circle shown in (A), magnified in (B).

## Use of Ca<sub>v</sub> Antibodies for Immunostaining of Mouse Cerebellum and Western Blots from Rat Brain

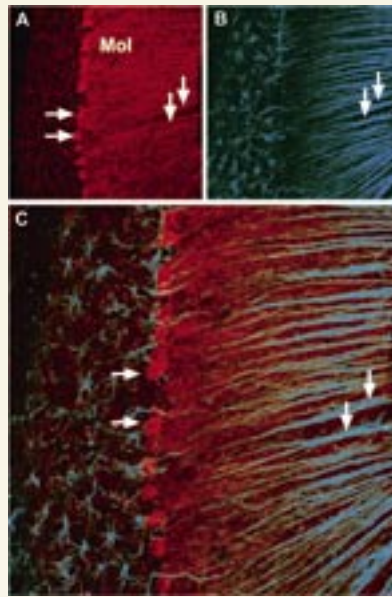
### Ca<sub>v</sub>1.2 (L-type)



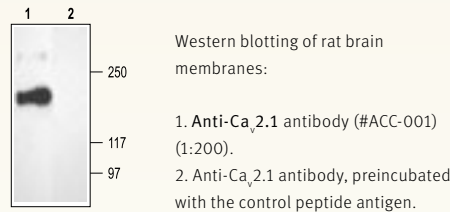
Immunohistochemical staining of Ca<sub>v</sub>1.2 channel with Anti-Ca<sub>v</sub>1.2 antibody (#ACC-003) in mouse cerebellum. (A) Ca<sub>v</sub>1.2 channel (red) appears in Purkinje cells (horizontal arrows) and is distributed diffusely in the molecular layer (Mol) including in Purkinje dendrites (vertical arrows). (B) staining of Purkinje nerve cells with mouse anti calcium binding protein (green) in the section demonstrates the location of dendrites in the molecular layer. (C) Confocal merge of Ca<sub>v</sub>1.2 and CBD28K.



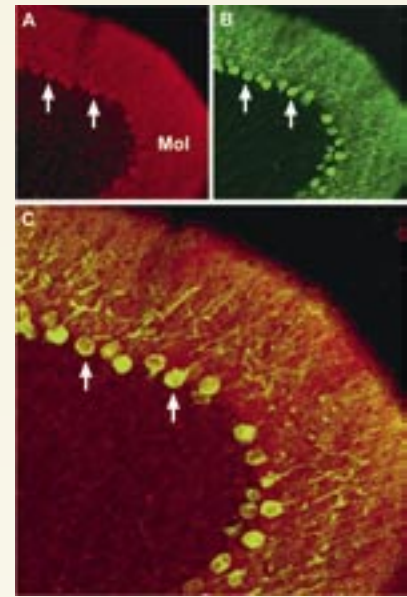
### Ca<sub>v</sub>2.1 (P/Q-type)



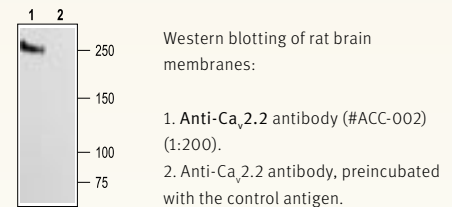
Immunohistochemical staining of Ca<sub>v</sub>2.1 channel with Anti-Ca<sub>v</sub>2.1 antibody (#ACC-001) in mouse cerebellum. (A) Ca<sub>v</sub>2.1 channel (red) appears in Purkinje cells (horizontal arrows) and is distributed diffusely in the molecular layer (Mol) including in astrocytic fibers (vertical arrows). (B) staining of astrocytic fibers with glial fibrillary acidic protein (blue - originally green digitally edited to blue) in the section demonstrates the location of astrocytic fibers in the molecular layer. (C) Confocal merge Ca<sub>v</sub>2.1 and GFAP.



