Modulated by Gasotransmitters – BK channels

CHAPTER · JANUARY 2012

READS
32

5 AUTHORS, INCLUDING:

Anton Hermann
University of Salzburg, Cell …

112 PUBLICATIONS **2,155**
CITATIONS

SEE PROFILE

Chapter 6
Modulated by Gasotransmitters: BK Channels

Anton Hermann, Guzel F. Sitdikova and Thomas M. Weiger

Abstract Calcium-activated potassium BK channels interconnect cellular activity, calcium signaling, and cell metabolism. Major virtues of these channels are their adaptability to different functions, their versatile physiology, and their capacity being modulated. The channels are present in a large variety of cells and organs in different forms of life from bacteria to men. Scientists attracted to these channels have produced a great wealth of information regarding their structure and function. Mutations at channels proteins are involved in a number of diseases (channelopathies), like diabetes, epilepsy, or heart failure. The gasotransmitters NO, CO, and H_2S all act on BK channels directly or indirectly via signaling pathways. In this chapter, we will briefly summarize some of the basic properties of BK channels and focus on aspects of BK channel modulation by gasotransmitters and their implications in physiology and pathophyiology.

Keywords Calcium-activated potassium channel · BK channel · Nitric oxide (NO) · Carbon monoxide (CO) · Hydrogen sulfide (H_2S)

Abbreviations

ACA	Acetaldehyde
Ach	Acetylcholine
BK	Maxi calcium-activated potassium channel
cAMP	Cyclic adenosinemonophosphate
cGMP	Cyclic guanosinemonophosphate

A. Hermann (✉) · T. M. Weiger
Department Cell Biology, Division Cellular and Molecular Neurobiology, University Salzburg, Hellbrunnerstr. 34, A-5020 Salzburg, Austria
e-mail: anton.hermann@sbg.ac.at

G. F. Sitdikova
Department of Human and Animal Physiology, Kazan Federal University, Kazan 420008, Russia

A. Hermann et al. (eds.), *Gasotransmitters: Physiology and Pathophysiology*,
DOI: 10.1007/978-3-642-30338-8_6,

CBS	Cystathionine β-synthase
CREB	Cyclic AMP response element-binding protein
CSE	Cystathionine γ-lyase
DTT	1,4-dithio-DL-threitol
DTNB	5,5'-dithiobis 2-nitrobenzoic acid
EET	Epoxyeicosatrienoic acid
ER	Estrogen receptor
EtOH	Ethanol
G-protein	Guanosine triphosphate (GTP) binding protein
20-HETE	20-hydroxyeicosatetraenoic acid
H_2S	Hydrogen sulfide
HS^-	Hydrogen sulfide anion
HO	Heme oxygenase
IK	Intermediate conductance K^+ channel
K_{ATP}	Adenosine-triphosphate dependent K^+ channel
LTP	Long-term potentiation
NaHS	Sodium hydrogen sulfide
NOS	NO synthase
NMDA	N-methyl D-aspartate
PKA, PKC, PKG,	protein kinase A, C, G
PDE	Phosphodiesterase
PS	Phosphatiylserine
P_{open}	Open probability
RCK	Regulatory domain of K^+ conductance
SK	Small conductance K^+ channel
sGC	Soluble guanylyl cyclase
Slob	Slo binding protein
STREX	Stress-axis regulated exon

Ions were the mighty tools live found in the sea when it was created there

Albert Szent-Györgyi, Nobel prize for Physiology and Medicine, 1937.

6.1 Ion Channels

Ion channels are integral membrane proteins constituting hydrophilic pores through lipid bilayers allowing ions to pass according to their electrochemical gradient. Ion channels are found early in the evolution of life and are essential for functioning of every living cell. Their array of operations range from using stored potential energy in the ion gradients across membranes, from osmo-regulation to the modulation of bioelectric processes, such as, sensory transduction, action potential generation and

propagation, synaptic transmission to muscle contraction, control of hormone release, or cell cycle coordination (Hille 2001; Armstrong 2003; Catterall 2010, 2011). Many ion channels are highly selective for a certain type of ion, such as K^+, Na^+, Ca^{2+}, or Cl^-, others are less selective and for example, allow to pass different cations such as excitatory acetylcholine (Ach) or N-methyl D-aspartate (NMDA) receptors. This property is related to a selectivity filter within the channel pore. Conformational changes allow these proteins to switch between closed and open states—known as channel gating. The equilibrium between these conformational states determines the amount of current that flows across the membrane as a function of time. Channel gating can be initiated by changes of the voltage across the membrane, by binding of ligands, such as neurotransmitters, hormones, intracellular messengers like Ca^{2+} or cyclic nucleotides, mechanical stress to the protein or via the cytoskeleton linked to channels, or by covalent modifications, such as protein phosphorylation, nitrosylation, carboxylation, or sulfhydration (Levitan 1999; Weiger et al. 2002; Hou et al. 2009; Hermann et al. 2012). Modification of channel gating comprises a large time range from milliseconds to hours or days. Long-term changes of the electrical excitability of neurons may be considered as a kind of cellular memory. Mutations at ion channels are involved in causing a number of diseases (channelopathies), like diabetes, epilepsy, heart failure, myotonia, or deafness to name a few (Shieh et al. 2000; Ashcroft 2006; Catterall et al. 2008; Kullmann 2010). Ion channels can be blocked by chemical agents or by peptide toxins which can be used as tools for separation of ion currents or for identification of certain types of channels. Patch clamp techniques allow the study of ion channels while these proteins are at work and together with molecular biology techniques that enable to produce alterations at the proteins to the exchange of a single amino acid it is possible to investigate intimate details of their structure and function.

6.2 Calcium-Activated Potassium Channels

A notable number of ion channels can be activated or modulated by Ca^{2+}. This property is based on either directly sensing alterations of intracellular Ca^{2+} or is mediated by Ca^{2+} binding proteins associated with these channels. Ca^{2+}-activated K^+ channels which are most prominent among those channels are found in a wide variety of excitable and non-excitable cells and in many species. They are broadly divided into three subfamilies mainly defined by their biophysical and pharmacological properties into SK (small conductance, 2–25 pikoSiemens (pS) (Blatz and Magleby 1986; Park 1994), IK (intermediate conductance, 25–100 pS) (Ishii et al. 1997) and BK (big conductance, 200–300 μS) (Marty 1981). The various types of SK, IK, or BK channels can be expressed in a single cell either alone or in combination, such as in the nervous or the vascular system (Thompson and Begenisich 2009). In this chapter, we will mainly focus on Ca^{2+}-activated "BK" channels and provide some information on their structure, function, and modulation which may bear on the further discussion of gasotransmitter actions.

6.3 BK Channels

BK (big K^+) channels are also referred to as large conductance Ca^{2+}-activated K^+ channels, MaxiK, BK_{Ca}, Slo1, $K_{Ca}1.1$, or KCNMA1 (Wei et al. 2005). The term Slo channels is derived from "Slowpoke", a gene that was first cloned from the fruit fly *Drosophila* (Atkinson et al. 1991) and later from a variety of other organisms (Adelman et al. 1992; Butler et al. 1993; Tseng-Crank et al. 1994; Ha et al. 2000; Salkoff et al. 2006). The Slo family includes three genes which express Ca^{2+} dependent channels. Some members of this group are insensitive to internal Ca^{2+} but are activated by internal Na^+ and Cl^- (Kameyama et al. 1984; Niu and Meech 2000; Yuan et al. 2003). Only a single Slo1 locus in the human genome (10q22.3) gives rise to multiple types of BK channels through RNA splicing at several different sites (Butler et al. 1993; Tseng-Crank et al. 1994; Yu et al. 2006).

BK Channels are present in a great variety of cells from bacteria to men as well as in many tissues, such as sensory, muscle, vascular, or the nervous system. BK channels have the largest single channel conductance of all K^+ channels (Latorre at al. 1989). Since Ca^{2+} is an important intracellular messenger involved in regulating a huge variety of enzymes these channels are linked to cell metabolism or to alteration of gene expression. The channels have been studied in great detail concerning their biophysical, physiological, pathophysiological, pharmacological, structural, and functional properties (for recent reviews see Salkoff et al. 2006; Ghatta et al. 2006; Cui et al. 2009; Wu et al. 2010; Lee and Cui 2010; Grimm and Sansom 2010; Hill et al. 2010; Berkefeld et al. 2010; Cui 2010).

BK channels are abundantly expressed in the brain (Knaus et al. 1996; Wanner et al. 1999) where they were found in virtually all cellular compartments—somatodendritic, axonal, as well in pre- and postsynaptic terminals (Sailer et al. 2006; Kaufmann et al. 2010). The activity of BK channels plays an important role in controlling action potential spike shaping and discharge activity, neurotransmitter release, hormone secretion, or vasoconstriction (Storm 1987; Lancaster and Nicoll 1987; Crest and Gola 1993). Activation of the channels drives the membrane toward the K^+ equilibrium potential and this way facilitates repolarization of the membrane potential providing a negative feedback for voltage-gated Ca^{2+} channels (Raffaelli et al. 2004; Hu et al. 2001; Robitaille and Charlton 1992; Lancaster and Adams 1986; Bielefeldt and Jackson 1994; Shao et al. 1999; Pedarzani et al. 2000; in Weiger et al. 2002; Faber and Sah 2003; Greffrath et al. 2004; Gu et al. 2007). Closing of Ca^{2+} channels terminates Ca^{2+} influx and causes internal Ca^{2+} to decay which in turn closes Ca^{2+}-activated K^+ channels. Such a negative feedback system was already described for endogenous bursting discharge activity in *Aplysia* pacemaker neurons (Gorman et al. 1981, 1982; Gorman and Hermann 1982). BK channels involved in governing electrical discharge activity have been found in a number of preparations, such as in rat adrenal chromaffin cells (Lingle et al. 1996), in rat pituitary somatotrophs (Van Goor et al. 2001), or in hair cells of the vertebrate auditory system (Fettiplace and Fuchs 1999; Navartanam et al. 1997). BK and voltage dependent Ca^{2+} channels often

coassemble into macromolecule complexes as first reported in *Helix* neurons (Gola and Crest 1993) and later also in other preparations (Berkefeld et al. 2006, 2010; Fakler and Adelman 2008) providing effective interaction of the channels by close association.

