

Ca²⁺-Dependent K⁺ (K_{Ca}) Channels: At the Crossroads of Cell Metabolism

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K⁺ channels are the largest and most diverse superfamily of ion channels. They are ubiquitously expressed in both excitatory and non-excitatory cells where they play a role in an assortment of different physiological functions such as cell proliferation and apoptosis, neuro- and cardio-protection, neuronal excitability, muscle contraction and salt secretion. Among this diversity the Ca²⁺-dependent K⁺ channel (K_{Ca}) subfamily is unique in that they integrate changes in intracellular Ca²⁺ concentrations with membrane excitability in both neuronal and non-neuronal cell types.

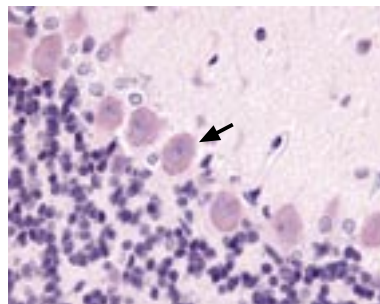
Introduction

The K_{Ca} channel subfamily of K⁺ channels can be classified into three groups based on their biophysical characteristics and single channel conductance (see Table for the current nomenclature). The large conductance (100-300 pS) K_{Ca} group includes the K_{Ca}1.1 channel, the intermediate conductance (25-100 pS) consists of the K_{Ca}3.1 channel and the small conductance (2-25 pS) group comprises the K_{Ca}2.1, K_{Ca}2.2 and K_{Ca}2.3 channels. The large conductance K_{Ca}1 group probably also includes the products of three other novel genes: K_{Ca}4.1 (or KCNT1, Slack), K_{Ca}4.1 (KCNT2) and K_{Ca}5.1 (KCNMC1, *slo-3*), some of which likely function as Na⁺-dependent K⁺ channels and will not be further discussed in this review.

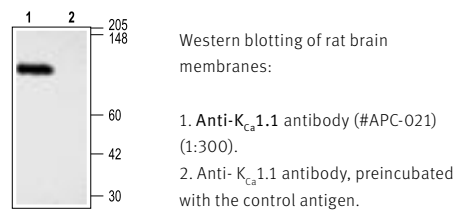
All K_{Ca} channels open in response to an increase in intracellular Ca²⁺ in the micromolar range while the K_{Ca}1.1 channel is the only one that can also be activated by membrane depolarization. The K_{Ca}1.1 is also unique in its topology, which includes seven transmembrane domains with an extracellular N-terminus and differs from that of the other K_{Ca} channels that resemble the structure of the voltage-gated K⁺ channels (six transmembrane domains with intracellular N- and C-termini). The functional channel of all the K_{Ca} family members is a multimeric protein composed of four pore-forming subunits with (in the case of the K_{Ca}1.1 channel) an occasional auxiliary (β) subunit.

K_{Ca} channels are expressed in virtually all cells where they integrate cellular metabolism with

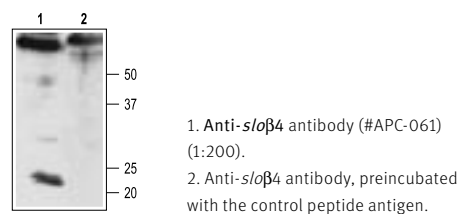
Expression of K_{Ca}1.1 in Rat Cerebellum



Immunohistochemical staining of K_{Ca}1.1 channel with Anti-K_{Ca}1.1 (1098-1196) (BK_{Ca}) antibody (#APC-021) in rat cerebellum. Picture showing the Purkinje layer. Note that Purkinje Cells (arrow) show an intense staining. Reaction product is pale red and counterstain is hematoxylin. Immunohistochemistry data provided by LifeSpan Biosciences, Seattle, USA.