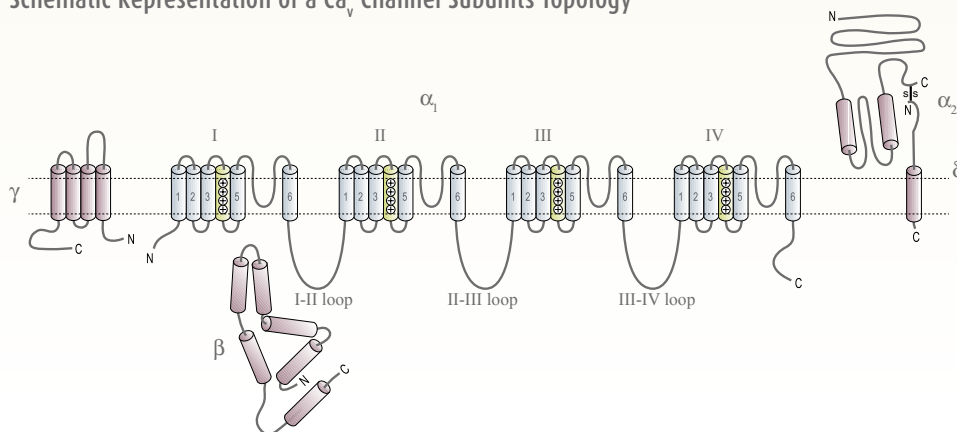
### Ca<sub>v</sub>2.2 (N-type)



Immunohistochemical staining of Ca<sub>v</sub>2.2 channel with Anti-Ca<sub>v</sub>2.2 antibody (#ACC-002) in mouse cerebellum. (A) Ca<sub>v</sub>2.2 channel (red) appears in Purkinje cells (arrows) and is distributed diffusely in the molecular layer (Mol). (B) staining of Purkinje nerve cells with mouse anti calcium binding protein (green) demonstrates the restriction of Ca<sub>v</sub>2.2 to cell bodies but not to dendrites in the molecular layer. (C) Confocal merge of Ca<sub>v</sub>2.2 and CBD28K.



## Schematic Representation of a Ca<sub>v</sub> Channel Subunits Topology



### Epitopes of Ca<sub>v</sub> Antibodies

Channel	Species	Epitope	Putative Location	Product #
Ca <sub>v</sub> 1.2	Rat	848-865	II-III loop	#ACC-003
Ca <sub>v</sub> 1.3	Rat	859-875	II-III loop	#ACC-005
Ca <sub>v</sub> 2.1	Rat	865-881	II-III loop	#ACC-001
Ca <sub>v</sub> 2.2	Rat	851-867	II-III loop	#ACC-002
Ca <sub>v</sub> 2.3	Rat	892-907	II-III loop	#ACC-006
Ca <sub>v</sub> 3.1	Rat	1-22	N-terminal	#ACC-021
Ca <sub>v</sub> 3.3	Rat	1053-1067	II-III loop	#ACC-009
β <sub>3</sub>	Rabbit	463-477		#ACC-008
α <sub>2</sub> δ <sub>1</sub>	Rabbit	27-41		#ACC-015
γ <sub>2</sub>	Mouse	213-228		#ACC-012

