Ion Channels and Oxygen Sensing in the Carotid Body

Noemí Bronstein, Ph.D.

Oxygen is an absolute requirement of all mammalian cells. Practically every cell is able to sense a decrease in oxygen tension and responds by regulating the expression and/or function of several genes that, in a matter of hours or days, reduce oxygen dependency. However, at the organismal level, a decrease in oxygen is immediately detected and, within seconds, compensatory mechanisms (e.g., increased breathing) are activated. How decreased oxygen levels (or hypoxia) are sensed at the systemic level and what the critical role of ion channels is in this process is the subject of this review.

Introduction

An adequate supply of oxygen is essential for all mammalian cells, which have built-in processes aimed at coping with hypoxia, a decrease in the availability of oxygen. From the systemic point of view, specialized oxygen sensors in the body are able to detect even slight decreases in oxygen levels in the blood and respond by rapidly stimulating breathing and increasing blood pressure so that normal oxygen tension is maintained in vital organs.

These specialized oxygen-sensing receptors are localized in tiny chemosensory organs known as carotid bodies, strategically located in the common carotid artery (the main artery leading oxygenated blood to the brain).[1,2] The carotid body consists of two cell types: glomus or type I cells and sustentacular or type II cells. Glomus cells have a neuronal phenotype and are the cells responsible for oxygen sensing while sustentacular cells have a phenotype more resembling glia cells and likely play a supporting role.[1] The carotid body is heavily innervated by afferent sensory fibers of the sinus nerve that connect to the brain stem respiratory center.

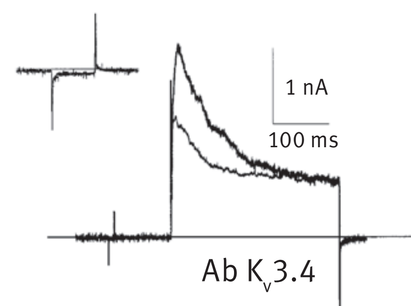
The current paradigm for hypoxia sensing and response in the carotid body involves three steps. The first step is that decreasing levels of oxygen are detected by molecular sensors in glomus cells that then inhibit K^+ channels in the cell membrane. In the second step, depolarization of the cell membrane due to inhibition of K^+ channels activates voltage-dependent Ca^{2+} channels, resulting in Ca^{2+} influx. Finally, as a result of the rise in intracellular Ca^{2+}, exocytosis of neurotransmitters occurs. This activates the sensory afferent fibers that relay the signal input to the respiratory center, which responds accordingly by increasing lung ventilation (see Figure 2 for a schematic model).[1,2]

This brief review will concentrate mainly on the role of ion channels in the three steps involved in the sensing and response to low levels of oxygen by the carotid body, the specialized hypoxia sensory organ.

Step 1: K^+ Channels and the Sensing of Oxygen Tension

The first step of the carotid body (and the systemic) response to hypoxia is the exquisite sensing of an even slight decrease in the levels of oxygen tension. The nature of the oxygen sensors in the glomus cells of the carotid body is a matter of intense study and debate. Two mechanisms have been put forward to describe the transduction pathway of oxygen sensing in the carotid body: the metabolic hypothesis and the membrane hypothesis. The metabolic hypothesis proposes that oxygen-sensing proteins in the mitochondria or the cytoplasm are able to respond to low levels of oxygen and are somehow coupled to the opening of voltage-dependent Ca^{2+} channels. These putative oxygen-sensing proteins are thought to be heme-containing proteins such as mitochondrial cytochrome oxidases or non-mitochondrial enzymes such as heme oxygenase 1 and 2 (HO-1 and HO-2).[3] Alternatively, the membrane hypothesis proposes that reduced

Figure 1. Immunological Blockade of Fast-Inactivating K^+ Currents in Rabbit Carotid Body Chemoreceptor Cells



Representative recordings of outward currents of chemoreceptor cells obtained with pulses to +40mV, before (thick traces) and after (thin traces) dialysis of **Anti-K_v3.4** (#APC-019) antibodies.
Adapted from reference #17, with the kind permission of the *J. Physiol.*

oxygen levels directly inhibit K^+ channels present in the membrane of glomus cells. Inhibition of K^+ channels depolarizes the membrane potential, which in turn activates voltage-dependent Ca^{2+} channels.[3] Possible interactions between the metabolic and the membrane sensory pathways have also been offered (see below).