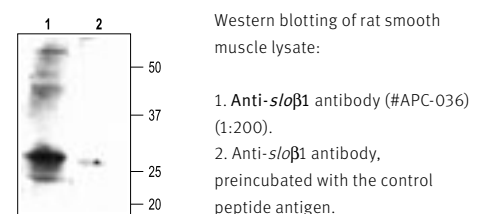
Western Blotting of Rat Brain Membranes with Anti-*slo*β4



Expression of *slo*β1 in Rat Pulmonary Artery



Immunohistochemical staining of *slo*β1 with Anti-*slo*β1 (KCNMB1) antibody (#APC-036) in rat pulmonary artery smooth muscle cells. (A) Transversal section of the pulmonary artery. Arrows show strongly stained myocytes. (B) Enlargement. DAB product is brown and the counterstain is Cresyl Violet.



membrane excitability thus contributing to various and diverse physiological outcomes. In this review we will summarize the biophysical characteristics of these channels and some of their physiological functions.

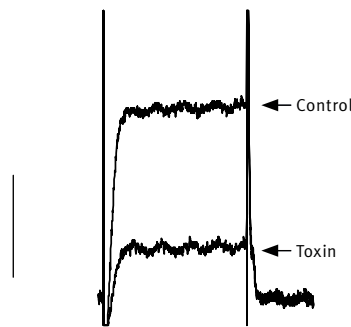
1. K_{Ca} 1.1: Modulating Smooth Muscle Tone and Neurotransmitter Release

General Considerations

The K_{Ca} 1.1 channel is by far the most studied of the K_{Ca} subfamily. The channel is ubiquitously expressed in almost all cell types where it participates in an astounding array of physiological functions. It was first characterized in *Drosophila* as the *slowpoke* channel and later identified in mouse and humans.¹ Given the fact that native currents of the K_{Ca} 1.1 channel with very different properties were known at the time, it was surprising that only one gene corresponding to the channel had been identified. Moreover, the K_{Ca} 1.1 channel gene is remarkably conserved among different species in mammals, suggesting that there is evolutionary pressure to maintain its optimized function.^{1,2} The different native channel properties found in various tissues can

be explained, for instance, by association of the channel with modulatory subunits and/or by alternative splicing. Indeed, both mechanisms account for the observed K_{Ca} 1.1 variability but the former has been more extensively examined. Four auxiliary β subunits have been identified that share a membrane topology consisting of

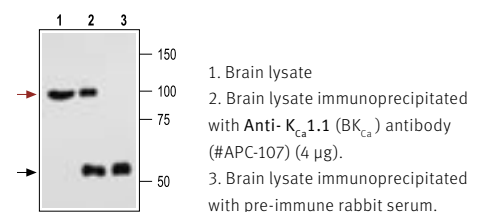
Inhibition of K_{Ca} 1.1 Channels by rCharybdotoxin



The effect of 100 nM rCharybdotoxin (#RTC-325) on K_{Ca} 1.1 (*mSlo*) expressed in *Xenopus* oocytes. Superimposed traces before and during perfusion of the toxin. Membrane holding potential was -100 mV, stepped every 15 s. to $+20$ mV for 100 ms. The vertical bar represents 0.1 μ A for K_{Ca} 1.1.

two transmembrane domains, an extracellular loop and cytoplasmic N- and C-termini (see Table) and have different expression patterns. The first regulatory subunit (now termed *sloβ1*) was identified in smooth muscle preparations on the basis of its high affinity for Charybdotoxin (CTX) a known peptide blocker of K_{Ca} 1.1 (see Table).^{3,4} As a whole, the four regulatory subunits increase the sensitivity of the pore-forming K_{Ca} 1.1 subunit to Ca^{2+} and voltage and they can also change its pharmacology and/or act as receptors for drugs.