6.3.1 BK Channels: Structure and Function

The structure and function of BK channels has already been resolved in great detail. BK channels have a tetrameric structure with four independent alpha (α)-subunits (Fig. 6.1) which are able to form functional channels. A monomeric α-subunit is composed of about 1,200 amino acids with seven hydrophobic transmembrane helical segments passing through the membrane. The overall structure of the α-subunit is similar to other voltage-dependent K^+ channels. Multiple splice variants of the α-subunit have been identified resulting in a great variety of channel properties in various cell types (Fodor and Aldrich 2009). Major deviations from the basic structure of voltage-dependent K^+ channels concerns (1) the N-terminus (amino terminal) with an additional transmembrane helical segment S0 that precedes the segments S1–S6 and therefore renders the N-terminus at the extracellular side of the membrane (Meera et al. 1997), and (2) a large intracellular C-terminus (carboxyl terminal) which comprises approximately two-thirds of the protein (Atkinson et al. 1991) with two RCK domains (regulatory domain of K^+ conductance) (Fig. 6.1) containing Ca^{2+} binding sites which confer Ca^{2+} sensitivity to the channels (Schreiber and Salkoff 1997; Jiang et al. 2001; Yusifov et al. 2008; Yuan et al. 2010; Wu et al. 2010). Critical amino acid residues for Ca^{2+} activation in RCK1 are an aspartic acid (D367) and two histidine (H365 and H 394) residues, as well as in RCK2—the Ca^{2+} bowl forming an EF-hand-like motif—the aspartic acids D895 and D897 and D894. The latter is not in direct contact with Ca^{2+} ions but forms salt bridges (Yuan et al. 2010, Wu et al. 2010). The transmembrane segments S1–S4 bear charged amino acids which are functionally distributed on these segments and are part of the voltage sensor of the channels. The highly charged S4 segment serves as the main voltage sensor as in many other voltage-activated channels (Ma et al. 2006). The pore forming loop between segments S5–S6 have a conserved amino acid sequence at the selectivity filter (glycine-tyrosine-glycine—GYG) typical also for many other types of K^+ channels (Fig. 6.1). Binding of Ca^{2+} to the RCK domain(s) causes dilation of a ring structure that controls the position of the cytoplasmic pore gate (Jiang et al. 2002; Ye et al. 2006; Wang and Sigworth 2009; Yuan et al. 2010). A peptide linker between the pore gate and the RCK domains appears to act as a mechanical spring which pulls the gate open (Niu et al. 2004). Thus, channel gating includes an allosteric mechanism including voltage (depolarization) and chemical (Ca^{2+} binding) forces transmitted into mechanical forces to open the channel. The C-terminal region is also prominent for interactions with various channel modulatory proteins, such as protein kinases, phosphatases, slob, G-proteins, or heme

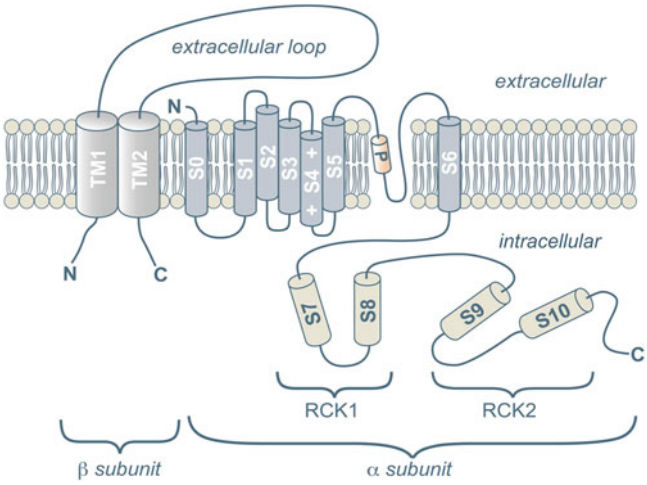

Fig. 6.1 Schematic illustration of the membrane topology of BK channel α- and *β*-subunits. Voltage sensing is operated by segments *S1–S4* with the positively charged *S4* being the dominant sensor. The pore gate loop is formed between the segments *S5* and *S6*, and the cytosolic domain contains *RCK1* and *RCK2* with various Ca^{2+} binding sites. Gasotransmitters appear to interact in particular with amino acid residues in the C-terminus. (graphic by A. Zankl)

(Isacson et al. 2007; Tian et al. 2003; Widmer et al. 2003; Zhou et al. 2003; Ragsdale and Yi 2011; Sokolowski et al. 2011), and see below.

Molecular and functional diversity of BK channels is achieved by splice variants of the Slo1 mRNA (Tseng-Crank et al. 1994; Navaratnam et al. 1997; Xie and McCobb 1998; Hall and Armstrong 2000). Via alternative splicing the pore forming α-subunit can at its C-terminus acquire a cysteine-rich 59 amino acid insert between RCK1 and RDK2 domains termed stress-axis regulated exon (STREX). STREX causes BK channels to activate at more negative potentials, enhances activation, and decreases deactivation which in summo leads to increased repetitive firing of action potentials.

6.3.2 BK Channel: Pharmacology

BK channels can be blocked by a variety of toxins and drugs. The most specific blocker at hand is iberiotoxin from scorpion venom. But also charybdotoxin (also from scorpion), paxilline (a mycotoxin from penicillium fungi), or extracellular submillimolar concentrations of tetraethylammonium (TEA, a quaternary ammonium cation) as initially reported for mollusc Ca^{2+}-activated K^+ currents (Hermann and Gorman 1979, 1981) block BK channels. Some BK channel subtypes found in rat brain plasma membrane vesicles are resistant to charybdotoxin (Reinhart et al. 1989). These channels are characterized by very slow gating and do not exhibit

intrinsic inactivation. Later it was found that the reason for this difference in channel characteristics appears to reside in the auxiliary β4-subunit which makes the channel resistant to charybdotoxin and iberiotoxin (Wallner et al. 1999; Weiger et al. 2000).

Natural polyamines (putrescine, spermidine, spermine) which are present in all cells and play important roles in their functioning also block BK channels (Drouin and Hermann 1994; Weiger and Hermann 1994; reviewed in Weiger and Hermann 2009). The polyamines are effective only if applied to the internal side of the membrane, except 1,12 diaminododecane an artificial diamine, which was found to act as a blocker from the extracellular face at the channel (Weiger et al. 1998). From in silico molecular modeling it was hypothesized that dehydration of the molecules was a determining factor for interaction with the channels. Recent findings indicate that a block of BK channels by polyamines appears to be involved in a overactive human bladder syndrome and by preventing polyamine synthesis BK channel activity could be restored to normal (Li et al. 2009). The mechanism of the polyamine block of BK channels is linked to the ring of negative charges at the inner vestibule of the channels (Zhang et al. 2006b).

Compounds that open K^+ channels are interesting in particular to pharmacologists as possible useful therapeutic tools (Nardi and Olesen 2008). Compounds were tested so far as stroke neuroprotectants, for treatment of urinary incontinence and erectile dysfunction (Shieh et al. 2000). As BK channel openers compounds, such as phloretin, a natural phenol found in apples, or related drugs such as NS1619 or BMS-204352 (Bristol-Mayer) have been identified. In vascular tissue it was found that the compound BMS-191011, a selective BK channel opener, specifically dilates rat retinal arterioles improving retinal circulation hence acting as a neuroprotectant in the retina with no apparent cardiovascular side effects (Mori et al. 2011). BK channel open probability is also increased by ethanol (Dopico et al. 1996; Jakab et al. 1997; reviewed in Hermann et al. 2012). Acetaldehyde (ACA) as the primary metabolite of ethanol oxidation appears to mimic EtOH effects or to interfere with its actions on the nervous system (reviewed in Hunt 1996; Quertemont et al. 2005; Correa et al. 2012). Studies from our laboratory indicate that intracellular ACA abolished the ethanol related increment of BK channel activity (Handlechner et al. 2008, 2011). From these findings we speculate that ACA may counteract the effect of ethanol and potentiate tolerance to ethanol. The effect of ACA on BK channels appears particularly relevant to the present thematic since ACA shows some aspects of a gasotransmitter and hence may be added to this category.

The direct opening of BK channels by appropriate drugs appears interesting as a further potential therapeutic approach (Nardi and Olesen 2008). For instance the compound BMS-191011 appears a selective BK channel opener in vascular tissue (Mori et al. 2011). It specifically dilates rat retinal arterioles improving retinal circulation which makes it a useful neuroprotectant in the retina. Another drug, puerarin, an isoflavone contained in the plant *Pueraria lobata Ohwi* (Leguminosa), used in therapy of cardiovascular diseases etc., also increases BK channels open probability and exhibits vasodilatory action (Sun et al. 2007). Furthermore, BK

channels are activated by inositol-1,4,5-trisphosphate (IP_3) which increases the BK channel apparent sensitivity to Ca^{2+} and this way stimulates the channels (Zhao et al. 2010). Epoxyeicosatrienoic acid (EET) and derivatives, metabolites of arachidonic acid, are "endothelium-derived hyperpolarizing factors" which activate coronary smooth muscle BK channels to cause vascular relaxation (in Edwards et al. 2010). Variations in the phenotype of BK channels between tissues, between cells and even in the same cell are expressed under different hormonal conditions (Benkusky et al. 2000). Sex hormones for example are in the category of BK channel openers (Dick and Tune 2010). The field of BK channel openers is still at its infancy but its pharmacological potential appears promising.

6.3.3 BK Channel Subunits

BK channels can be modulated by a wide variety of intra- and extracellular factors which allow fine-tuning of BK currents to the needs of a particular cell/organ. Four auxiliary β-subunits ($\beta1$–$\beta4$) associate with the α-subunits (Fig. 6.1) (Wallner et al. 1996; Meera et al. 1996; Orio et al. 2002). β-subunits are expressed through activation of four different genes in different tissues, such as smooth muscle, adrenal chromaffin cells or neurons, and modify voltage sensitivity, current kinetics and pharmacological properties of BK channels (Wallner et al. 1996, 1999). β-subunits are also responsible for tissue specificity, alter channel activity by activation of protein kinases, confer hormone (estradiol) activation, and can alter toxin binding to the channel (Tseng-Crank et al. 1996). They are involved in current inactivation by a flexible N-terminal chain and ball structure which eventually occludes the channel (Bentrop et al. 2001; Xia et al. 2003). In the brain $\beta4$-subunits for example inhibit BK channel activation and slow channel kinetics (Ha et al. 2004; Brenner et al. 2005; Weiger et al. 2000), make BK channels resistant to peptide blockers such as charybdotoxin and iberiotoxin (Meera et al. 2000; Behrens et al. 2000) and mutations at β-subunits are associated with idiopathic generalized epilepsy (Lorenz et al. 2007).

In addition the so-called Slo binding proteins (Slobs) attach to and modulate Slo channels (Schopperle et al. 1998; Zhou et al. 1999; Zeng et al. 2005; Zeng et al. 2006). Some Slobs like Slob 57 shift the voltage dependence to more depolarized voltages and cause inactivation of the channels which makes them close faster (Zeng et al. 2006). Other Slobs like Slob71 or Slob 53, shift voltage dependence in the opposite direction, i.e. to less depolarized voltages but have no effect on channel kinetics (Zeng et al. 2005). Physiologically interesting is the fact that one of the Slobs (Slob57) cycles in vivo (Jaramillo et al. 2004) indicating that BK channel activity changes as a function of day time imparting circadian rhythmicity to neurons.

Some BK channels in addition to Ca^{2+} and voltage can be activated by stretch. Stretch-activated BK channels (SAKCaC) (Kawakubo et al. 1999; Gasull et al. 2003) are expressed in a variety of tissues such as in myocytes or neurons, and

modulate vascular smooth muscle tone and endocrine cell secretion. There is evidence that also the STREX insert between RCK1 and RCK2 domains at the channel's C-terminal α-subunit confers stretch sensitivity to the channels (Kawakubo et al. 1999; Tang et al. 2003a). However, other BK channels lacking the STREX insert remain sensitive to membrane stretch suggesting that additional structures of the channel may be responsible for mechanical coupling to the cell membrane (Wang et al. 2010).

