

The Role of Ion Channels in Neurodegeneration

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Neurodegenerative diseases take an enormous toll on society as well as on individuals. Very limited treatments for these diseases exist, since their molecular mechanisms are not well understood. Several ion channels, a group of membrane spanning proteins that regulate ion content and membrane potential in cells, have been implicated as important players in these diseases. While many Ca^{2+} conducting channels (Ca_v , P2X or glutamate receptors) may contribute to glutamate overload and excitotoxicity directly, K^+ channels often regulate the membrane potential controlling the Ca^{2+} signal indirectly. Below, we review the use of Alomone Labs' products in research related to the role ion channels play in these diseases.

Sodium, potassium, and calcium channels, as well as the glutamate receptors NMDA and AMPA have all been implicated in various neurodegenerative diseases. One of the main factors in neurotoxicity is glutamate overload.¹ Glutamate is the primary excitatory neurotransmitter of the nervous system. Following glutamate release, postsynaptic responses occur through both metabotropic and ionotropic receptors. However, in 1957, excess glutamate was shown to be toxic. The term "excitotoxicity" was coined to represent the neurotoxicity caused by excess of excitatory neurotransmitters.² It is now well accepted that a strong relationship exists between excessive Ca^{2+} influx and glutamate-triggered neuronal injury.³ The NMDA receptor in particular has been implicated in this process⁴ as well as the P2X7 receptor. P2X7 receptors are localized to the excitatory terminals in the hippocampus, as shown by immunohistochemistry using **Anti-P2X7** antibody (#APR-004).⁵ Calcium overload can trigger many downstream neurotoxic cascades including activation of proteases, protein kinases, nitric oxide synthetase, calcineurins, which leads to increased production of toxin-reactive oxygen species, alteration in the cytoskeleton, mitochondrial dysfunction, and activation of genetic signals leading to cell death.¹ The pervasive involvement of Ca^{2+} in neuronal function suggested that altered Ca homeostasis may be a fundamental mediator of age related changes in the nervous system.⁶

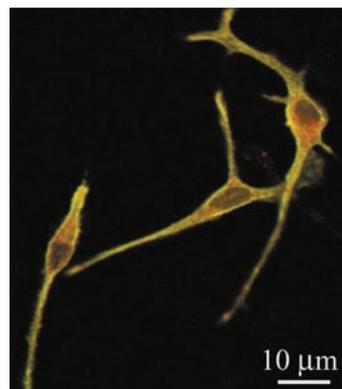
Alzheimer's disease is a progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions such as memory and learning. It is the most common cause of dementia. The neurodegeneration in Alzheimer's disease is postulated to involve the loss of acetylcholine

receptors from the basal forebrain cholinergic neurons (BCFN)⁷, whose numbers are shown to decrease early in the disease process. In addition, potassium channels, specifically $\text{K}_v3.1$ and $\text{K}_v2.1$ have been implicated. Immunohistochemical techniques, using **Anti- $\text{K}_v3.1$** antibody (#APC-014) and **Anti- $\text{K}_v2.1$** antibody (#APC-012) were used to investigate the expression of these channels and both were found to be expressed in the BCFN.⁷ Basal forebrain neurons are susceptible to changes associated with aging and related dysfunctions, such as Alzheimer's. The involvement of the smooth endoplasmic reticulum (SER) was investigated using the SER Ca^{2+} uptake blocker, **Thapsigargin** (#T-650), however it was not found to mediate the age-related changes.⁶

The accumulation of plaques of amyloid beta (a peptide of 39–43 amino acids) is a hallmark of the disease and much effort has been expended to understand how these plaques interfere in the normal functioning of the brain. It has been suggested that these amyloid plaques form calcium-conducting ion channels that cause rapid neurodegeneration due to calcium overload.⁸ In addition, the plaques have been postulated to interfere with neuronal signaling via the nicotinic acetylcholine receptor in the early stages of the disease.⁷ The stimulatory effect of amyloid beta was partially dependent on voltage gated Ca^{2+} channels at low concentrations, as shown by the ability of a mixture of Ca^{2+} channel blockers, **ω -Agatoxin-TK** (#A-530), **ω -Conotoxin MVIIC** (#C-150) and **ω -Conotoxin GVIA** (#C-300) to partially attenuate increases in Ca^{2+} concentration in isolated hippocampal nerve endings in the rat.⁷ A-type K^+ channels have been implicated in the onset of LTP in mammalian neurons, which is thought to underlie learning and memory, which are progressively impaired in Alzheimer's disease. To determine which channels underlie

these currents in a drosophila model, specific blocker of the $\text{K}_v4.2$ channel, **Phrixotoxin-2** (#P-700) and specific blocker of the Shaker channel **α -Dendrotoxin** (#D-350) were used. Treatment of cells with amyloid peptide altered the kinetics of the current and caused a decrease in neuronal viability.⁹ Glutamate toxicity has