Immunoprecipitation of Rat Brain with Anti- K_{Ca} 1.1



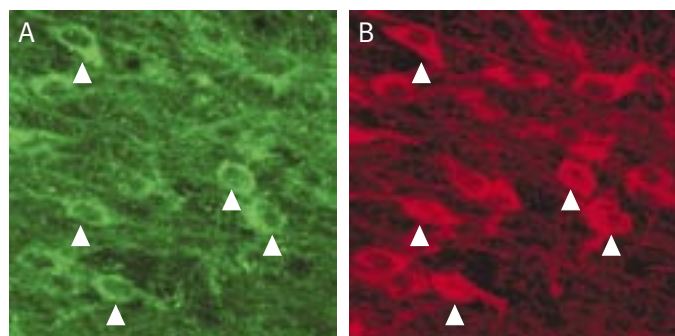
The upper arrow indicates the K_{Ca} 1.1 channel while the lower arrow indicates the IgG heavy chain. Western blotting was performed with Anti- K_{Ca} 1.1 antibody.

The K_{Ca} Family Members and Auxiliary Subunits

Current name	Other names	Subfamily	Topology	Gating	Expression	Active toxins
K_{Ca} 1.1	BK_{Ca} , KCNMA1, <i>slo</i> , Maxi-K	Large conductance pore-forming subunit		Rise in intracellular Ca^{2+} and/or membrane depolarization	Broadly expressed.	BmBKTx1, BmTx1*, BmTx2*, Butantoxin®, Charybdotoxin*, ClITx1, Iberitoxin, Kaliotoxin* [@] , Kbot1* [@] , Martentoxin, Noxiustoxin*, Slotoxin,
K_{Ca} 2.1	SK1, KCNN1, K_{Ca} 1	Small conductance pore forming subunit		Rise in intracellular Ca^{2+}	Central nervous system	Apamin, BmP05, BmSKTx1, P01, Scyllatoxin, TSK, Kbot1, Pi1* [@] , Pi4 [@]
K_{Ca} 2.2	SK2, KCNN2, K_{Ca} 2					Apamin, BmP05, BmSKTx1, P01, Scyllatoxin, Tamapin, TSK, Kbot1, Pi1* [@] , Pi4 [@]
K_{Ca} 2.3	SK3, KCNN3, K_{Ca} 3					Apamin, BmP05, BmSKTx1, P01, Scyllatoxin, TSK, Kbot1, Pi1* [@] , Pi4 [@]
K_{Ca} 3.1	SK4, KCNN4, IK_{Ca} , $IK1$	Intermediate conductance pore forming subunit			Cells of the hematopoietic system (i.e. red and white blood cells), colon, salivary glands	Charybdotoxin*, Kaliotoxin* [@] , OSK1* [@] , Maurotoxin
<i>sloβ</i> 1	BKβ1, KCNMB1	Regulatory β subunit of the K_{Ca} 1.1 channel			Smooth muscle with higher expression in vascular smooth muscle cells	
<i>sloβ</i> 2	BKβ2, KCNMB2				Chromaffin cells, brain	
<i>sloβ</i> 3	BKβ3, KCNMB3				Testis, pancreas, spleen	
<i>sloβ</i> 4	BKβ4, KCNMB4				Brain	

Symbols denote other channels that are also blocked by the toxin.
 $\&$ K_{V} 1.1, @ K_{V} 1.2, * K_{V} 1.3, # *ShakerB* (*Drosophila* K_{V} 1 homologue)

Expression of $K_{Ca}2.3$ in Dopaminergic Neurons (Mouse *Substantia nigra*)



Immunohistochemical staining of $K_{Ca}2.3$ with Anti- $K_{Ca}2.3$ antibody (#APC-025) (A) in mouse *substantia nigra pars compacta*. In (B), tyrosine hydroxylase staining shows dopaminergic neurons. Triangles point at cells with co-localization.