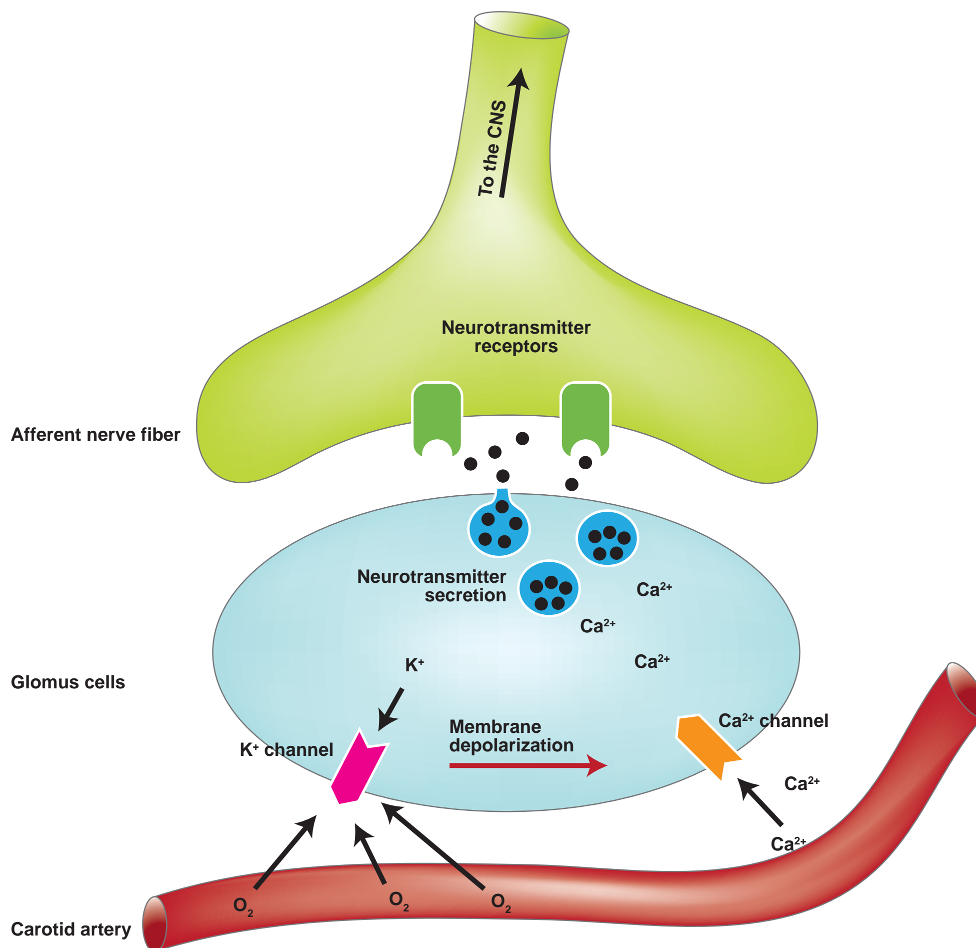
As mentioned above, there is general agreement that hypoxia inhibits K^+ channel conductance in carotid body glomus cells and, as a consequence, the cell membrane is depolarized and voltage-dependent Ca^{2+} channels are activated. In accordance with this hypothesis, it has been shown that K^+ channels blockers such as Charybdotoxin, TEA, 4-AP, and Iberiotoxin can mimic the hypoxic effect and induce depolarization of glomus cells.[1] Less agreed upon is the identity of this crucial K^+ channel. It is now clear that there are species-based differences concerning the main or dominant K^+ conductance in glomus cells; i.e., a K^+ channel identified as central to oxygen sensing in the carotid body of the rat is not necessarily the one with a key role in rabbit or mouse. Alternatively, it has been shown that glomus cells express a variety of K^+ channels, several of which can be individually inhibited by hypoxia, making it difficult to establish which is the relevant one (or ones).[3,4] The general consensus, however, is that multiple K^+ channels can function as oxygen sensors and that several K^+ channels perform this function simultaneously.