Membrane Localization of $\text{K}_v1.3$ in Rat Microglial Cultures



Representative confocal immunofluorescence images of rat microglia showing colocalization of the membrane-delimited marker, OX-42, with $\text{K}_v1.3$. OX-42 primary antibody was used with a biotinylated secondary antibody and FITC-conjugated streptavidin (green labeling), and **Anti- $\text{K}_v1.3$** (#APC-002) primary antibodies were used with a Cy3-conjugated secondary antibody (red labeling). For each cell, the same confocal plane was used for acquisition, thus colocalization of channel and microglial membrane is represented by yellow regions in the merged images.

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also been postulated, as the NMDA receptor antagonist, memantine, has been approved for the treatment of Alzheimer's.¹⁰

Damage by reactive oxygen species caused by the activation of microglia has been documented in Alzheimer's disease. Several K⁺ channels have been shown to be involved in this respiratory burst by blocking current in cultured rat glia using the specific K⁺ channel blocker **rAgitoxin-2** (#RTA-420).¹¹ Blockage of the respiratory burst by rAgitoxin-2 further demonstrated the involvement of K⁺ channels. Western blot analysis of microglial lysates using **Anti-K_v1.3** antibody (#APC-002) **Anti-K_v1.5** antibody (#APC-004) and **Anti-K_{ca}2.3** antibody (#APC-103) and confocal imaging corroborated these findings. K_v1.3 blockers **rCharybdotoxin** (#RTC-325), rAgitoxin-2 and α-Dendrotoxin reduce neuron killing by microglia as shown by TUNEL analysis of neurons treated by activated microglia.¹² K_{ca}3.1 is highly expressed in microglia, as shown by immunoblotting with **Anti-K_{ca}3.1** antibody (#APC-034) and has been shown to be a possible therapeutic target in acute and chronic neurodegenerative disorders.¹³

Familial amyloidotic polyneuropathy (FAP) is a neurodegenerative disease that occurs in the PNS and is characterized by extracellular deposition of amyloid fibrils composed of misfolded transthyretin (TTR). The disruption of Ca²⁺ homostasis by TTR thru N-type Ca²⁺ channels has been proposed as the mechanism for its cytotoxicity based on the finding that the specific blocker, Conotoxin GVIA significantly reduced the TTR-induced increased in internal Ca²⁺ concentration.¹⁴