The physiological role of the β subunits will be discussed in more detail below. As mentioned above, alternative splicing of the $K_{Ca}1.1$ that accounts for physiological differences has been identified in various tissues such as adrenal chromaffin cells, brain and human gliomas.⁵⁻⁷

At least six sites for alternative splicing have been identified in the mouse $K_{Ca}1.1$ transcript. Functional properties of the different splice variants are only starting to emerge but changes in Ca^{2+} sensitivity and/or slowed channel activation has been described for some of the different variants. In addition, the $K_{Ca}1.1$ can be modulated by a large array of cellular signaling pathways including protein phosphorylation and/or dephosphorylation, G-proteins and nitric oxide.⁸⁻¹⁰ Regulation of the $K_{Ca}1.1$ channel by protein phosphorylation has been more thoroughly addressed. Although some tissue specific differences have been detected, for the most part channel phosphorylation via protein kinase A (PKA) and protein kinase G (PKG) seems to stimulate channel activity in smooth muscle by altering the responsiveness of the channel to Ca^{2+} .⁸ In addition, several proteins have been identified that can associate with the $K_{Ca}1.1$ channel and include Syntaxin 1A, $\beta 2$ adrenergic receptors and β -catenin.¹¹⁻¹³ These proteins can affect the distribution of the channel within the cell; thus changing the current modulation and subsequent physiological outcome. It seems conceivable that as better biochemical and molecular tools became available the list of proteins found to be associated with the $K_{Ca}1.1$ channel will steadily grow.

Physiological Significance

As the complex modulation of the $K_{Ca}1.1$ channel would suggest, the activity of the channel profoundly influences several physiological functions in various tissues. That is not surprising if one considers that the channel sits at the crossroads of two pathways that profoundly affect all cell function: changes in cytosolic Ca^{2+} levels and membrane potential. We will briefly consider two fields in which the importance of the $K_{Ca}1.1$ channel at the physiological level has

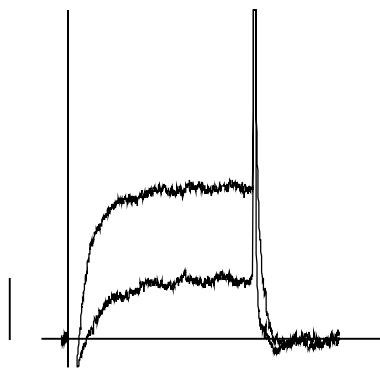
been more extensively studied: modulations of smooth muscular tone and Ca^{2+} -dependent neurotransmitter release. $K_{Ca}1.1$ channels have been identified in a variety of smooth muscle preparations including vascular, urinary bladder, uterine and others. In all smooth muscle preparations, the channel appears to be functionally coupled with the $slo\beta 1$ auxiliary subunit that is exclusively expressed in smooth muscle. Simply put, smooth muscle cells contract as a result of an increase in the intracellular Ca^{2+} concentration. This Ca^{2+} increase activates the Ca^{2+} -calmodulin-dependent protein kinase, which initiates a biochemical cascade that eventually results in muscular contraction. The intracellular Ca^{2+} increase is mediated by the opening of ryanodine-receptors in the sarcoplasmic reticulum (Ca^{2+} sparks) and/or the opening of voltage-dependent Ca^{2+} channels (VDCCs) in the plasma membrane. Both the rise in intracellular Ca^{2+} and the membrane depolarization (that opens the VDCCs) will activate the $K_{Ca}1.1$ channel that responds with an efflux of K^+ and a concomitant hyperpolarization of the cell membrane potential. This in turn, will close the

membrane VDCCs thus effectively working as a negative feedback mechanism on contraction and inducing muscle relaxation. Indeed, inhibition of $K_{Ca}1.1$ channel activity in vascular smooth muscle preparations with **Iberiotoxin** (a specific channel blocker, see Table) has been shown to induce membrane depolarization and vasoconstriction.¹⁴ Conversely, $K_{Ca}1.1$ channel openers would act as relaxation factors of vascular smooth muscle, inducing membrane hyperpolarization and closure of Ca^{2+} channels. Indeed, several known endogenous vasodilators such as nitric oxide, atrial natriuretic factor, β adrenergic agonists, etc. produce their vasorelaxing effect by directly or indirectly (via activation of PKA and/or PKG) activating the $K_{Ca}1.1$ channel.^{15, 16}