K^+ channels that have been implicated as oxygen sensors in glomus cells will now be examined in some detail.

a) Ca^{2+}-Dependent K^+ Channels: $K_{Ca}1.1$ (BKCa) Channel:

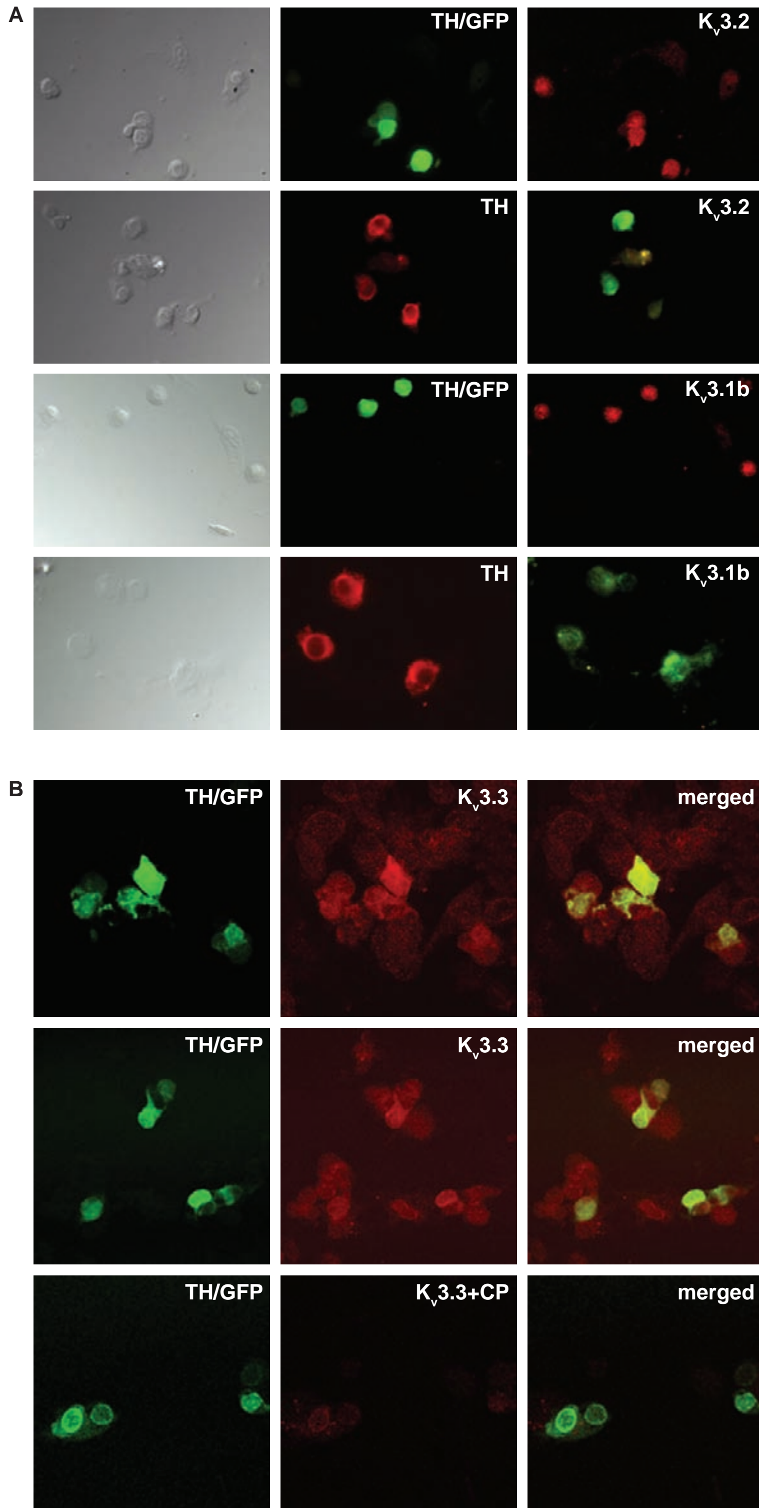
The $K_{Ca}1.1$ channel is a high conductance Ca^{2+} and voltage-activated K^+ channel known to regulate many physiological functions, including smooth muscle contraction, neurotransmission, and endocrine secretion.[5]It has been shown to be inhibited by hypoxia in both native and recombinant settings and is probably more dominant as an oxygen sensor in the rat carotid body than in other species.[4,6,7] Whether this channel is directly modulated by low oxygen tension or whether it is in close contact with an oxygen-sensing molecule is still unclear, as evidence for both cases has been reported. It was recently reported that the $K_{Ca}1.1$ channel co-immunoprecipitated with the HO-2 protein, an