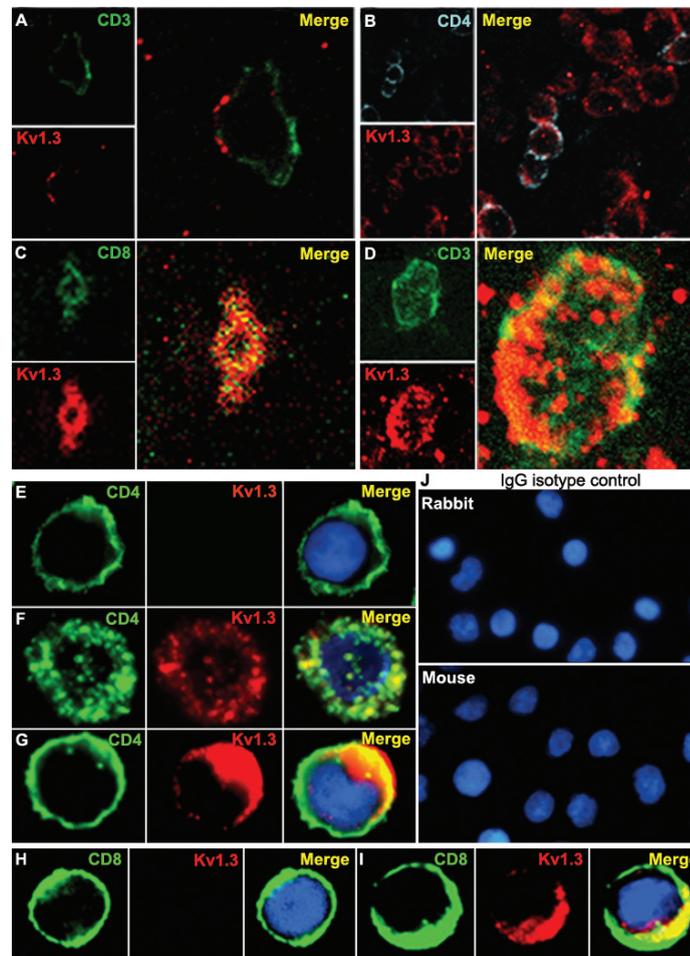
Amyotrophic Lateral Sclerosis (ALS) is a chronic, progressive disease marked by gradual degeneration of the nerve cells in the central nervous system that control voluntary muscle movement. The disorder causes muscle weakness and atrophy. The cause is unknown, and there is no known cure. It has been found that the motoneurons which innervate tongue muscles are vulnerable to degeneration in ALS and this is linked to the differential expression of voltage activated Ca²⁺ channels.¹⁵ It was found that there is a 3.5 fold greater expression of P/Q type current in these motoneurons as opposed to those which innervate extraocular muscles as was shown by immunolabelling using **Anti-Ca_v2.1** antibody (#ACC-001). Identity of the channels was confirmed by determining the sensitivity of the Ca²⁺ currents to channel blockage using the N-type blocker ω-ConotoxinGVIA and the P/Q blocker ω-Agatoxin-TK.

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system in which gradual destruction of myelin occurs in patches throughout the brain or spinal cord (or both), interfering with the nerve pathways and causing muscular weakness, loss of coordination and

speech and visual disturbances. MS is the most common neurological cause of disability in young adults in industrialized societies.¹⁶ Recent studies have identified changes in the expression pattern of specific Na⁺ channel isoforms as an important contributor to remission and progression in MS, and there is evidence suggesting that aberrantly expressed Na⁺ channels might also contribute to cerebellar dysfunction in MS.¹⁶ Changes that have, in the past, been attributed to the

demyelination may, in fact, be heavily dependent upon the changes in ion channels.¹⁷ It has been suggested that K_v3.1b interferes with conduction in demyelination axons.¹⁸ The presence of K_v3.1b in CNS nodes has been shown using **Anti-K_v3.1b** antibody (#APC-014). The expression of K_v1.3 in postmortem MS brain tissue has been shown by immunohistochemical analysis and confocal microscopy using Anti-K_v1.3 antibody.¹⁹ EAE is widely used experimental model for MS. In

Immunohistochemical Staining of K_v1.3 in Human MS Brain



Immunohistochemical staining of K_v1.3 in human MS brain floating sections using **Anti-K_v1.3** antibody (#APC-002). Confocal microscopy of K_v1.3 and CD3/CD4 in MS brain tissue. Confocal microscopic images of 20-μm floating sections of postmortem MS brain tissue. (A and B) Parenchymal infiltrate with positive CD3 and punctate K_v1.3 staining in the membrane. (C) A cluster of lymphocytes stained positively for K_v1.3 and CD4, as well as occasional CD8 (Inset). (D) CD3⁺ cells showed extensive K_v1.3 and CD3 colocalization in the membrane. Immunofluorescent staining of PB-derived T cells concentrated on a slide by cytospin showed membrane patterns of staining of CD4, CD8, and K_v1.3. (E) Day 7-activated naive and TCM are CD4⁺, CCR7⁺ (data not shown) and K_v1.3⁺. (F) Chronically stimulated resting TEM were CD4⁺, CCR7⁺ (data not shown) and expressed K_v1.3 in the membrane but with minimal colocalization with CD4. (G) TEM that had been recently activated expressed increased amounts of K_v1.3 and demonstrated more colocalization with CD4 similar to the brain tissue lymphocyte in D. (H) Naive CD8⁺ T cells expressed no K_v1.3 but, when chronically stimulated and activated (I), exhibited intense K_v1.3 expression and colocalization with CD8. (J) Isotype controls using nonspecific rabbit primary antibody followed by usual secondary label and with primary rabbit anti-human and nonspecific labeled mouse anti-rabbit secondary antibody showed no background staining.