One of the most intriguing aspects of the involvement of the $K_{Ca}1.1$ channel in smooth muscle tone regulation is the involvement of the $\beta 1$ auxiliary subunit. Studies with $slo\beta 1$ knockout mice have demonstrated that loss of this regulatory subunit produce hypertension and cardiac hypertrophy, probably because loss of this subunit decreases the Ca^{2+} sensitivity of the $K_{Ca}1.1$ channel, which can no longer respond to endogenous Ca^{2+} sparks.^{17, 18} Conversely, a recent study showed that a commonly found gain-of-function $slo\beta 1$ variant has a protective effect against human diastolic hypertension. The $slo\beta 1$ variant does so by further increasing the apparent Ca^{2+} and voltage-activation sensitivity of the pore forming $K_{Ca}1.1$ channel.¹⁹

Although the widespread expression of the $K_{Ca}1.1$ channel in the nervous system has long been acknowledged, the functional role of these channels in the brain is largely unknown.²⁰ Similarly to their function in smooth muscle tone regulation, $K_{Ca}1.1$ channels are believed to function as a feedback inhibition mechanisms that initiates membrane repolarization and prevents additional Ca^{2+} entry through VDCC in neurons and hence further neurotransmitter release. Thus, the $K_{Ca}1.1$ channel is believed to act in the brain as an "emergency break" in situations that involve excessive depolarization and Ca^{2+} entry in pathological situations such as ischemia (reduced blood flow) or epilepsy.²¹

Inhibition of $K_{Ca}1.1$ Channels by Iberiotoxin



$K_{Ca}1.1$ channel currents ($5 \text{ mM } K^+$) from *Xenopus* oocytes, before and during application of 100 nM iberiotoxin (#RTI-400). Holding potential, -100 mV , test potential, $+50 \text{ mV}$ for 100 ms. The vertical bar represents $0.1 \mu\text{A}$.

2. $K_{Ca}2$: Modulating Neuronal Excitability

General Considerations

As mentioned above, the small conductance Ca^{2+} -activated K^+ ($K_{Ca}2$) channel subfamily comprises three highly homologous members: $K_{Ca}2.1$, $K_{Ca}2.2$ and $K_{Ca}2.3$ (see Table for the alternative terminology).²² They have a similar topology to the voltage-activated K^+ (K_V) channels but display only two positively charged amino acids at the S4 segment while K_V channels typically display seven. This difference probably accounts

for the observed voltage insensitivity of the K_{Ca2} channels. K_{Ca2} channels are therefore exclusively activated by increasing cytosolic Ca^{2+} concentration.²³ In fact, very low levels of intracellular Ca^{2+} (300-700 nM) can open the K_{Ca2} channels very rapidly (5-15 ms). Hence, the K_{Ca2} channels are highly sensitive and fast Ca^{2+} sensors resembling other known Ca^{2+} -binding proteins. This type of Ca^{2+} -dependent activation is achieved by the constitutive binding of the K_{Ca2} channels to calmodulin, a highly expressed Ca^{2+} -binding protein via a calmodulin-binding domain situated at the cytoplasmic C-termini (see Table).²⁴

Several studies have detected heteromeric assembly of the K_{Ca2} subunits (and even with the $K_{Ca3.1}$ subunit) in heterologous expression systems, although whether this occurs in native tissues is less clear.²³ Pharmacologically, the K_{Ca2} channels are the only known targets of the bee venom toxin **Apamin**, with $K_{Ca2.1}$ being the least sensitive, $K_{Ca2.2}$ the most sensitive and $K_{Ca2.3}$ showing intermediate sensitivity.²⁵