6.3.4 Posttranslational Modifications at BK Channels

Posttranslational modifications have been recognized as important means contributing to the functional fine-tuning of BK channels which also includes the array of gasotransmitter actions. Protein kinases/phosphatases and G-proteins are involved in physiological processes, such as transmitter release, hormone secretion, or muscle contraction (Chung et al. 1991; Levitan 1994; Bielefeldt and Jackson 1994; Schubert and Nelson 2001; Tian et al. 2004; Dai et al. 2009; Zhou et al. 2010). BK channels can be activated by internal GTP or GTPγS (a non-hydrolysable GTP analogue) in the presence of Mg^{2+}, characteristic for a G-protein mediated mechanism (Toro et al. 1990). BK channels can also be directly modulated by G-proteins independent of phosphorylation (in Dai et al. 2009). BK channels of rat pituitary GH4C1 cells are stimulated by cGMP-dependent protein kinase (PKG) but are inhibited by protein kinase A (PKA) (White et al. 1991, 1993) and by protein kinase C (PKC) (Shipston and Armstrong 1996; Hall and Armstrong 2000). PKA activation is generally found in smooth muscles and neurons whereas deactivation is reported in neuroendocrine cells (in Salkoff et al. 2006). Alternative spliced BK channels containing a STREX insert were inhibited by PKA (Shipston et al. 1999), whereas BK channels devoid of splice inserts were activated by PKA thus providing a molecular switch to determine sensitivity of the channels to phosphorylation. BK channel activity lacking the STREX exon is increased only after phosphorylation at all 4 serine sites (869 or 899, depending on the isoform) of the α-subunit. BK channel activity is decreased, however, with phosphorylation of only one serine (4) site of the STREX insert (Tian et al. 2004). Phosphorylation sites are located on α- as well as on β-subunits. PKC phosphorylation of BK channels at a site located between RCK1 and RCK2 domains inhibits open-state probability which depends on sequential phosphorylation of two distinct serines in the C-terminus. Dephosphorylation by protein phosphatases provide the antagonistic part of the regulatory cycle (Levitan 1994; Weiger et al. 2002; Dai et al. 2009; Perry and Sandle 2009). In rat pituitary tumor (GH4C1) cells the neuropeptide somatostatin which inhibits secretion in a variety of cells stimulates BK channels through protein dephosphorylation (White et al. 1991, 1993). Notably, the movement of a voltage sensor domain may activate lipid phosphatases as reported in an ascidian non-channel forming protein (Murata et al. 2005; Hossain et al. 2008).

BK channel activity is also influenced by their lipid surrounding. This has been studied by insertion of the channels into artificial lipid bilayer membranes using different types of lipids. For example, the probability of channel opening (Po) was significantly greater in phosphatidylethanolamine (PE) compared to phosphatidylserine (PS) at the same Ca^{2+} concentration and voltage (Moczydlowski et al. 1985). Also bilayer thickness and specific lipids such as sphingomyelin, which cluster in microdomains have been identified as critical factors that modulate BK channel conductance (Yuan et al. 2004). Beside lipids cholesterol is a major component of cell membranes in animals. BK channels are generally inhibited by accessory cholesterol in native and in reconstituted cell membranes by shortening mean open and extending mean closed times whereas depletion of membrane cholesterol results in an increase of channel open probability (Bolotina et al. 1989; Chang et al. 1995; Crowley et al. 2003; Lin et al. 2006; Bukiya et al. 2008). Since gasotransmitters are small molecules and lipid soluble it will be important to study their effects on the level of lipid bilayer–BK channel interaction in more detail.

6.3.5 BK Channelopathies

Channelopathies are gene mutations that cause ion channel malfunction which may be linked to organ malfunction (for recent reviews see Rolim et al. 2010; Catteral 2010; Kullman and Waxman 2010; Lee and Cui 2010). Mutations, elevation, or deletion of BK channels were found to be associated with epilepsy, paroxysmal disorder, cerebellar ataxia, hearing loss, autism, mental deficiency, chronic hypertension, or in erectile dysfunction (Werner et al. 2005; Brenner et al. 2005; Sausbier et al. 2004, 2005; Rüttiger et al. 2004; Du et al. 2005; Laumonnier et al. 2006). Various β-subunits were found to modulate BK channels differently and therefore may contribute to channelopathies (Brenner et al. 2000, 2005; Lee and Cui 2010). BK channel mRNA expression is lower in the prefrontal cortex of schizophrenic, autistic, and mentally retarded persons (Zhang et al. 2006b; Laumonnier et al. 2006). Mutation at the α-subunit which is associated with idiopathic generalized epilepsy and paroxysmal dyskinesia (Lorenz et al. 2007) appear to result from augmented Ca^{2+} sensitivity at the RCK1 binding site together with mutations at the brain specific β4-subunit. Mutant BK channels were found in humans to increase excitability by causing a more rapid repolarization of action potentials which in turn limits the amount of Ca^{2+} flowing into the cell. Less Ca^{2+} means that SK channels will be activated to a lesser degree which leads to a shorter period in which the cells are hyperpolarized resulting in an increased discharge of action potentials which may lead to epilepsy, paroxysmal movement disorders, or alcohol dependent initiation of dyskinesias (Du et al. 2005; Brenner et al. 2005).

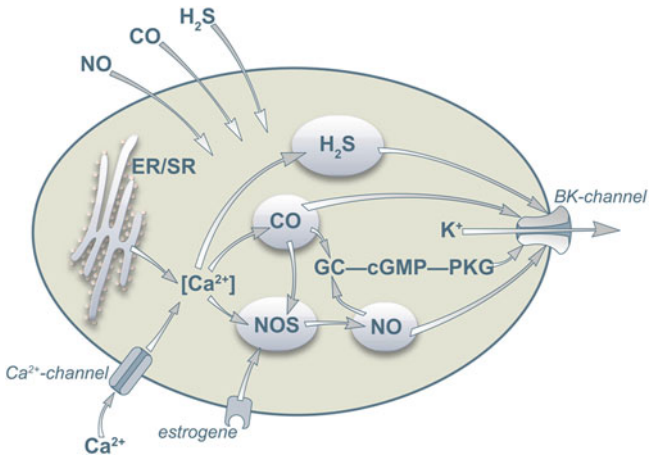

Fig. 6.2 Schematic of gasotransmitter action on BK channels. NO, CO, and H_2S from external sources may pass the plasma membrane or can be enzymatically generated via a common Ca^{2+} dependent mechanism from the substrates L-arginine, heme, or cysteine, respectively. NO and CO may act through a sGC—cGMP—PKG pathway. All gasotransmitters may directly interact with BK channels at different sites or channel associated proteins (possibly by nitrosylation, carboxylation, or sulfhydration). (graphic by A. Zankl)

6.4 Gasotransmitters: BK Channels

Gasotransmitters have been established as a further important group of signaling molecules. The history of their discovery appears as one of the most fascinating recent scientific achievements in the life sciences. The development of appropriate ideas, some dating back centuries, have been covered in recent reviews (in Kajimura et al. 2010; Moody and Calvert 2011; Wang et al. 2010; Mustafa et al. 2009b). In this section we will summarize some details of the action of gasotransmitters on BK channels.

6.5 BK Channels: Modulation by Nitric Oxide (NO)

Nitric oxide (NO) activates many enzymes and ion channels either directly by interaction with the channel proteins or indirectly via intracellular signaling pathways (Fig. 6.2). NO was the first gaseous transmitter identified and the first shown to act at BK channels. NO has been established as retrograde messenger which from its site of postsynaptic generation diffuses back and acts at the presynaptic side where it can alter transmitter release (Malen and Chapman 1997; Bon and Garthwaite 2003; in Garthwaite 2010; Szabadits et al. 2011) and affect learning and memory (Edwards and Rickard 2007; Paul and Ekambaram 2011). BK channels at synaptic terminals are therefore prominent targets of NO for shaping transmitter release.

There is a large body of studies to indicate that NO activates BK channels (for recent reviews see Tanaka et al. 2004; Edwards and Rickard 2007; Feletou 2009, Edwards et al. 2010). The NO-induced activation of BK channels occurs by various ways: (1) **directly** by interaction of NO with BK channels, or (2) **indirectly** via a NO activated sGC–cGMP–PKG phosphorylation pathway (Fig. 6.2), by other intermediate proteins or by preventing the formation of endogenous inhibitors. Evidence for **direct** action of NO on BK channels was obtained by single channels recordings of cell-free membrane patches form vascular smooth muscle (Bolotina et al. 1994), from intestine mesentery artery (Mistry and Garland 1998) and from isolated rat brain synaptosomes inserted into planar lipid bilayers (Shin et al. 1997). Also in posterior pituitary nerve terminals activation of BK channels by NO persisted in the presence of sGC inhibitors or under ATP/GTP free conditions (Ahern et al. 1999). In this preparation NO activated BK channels almost independent of voltage and cytoplasmic Ca^{2+} rendering channels active even at very low-nanomolar Ca^{2+} concentrations. It was concluded that NO modified BK channels may suppress discharge activity of action potentials and inhibit hormone secretion.

NO also increases the open probability of BK channels from rat brain directly in a concentration dependent manner followed by a prolonged suppression of channel activity after NO wash out (Lee et al. 2006). In further experiments using N-ethylmaleimide (NEM), which alkylates free sulfhydryl groups of cysteines and irreversibly suppresses BK channel activity, NO could still activate BK channels via direct chemical modification—probably via S-nitrosylation (Lee et al. 2006). Intermittent hypoxia which may occur during breathing disorders such as sleep apnea appears to involve a NO–BK mechanism of action in hippocampal cells (Tjong et al. 2008a). During chronic intermittent hypoxia down regulation of neuronal NO synthase expression impairs NO release which decreases the open probability of BK channels. NO donors restored the activity of BK channels of these cells which was prevented by blockers of S-nitrosylation but not by inhibition of the sGC–cGMP pathway, again indicating a direct NO-dependent mechanism. Melatonin which is rhythmically released in a circadian manner from the pineal gland is well-known for its neuroendocrine functions and as an antioxidant and radical scavenger. In hippocampal CA1 neurones during hypoxia neuronal NO synthase and concomitantly BK channels are significantly reduced. Melatonin ameliorates NO production and BK channel activity via an antioxidant mechanism (Tjong et al. 2008b).

In the vascular system BK channels composed of α- and β1-subunits are preferentially expressed in smooth muscle cells whereas other Ca^{2+} activated K^+ channels (SK and IK) are preferentially expressed in endothelial cells (in Feletou 2009). Insulin resistance may cause severe cardiovascular diseases where BK channels and NO appear to play a pivotal role (Li et al. 2011). In insulin resistant rats BK currents were decreased in vascular smooth muscle related to down regulation of the auxiliary β1 subunit, whereas NO concentration was compensatory increased. It should be noted that also a variety of other K channels in smooth muscles not included in this overview can be activated to cause hyperpolarisation and relaxation.

NO has also been reported to **indirectly** activate BK channels via a cGMP pathway as in a variety of vascular smooth muscles (Williams et al. 1988 (aorta); Robertson et al. 1993 (cerebral artery); Archer et al. 1994; George and Shibata 1995 (coronary artery); Alioua et al. 1995 (trachea); Darkow et al. 1997 (coronary artery); Nagaoka et al. 2007 (retinal arterioles) or in human glomerular mesangial cells located within corpuscle capillaries of the kidney (Stockand and Sansom 1996). The carotid body, a chemosensory organ that detects changes in arterial blood O_2, CO, and H^+, is regulated by NO released from efferent nerves or from vascular endothelium. NO inhibits sensory activity of carotid body cells by enhancing BK channel activity through a sGC–cGMP–PKG-dependent mechanism (Silva and Lewis 2002). Further investigation of a NO-induced cGMP-mediated effect on BK channels expressed in HEK293 cells on the molecular level showed that point mutation at Ser-1072, a high-affinity PKG phosphorylation site in BK channels, abolished the effect of NO as well as PKG enhanced BK channel open probability (Fukao et al. 1999). This study provides evidence of a NO-induced PKG-dependent direct phosphorylation of BK channels. Resveratrol, is another antioxidant which is produced by several plants and became famous because it is contained in red vine and its possible beneficial cardiovascular effects. The drug was found to induce dilation of retinal arterioles mediated by the release of NO from the endothelium and a subsequent activation of sGC and of BK channels in smooth muscles (Nagaoka et al. 2007).