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this model it has been shown that cell damage does not lead to an increase in endocannabinoid-mediated neuroprotection (as occurs in normal cells) because of disruption in the functionality of P2X7 receptors in the microglia caused by interferon-gamma. This was shown by immunoprecipitation experiments using **Anti-P2X7** antibody (#APR-004) in primary microglia cultures. These experiments showed that the overall expression of the receptors was not changed nor was their expression at the plasma membrane affected. It has been proposed that voltage gated Na⁺ channels can provide a route for Na⁺ influx into axons which triggers influx of damaging levels of intra-axonal Ca²⁺.²⁰ The molecular identities of the channels involved has been investigated by immunocytochemistry using **Anti-Na_v1.2** antibody (#ASC-002) and **Anti-Na_v1.6** antibody (#ASC-009) in the spinal columns of EAE mice. A significant increase in the number of demyelinated axons demonstrating Na_v1.2 and Na_v1.6 staining was shown. *Shiverer* mice have been widely used as a non-injury model in remyelination studies.²¹ The specific functional role of K_v1.1 and K_v1.2 in these mice was studied using **Dendrotoxin-I** (#D-390) and **Dendrotoxin-K** (#D-400). Distribution and changes in expression were studied using **Anti-K_v1.1** antibody (#APC-009) and **Anti-K_v1.2** antibody (#APC-010).

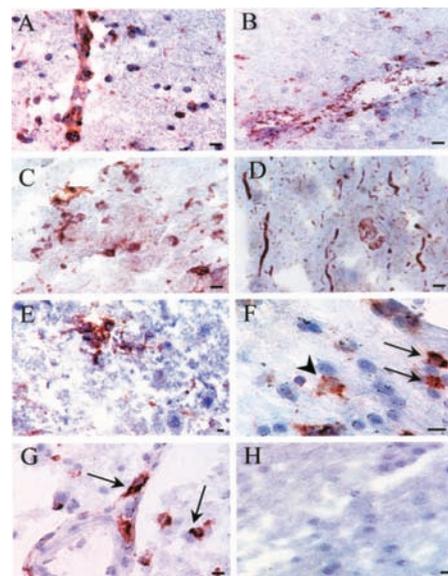
Parkinson's disease (PD) is a slowly progressive degenerative disorder of the central nervous system characterized by slowness or poverty of movement (bradykinesia), rigidity, postural instability, and tremor primarily while at rest. Potassium channels have been implicated in the pathogenesis of PD. K_{ATP} channels comprised of K_v6.2 and Sur1 are abundantly expressed in substantia nigra dopamine neurons, which are the type of neurons that show degradation in Parkinson's disease.²² GIRK-2 has been shown to be linked to the degeneration of dopaminergic neurons. Ventral mesencephalic cultures positive for GIRK-2, as shown by immunocytochemistry using **Anti-K_v3.2** antibody (#APC-006) were more vulnerable to MPP⁺-induced neurotoxicity.²³ The weaver mutation causes neuronal degradation and severe motor dysfunction caused by alterations in the inward rectifier channel and is often used as a model for PD. A population of granule cells expressed an inwardly-rectifying channel which was suggested to be GIRK-2 due to its sensitivity to **QX-314** (#Q-100).²⁴

Duchenne muscular dystrophy (DMD) is a form of muscular dystrophy that is characterized by decreasing muscle mass and progressive loss of muscle function in male children. It is the most common congenital human

neuromuscular disease. It is caused by a mutation in the dystrophin gene, a protein which forms a transmembrane complex linking the cytoskeleton to extracellular proteins in many tissues. In dystrophin mutants immunostaining using **Anti-GABA_Aα1** antibody (#AGA-001) has shown that the size and number of GABA receptor clusters are decreased at cerebellar inhibitory synapses.²⁵

Recently, mutations in ion channels have been shown to play a role in spinocerebellar ataxias. Spinocerebellar ataxia (SCA) is one of a group of genetic disorders characterized by slowly progressive incoordination of gait and is often associated with poor coordination of hands, speech, and eye movements. In SCA13, mutations in K_v3.3 have been shown to have a key role and to