Physiological Significance

Based on their biophysical properties and central nervous system distribution, the K_{Ca2} channels have long been implicated in the regulation of neuronal excitability. As mentioned above for the $K_{Ca1.1}$ channel, Ca^{2+} enters neurons through VDCCs during an action potential (AP). Following the AP a membrane hyperpolarization occurs termed afterhyperpolarization (AHP), which dampens neuronal excitability. Several types of AHP are temporally distinguished, the fast (fAHP), the medium (mAHP) and the slow (sAHP) while the importance of each AHP depends on the type of neuron. K_{Ca2} channels are believed to underlie the mAHP meaning that they are involved in the control of firing rate (the number of APs generated over a unit of time) and of firing pattern (the way the APs are distributed over time).²⁶ These properties imply that in different neuronal populations, K_{Ca2} activity will produce different outputs. For example, midbrain dopaminergic neurons have a prominent mAHP that is mediated by K_{Ca2} channels (particularly $K_{Ca2.3}$) that control firing rate and subsequent dopamine secretion.²⁷ Since malfunction of these neurons is involved in several pathological disorders such as Parkinson's disease and schizophrenia, modulators of the $K_{Ca2.3}$ channels have been proposed to be of therapeutic value in these diseases.²⁶

$K_{Ca3.1}$: Modulating Lymphocyte Activation

General Considerations

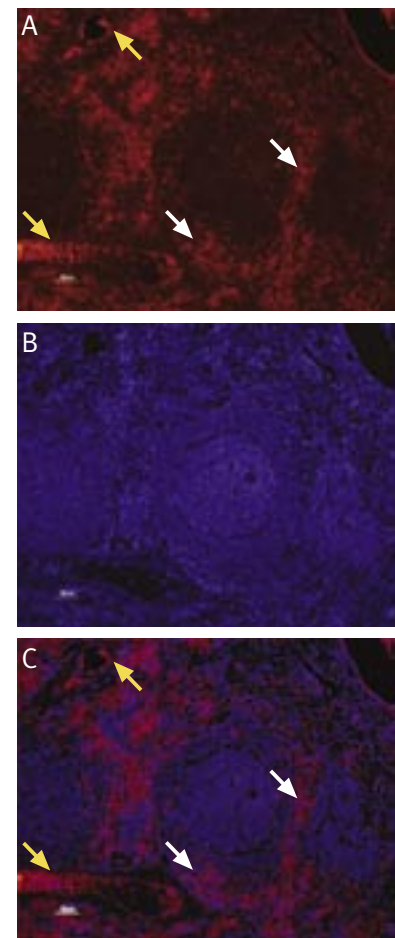
The $K_{Ca3.1}$ channel is the lone member of the Ca^{2+} -dependent K^+ family of intermediate conductance. Ironically, this channel is the least studied of

the K_{Ca} family even though it was the first one to be identified as the Ca^{2+} -dependent K^+ channel present in human erythrocytes where it is also known as the Gardos channel.²⁸ The channel has the same basic topology of the K_{Ca2} subfamily and like them is constitutively bound to calmodulin. The channel is extremely sensitive to intracellular Ca^{2+} concentrations with an activation threshold of 200-300 nM.²⁹ The tissue distribution of the channel also varies substantially from that of the K_{Ca2} subfamily. While the latter is expressed mainly in the central nervous system, the $K_{Ca3.1}$ channel is found exclusively in the periphery, in cells of hematopoietic origin, colon and salivary glands. Pharmacologically there are also marked differences, as the $K_{Ca3.1}$ channel is insensitive to apamin, the paramount channel blocker for the small conductance family. Instead, the channel can be blocked by the peptide toxins **Charybdotoxin** (that also blocks $K_{Ca1.1}$) and **Maurotoxin** (that also blocks $K_{Ca1.2}$) (see Table).