Figure 2. Schematic Model of Oxygen Sensing in the Carotid Body



A decrease in oxygen levels will produce (directly or indirectly) an inhibition of glomus cells K^+ channels. This will depolarize the cell membrane and as a consequence open voltage-dependent Ca^{2+} channels. The subsequent increase in intracellular Ca^{2+} concentration will then induce Ca^{2+} - dependent exocytosis of vesicles containing neurotransmitters. These neurotransmitters bind and activate receptors on the nerve endings of afferent neurons initiating action potentials that will convey the information to the central nervous system (CNS).

Figure 3. Expression of K_v3.1b, K_v3.2, and K_v3.3 in Mouse Carotid Body Chemoreceptor Cells



A. The presence of K_v3.2 and K_v3.1b in tyrosine hydroxylase (TH)-expressing cells was shown both by immunofluorescence labeling of TH–GFP cells and by double labeling with TH and **Anti-K_v3.2** (#APC-011) and **Anti-K_v3.1b** (#APC-014) antibodies.
B. Immunofluorescence labeling of K_v3.3 with **Anti-K_v3.3** antibody (#APC-102) in mouse carotid body chemoreceptor cells shows the expression of K_v3.3 in every GFP-positive cell (yellow in the merged panels). The specificity of the K_v3.3 labeling was confirmed by the loss of K_v3.3 tagging in cells preincubated with the control peptide (CP). In this case, there is no color change in the merged panel compared to the TH/GFP panel.
Adapted form reference #15, with the kind permission of Dr. Pérez-García of Departamento de Bioquímica y Biología Molecular y Fisiología, Facultad de Medicina, Universidad de Valladolid, Spain and the *J. Physiol.*

enzyme that breaks down its heme component to produce carbon monoxide (CO), biliverdin, and iron in the presence of oxygen. CO is a known activator of K_{Ca}1.1 channels and therefore, in the presence of oxygen, CO is produced and K_{Ca}1.1 channels are maintained in the open configuration. When oxygen levels drop, CO production decreases and therefore the channels are inhibited.[8] A more recent report proposes a key role for the AMP-activated protein kinase (AMPK) in mediating chemotransduction by hypoxia, among other things, by the phosphorylation and hence inhibition of K_{Ca}1.1 channels. AMPK is a serine/threonine kinase that is activated by a rise in the AMP/ATP ratio, a situation that occurs in response to metabolic stress, e.g., when levels of ATP drop following the inhibition of oxidative mitochondrial phosphorylation. Hence, a decrease in oxygen levels activates AMPK, which in turn inhibits K_{Ca}1.1 channels.[9]

b) K_{2P} Channels:

Two-pore (2P) K^+ channels form a family that includes at least sixteen members. These channels show little time or voltage dependence and are considered to be “leak” or “background” K^+ channels, thereby generating background currents that help set the membrane resting potential and cell excitability. K_{2P} channels are implicated in oxygen sensing in the carotid body. Electrophysiological recordings as well pharmacological experiments in isolated glomus cells demonstrated the presence of background K^+ currents in these cells and that the current was inhibited by hypoxia.[10] Expression of several members of the K_{2P} channel family has been detected in glomus cells, including K_{2P}3.1 (TASK-1), K_{2P}5.1 (TASK-2), K_{2P}9.1 (TASK-3), and K_{2P}4.1 (TRAAK).[11] Most reports focused on the K_{2P}3.1 channel as the most likely candidate to be the background K^+ channel responsive to oxygen levels, as it functions in this role in several cell types.[12,13] Interestingly, AMPK, which inhibits the activity of K_{Ca}1.1 channels, has also been shown to regulate the activity of K_{2P}3.1 channels.