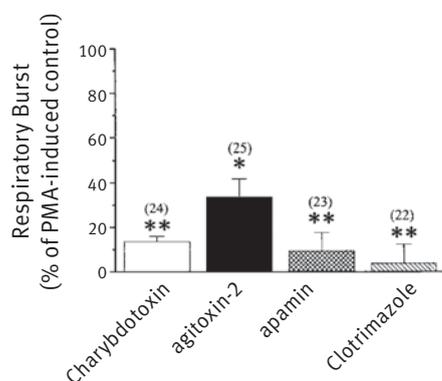
Expression of K_v1.3 in White and Grey Matter in Human MS Brain



Immunohistochemical staining of K_v1.3 in normal appearing white and grey matter in human MS brain using **Anti-K_v1.3** antibody (#APC-002). MS brain cryostat sections that were grossly uninvolved were examined for K_v1.3 expression. (A) K_v1.3 deposits were found on perivascular and parenchymal inflammatory cells in the normal appearing white matter. (B) Many of these cells stained positively for CD68. (C) K_v1.3 staining was also seen on parenchymal cells in the grey matter. (D) Phosphorylated neurofilament staining showed axonal fragmentation and swelling in a normal appearing grey matter area, which was a consecutive section for the K_v1.3 staining seen only on inflammatory cells in C. (E) Some of the cells were branched process bearing cells with an appearance suggestive of microglia. (F) Double labeling identified some K_v1.3⁺ cells as CD68⁺ cells (arrows red-K_v1.3, dark brown CD68); not all CD68 cells expressed K_v1.3 (arrowheads). (G) Double labeling with CD3 (dark brown) and K_v1.3 (red) was also clearly seen. Not all K_v1.3-expressing cells are CD68 positive. (H) Control of the immunoperoxidase reaction. (Scale bar, 20 μm in A, B, D, G, and H; 50 μm in C and E; and 10 μm in F.)

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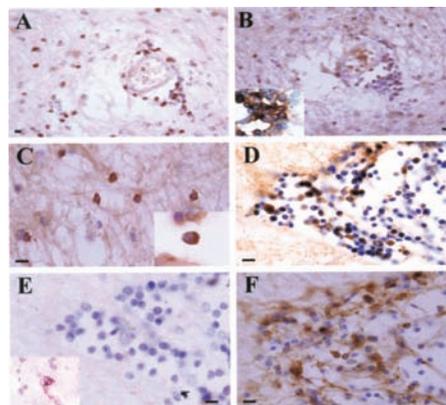
K⁺ Channel Blockers Reduce the PMA-Induced Respiratory Burst in Rat Microglia



Microglia were incubated in 2 mM DHR 123 and the fluorescence monitored for 5 min to ensure a stable baseline. A K⁺ channel blocker was perfused into the bath, the fluorescence recorded continuously for a further 5 min, then the bath was perfused with the blocker plus 100 nM PMA. The fluorescence signal from several cells in each field was monitored for a further 45 min, and the final average value compared with control cells from the same batches (number of cells from at least 3 rat litters indicated). The drug concentrations were 50 nM **rCharybbotoxin** (#RTC-325), 5 nM **rAgitoxin-2** (#RTA-420), 1.2 nM Apamin, and 500 nM Clostrimazole. *P, 0.05 and **P, 0.001, values significantly different from controls.

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Expression of K_v1.3 in Inflammatory Cells in Human MS Brain



Immunohistochemical staining of K_v1.3 in inflammatory cells in human MS brain using **Anti-K_v1.3** antibody (#APC-002). Paraffin sections were stained by indirect immunoperoxidase for K_v1.3, CD3, CD4, CCR7, and CCR5. Areas used in sectioning were from a white matter plaque. There were many perivascular inflammatory cells that stained positively for CD3 (A), K_v1.3 (B), and CD4 (B Inset) on consecutive sections. (C) K_v1.3 was also localized on inflammatory cells in the white matter parenchyma (Inset reveals membrane polarization of K_v1.3 staining). (D) Consecutive sections through another perivascular infiltrate revealed numerous K_v1.3⁺ inflammatory cells, which were predominantly CCR7⁺ (E) (Inset reveals rare CCR7 positive staining), and CCR5⁺ (F). (Scale bar, 50 μm in A and B and 20 μm in C, D, E, and F.)