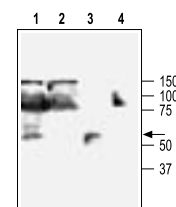
Physiological Significance

Since its functional identification in human erythrocytes the physiological significance of the $K_{Ca3.1}$ channel has primarily been studied in cells of hematopoietic origin. In normal resting T-lymphocytes levels of the $K_{Ca3.1}$ channel are relatively low and it is believed that the voltage-dependent K^+ channel $K_{Ca1.3}$ is the main channel responsible for maintaining the cell membrane potential. However in activated T-lymphocytes the levels of $K_{Ca3.1}$ are markedly upregulated.³⁰ In order to be properly activated, that is capable of proliferation and differentiation into an effector T-lymphocyte, the cells must be able to maintain a sustained Ca^{2+} entry for at least a few hours. Because a high and steady Ca^{2+} entry would eventually dissipate the electrochemical force for additional Ca^{2+} entry, the opening of the $K_{Ca3.1}$ channels and the concomitant efflux of K^+ would provide a hyperpolarization effect that would aid in the maintenance of the Ca^{2+} entry.³¹ All this implies that specific blockers of the $K_{Ca3.1}$ channel would be able to prevent T-lymphocyte proliferation.³² Indeed, several *in vitro* studies show that this is the case.^{33, 34} Moreover, recent studies have shown that *in vivo* blockage of the $K_{Ca3.1}$ channel can be useful in pathological situations that involve excessive T-lymphocyte-mediated activation. These include T-lymphocyte-mediated autoimmune diseases such as multiple sclerosis and T-lymphocyte-mediated inflammation among others.^{35, 36}

Expression of $K_{Ca3.1}$ in Rat Spleen

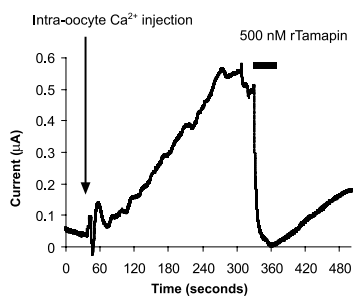


Immunohistochemical staining of $K_{Ca3.1}$ with Anti- $K_{Ca3.1}$ antibody (#APC-064) in rat spleen. (A) and (C) Secondary (activated) follicle in the spleen white pulp showing intense staining of Marginal Zone and Periarteriolar T-lymphocytes (white and yellow arrows, respectively); note that cells in the red pulp and B lymphocytes in the germinal center are not stained. (B) The counterstain is Hoechst 33324.



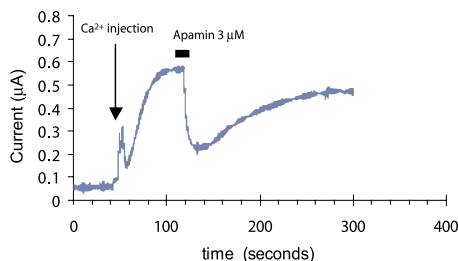
Western blotting of HEK-293- $K_{Ca3.1}$ (1, 2) and K562 (3, 4) cells: 1, 3. Anti- $K_{Ca3.1}$ antibody (#APC-064) (1:200). 2, 4. Anti- $K_{Ca3.1}$ antibody, preincubated with the control peptide antigen.

Inhibition of $K_{Ca}2$ K^+ Channels by rTamapin



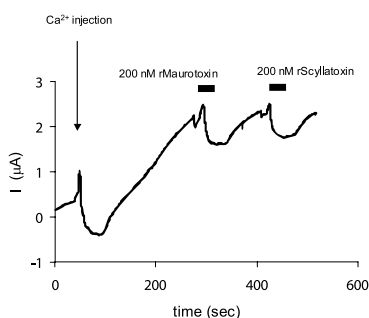
Tamapin is a 31 amino acid peptidyl toxin, isolated from the venom of the Indian red scorpion, *Mesobuthus tamulus*. Activation of rTamapin (#RTT-400) sensitive outward current by intracellular Ca²⁺ injection into *Xenopus oocytes* expressing SK2 ($K_{Ca}2.2$) channels. The arrow and vertical bar represents time of intracellular injection and period of toxin perfusion, respectively.