c) Voltage-Dependent K^+ Channels (K_v):

K_v channels comprise a large and heterogeneous superfamily of channels with K^+ conductance in response to changes in cell membrane potential. Several members have been characterized as oxygen-responsive, thus fitting the criteria for K^+ channels able to depolarize glomus cell membranes and activate voltage-dependent Ca^{2+} channels in response to hypoxic conditions.[14] These include K_v1.2, K_v1.5, K_v2.1, members of the K_v3 and K_v4 subfamilies, as well as the K_v11 (erg) subfamiliy.

The molecular identity of the most relevant K_v channels that function as oxygen sensors in the carotid body has been confounded by several

factors including the animal species studied, the ability of K_v channels to form heterodimers, and/or the presence of auxiliary b subunits that change the biophysical properties of the channels. For example, in the mouse, the K_v3 channel subfamily appears as the most likely candidate to be the oxygen-sensitive K^+ channels in the carotid body as demonstrated using a combination of electrophysiological, RT-PCR, and immunostaining methods.[15] Conversely, in rabbits, members of the K_v4 subfamily appear to be the main contributors to oxygen-sensitive outward K^+ currents.[16,17] In addition, K^+ currents characteristic of members of the ether-a-go-go (erg, K_v11 subfamily) have been also detected in the carotid body of both rats and rabbits.[18,19] In this regard, it is interesting that K_v11 subfamily members contain a Per Arnt Sim (PAS) domain at their cytoplasmic N-terminus. The PAS domain is highly conserved among redox-sensitive proteins such as the HIF transcription factors.[20]

Step 2: Ca^{2+} Channels and the Influx of Extracellular Ca^{2+} in Response to Hypoxia

As mentioned above, a drop in oxygen concentration to hypoxic levels inactivates K^+ channels (either directly or indirectly) and this produces a depolarization of the cell membrane. This depolarization activates voltage-dependent Ca^{2+} channels and produces an influx of extracellular Ca^{2+}. Similarly to other secretory systems, an increase in intracellular Ca^{2+} induces the release of neurotransmitters. These neurotransmitters in turn activate receptors in nerve sensory afferents and initiate nerve activation. The notion that influx of extracellular Ca^{2+} through voltage-dependent Ca^{2+} channels is necessary for the transduction process of oxygen sensing in the carotid body is well established. Indeed, removal of extracellular Ca^{2+} abolished the release of neurotransmitters evoked by hypoxia.[21] However, the molecular identity of the Ca^{2+} channel involved in this process is not well established. As discussed above, probably more than one voltage-dependent Ca^{2+} channel is involved in the transduction process of hypoxia and some differences between species may also exist. Pharmacological experiments using various voltage-dependent Ca^{2+} channel blockers show that L-type Ca^{2+} channels are important in this process although N- and P/Q- type channels have also been described.[22,23] Pharmacological evidence also suggests the participation of other types of Ca^{2+} channels since, at least in some instances, inhibitors of voltage-dependent Ca^{2+} channels fail to completely block Ca^{2+} influx. The candidates likely involved in this Ca^{2+} influx are members of the transient receptor potential (TRP) channel family. Three major subgroups of TRP channels have been identified: TRPC (canonical), TRPV (vanilloid), and TRPM (melastatin). The TRPC channels are activated downstream of PLC activation, which is coupled to G protein-coupled receptor signaling. Several members of the TRPC family have been identified in glomus cells as well as in the afferent nerve terminals, although their physiological relevance to the hypoxic response is not clear.[29]

Step 3: Neurotransmitter Release and Afferent Nerve Activation in Response to Hypoxia

The last step in the sensing of hypoxia by the carotid body is the release of neurotransmitters and the activation of the afferent neurons that innervate the carotid body. Not surprisingly, several classes of neurotransmitters have been implicated in this process. The neurotransmitters involved have been broadly classified as either "conventional" or "unconventional". Conventional neurotransmitters are those stored in synaptic vesicles that undergo exocytosis in response to a hypoxic stimulus and include acetylcholine (ACh), ATP, catecholamines (dopamine and norepinephrine), substance P, endothelin-1 (ET-1), and others.[3,24] Neurotransmitters classified as "unconventional" are those generated by enzymatic reactions and include gas signaling molecules such as nitric oxide (NO) and carbon monoxide (CO).[3,24]