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alter the channel properties, leading to a change in the firing patterns of neurons, explaining the physiological manifestations of the disease.²⁶ In a different type of ataxia, SCA63, a degenerative disorder of the cerebellum characterized by nearly selective and progressive death of Purkinje cells, the mutation is in the $\alpha 1A$ subunit of the neuronal P/Q-type voltage-gated calcium channel.²⁷ This mutation leads to an expanded region of glutamine residues that shifts the voltage dependence of channel activation and rate of inactivation and impairs normal G-protein regulation of P/Q channels. Using the specific antibody Anti-Ca_v2.1 antibody has been shown that this pathological expansion can be expressed in multiple isoforms of the Ca_v2.1 subunit.

An important aspect of these findings is that the underlying mechanisms for many neurodegenerative diseases was thought to lie in accumulation of misfolded, aggregated proteins; the involvement of ion channels in neurodegenerative disease opens up a whole new avenue of therapeutic possibilities.¹⁷

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Related Products

Compound	Product #
Antibodies to Voltage-Gated Ca²⁺ Channels	
Anti-Ca _v 2.1 ($\alpha 1A$)	ACC-001
Anti-Ca _v 2.2 ($\alpha 1B$)	ACC-002
Anti-Ca _v 1.2 ($\alpha 1C$)	ACC-003
Anti-Ca _v 1.2-ATTO-488	ACC-003-AG
Anti-human Ca _v 1.2 ($\alpha 1C$)	ACC-022

Anti-Ca _v 1.2a ($\alpha 1C$ Cardiac)	ACC-013
Anti-Ca _v 1.3 ($\alpha 1D$)	ACC-005
Anti-Ca _v 2.3 ($\alpha 1E$)	ACC-006
Anti-Ca _v 3.1 ($\alpha 1G$)	ACC-021
Anti-Ca _v 3.2 ($\alpha 1H$)	ACC-025
Anti-Ca _v 3.3 ($\alpha 1I$)	ACC-009
Anti-Ca _v pan $\alpha 1$	ACC-004

Antibodies to Voltage-Gated Na⁺ Channels

Anti-Na _v 1.1	ASC-001
Anti-Na _v 1.2	ASC-002
Anti-Na _v 1.3	ASC-004
Anti-Na _v 1.4	ASC-020
Anti-Na _v 1.5	ASC-005
Anti-human Na _v 1.5	ASC-013
Anti-Na _v 1.6	ASC-009
Anti-Na _v 1.7	ASC-008
Anti-Na _v 1.8	ASC-016
Anti-Na _v 1.9	ASC-017
Anti-Pan Na _v	ASC-003
Anti-Na $\beta 2$	ASC-007

Antibodies to Voltage Activated K⁺ Channels

Anti-K _v 1.1	APC-009
Anti-K _v 1.2	APC-010
Anti-K _v 1.3	APC-002
Anti-K _v 1.3 (extracellular)	APC-101
Anti-K _v 1.3 (extracellular)-FITC	APC-101-F
Anti-K _v 1.4	APC-007
Anti-K _v 1.5	APC-004
Anti-K _v 1.6	APC-003
Anti-K _v 1.7	APC-063
Anti-K _v 2.1	APC-012
Anti-K _v 2.2	APC-120
Anti-K _v 3.1b	APC-014
Anti-K _v 3.2	APC-011
Anti-K _v 3.3	APC-102
Anti-K _v 3.4	APC-019
Anti-K _v 4.1	APC-119
Anti-K _v 4.2	APC-023
Anti-K _v 4.3	APC-017
Anti-K _v 7.1 (KCNQ1)	APC-022
Anti-K _v 7.2 (KCNQ2)	APC-050
Anti-K _v 7.3 (KCNQ3)	APC-051
Anti-K _v 10.1 (EAG-1)	APC-104
Anti-KV10.2 (EAG-2)	APC-053
Anti-K _v 11.1 (erg1)	APC-016
Anti-hK _v 11.1 (HERG)	APC-062
Anti-K _v 11.1 (HERG) (extracellular)	APC-109
Anti-K _v 11.1 (HERG) (extracellular) FITC	APC-109-F
Anti-K _v 11.2 (erg2)	APC-114
Anti-K _v 11.3 (erg3)	APC-112
Anti-K _v 12.1 (Elk1)	APC-113