Inhibition of $K_{Ca}2.2$ (SK2) Channels by Apamin



Voltage clamped whole oocyte current was recorded continuously under low Cl⁻ concentration at 5 mV holding potential. At the indicated time 10 nl of 100 mM Ca²⁺ was injected into the oocyte and an outward current developed. A minute later 3 µM Apamin (#A-200) was perfused into the bath, resulting in about 60% inhibition in the amplitude of this Ca²⁺ dependent current, which was nearly completely recovered upon toxin wash.

Inhibition of $K_{Ca}2$ K^+ Channels by rMaurotoxin and rScyllatoxin



Scyllatoxin is a 31 amino acid toxin, originally isolated from the venom of the scorpion *Leiurus quinquestriatus hebraeus*. Maurotoxin is a 34 amino acid toxin, originally isolated from the venom of the scorpion *Scorpio Maurus palmatus*, and is classified as α -KTx6.2 scorpion toxin family. Inhibition of $K_{Ca}2.2$ channels expressed in *Xenopus oocytes* by rScyllatoxin (#RTS-370) and by rMaurotoxin (#RTM-340). Continuous current recording at holding potential +5 mV with low Cl⁻ content in the bath solution. An outward current (upward deflection) carried out by K⁺ ions flowing via $K_{Ca}2.2$ channels develops following an intra-oocyte Ca²⁺ injection (arrow). Both recombinant toxins partially and reversibly depressed the K⁺ current at 200 nM. Periods of toxin perfusion are marked by the horizontal bars.

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Related Products

Compound	Product #
Antibodies	
Anti-K _{Ca} 1.1 (1098-1196) (BKCa)	APC-021
Anti-K _{Ca} 1.1 (1184-1200) (BKCa)	APC-107
Anti-K _{Ca} 2.1 (SK1)	APC-039
Anti-K _{Ca} 2.2 (SK2)	APC-028
Anti-K _{Ca} 2.3 (N-term) (SK3)	APC-025
Anti-K _{Ca} 2.3 (C-term) (SK3)	APC-103
Anti-K _{Ca} 3.1 (SK4)	APC-064
Anti-sloβ1 (KCNMB1)	APC-036
Anti-sloβ4 (KCNMB4)	APC-061
Anti-Ca _v 2.1 (α _{1A})	ACC-001
Anti-Ca _v 2.2 (α _{1B})	ACC-002
Anti-Ca _v 1.2 (α _{1C})	ACC-003
Anti-human Ca _v 1.2 (α _{1C})	ACC-022
Anti-Ca _v 1.2a (α _{1C} Cardiac)	ACC-013
Anti-Ca _v 1.3 (α _{1D})	ACC-005
Anti-Ca _v 2.3 (α _{1E})	ACC-006
Anti-Ca _v 3.1 (α _{1F})	ACC-021
Anti-Ca _v 3.3 (α _{1I})	ACC-009
Anti-Ca _v pan α1	ACC-004
Anti-Caβ3	ACC-008
Anti-Caγ2	ACC-012
Anti-Ca _v α2δ-1	ACC-015
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-Syntaxin 1	ANR-002
Blockers	
Apamin	A-200
rCharybodotoxin	RTC-325
rIberiotoxin	RTI-400
rKaliotoxin-1	RTK-370
rMaurotoxin	RTM-340
rNoxiustoxin	RTN-340
rScyllatoxin	RTS-370
rSlotoxin	RTS-410
rTamapin	RTT-400
Activators	
Isopimaric Acid	I-370
Pimaric Acid (PiMA)	P-270