## Channelopathies, Toxins and Clinical Ca<sub>v</sub> Channel Blockers

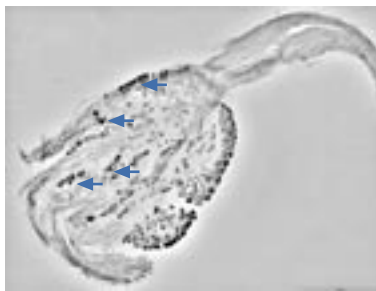
Mutations in Ca<sub>v</sub> channel genes are linked to several inherited neuronal (Ca<sub>v</sub>2.1) and muscular diseases (Ca<sub>v</sub>1.1)<sup>32</sup> as well to a multisystemic syndrome involving autism (Ca<sub>v</sub>1.2).<sup>33</sup> The latter exemplifies the general role played by this L-type channel in regulating Ca<sup>2+</sup> metabolism in excitable as well in non-excitable tissues (such as bone and lung). Although these mutations are rare, pharmacological interventions that target Ca<sub>v</sub> channels are widely used in the clinic,<sup>34-37</sup> among them antihypertensive drugs acting on smooth muscle Ca<sub>v</sub>1.2 channels or anticonvulsant drugs that target brain T-type channels. Recently, the FDA has approved Prialt™ (ziconotide) a synthetic version of ω-Conotoxin MVIIA, as a painkiller for some indications.<sup>38, 39</sup>

One of the first methods used to differentiate among voltage dependent Ca<sup>2+</sup> channels in assessing their particular physiological roles, is based on differential pharmacological sensitivities. Particularly, the differentiation between the presynaptic Ca<sub>v</sub>2 subfamily isoforms was facilitated due to specific toxin sensitivities. The cone snail peptides ω-Conotoxin GVIA and ω-Conotoxin MVIIA<sup>40</sup> inhibit the Ca<sub>v</sub>2.2 channel potently and specifically, while the spider toxin ω-Agatoxin IVA<sup>41</sup> is specific for Ca<sub>v</sub>2.1. Later, the tarantula peptide, SNX-482<sup>42</sup> was shown to be a specific blocker of Ca<sub>v</sub>2.3, which was associated with the toxin resistant R-type current. These toxins were used to block transmission in different synapses.<sup>43-45</sup>

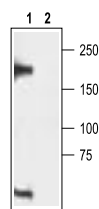
Other compounds that block Ca<sub>v</sub> channels are very useful in differentiating between subfamilies but have little selectivity toward specific isoforms within the subfamily. The Ca<sub>v</sub>1 subfamily proteins are often referred to as DHP receptors, as this group of chemical compounds interacts specifically with Ca<sub>v</sub>1 channels either as antagonists (such as nimodipine) or agonists (i.e. (-)-Bay K 8644). Other examples include, the scorpion peptide kurtoxin, that blocks all three T-type channels with similar potencies, but has little effect on other Ca<sub>v</sub> channels.<sup>(46, 47)</sup> In a similar manner Calcicludine<sup>48, 49</sup> and Calciseptine<sup>50, 51</sup>, toxins purified from the venom of the green and black mamba respectively, block L-type channels specifically, but little is known regarding their selectivity between Ca<sub>v</sub>1 subfamily channels.

Acknowledgements: We thank Annette C. Dolphin, Ph.D. from Department of Pharmacology, UCL, UK for her helpful comments.

### Expression of Ca<sub>v</sub>1.3 in Rat DRG



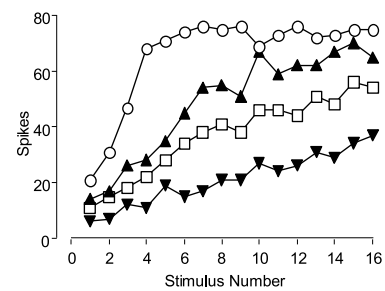
Staining of Ca<sub>v</sub>1.3 in adult rat dorsal root ganglion (DRG) with Anti-Ca<sub>v</sub>1.3 antibody (#ACC-005). Staining (black) appeared mostly in clusters of cells (arrows) with variable intensity, within the ganglion; not in the roots.