The specific role of each neurotransmitter has been difficult to elucidate because of differences between species as well as the presence of autocrine circuits in glomus cells. ACh and probably ATP are believed to be the major neurotransmitters mediating nerve activation following hypoxia.[25,26] ACh binds to both nicotinic and muscarinic receptors in nerve endings of neurons innervating glomus cells. ACh is probably co-released with ATP, which binds to purinergic receptors in the afferent neurons, most probably P2X2 and P2X3.[27,28]

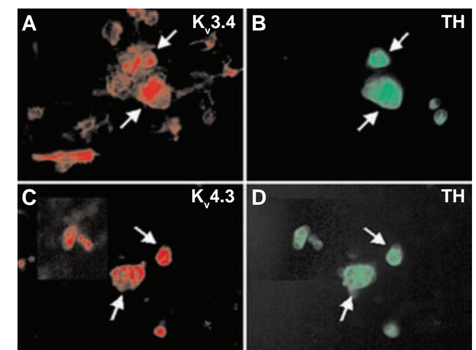
Conclusions

Maintaining sufficient levels of oxygen in tissues is a homeostatic challenge for the organism. The carotid body is the key organ involved in the sensing and responding to even small changes in oxygen levels. It should be noted that there are other oxygen-sensing specialized tissues in the body, such as the neuroepithelial bodies in the lung that present a similar structure and function as the carotid body but are less well studied.[30]

More controversial is whether pulmonary vasoconstriction in response to hypoxia is the result of the direct action of low oxygen levels on pulmonary artery smooth muscle cells (PASMC) or whether the neuroepithelial bodies in the lung indirectly mediate this effect. In any case, hypoxia inhibits K^+ currents in PASMCs causing membrane depolarization, opening of voltage-dependent Ca^{2+} channels, and smooth muscle contraction.[30] The voltage-dependent K^+ channel $K_v1.5$ has a central role in smooth muscle-mediated pulmonary vasoconstriction as demonstrated by gene transfer experiments.[31]

What is clear is that the exquisite sensitivity of the carotid body and other oxygen-sensitive tissues to changes in oxygen levels and its ability to rapidly relay this information to the central nervous system is dependent on the careful orchestration of several classes of ion channels. The challenge for understanding their complex relationships and interactions is still on.

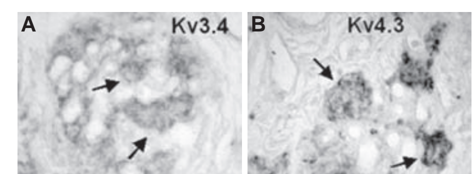
Figure 4. Expression of $K_v3.4$ and $K_v4.3$ in Rabbit Carotid Body Chemoreceptor Cells



Expression of $K_v3.4$ (A) and $K_v4.3$ (C) in cultured rabbit chemoreceptor cells was demonstrated using **Anti-K_v3.4** (#APC-019) and **Anti-K_v4.3** (#APC-017) antibodies (red). Colocalization with tyrosine hydroxilase (TH)-expressing cells (green), a marker of chemoreceptor cells, (B, and D) is marked by arrows.

Adapted from reference #17, with the kind permission of the *J. Physiol.*

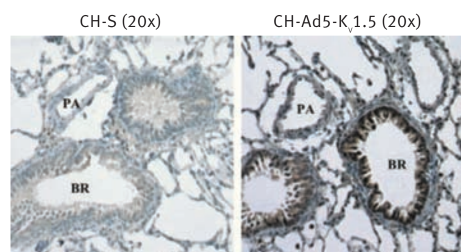
Figure 5. Expression of $K_v3.4$ and $K_v4.3$ in Rabbit Carotid Body



Paraffin-embedded sections of rabbit carotid body were stained with **Anti-K_v3.4** (#APC-019) and **Anti-K_v4.3** (#APC-017) antibodies (A, and B, respectively). Carotid body glomeruli appear stained with the antibodies (arrows).