In addition to a multitude of various neurohumoral factors the NO–cGMP–PKG–BK pathway is also involved in erectile function and dysfunction of males and females. NO released from nonadrenergic-noncholinergic nerves (NANC) activates sGC signaling with final PKG-dependent phosphorylation of BK channels which hyperpolarizes arterial and cavernosal smooth muscles. This leads to closure of voltage-dependent L-type Ca^{2+} channels and the reduction of the cytosolic Ca^{2+} concentration causing relaxation. This way the corpora covernosa are flooded with blood and by restriction of venous drainage arterial blood pressure raises above systemic pressure which leads to erection (Fan et al. 1995; Archer 2002; Gragasin et al. 2004; Feletou 2009). Other NO-dependent mechanisms, like the reduction of internal Ca^{2+}, other types of K^+ channels (SK, IK, adenosine-triphosphate dependent K^+ channels (K_{ATP}), or voltage-activated K^+ channels), expressed in different cell types, or electrical coupling of smooth muscle cells may also contribute to relaxation but are not further considered in this context.

NO can also **indirectly** activate BK channels by other intermediate products. Endothelium-derived factors such as cytochrome P450-derived epoxyeicosatrienoic acids, prostacyclin, or lipoxygenase hyperpolarize smooth muscle cells by activating BK channels possibly via a receptor activated phosphorylation pathway. In contrast, cytochrome P450-derived 20-hydroxyeicosatetraenoic acid (20-HETE) and various endothelium-derived contracting factors inhibit BK channels causing subsequent activation of voltage-dependent Ca^{2+} channels, thus depolarizing and contracting the vascular smooth muscle cells. Hence, NO by inhibiting cytochrome 450 dependent formation of 20-HETE can activate BK channels and thus may reduce infarct after ischemic stroke and reverse vasospasm (reviewed in Feletou 2009).

Activation of BK channel α-subunits expressed in human embryonic kidney (HEK293) cells or in cerebrovascular smooth muscle cells has been found to be involved in NO-induced apoptosis (Ma et al. 2010; Xie et al. 2010). This effect appears specific to BK activation since native HEK cells which are devoid of these channels, or if BK channels were blocked, the apoptotic effect after NO application was absent. If this NO–BK channel mechanism also plays a role in any native physiological system, as well as the question which role other auxiliary proteins like β-subunits or slob may play in the apoptotic pathway remains to be investigated. The interaction between NO and BK channels may also be governed by alteration of the Ca^{2+} concentration in the cytosol. NO liberated from arterial endothelial cells induces Ca^{2+} sparks (elementary release of Ca^{2+} units) through ryanodine-sensitive Ca^{2+} channels in the sarcoplasmatic reticulum (Perez et al. 2001; Mandala et al. 2007). The increase of Ca^{2+} activates nearby BK channels which leads to hyperpolarization and dilatation of vascular smooth muscles.

6.5.1 NO–BK: Hormones

Steroid hormones have been found to act through a non-genomic, NO-mediated mechanism (Fig. 6.2). 17β-estradiol for example, induces release of NO and activation of BK channels in coronary arterioles predominantly during ischemic conditions (Node et al. 1997). NO activation may comprise estrogen binding to a plasma membrane estrogen receptor (ERα) (Chambliss et al. 2000) which through signaling pathways leads to phosphorylation of eNOS and NO production (Li et al. 2007) (Fig. 6.2). Furthermore, in coronary artery endothelium cells and smooth muscles the process appears to involve a NO–cGMP-dependent stimulation of BK channels (Wellman et al. 1996; Darkow et al. 1997). It was proposed therefore that estrogens are involved in the regulation of vascular tone in heart and through its vasodilatory effect may exert protection against cardiovascular disease which appears particularly beneficial to woman before menopause (White et al. 1995). Activation of the cGMP signaling pathway to stimulate BK channels may also comprise cross-activation through cAMP via metabolites of archidonic acid (White et al. 2000; Zhu et al. 2002).

6.5.2 NO–BK Disorders

Disorders in the NO–BK channel pathway can emerge at a multitude of levels including deficiency of NO production (which again can be multifarious) (in Mason and Cockcroft 2006), the up- or degradation of sGC–cGMP–PKG pathway with its amplifying properties (reviewed in Francis et al. 2010) or the expression of a low quantity or different variants of BK channels. Thus an equal amount of therapies on these various levels appears predictable. A drug that has been already

used by the inventor of dynamite, Alfred Nobel for treatment of his angina pectoris, is nitroglycerin although its mechanism of action was unknown at that time (Marsh and Marsh 2000). The compound is still in use today and has been found later to release NO by a bioactivation process and to cause vasorelaxation through an increase of cGMP and BK channel activation (Ignarro et al. 1999; Gruhn et al. 2002; Martínez-Ruiz et al. 2011). A more recent therapy commercially available is the employment of phosphodiesterases (PDE5) inhibitors, such as sildenafil (Viagra®) or similar drugs, in erectile dysfunction that inhibit the breakdown of cGMP which leads to an increase of BK channel activity. Further therapies may involve NO donors, BK channel activators, stimulation of BK channels expression, or augmentation of BK channels by gene transfer (Melman et al. 2006). On the other hand, drugs blocking BK channels could help in the treatment of hypotension as in circulatory shock conditions (Zhao et al. 2007). Aging decreases BK channel expression and the magnitude of ion currents of rat coronary arterial smooth muscles (Marijic et al. 2001; in Feletou 2009). Aging and cardiovascular diseases are also associated with endothelial dysfunctions involving a decrease in NO bioavailability, alterations of EDHF-mediated responses, and/or enhanced production of endothelium-derived contracting factors (in Feletou 2009). cDNA injections into the corpora cavernosa for expression of BK channels or an adenoviral vector containing the genes for expression of eNOS increased erections of aged animals indicating gene therapy as a possible useful treatment in erectile dysfunction (Christ et al. 1998; Champion et al. 1999).

6.6 BK Channels: Modulation by Carbon Monoxide (CO)

The generation, physiological, and pathophysiological functions of CO have been covered in the chapter "The role of CO as a gasotransmitter in cardiovascular and metabolic regulation" of this book by Ashley Untereiner, Lingyun Wu, and Rui Wang and has been reviewed previously (Verma et al. 1993; Wang et al. 1997a; Roberts et al. 2004; Ryter and Ottenbein 2004; Wu and Wang 2005; Kim et al. 2006; Cutajar and Edwards 2007; Stec et al. 2008; Ryter and Choi 2010; Durante 2010; Leffler et al. 2011). CO action on synaptic transmission, emphasizing the neuromuscular junction is presented by Guzel Sitdikova and Andrey Zefirov in their contribution. Here we will cover some CO functions focusing on its actions at BK channels. CO is produced via three types of heme oxygenase enzymes (HO-1, 2, or 3; the production and functions of HO-3, however, is still elusive). The enzymes are either inserted into membranes (plasma membrane, endoplasmatic reticulum, the nuclear envelope) or HO-2 being directly associated with BK channels. There is general agreement that CO increases the activity of BK channel α-subunits in the absence of β-subunits (Riesco-Fagundo et al. 2001; Wu et al. 2002; Xi et al. 2004; Williams et al. 2004; Bolognesi et al. 2007; Telezhkin et al. 2011). CO has been postulated to act via various pathways on BK channels: (1) activation of the sGC–cGMP–PKG cascade (Komuro et al. 2001; Gagov et al.

2003; Boehning and Synder 2003; Dong et al. 2007) suggesting phosphorylation of BK channels or activation of the Na^+/Ca^{2+} exchanger, (2) via CO binding to heme associated with BK channels (Jaggar et al. 2002, 2005), or (3) by direct binding of CO to and affecting BK channels (Wang et al. 1997b; Riesco-Fagundo et al. 2001; Dong et al. 2007; Wang and Wu 2003; Hou et al. 2008) causing conformational alterations of the channel protein or by changing the channel's Ca^{2+} sensitivity.

Blood oxygen (O_2) level is being constantly monitored by glomus cells in the carotid bodies within the carotid arteries. Under normoxia the enzyme heme oxygenase-2 (HO-2) binds O_2 and generates CO at low micromolar concentration which activates BK channels and causes glomus cells to hyperpolarize and to remain inactive (Williams et al. 2004). This line of evidence is supported by the in vitro findings of HO-2 being part of the BK channel complex, by knockdown of HO-2 expression reducing channel activity and by CO reestablishing BK activity. Under hypoxia CO production comes to a halt and by closing of BK channels electrical excitable glomus cells depolarize by activation of voltage-dependent Na^+ and Ca^{2+} channels. Cells produce action potentials which signal to the brain and eventually lead to an increase of breathing frequency. However, the role of CO–BK activation in oxygen sensing in vivo has been questioned since HO-2 knockout mice exhibit normal responsiveness to hypoxia (Ortega-Saenz et al. 2006). Also the alternatively spliced cysteine-rich STREX insert into the carboxy terminal of the BK channel α-subunit appears essential for oxygen sensing since mutation of a serine residue within the STREX exon abolished hypoxia sensitivity (McCartney et al. 2005). From these experiments it appears that HO-2 is unlikely to mediate regulation of BK channels and therefore may be not a universal oxygen sensor. Hence, sensing of O_2 probably may involve other mechanisms, including cross-excitation to H_2S (Peng et al. 2010), other ion channels or enzymes (Peers et al. 2010).

Arachidonic acid is metabolised in endothelial cells by cytochrome P450 epoxygenases to epoxyeicosatrionic acid (EETs). One of the EETs, namely 11,12-EET, through activation of HO-system causes an increase of endogenous generation of CO and activation of BK channels (Sacerdoti et al. 2006). This mechanism appears involved in mesenteric vasodilatation and increased mesenteric microcirculation. Interestingly EETs have no effect on BK channels from vascular smooth muscles in inside-out patches indicating that EETs do not directly activate BK channels. EETs can also activate BK channels by stimulation of the transient receptor potential channel (TRPV4) and the subsequent induction of spontaneous transient outward currents (Earley et al. 2005).

In mesenteric arteries of cirrhotic rats BK α-subunits are over-expressed which has been suggested to be due to upregulation of HO and increased CO production causing an increased response to acetylcholine (Bolognesi et al. 2007). CO in turn may be responsible for increased expression of BK channels (Bolognesi et al. 2007; Wu and Wang 2005). Indeed, the gas may have therapeutic benefits since continuous inhalation of low concentrations of CO attenuates hypoxic pulmonary artery vasoconstriction by activation of BK channels (Dubuis et al. 2005; Ryter and Choi 2010).

As already outlined (see Chapter by Untereiner et al.) a major target of present investigations in CO-mediated BK channel activation is the vascular system (Wang and Wu 2003; Ryan et al. 2006, Dong et al. 2007, reviewed in Leffler et al. 2011). A study on pig cerebral arterioles stimulated by glutamate is mediated by the CO–BK activation mechanism but differs to a hypoxia-induced dilation, where activation of CO–BK channels or via sGC activation surprisingly appear not to be involved (Kanu and Leffler 2007). CO at nanomolar concentrations augments BK channel frequency and amplitude in cerebral arterioles by increasing the coupling to Ca^{2+} sparks since ryanodine, a blocker of Ca^{2+} sparks, abolished CO dilatation (Jaggar et al. 2002). How the amplitude of BK currents is increased remains elusive!