Western blotting of rat brain membranes proteins:

1. Anti-Cav1.3, (#ACC-005) (1:200).
2. Anti-Cav1.3, preincubated with the control peptide antigen.

### SNX-482 Effects in a Pain Model

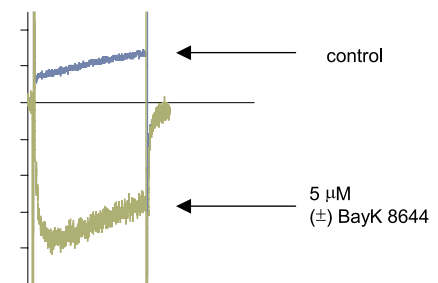
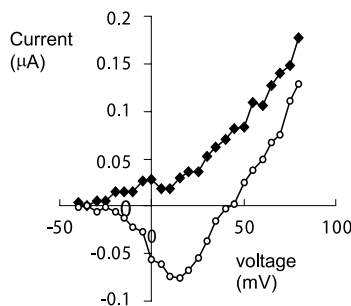


○ Pre - drug control    □ SNX -482 1.5 μg  
 ▲ SNX -482 0.5 μg    ▼ SNX -482 4 μg

Dose-related effects of SNX-482 (#S-500) on the wind-up of spinal neurons in Spinal Nerve Ligated (SNL) rats. The number of action potentials evoked per stimulus were plotted against the stimulus number, before and after drug administration in a single dorsal horn neuron. SNX-482 produced dose-related inhibitions of the wind-up of spinal neurons in SNL rats.

Acknowledgements: Stephens, G.J. Matthews, E. & Dickenson, A.H. (2003) *Soc. for Neurosci. Abst.* 33:589.10 Dept. of Pharmacology, University College London, UK.

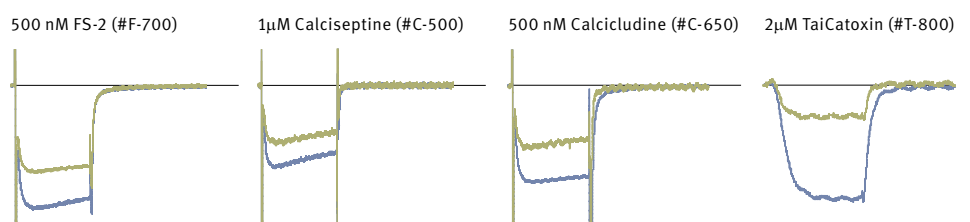
### Electrophysiological Detection of Ca<sub>v</sub>1 Current Induction by (±)-Bay K 8644



The effect of 5 μM (±)-Bay K 8644 (#B-350) on heterologously expressed L-type Ca<sup>2+</sup> currents (Ca<sub>v</sub>1.2 / α2δ1 / β2a, RNA injected into *Xenopus* oocytes). Left: I-V relation before (diamonds) and during (circles), bath perfusion of the compound. Right: Current response to 200 ms depolarization to +20mV (from holding potential of -100 mV) before (blue) and during (green) perfusion of the drug.

### Ca<sub>v</sub>1 (L-type) Channels Peptide Blockers

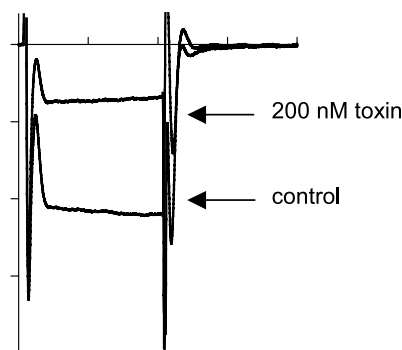
Inhibition of Ca<sub>v</sub>1.2 (α1C) channel currents in *Xenopus* oocytes by different peptide toxins



Each panel shows superimposed currents before (blue) and during bath perfusion of the indicated toxin (green).