Antibodies to Ca²⁺ Activated K⁺ Channels

Anti-K _{Ca} 1.1 (1098-1196)	APC-021
Anti-K _{Ca} 1.1 (1184-1200)	APC-107
Anti-K _{Ca} 2.1	APC-039
Anti-K _{Ca} 2.2	APC-028
Anti-K _{Ca} 2.3 (N-term)	APC-025
Anti-K _{Ca} 2.3 (C-term)	APC-103
Anti-K _{Ca} 3.1	APC-064

Antibodies to Inward Rectifier K⁺ Channels

Anti-K _{ir} 1.1	APC-001
Anti-K _{ir} 2.1	APC-026
Anti-K _{ir} 2.2	APC-042
Anti-K _{ir} 2.3	APC-032
Anti-K _{ir} 3.1	APC-005
Anti-K _{ir} 3.2	APC-006
Anti-K _{ir} 3.3	APC-038
Anti-K _{ir} 3.4	APC-027
Anti-K _{ir} 4.1	APC-035
Anti-K _{ir} 4.2	APC-058
Anti-K _{ir} 6.1	APC-105
Anti-K _{ir} 6.2	APC-020

Antibodies to Ligand-Gated Channels

Anti-GABA (A) $\alpha 1$	AGA-001
Anti-GABA (A) $\alpha 2$	AGA-002

Anti-GABA (A) $\alpha 3$	AGA-003
Anti-GABA (A) $\alpha 6$	AGA-004
Anti-GABA(A) $\gamma 2$	AGA-005
Anti-P2X1	APR-001
Anti-P2X2	APR-003
Anti-P2X3	APR-016
Anti-P2X4	APR-002
Anti-P2X5	APR-005
Anti-P2X7	APR-004

Voltage-Gated Ca²⁺ Channel Blockers

ω -Agatoxin IVA	A-500
ω -Agatoxin TK	A-530
Calciclude	C-650
Calciseptine	C-500
ω -Conotoxin GVIA	C-300
ω -Conotoxin MVIIA	C-670
ω -Conotoxin MVIIC	C-150
FS-2	F-700
ω -Grammotxin SIA	G-450
PLTX-II	P-510
SNX-482	S-500
TaiCatoxin	T-800

K⁺ Channel Blockers

rAa1	RTA-400
rAgitoxin-1	RTA-150
rAgitoxin-2	RTA-420
rAgitoxin-3	RTA-390
Apamin	A-200
BDS-I	B-400
BDS-II	B-450
rBeKm-1	RTB-470
rCharybdotoxin	RTC-325
α -Dendrotoxin	D-350
β -Dendrotoxin	D-360
γ -Dendrotoxin	D-370
δ -Dendrotoxin	D-380
Dendrotoxin-I	D-390
Dendrotoxin-K	D-400
E-4031	E-500
rErgotoxin-1	RTE-450
rHeteropodatoxin-2	RTH-340
rHogotoxin-1	RTH-400
rIberiotoxin	RTI-400
rKaliotoxin-1	RTK-370
rLq2	RTL-550
MCD-Peptide	M-250
rMargatoxin	RTM-325
rMaurotoxin	RTM-340
rNoxiustoxin	RTN-340
rOsK-1	RTO-150
Paxilline	P-450
Penitrem A	P-650
Phrixotoxin-2	P-700
Stromatoxin-1 (rSCTx-1)	RTS-350
rScyllatoxin	RTS-370
rSlotoxin	RTS-410
Stichodactyla Toxin (ShK)	S-400
rTamapin	RTT-400
rTertiapin	RTT-250
rTertiapin-Q	RTT-170
rTityustoxin Ka	RTT-360
Verruculogen	V-500

Intracellular Ca²⁺ Mobilizers

A23187	A-600
Anhydronodine	A-510
Cyclopiazonic Acid	C-750
Imperatoxin A	I-300
rMaurocalcine	RTM-100
Ochratoxin A	O-400
Ryanodine	R-500
tBuBHQ	T-220
Thapsigargin	T-650
Thapsigargin Epoxide	T-670

Ca²⁺ Ionophores

A23187	A-600
Ionomycin	I-700