Astrocytes, with their end-feet contact to arterioles, activate cerebral arteriole myocytes contributing to the regulation of cerebral blood flow. Glutamate stimulated CO production by astrocytes activates myocyte BK channels and causes dilation of arterioles in the brain (Li et al. 2007). NO and CO differ in respect to their effect on BK channels. In vascular smooth muscle BK channel β-subunits appear not necessary for CO activation but appear essential for NO activation. Pretreatment of the channels with NO prevented the effect of subsequent CO application (Wu et al. 2002). In human umbilical vein endothelial cells BK channels are activated by both CO and NO and it was suggested that at low concentrations of CO the activation of the channels is partially mediated by NO (Dong et al. 2007). Furthermore, cross reaction of CO induced release of NO (Thorup et al. 1999, Gomes et al. 2004, 2010) and vice versa (Durante et al. 1997) have been reported. A study of Wang and Wu (2003) indicates that NO and CO act at different amino acid residues to affect BK channels and hence may play a role in tailoring the functional status of the channels. CO and NO exhibit many similar functions such as in apoptosis, inflammation, proliferation, or neurotransmission. NO can activate CO production by stimulating gene expression (Durante et al. 1997; Durante 2010) whereas prolonged elevated CO in neonate piglets reduces NO by inhibiting NOS apparently constituting a negative feedback system to control vascular tone (Knecht et al. 2010; cf. Leffler et al. 2011). Crosstalk of gasotransmitters has been discussed recently in Kajimura et al. 2010; Moody and Calvert 2011; and in Untereiner et al., this book).

The topological location of specific amino acid residues of BK channels targeted by CO is a matter of further intense discussion and investigation. First indication for a site of CO action on BK channels was obtained by using chemical modification of specific amino acids. Diethyl pyrocarbonate, a chemical reagent directed against histidine residues applied to outside-out patches, annihilated the CO induced increase of open probability of BK channels of vascular smooth muscle (Wang and Wu 1997). However, the precise identity of the site(s) of CO interaction could not be determined with certainty. In other studies it was shown that CO may affect BK channels indirectly.

CO is known to activate sGC at high micromolar concentrations whereas NO is active at nanomolar concentrations. However, CO does not increase cGMP levels of pig cranial arterioles but causes dilatation of arterioles by the available

minimum background concentration of cGMP indicating only a minor contribution of a sGC–cGMP–BK mechanism of action (Leffler et al. 1999).

CO binding to heme which is endogenously linked to a histidine residue within a heme binding site located between the two RCK domains at the C terminal of the BK channel α-subunit (Tang et al. 2003b) switches heme from being a channel inhibitor to a channel activator (Jaggar et al. 2002, 2005). However, several lines of evidence suggest that heme is not the (only) CO sensor. Oxidation of heme did not alter the channel's sensitivity to CO and mutations at heme binding sites were not able to suppress CO activation (Williams et al. 2008; Hou et al. 2008). Replacing of the S9–S10 domains of the C terminus (Williams et al. 2008) or mutations of an aspartic acid (D367) and two histidine (H365 and H 394) residues located at the cytoplasmic RCK1 totally abolished CO sensitivity (Hou et al. 2008). Also mutation at aspartic acid D367, a probable further high-affinity Ca^{2+} sensor in RCK1, rendered the channel insensitive to CO, suggesting that this site is another essential part of the CO sensor while another low-affinity Ca^{2+} sensing site at RCK1 had no effect on CO sensing (Hou et al. 2008). These mutations failed to alter the sensitivity of the channel to hemin, indicating that CO and hemin act via different mechanisms at BK channels. Since these mutations are located near the high-affinity Ca^{2+} sensor of the channels it was proposed that CO mimics the effect of Ca^{2+}. Notably, CO increased the open probability of channels in excised patches in the virtual absence of Ca^{2+} and does not require activation of the voltage sensor (Hou et al. 2008). The report also states that CO was ineffective on small conductance Ca^{2+}-activated K^+ channels (SK) which have a different Ca^{2+} activating mechanism and NO does not stimulate the BK channel. Since the RCK1 domain accommodates Ca^{2+} (as well as Mg^{2+} and Zn^{2+}), CO and H^+, it has been termed a "multi-ligand" sensor (Hou et al. 2009). The fact, that CO at saturating Ca^{2+} concentrations is able to further increase BK channel open probability (Williams et al. 2008), however, appears difficult to reconcile with this notion. In a recent publication by Telezhkin et al. (2011) the pros and in majority the contras of a hypothesis on the mechanisms of CO action so far at hand are discussed. Further experiments presented in this article showed that cyanide reversibly prevents channels activation by CO. Cyanide appears to bind to, but not to activate the channels. Cyanide appears not to bind to heme and hence also makes the heme hypothesis more unlikely. The study rather suggests that CO activation is conferred to BK channels by interaction with cysteine residues, in particular C911, within the RCK2 domain close to the Ca^{2+} bowl where it may be involved in formation of a metallocluster which binds to and activates the channels. However, such an integrated binding site is not indicated in the bacterial MthK channel, a basic BK structured channel (Jiang et al. 2002). From these and some other results it now appears that the C-terminal of the α-subunit may be a major target of CO binding although further heterogeneous sites at BK channels may contribute to the implicated conformational changes leading to channel activation. Alterations of other amino acids at BK channels which prevent CO activation may lead to rigidity of channel conformation but may not affect a primer CO binding site. Hence these experiments are sometimes difficult to interpret and therefore the

exact nature of CO action on BK channels is still not entirely clear. Nevertheless, it appears possible to predict that the various experimental data already at hand and to be produced in near future will crystallize and soon allow to furnish a solid hypothesis for a mechanism of CO–BK channel activation.

Some further questions, therefore, still deserve further exploration: The detailed mechanism of direct CO action at BK channels, at which site(s) of the channel does CO attach to modify channel functioning and which role may carboxylation of amino acids play? Although there appears general agreement that CO increases BK channels by activation of α-subunits, interaction with the various β-subunits still remains to be more fully examined. CO-mediated activation of BK channels regulating vascular tone appears of particular interest in pharmacology and therapy. In addition, the role of CO in higher nervous functions, such as learning and memory shall to be investigated in more detail in particular its effect on ion channels.

6.7 BK Channels: Modulation by Hydrogen Sulfide (H_2S)

A summary of the function of H_2S in physiology, pathophysiology and pharmacology has been reviewed in recent publications and has been covered by Hideo Kimura in the chapter on "Physiological and pathophysiological functions of hydrogen sulfide", in this book. In the present section we summarize some knowledge about the action of H_2S on Ca^{2+}-activated K^+ channels—in particular on BK channels which is rather scarce so far.

H_2S is endogenously produced in many cells and tissues from the amino acid L-cysteine. The enzymatic production of H_2S through cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), or cysteine aminotransferase (CAT)/3-mercaptopyruvat sulfurtransferase (3MST) has been summarized in various reports (Łowicka and Bełtowski 2007; Shibuya et al. 2009; Ishigami et al. 2009; Renga 2011) and is described in detail by Kimura in the present communication. Similar to the other gasotransmitters NO or CO, H_2S is water and lipid soluble and therefore easily diffuses in the cytosol and is able to pass membranes. The biology, physiology, pathophysiology, and pharmacology of H_2S has been reviewed in an impressive amount of recent publications (Mustafa et al. 2009a; Mancardi et al. 2009; Caliendo et al. 2010; Wallace 2010; Tan et al. 2010; Gadalla and Snyder 2010; Wang 2011; Kimura 2011; Hu et al. 2011; Bucci and Cirino 2011; Wang 2011). Evidence is accumulating that H_2S plays a crucial role in oxygen sensing (Olson et al. 2008; Olsen and Whitfield 2010; reviewed in Peers et al. 2010). In carotid body chemoreceptors H_2S appears to block BK channels causing excitation of glomus cells (Li et al. 2010). In CSE knockout animals or after inhibition of CSE carotid chemoreceptors responses to hypoxia were severely impaired (Peng et al. 2010). Under normoxia heme oxygenase-2 (HO-2) dependent CO generation appears to suppress H_2S production whereas the lack of oxygen under hypoxia, where CO generation is depressed, H_2S production is increased. H_2S generation in

the carotid body appears to require interaction of the H_2S producing enzyme CSE with HO-2 which generates CO. Carotid body aberrations appear to play a role in sleep apneu which causes intermittent hypoxia and via increase of sympathetic nerve activity may lead to blood pressure elevation (Peng et al. 2010).

H_2S, via BK channel activation dilates endothelium mesenteric arteries causing hyperpolarization of vascular smooth muscles and a decrease of myogenic tone (Jackson-Weaver et al. 2011). In intermittent hypoxia, a model of sleep apnea, the authors report on depression of endothelial CSE and hence H_2S causing depolarization of vascular smooth muscles and increase of myogenic tone. Elucidation of the signaling pathway could help targeting vascular dysfunction and hypertension in sleep apnea to provide pharmacological tools for therapy. Clearly there appears substantial evidence now of H_2S-mediated sensing of oxygen in carotid bodies involved in regulation of oxygen requirements. Nevertheless, other mechanisms are also under discussion, such as H_2S activating of ATP-dependent K^+ channels (Fitzgerald et al. 2011) or activation of AMP-activated protein kinase inhibiting BK channels (in Peers et al. 2010).

We used GH cells (growth hormone releasing cells) from a rat pituitory tumor cell line to investigate the effect of H_2S on BK channels (Sitdikova et al. 2010). Sodium hydrogen sulfide (NaHS) was used as H_2S donor. NaHS dissociates to Na^+ and HS^- (hydrogen sulfide anion) in solution and HS^- associates with H^+ to produce H_2S. In a solution of pH 7.4 approximately one-third of NaHS exists as H_2S and the remaining two-thirds are present as HS^- (Beauchamp et al. 1984; Reiffenstein et al. 1992). Our recent measurements using a H_2S sensor and taking the salinity of the solution and evaporation of H_2S into account indicate that an effective concentration of $\sim$50 μM H_2S is obtained from a 300 μM NaHS solution (Sitdikova et al. unpublished results). Since H_2S is highly diffusible NaHS solutions were prepared shortly before use and were usually applied for 3–5 minutes. Because H_2S is permeable to the plasma membrane it can be assumed that during single cell recordings, as well as in various other patch clamp configurations, H_2S concentrations are similar to the H_2S concentration in the bath solution.

H_2S dose-dependently increased single channel open probability (P_{open}) of BK channels (Sitdikova et al. 2010). The dose-response relationship revealed a low and a high range of effective H_2S concentrations. The Hill coefficient for the low H_2S dose was 0.82 and the effective concentration (EC) 90.14 μM, and the high dosage range had a Hill coefficient of 3.26 and an EC of 1664 μM. Both, low and high concentrations of NaHS were fully reversible within minutes after wash out. The effect of H_2S was transient similar to the action of ethanol on BK channels (Jakab et al. 1997) indicating the development of time-dependent tolerance. The mechanism by which H_2S increases P_{open} is presently unknown. The fast onset of the H_2S effect after application within seconds, but also the rapid decrease after wash out of the drug, appears to favor a direct effect at the channel protein. To study the effect of H_2S on BK channel sensitivity to intracellular Ca^{2+} we used a range of Ca^{2+} concentrations at a constant membrane potential. These experiments showed that there was no difference in H_2S effects on BK channel activity at different Ca^{2+} concentrations applied to the internal face of the channels. Hence,

H_2S appears not to interfere at the Ca^{2+} binding sites of the channel. Since BK channels of GH cells are not accompanied by β4-subunits, as indicated by the rapid iberiotoxin block (Behrens et al. 2000), these auxilliary subunits also do not appear targets of H_2S in GH cells.