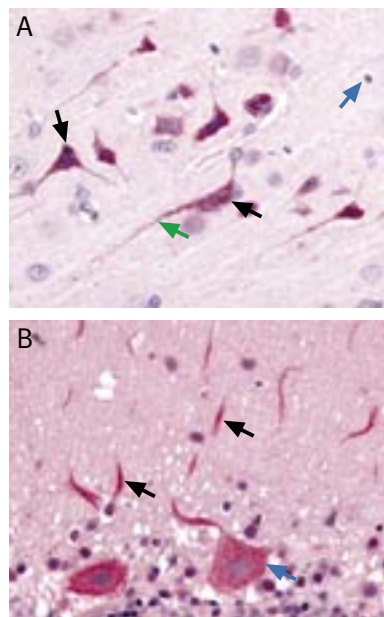
## ω-Conotoxin MVIIA-

### A Potent Blocker of N-type Channels

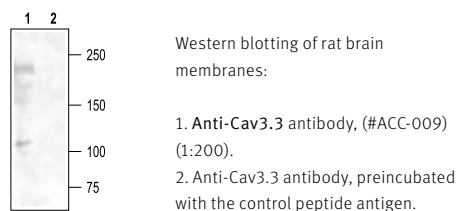


Inhibition of Ca<sub>v</sub>2.2 channels expressed in *Xenopus* oocytes by ω-Conotoxin MVIIA (#C-670). Traces before or during perfusion of 200 nM toxin.

### Expression of Ca<sub>v</sub>3.3 (T-type) in Rat Brain Cortex and Cerebellum



Immunohistochemical staining of Ca<sub>v</sub>3.3 channel with Anti-Ca<sub>v</sub>3.3 antibody (#ACC-009) in rat brain cortex and cerebellum. (A) Picture showing the third layer of the brain cortex. Pyramidal neurons cells (black arrow) and their axons (green arrow) shows strong staining. However, glial cells (blue arrows) show no staining at all. (B) Picture showing the Purkinje layer of the rat cerebellum. Note that Purkinje cells (blue arrows) and their axons (black arrows) were strongly stained. Staining product is red and counterstain is hematoxylin. Immunohistochemistry data provided by LifeSpan Biosciences, Seattle, USA.



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## Related Products

Compound	Product #
<b>Antibodies</b>	
Anti-Ca <sub>v</sub> 2.1 (α <sub>1a</sub> )	ACC-001
Anti-Ca <sub>v</sub> 2.2 (α <sub>1b</sub> )	ACC-002
Anti-Ca <sub>v</sub> 1.2 (α <sub>1c</sub> )	ACC-003
Anti-human Ca <sub>v</sub> 1.2 (α <sub>1c</sub> )	ACC-022
Anti-Ca <sub>v</sub> 1.2a (α <sub>1c</sub> Cardiac)	ACC-013
Anti-Ca <sub>v</sub> 1.3 (α <sub>1d</sub> )	ACC-005
Anti-Ca <sub>v</sub> 2.3 (α <sub>1e</sub> )	ACC-006
Anti-Ca <sub>v</sub> 3.1 (α <sub>1f</sub> )	ACC-021
Anti-Ca <sub>v</sub> 3.3 (α <sub>1g</sub> )	ACC-009
Anti-Ca <sub>v</sub> pan α1	ACC-004
Anti-Caβ3	ACC-008
Anti-Caγ2	ACC-012
Anti-Ca <sub>v</sub> α2δ-1	ACC-015
Anti-SNAP-25	ANR-001
Anti-Syntaxin 1	ANR-002
Anti-Syntaxin 2	ANR-008
Anti-Syntaxin 3	ANR-005
Anti-Syntaxin 4	ANR-004
Anti-Synaptotagmin I	ANR-003
Anti-VAMP-2	ANR-007
<b>Blockers</b>	
ω-Agatoxin IVA	A-500
ω-Agatoxin TK	A-530
Calcicludine	C-650
Calciseptine	C-500
ω-Conotoxin GVIA	C-300
ω-Conotoxin MVIIA	C-670
ω-Conotoxin MVIIIC	C-150
ω-Conotoxin SVIB	C-570
FS-2	F-700
ω-Grammotoxin SIA	G-450
PLTX-II	P-510
SNX-482	S-500
TaiCatoxin	T-800
<b>Activator</b>	
(±)-Bay K 8644	B-350