Adapted from reference #17, with the kind permission of the *J. Physiol.*

Figure 6. Expression of K_v1.5 in the Lungs of Rats Undergoing Chronic Hypoxia



Paraffin-embedded sections of rat lung were stained with **Anti-K_v1.5** antibody (#APC-004). Staining (brown color) in the chronic hypoxia treated group (left panel) were compared to staining in the group that underwent gene transfer with an adenovirus carrying the human K_v1.5 gene (right panel). Adapted from reference #31, with the kind permission of the journal *Circulation*.

References:

1. López-Barneo, J. *et al.* (2001) *Annu. Rev. Physiol.* **63**, 259.
2. Prabhakar, N.R. (2000) *J. Appl. Physiol.* **88**, 2287.
3. Prabhakar, N.R. (2006) *Exp. Physiol.* **91**, 17.
4. Kemp, P.J. (2006) *Exp. Physiol.* **91**, 829.
5. Lu, R. *et al.* (2006) *J. Physiol.* **570**, 65.
6. Riesco-Fagundo, A.M. *et al.* (2001) *Circ. Res.* **89**, 430.
7. Lewis, A. *et al.* (2002) *J. Physiol.* **540**, 771.
8. Williams, S.E. *et al.* (2004) *Science* **306**, 2093.
9. Wyatt, C.N. *et al.* (2007) *J. Biol. Chem.* **282**, 8092.
10. Buckler, K.J. *et al.* (2000) *J. Physiol.* **525**, 135.
11. Yamamoto, Y. *et al.* (2002) *Brain Res.* **950**, 304.
12. Hartness, M.E. *et al.* (2001) *J. Biol. Chem.* **276**, 26499.
13. Gurney, A.M. *et al.* (2003) *Circ. Res.* **93**, 957.
14. Patel, A.J. and Honoré, E. (2001) *Eur. Respir. J.* **18**, 221.
15. Pérez-García, M.T. *et al.* (2004) *J. Physiol.* **557**, 457.
16. Pérez-García, M.T. *et al.* (2000) *J. Neurosci.* **20**, 5689.
17. Sanchez, D. *et al.* (2002) *J. Physiol.* **542**, 369.
18. Overholt, J.L. *et al.* (2000) *J. Neurophysiol.* **83**, 1150.
19. Kim, I. et al. (2005) *J. Appl. Physiol.* **98**, 1469.
20. Taylor, B.L. and Zhulin, I.B. (1999) *Microbiol. Mol. Biol. Rev.* **63**, 479.
21. Shirahata, M. and Fitzgerald, R.S. (1991) *J. Appl. Physiol.* **71**, 1062.
22. Overholt, J.L. and Prabhakar, N.R. (1997) *J. Neurophysiol.* **78**, 2467.
23. Rocher, A. *et al.* (2005) *J. Physiol.* **562**, 407.
24. Lahiri, S. *et al.* (2006) *Prog. Biophys. Mol. Biol.* **91**, 249.
25. Fitzgerald, R.S. (2000) *Respir. Physiol.* **120**, 89.
26. Zhang, M. *et al.* (2000) *J. Physiol.* **525**, 143.
27. Prasad, M. *et al.* (2001) *J. Physiol.* **537**, 667.
28. Campanucci, V.A. *et al.* (2006) *J. Neurosci.* **26**, 9482.
29. Buniel, M.C.F. *et al.* (2003) *J. Comp. Neurol.* **464**, 404.
30. Weir, E.K. *et al.* (2005) *N. Engl. J. Med.* **353**, 2042.
31. Pozeg, Z.I. *et al.* (2003) *Circulation* **107**, 2037.