Redox modification is among the recognized mechanisms for cellular effects of H_2S (Kimura and Kimura 2004; Zhao et al. 2001; Yang et al. 2005; Kawabata et al. 2007; Kabil and Banerjee 2010). In our experiments the increase of BK channels activity by H_2S was impeded after application of the reducing agent dithiothreitol (DTT) to cytoplasmic side of the channel. In the oxidized state after application of thimerosal BK channel P_{open} was further increased by H_2S. From these experiments we suggested that H_2S acts at BK channel sulfhydryl groups and hypothesized that the increase of BK channel P_{open} is mediated by a redox modulation of cysteine or some other residue(s). Cysteine residues available for redox modulation are located at the cytoplasmic side of the channel since the reducing agent DTT and the oxidizing agent thimerosal alter BK channel activity only when applied to the intracellular side of the patch membrane (Erxleben et al. 2002; Wang et al. 1997c). We hypothesize that the activation of BK channels by H_2S causes shortening of action potentials which will decrease hormone secretion of GH cells.

In contrast to our results BK channels expressed in HEK293 cells were inhibited by H_2S (Telezhkin et al. 2009, 2011). On the other hand, in vascular smooth muscle H_2S causes BK channel-dependent dilatation and hyperpolarization (Jackson-Weaver et al. 2011) and activates BK channels in cultured endothelial cell (Zuidema et al. 2010). To date no explanation on these differences in the response to H_2S are given but might be related to different BK channel splice variants or may be due to a different phosphorylation or redox state of the channels. Further studies will have to resolve these questions and will have to identify the target(s) of H_2S at BK channels and which role protein modifications may play in the tailoring the BK channel response. Preliminary results of our lab indicate that the phosphorylation status of the channel may play role in the observed different responses to H_2S (Sitdikova et al. in preparation).

BK channel could be also indirectly modulated by H_2S via changes of internal Ca^{2+} through entry via Ca^{2+} channels or liberation of Ca^{2+} from intracellular stores. Indeed H_2S by activating Ca^{2+} entry through L-type Ca^{2+}-channels increases the cytosolic Ca^{2+} concentration in neurons (García-Bereguiaín et al. 2008) and also increases intracellular Ca^{2+} concentrations and induces Ca^{2+} waves in cultured astrocytes as well as in hippocampal slices (Nagai et al. 2004). In rat cardiomyocytes H_2S decreased mechanical contractions by inhibition of L-type calcium channels (Sun et al. 2008). In addition H_2S has been identified as a nociceptive messenger through activation of T-type Ca^{2+} channels in peripheral tissues, particularly during inflammation (Kawabata et al. 2007). T-type calcium channels are also involved in pain processing of spinal nociceptive neurons (Maeda et al. 2009), in colon (Matsunami et al. 2009) and pancreas (Nishimura et al. 2009) while analgesia appears to be due to activation of ATP-sensitive K^+ channels (K_{ATP}) channels.

H_2S is also synthesized in lower vertebrates (Olson et al. 2008) and in invertebrates such as in clams and worms predominately via the enzyme CBS (Julian et al. 2002; Gainey and Greenberg 2005) or in the brain of the honeybee, *Apis mellifera*, (Watanabe et al. 2007). In the pond snail *Lymnaea stagnalis* low levels of H_2S (100 μM) diminished the ability to learn and remember but did not prevent memory consolidation (Rosenegger et al. 2004). In our own studies using identified neurons of the snail, *Helix pomatia*, H_2S increased Ca^{2+}-activated K^+ currents (with similar characteristics to BK channel currents), as well as voltage-dependent K^+ currents and reduced the Ca^{2+} inward current which alters the shape and time course of action potentials (Hermann et al. 2010). These findings may help to explain some of the effects of H_2S on learning and memory.

6.7.1 BK Channels and Oxygen

Although oxygen is not a gasotransmitter by definition, it is nevertheless a very important gas which occurs naturally in our environment and is mandatory for most forms of life on earth as we know it. BK channels have been identified as one of the main sensors of hypoxia in the body. However, the responsiveness of native BK channels to changes in oxygen tension is diverse, and the nature of oxygen sensing mechanisms of BK channels can be manifold. BK channels are in some tissues completely insensitive to hypoxia like in ear arterial smooth muscle cells while in other tissues like the carotid body BK channel activity is decreased by hypoxia (Jovanović et al. 2003; Riesco-Fagundo et al. 2001; Williams et al. 2004). During chronic hypoxia the expression of charybdotoxin sensitive Ca^{2+}-activated K^+ channels in carotid body chemoreceptor cells might be even completely abolished as reported by Wyatt et al. 1995. But their study also indicates that these channels are not the exclusive O_2 sensors in these cells. Similar results were obtained by Gao et al. 2002. This group studied CA1 pyramidal cell BK channels from normoxic or chronic hypoxic rats. They found a lowered expression of BK channels in hypoxic cells as well as a reduced activity of the remaining channels. This effect was partially recovered by oxidizing but not by reducing agents, suggesting the involvement of a redox mechanism. McCartney et al. 2005 showed that the sensitivity to hypoxia on the molecular level is conferred by the STREX exon insert to the channels. A lack of oxygen caused the channel to shut down. The authors claimed that this sensitivity is CO independent and not due to a redox mechanism; however, it was calcium-dependent. They further indicate that a single serine residue (S24) as well as the flanking cysteines (C23, C25) in the STREX exon are mandatory for the modulatory action of STREX under hypoxia.

Two major pathways how BK channels may be involved in oxygen sensing are offered by todays research as already outlined above. First, BK channels may act as indirect sensors of oxygen via the redox effect of H_2S on the channels (Olson et al. 2008, 2010). Second as found by Riesco-Fagundo et al. 2001 and Williams

et al. 2004, BK channels may mediate oxygen tension via a CO-dependent mechanism. While these two mechanisms are as of today known it cannot be excluded that β-subunits or other cytosolic factors might be involved in the oxygen sensing of BK channels. It should be also mentioned that BK channels are most likely not the only oxygen sensors in cells but most likely one of many. For instance Roth et al. 2009 found in the mouse pulmonary vascular system an oxygen sensing pathway which is BK channel independent.

The cytosolic redox status can also modulate directly channel activity. BK channels are modulated by the redox state of critical amino acids (DiChiara and Reinhart 1997; Wang et al. 1997c; Gong et al. 2000). For instance reactive oxygen species (ROS) profoundly inhibit BK channel activity by decreasing their Ca^{2+} sensitivity (Tang et al. 2004). The reduced Ca^{2+} sensitivity was attributed to the modification of a cysteine residue near the Ca^{2+} bowl. Cysteine residues involved in redox modulation appear to be located at the cytoplasmatic side of the channel (Erxleben et al. 2002; Wang et al. 1997c). Indeed, a key site of channel protein modulation by redox signaling in ion channel proteins are the sulfhydryl groups (SH) of cysteine. Disulfide bonds which are modified in consequence of an oxidation or reduction may alter the protein structure and eventually lead to a change in channel activity as observed for BK channels in the hippocampus (Hepp et al. 2005). When SH groups of BK channels were oxidized with 5,5'-dithiobis 2-nitrobenzoic acid (DTNB) the channel activity was raised whereas the reduction of the channel protein by 1,4-dithio-DL-threitol (DTT) blocked BK channel activity. Augmentation of BK channel activity was protective against brain hypoxia in their experimental setup suggesting that oxidation of BK channel SH groups could mediate a neuroprotective effect. In contrast, the redox properties of BK channels were found to be the other way round, since for instance in rat chemoreceptor cells reduction of the channels by DDT increased their activity while oxidation with 2,2'-dithiopyridine (DTDP) had the opposite effect (Riesco-Fagundo et al. 2001). Redox modulation is also supported by a number of studies reporting under reducing conditions the channel activity to be augmented (DiChiara and Reinhart 1997; Gong et al. 2000; Wang et al. 1997c). Furthermore, inclusion of the STREX exon makes the channels extremely sensitive to inhibition by oxidation (Erxleben et al. 2002). These complex and conflicting data concerning BK channel redox modulation might depend on the amino acid targeted (Tang et al. 2001). When they applied chloramine-T, which preferentially oxidizes methionine, they found the channel activity going up. In contrast, when they used hydrogen peroxide and cysteine-specific reagents like DTNB to oxidize the channel they observed a reduced activity of BK channels.

To conclude, BK channels serve as important sensors for oxygen tensions. Furthermore, redox modulation of BK channels may have important implication in diseases which are for instance accompanied by vascular constriction. As a fully functional and active BK channel is necessary for a beneficial vascular relaxation it might be of high relevance to develop pharmacological agents which function as channel openers opposing negatively effective redox mechanisms.

6.8 Synopsis

BK channels, present in almost all tissues, mediate or modulate a huge variety of physiological functions as well as pathophysiological conditions. Gasotransmitters, although they have some common targets, appear to act tissue-specific, which means they can also exert different, even opposite effects, in various tissues. The amount of work and knowledge of gasotransmitter actions on BK channels is already at a fair status concerning their mechanisms of action and interactions. Their implications for physiology, pathophysiology, and pharmacology certainly will also be formidable in the near future. Experiments using knockout animals showed that in all cases after elimination of appropriate enzymes the gases are no longer produced and the expected pathophysiological modifications emerged. In particular, it will be of interest to further follow investigations on the interactions (cross-reactions) of gasotransmitters. Taken granted that a large number of neurons and glial cells may be targeted by gasotransmitters in the brain the term "volume signaling" (Münch et al. 2010) has been suggested. Its impact on nervous function and information processing in the central nervous system remains to be investigated in detail and certainly will be of enormous impact for signalling theory. The concept of volume signaling may be also applied to other tissues, such as the peripheral nervous system, to receptor and muscle systems where fast and synergistic action is required. In pharmacology the development of new drugs modulating gaseous signaling and/or BK channels has potential in the treatment of diseases like high blood pressure, erectile dysfunction, or pain. New techniques are in the pipeline to determine gasotransmitters at extremely low concentrations (in the micro- to nanomolar range) in biological preparations (see Peng et al. chapter on "Methods for the detection of gasotransmitters"). Further methodical developments in particular in respect to sensitivity, selectivity, and reaction speed will be of further interest to fertilize scientific progress. Possibly also other gases, such as sulfur dioxide (SO_2^-), carbondioxide (CO_2), acetaldehyde (CH_3CHO), ammonia (NH_3), etc. may join the family of gasotransmitters, although they may lack some requirements such as membrane permeability, as lined out in the definition given by Untereiner et al., see chapter on CO. It may be necessary, therefore, to develop further new concepts and definitions to herd these gases. It also will be of great interest to shed some light on the role the gases may have played in the evolution of life, since they were available at these archaic times. Of course this will be speculative—but fascinating, and may add to the phrase coined by Albert Szent-Györgyi: "Ions **and gases** may have been the mighty tools live found in the sea when it was created there"!

Acknowledgments In commemoration of the fiftieth anniversary after re-establishment of the University of Salzburg in 1962 (founded 1622). Our work was supported by the University of Salzburg and the Stiftungs- und Förderungsgesellschaft der Universität Salzburg.

References

Adelman JP, Shen KZ, Kavanaugh MP et al (1992) Calcium-activated potassium channels expressed from cloned complementary DNAs. Neuron 9:209–216

Ahern GP, Hsu SF, Jackson MB (1999) Direct actions of nitric oxide on rat neurohypophysial K^+ channels. J Physiol (Lond) 520(Pt 1):165–176

Alioua A, Huggins JP, Rousseau E (1995) PKG-I alpha phosphorylates the alpha-subunit and upregulates reconstituted GKCa channels from tracheal smooth muscle. Am J Physiol 268:L1057–L1063

Archer SL (2002) Potassium channels and erectile dysfunction. Vascul Pharmacol 38:61–71

Archer SL, Huang JM, Hampl V et al (1994) Nitric oxide and cGMP cause vasorelaxation by activation of a charybdotoxin-sensitive K channel by cGMP-dependent protein kinase. Proc Natl Acad Sci USA 91:7583–7587

Armstrong CM (2003) Voltage-gated K channels. Sci STKE 2003:re10. doi: 10.1126/stke.2003.188.re10

Ashcroft FM (2006) From molecule to malady. Nature 440:440–447. doi:10.1038/nature04707

Atkinson NS, Robertson GA, Ganetzky B (1991) A component of calcium-activated potassium channels encoded by the Drosophila slo locus. Science 253:551–555

Beauchamp RO Jr, Bus JS, Popp JA et al (1984) A critical review of the literature on hydrogen sulfide toxicity. Crit Rev Toxicol 13:25–97. doi:10.3109/10408448409029321

Behrens R, Nolting A, Reimann F et al (2000) hKCNMB3 and hKCNMB4, cloning and characterization of two members of the large-conductance calcium-activated potassium channel beta subunit family. FEBS Lett 474:99–106

Benkusky NA, Fergus DJ, Zucchero TM, England SK (2000) Regulation of the Ca^{2+}-sensitive domains of the maxi-K channel in the mouse myometrium during gestation. J Biol Chem 275:27712–27719. doi:10.1074/jbc.M000974200

Bentrop D, Beyermann M, Wissmann R, Fakler B (2001) NMR structure of the "ball-and-chain" domain of KCNMB2, the beta 2-subunit of large conductance Ca^{2+}- and voltage-activated potassium channels. J Biol Chem 276:42116–42121. doi:10.1074/jbc.M107118200

Berkefeld H, Fakler B, Schulte U (2010) Ca^{2+}-activated K^+ channels: from protein complexes to function. Physiol Rev 90:1437–1459. doi:10.1152/physrev.00049.2009

Berkefeld H, Sailer CA, Bildl W et al (2006) BKCa-Cav channel complexes mediate rapid and localized Ca^{2+}-activated K^+ signaling. Science 314:615–620. doi:10.1126/science.1132915

Bielefeldt K, Jackson MB (1994) Phosphorylation and dephosphorylation modulate a Ca(2+)-activated K^+ channel in rat peptidergic nerve terminals. J Physiol (Lond) 475:241–254

Blatz AL, Magleby KL (1986) Single apamin-blocked Ca-activated K^+ channels of small conductance in cultured rat skeletal muscle. Nature 323:718–720. doi:10.1038/323718a0

Boehning D, Snyder SH (2003) Novel neural modulators. Annu Rev Neurosci 26:105–131. doi:10.1146/annurev.neuro.26.041002.131047

Bolognesi M, Sacerdoti D, Piva A et al (2007) Carbon monoxide-mediated activation of large-conductance calcium-activated potassium channels contributes to mesenteric vasodilatation in cirrhotic rats. J Pharmacol Exp Ther 321:187–194. doi:10.1124/jpet.106.116665

Bolotina V, Omelyanenko V, Heyes B et al (1989) Variations of membrane cholesterol alter the kinetics of Ca2(+)-dependent K^+ channels and membrane fluidity in vascular smooth muscle cells. Pflugers Arch 415:262–268

Bolotina VM, Najibi S, Palacino JJ et al (1994) Nitric oxide directly activates calcium-dependent potassium channels in vascular smooth muscle. Nature 368:850–853. doi:10.1038/368850a0

Bon CLM, Garthwaite J (2003) On the role of nitric oxide in hippocampal long-term potentiation. J Neurosci 23:1941–1948

Brenner R, Chen QH, Vilaythong A et al (2005) BK channel beta4 subunit reduces dentate gyrus excitability and protects against temporal lobe seizures. Nat Neurosci 8:1752–1759. doi:10.1038/nn1573

Brenner R, Peréz GJ, Bonev AD et al (2000) Vasoregulation by the beta1 subunit of the calcium-activated potassium channel. Nature 407:870–876. doi:10.1038/35038011

Bucci M, Cirino G (2011) Hydrogen sulphide in heart and systemic circulation. Inflamm Allergy Drug Targets 10:103–108

Bukiya AN, McMillan J, Parrill AL, Dopico AM (2008) Structural determinants of monohydroxylated bile acids to activate beta 1 subunit-containing BK channels. J Lipid Res 49:2441–2451. doi:10.1194/jlr.M800286-JLR200

Butler A, Tsunoda S, McCobb DP et al (1993) mSlo, a complex mouse gene encoding "maxi" calcium-activated potassium channels. Science 261:221–224

Caliendo G, Cirino G, Santagada V, Wallace JL (2010) Synthesis and biological effects of hydrogen sulfide (H_2S): development of H2S-releasing drugs as pharmaceuticals. J Med Chem 53:6275–6286. doi:10.1021/jm901638j

Catterall WA (2011) Voltage-gated calcium channels. Cold Spring Harb Perspect Biol 3:a003947. doi:10.1101/cshperspect.a003947

Catterall WA (2010) Ion channel voltage sensors: structure, function, and pathophysiology. Neuron 67:915–928. doi:10.1016/j.neuron.2010.08.021

Catterall WA, Dib-Hajj S, Meisler MH, Pietrobon D (2008) Inherited neuronal ion channelopathies: new windows on complex neurological diseases. J Neurosci 28:11768–11777. doi:10.1523/JNEUROSCI.3901-08.2008

Chambliss KL, Yuhanna IS, Mineo C et al (2000) Estrogen receptor alpha and endothelial nitric oxide synthase are organized into a functional signaling module in caveolae. Circ Res 87:E44–E52

Champion HC, Bivalacqua TJ, Hyman AL et al (1999) Gene transfer of endothelial nitric oxide synthase to the penis augments erectile responses in the aged rat. Proc Natl Acad Sci USA 96:11648–11652

Chang HM, Reitstetter R, Mason RP, Gruener R (1995) Attenuation of channel kinetics and conductance by cholesterol: an interpretation using structural stress as a unifying concept. J Membr Biol 143:51–63

Christ GJ, Rehman J, Day N et al (1998) Intracorporal injection of hSlo cDNA in rats produces physiologically relevant alterations in penile function. Am J Physiol 275:H600–H608

Chung SK, Reinhart PH, Martin BL et al (1991) Protein kinase activity closely associated with a reconstituted calcium-activated potassium channel. Science 253:560–562

Correa M, Salamone JD, Segovia KN et al (2012) Piecing together the puzzle of acetaldehyde as a neuroactive agent. Neurosci Biobehav Rev 36:404–430. doi:10.1016/j.neubiorev.2011.07.009

Crest M, Gola M (1993) Large conductance Ca(2+)-activated K^+ channels are involved in both spike shaping and firing regulation in Helix neurones. J Physiol (Lond) 465:265–287

Crowley JJ, Treistman SN, Dopico AM (2003) Cholesterol antagonizes ethanol potentiation of human brain BKCa channels reconstituted into phospholipid bilayers. Mol Pharmacol 64:365–372. doi:10.1124/mol.64.2.365

Cui J (2010) BK-type calcium-activated potassium channels: coupling of metal ions and voltage sensing. J Physiol (Lond) 588:4651–4658. doi:10.1113/jphysiol.2010.194514

Cui J, Yang H, Lee US (2009) Molecular mechanisms of BK channel activation. Cell Mol Life Sci 66:852–875. doi:10.1007/s00018-008-8609-x

Cutajar MC, Edwards TM (2007) Evidence for the role of endogenous carbon monoxide in memory processing. J Cogn Neurosci 19:557–562. doi:10.1162/jocn.2007.19.4.557

Dai S, Hall DD, Hell JW (2009) Supramolecular assemblies and localized regulation of voltage-gated ion channels. Physiol Rev 89:411–452. doi:10.1152/physrev.00029.2007

Darkow DJ, Lu L, White RE (1997) Estrogen relaxation of coronary artery smooth muscle is mediated by nitric oxide and cGMP. Am J Physiol 272:H2765–H2773

DiChiara TJ, Reinhart PH (1997) Redox modulation of hslo Ca^{2+}-activated K^+ channels. J Neurosci 17:4942–4955

Dick GM, Tune JD (2010) Role of potassium channels in coronary vasodilation. Exp Biol Med (Maywood) 235:10–22. doi:10.1258/ebm.2009.009201

Dong D-L, Zhang Y, Lin D-H et al (2007) Carbon monoxide stimulates the Ca2(+)-activated big conductance k channels in cultured human endothelial cells. Hypertension 50:643–651. doi:10.1161/HYPERTENSIONAHA.107.096057

Dopico AM, Lemos JR, Treistman SN (1996) Ethanol increases the activity of large conductance, Ca(2+)-activated K^+ channels in isolated neurohypophysial terminals. Mol Pharmacol 49:40–48
Drouin H, Hermann A (1994) Intracellular action of spermine on neuronal Ca^{2+} and K^+ currents. Eur J Neurosci 6:412–419
Du W, Bautista JF, Yang H et al (2005) Calcium-sensitive potassium channelopathy in human epilepsy and paroxysmal movement disorder. Nat Genet 37:733–738. doi:10.1038/ng1585
Dubuis E, Potier M, Wang R, Vandier C (2005) Continuous inhalation of carbon monoxide attenuates hypoxic pulmonary hypertension development presumably through activation of BKCa channels. Cardiovasc Res 65:751–761. doi:10.1016/j.cardiores.2004.11.007
Durante W (2010) Targeting heme oxygenase-1 in vascular disease. Curr Drug Targets 11:1504–1516
Durante W, Kroll MH, Christodoulides N et al (1997) Nitric oxide induces heme oxygenase-1 gene expression and carbon monoxide production in vascular smooth muscle cells. Circ Res 80:557–564
Earley S, Heppner TJ, Nelson MT, Brayden JE (2005) TRPV4 forms a novel Ca^{2+} signaling complex with ryanodine receptors and BKCa channels. Circ Res 97:1270–1279. doi:10.1161/01.RES.0000194321.60300.d6
Edwards G, Félétou M, Weston AH (2010) Endothelium-derived hyperpolarising factors and associated pathways: a synopsis. Pflugers Arch 459:863–879. doi:10.1007/s00424-010-0817-1
Edwards TM, Rickard NS (2007) New perspectives on the mechanisms through which nitric oxide may affect learning and memory processes. Neurosci Biobehav Rev 31:413–425. doi:10.1016/j.neubiorev.2006.11.001
Erxleben C, Everhart AL, Romeo C et al (2002) Interacting effects of N-terminal variation and strex exon splicing on slo potassium channel regulation by calcium, phosphorylation, and oxidation. J Biol Chem 277:27045–27052. doi:10.1074/jbc.M203087200
Faber ESL, Sah P (2003) Ca^{2+}-activated K+(BK) channel inactivation contributes to spike broadening during repetitive firing in the rat lateral amygdala. J Physiol (Lond) 552:483–497. doi:10.1113/jphysiol.2003.050120
Fakler B, Adelman JP (2008) Control of K(Ca) channels by calcium nano/microdomains. Neuron 59:873–881. doi:10.1016/j.neuron.2008.09.001
Fan SF, Brink PR, Melman A, Christ GJ (1995) An analysis of the Maxi-K+(KCa) channel in cultured human corporal smooth muscle cells. J Urol 153:818–825
Félétou M (2009) Calcium-activated potassium channels and endothelial dysfunction: therapeutic options? Br J Pharmacol 156:545–562. doi:10.1111/j.1476-5381.2009.00052.x
Fettiplace R, Fuchs PA (1999) Mechanisms of hair cell tuning. Annu Rev Physiol 61:809–834. doi:10.1146/annurev.physiol.61.1.809
Fitzgerald RS, Shirahata M, Chang I et al (2011) The impact of hydrogen sulfide (H(2)S) on neurotransmitter release from the cat carotid body. Respir Physiol Neurobiol 176:80–89. doi:10.1016/j.resp.2011.01.010
Fodor AA, Aldrich RW (2009) Convergent evolution of alternative splices at domain boundaries of the BK channel. Annu Rev Physiol 71:19–36. doi:10.1146/annurev.physiol.010908.163124
Francis SH, Busch JL, Corbin JD, Sibley D (2010) cGMP-dependent protein kinases and cGMP phosphodiesterases in nitric oxide and cGMP action. Pharmacol Rev 62:525–563. doi:10.1124/pr.110.002907
Fukao M, Mason HS, Britton FC et al (1999) Cyclic GMP-dependent protein kinase activates cloned BKCa channels expressed in mammalian cells by direct phosphorylation at serine 1072. J Biol Chem 274:10927–10935
Gadalla MM, Snyder SH (2010) Hydrogen sulfide as a gasotransmitter. J Neurochem 113:14–26. doi:10.1111/j.1471-4159.2010.06580.x
Gagov H, Kadinov B, Hristov K et al (2003) Role of constitutively expressed heme oxygenase-2 in the regulation of guinea pig coronary artery tone. Pflugers Arch 446:412–421. doi:10.1007/s00424-002-1003-x
Gainey LF Jr, Greenberg MJ (2005) Hydrogen sulfide is synthesized in the gills of the clam Mercenaria mercenaria and acts seasonally to modulate branchial muscle contraction. Biol Bull 209:11–20