Related Products

Antibodies to Ca^{2+} Activated K^+ Channels

Compound	Product #
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

Antibodies to Two Pore Domain K^+ Channels

Compound	Product #
Anti-K_{2P}1.1 (TWIK-1)	APC-110
Anti-K_{2P}2.1 (TREK-1)	APC-047
Anti-K_{2P}3.1 (TASK-1)	APC-024
Anti-K_{2P}4.1 (TRAAK)	APC-108
Anti-K_{2P}5.1 (TASK-2)	APC-037
Anti-K_{2P}6.1 (TWIK-2)	APC-040
Anti-K_{2P}9.1 (TASK-3)	APC-044
Anti-K_{2P}10.1 (TREK-2)	APC-055
Anti-K_{2P}13.1 (THIK-1) (extracellular)	APC-121
Anti-K_{2P}18.1 (TRESK) (extracellular)	APC-122

Antibodies to Voltage Activated K^+ Channels

Compound	Product #
Anti-K_v1.1	APC-009
Anti-K_v1.2	APC-010
Anti-K_v1.3	APC-002
Anti-K_v1.3 (extracellular)	APC-101
Anti-K_v1.3 (extracellular)-FITC	APC-101-F
Anti-K_v1.4	APC-007
Anti-K_v1.5	APC-004
Anti-K_v1.6	APC-003
Anti-K_v1.7	APC-063
Anti-K_v2.1	APC-012
Anti-K_v2.2	APC-120
Anti-K_v3.1b	APC-014
Anti-K_v3.2	APC-011
Anti-K_v3.3	APC-102
Anti-K_v3.4	APC-019
Anti-K_v4.1	APC-119
Anti-K_v4.2	APC-023
Anti-K_v4.3	APC-017
Anti-K_v7.1 (KCNQ1)	APC-022
Anti-K_v7.2 (KCNQ2)	APC-050
Anti-K_v7.3 (KCNQ3)	APC-051
Anti-K_v10.1 (EAG-1)	APC-104
Anti-KV10.2 (EAG-2)	APC-053
Anti-K_v11.1 (erg1)	APC-016
Anti-hK_v11.1 (HERG)	APC-062
Anti-K_v11.1 (HERG) (extracellular)	APC-109
Anti-K_v11.1 (HERG) (extracellular) FITC	APC-109-F
Anti-K_v11.2 (erg2)	APC-114
Anti-K_v11.3 (erg3)	APC-112
Anti-K_v12.1 (Elk1)	APC-113
Anti-K_v12.3 (Elk3)	APC-116

Antibodies to Voltage-Gated Ca^{2+} Channels

Compound	Product #
Anti-Ca_v2.1 (α1A)	ACC-001
Anti-Ca_v2.2 (α1B)	ACC-002
Anti-Ca_v1.2 (α1C)	ACC-003
Anti-Ca_v1.2-ATTO-488	ACC-003-AG
Anti-human Ca_v1.2 (α1C)	ACC-022
Anti-Ca_v1.2a (α1C Cardiac)	ACC-013
Anti-Ca_v1.3 (α1D)	ACC-005
Anti-Ca_v2.3 (α1E)	ACC-006
Anti-Ca_v3.1 (α1G)	ACC-021
Anti-Ca_v3.2 (α1H)	ACC-025
Anti-Ca_v3.3 (α1I)	ACC-009
Anti-Ca_vpan α1	ACC-004

Antibodies to TRPC Channels

Compound	Product #
Anti-TRPC1	ACC-010
Anti-TRPC3	ACC-016
Anti-TRPC4	ACC-018
Anti-TRPC5	ACC-020
Anti-TRPC6	ACC-017

Antibodies to Purinergic (P2X) Receptors

Compound	Product #
Anti-P2X1	APR-001
Anti-P2X2	APR-003
Anti-P2X3	APR-016
Anti-P2X4	APR-002
Anti-P2X5	APR-005
Anti-P2X6	APR-013
Anti-P2X7-extracellular	APR-008
Anti-P2X7-extracellular-FITC	APR-008-F
Anti-P2X7	APR-004
Anti-P2X7-ATTO-550	APR-004-AO

K^+ Channel Blockers

Compound	Product #
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
rErgtoxin-1	RTE-450
rHeteropodatoxin-2	RTH-340
rHongotoxin-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 Kα	RTT-360
Verruculogen	V-500

Voltage-Gated Ca^{2+} Channel Blockers

Compound	Product #
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 MVIIC	C-150
FS-2	F-700
ω-Grammotoxin SIA	G-450
PLTX-II	P-510
SNX-482	S-500
TaiCatoxin	T-800