Gao T-M, Fung M-L (2002) Decreased large conductance Ca(2+)-activated K(+) channel activity in dissociated CA1 hippocampal neurons in rats exposed to perinatal and postnatal hypoxia. Neurosci Lett 332:163–166

García-Bereguiaín MA, Samhan-Arias AK, Martín-Romero FJ, Gutiérrez-Merino C (2008) Hydrogen sulfide raises cytosolic calcium in neurons through activation of L-type Ca^{2+} channels. Antioxid Redox Signal 10:31–42. doi:10.1089/ars.2007.1656

Garthwaite J (2010) New insight into the functioning of nitric oxide-receptive guanylyl cyclase: physiological and pharmacological implications. Mol Cell Biochem 334:221–232. doi:10.1007/s11010-009-0318-8

Gasull X, Ferrer E, Llobet A et al (2003) Cell membrane stretch modulates the high-conductance Ca^{2+}-activated K^+ channel in bovine trabecular meshwork cells. Invest Ophthalmol Vis Sci 44:706–714

George MJ, Shibata EF (1995) Regulation of calcium-activated potassium channels by S-nitrosothiol compounds and cyclic guanosine monophosphate in rabbit coronary artery myocytes. J Investig Med 43:451–458

Ghatta S, Nimmagadda D, Xu X, O'Rourke ST (2006) Large-conductance, calcium-activated potassium channels: structural and functional implications. Pharmacol Ther 110:103–116. doi:10.1016/j.pharmthera.2005.10.007

Gola M, Crest M (1993) Colocalization of active KCa channels and Ca^{2+} channels within Ca^{2+} domains in helix neurons. Neuron 10:689–699

Gomes DA, Giusti-Paiva A, Ventura RR et al (2010) Carbon monoxide and nitric oxide modulate hyperosmolality-induced oxytocin secretion by the hypothalamus in vitro. Biosci Rep 30:351–357. doi:10.1042/BSR2009010

Gomes DA, Reis WL, Ventura RR et al (2004) The role of carbon monoxide and nitric oxide in hyperosmolality-induced atrial natriuretic peptide release by hypothalamus in vitro. Brain Res 1016:33–39. doi:10.1016/j.brainres.2004.04.047

Gong L, Gao TM, Huang H, Tong Z (2000) Redox modulation of large conductance calcium-activated potassium channels in CA1 pyramidal neurons from adult rat hippocampus. Neurosci Lett 286:191–194

Van Goor F, Li YX, Stojilkovic SS (2001) Paradoxical role of large-conductance calcium-activated K^+ (BK) channels in controlling action potential-driven Ca^{2+} entry in anterior pituitary cells. J Neurosci 21:5902–5915

Gorman AL, Hermann A (1982) Quantitative differences in the currents of bursting and beating molluscan pace-maker neurones. J Physiol (Lond) 333:681–699

Gorman AL, Hermann A, Thomas MV (1982) Ionic requirements for membrane oscillations and their dependence on the calcium concentration in a molluscan pace-maker neurone. J Physiol (Lond) 327:185–217

Gorman AL, Hermann A, Thomas MV (1981) Intracellular calcium and the control of neuronal pacemaker activity. Fed Proc 40:2233–2239

Gragasin FS, Michelakis ED, Hogan A et al (2004) The neurovascular mechanism of clitoral erection: nitric oxide and cGMP-stimulated activation of BKCa channels. FASEB J 18:1382–1391. doi:10.1096/fj.04-1978com

Greffrath W, Magerl W, Disque-Kaiser U et al (2004) Contribution of Ca^{2+}-activated K^+ channels to hyperpolarizing after-potentials and discharge pattern in rat supraoptic neurones. J Neuroendocrinol 16:577–588. doi:10.1111/j.1365-2826.2004.01204.x

Grimm PR, Sansom SC (2010) BK channels and a new form of hypertension. Kidney Int 78:956–962. doi:10.1038/ki.2010.272

Gruhn N, Boesgaard S, Eiberg J et al (2002) Effects of large conductance Ca(2+)-activated K(+) channels on nitroglycerin-mediated vasorelaxation in humans. Eur J Pharmacol 446:145–150

Gu N, Vervaeke K, Storm JF (2007) BK potassium channels facilitate high-frequency firing and cause early spike frequency adaptation in rat CA1 hippocampal pyramidal cells. J Physiol (Lond) 580:859–882. doi:10.1113/jphysiol.2006.126367

Ha TS, Heo M-S, Park C-S (2004) Functional effects of auxiliary beta4-subunit on rat large-conductance Ca(2+)-activated K(+) channel. Biophys J 86:2871–2882. doi:10.1016/S0006-3495(04)74339-8

Ha TS, Jeong SY, Cho SW et al (2000) Functional characteristics of two BKCa channel variants differentially expressed in rat brain tissues. Eur J Biochem 267:910–918

Hall SK, Armstrong DL (2000) Conditional and unconditional inhibition of calcium-activated potassium channels by reversible protein phosphorylation. J Biol Chem 275:3749–3754

Handlechner A, Weiger TM, Kainz V, Hermann A (2011) Acetaldehye and ethanol interactions on calcium activated potassium (BK) channels in Pituitary (GH3/GH4) cells. Alcohol Alcohol 46:3

Handlechner AG, Weiger TM, Kainz V, Hermann A (2008) Acetaldehyde blocks the augmenting action of ethanol on BK channels in pituitary (GH3) cells. Alcohol Clin Exp Res 32:29A

Hepp S, Gerich FJ, Müller M (2005) Sulfhydryl oxidation reduces hippocampal susceptibility to hypoxia-induced spreading depression by activating BK channels. J Neurophysiol 94:1091–1103. doi:10.1152/jn.00291.2005

Hermann A, Gorman AL (1981) Effects of tetraethylammonium on potassium currents in a molluscan neurons. J Gen Physiol 78:87–110

Hermann A, Gorman AL (1979) External and internal effects of tetraethylammonium on voltage-dependent and Ca-dependent K^+ currents components in molluscan pacemaker neurons. Neurosci Lett 12:87–92

Hermann A, Krahwinkler S, Weiger TM, Sitdikova G (2010) Hydrogen sulfide alters ion currents of mollusc neurons. FENS Abstr 5(163):13

Hermann A, Sitdikova G, Weiger TM (2012) BK-Channels focus on polyamines, ethanol/acetaldehyde and hydrogen Sulfide (H_2S). In: Kaneez FS (ed) Patch Clamp Technique, Intech, Croatia, pp 109–142. doi: 10.5772/35179

Hill MA, Yang Y, Ella SR et al (2010) Large conductance, Ca^{2+}-activated K^+ channels (BKCa) and arteriolar myogenic signaling. FEBS Lett 584:2033–2042. doi:10.1016/j.febslet.2010.02.045

Hille B (2001) Ion channels of excitable membranes, 3rd edn. Sinauer, Sunderland, Mass

Hossain MI, Iwasaki H, Okochi Y et al (2008) Enzyme domain affects the movement of the voltage sensor in ascidian and zebrafish voltage-sensing phosphatases. J Biol Chem 283:18248–18259. doi:10.1074/jbc.M706184200

Hou S, Heinemann SH, Hoshi T (2009) Modulation of BKCa channel gating by endogenous signaling molecules. Physiology (Bethesda) 24:26–35. doi:10.1152/physiol.00032.2008

Hou S, Xu R, Heinemann SH, Hoshi T (2008) The RCK1 high-affinity Ca^{2+} sensor confers carbon monoxide sensitivity to Slo1 BK channels. Proc Natl Acad Sci USA 105:4039–4043. doi:10.1073/pnas.0800304105

Hu H, Shao LR, Chavoshy S et al (2001) Presynaptic Ca^{2+}-activated K^+ channels in glutamatergic hippocampal terminals and their role in spike repolarization and regulation of transmitter release. J Neurosci 21:9585–9597

Hu L-F, Lu M, Hon Wong PT, Bian J-S (2011) Hydrogen sulfide: neurophysiology and neuropathology. Antioxid Redox Signal 15:405–419. doi:10.1089/ars.2010.3517

Hunt WA (1996) Role of acetaldehyde in the actions of ethanol on the brain–a review. Alcohol 13:147–151

Ignarro LJ, Cirino G, Casini A, Napoli C (1999) Nitric oxide as a signaling molecule in the vascular system: an overview. J Cardiovasc Pharmacol 34:879–886

Isacson CK, Lu Q, Karas RH, Cox DH (2007) RACK1 is a BKCa channel binding protein. Am J Physiol Cell Physiol 292:C1459–C1466. doi:10.1152/ajpcell.00322.2006

Ishigami M, Hiraki K, Umemura K et al (2009) A source of hydrogen sulfide and a mechanism of its release in the brain. Antioxid Redox Signal 11:205–214. doi:10.1089/ARS.2008.2132

Ishii TM, Silvia C, Hirschberg B et al (1997) A human intermediate conductance calcium-activated potassium channel. Proc Natl Acad Sci USA 94:11651–11656

Jackson-Weaver O, Paredes DA, Gonzalez Bosc LV et al (2011) Intermittent hypoxia in rats increases myogenic tone through loss of hydrogen sulfide activation of large-conductance Ca(2+)-activated potassium channels. Circ Res 108:1439–1447. doi:10.1161/CIRCRESAHA.110.228999

Jaggar JH, Leffler CW, Cheranov SY et al (2002) Carbon monoxide dilates cerebral arterioles by enhancing the coupling of Ca^{2+}sparks to Ca^{2+}-activated K^+ channels. Circ Res 91:610–617

Jaggar JH, Li A, Parfenova H et al (2005) Heme is a carbon monoxide receptor for large-conductance Ca^{2+}-activated K^+ channels. Circ Res 97:805–812. doi:10.1161/01.RES.0000186180.47148.7b

Jakab M, Weiger TM, Hermann A (1997) Ethanol activates maxi Ca^{2+}-activated K^+ channels of clonal pituitary (GH3) cells. J Membr Biol 157:237–245

Jaramillo AM, Zheng X, Zhou Y et al (2004) Pattern of distribution and cycling of SLOB, Slowpoke channel binding protein, in Drosophila. BMC Neurosci 5:3. doi:10.1186/1471-2202-5-3

Jiang Y, Lee A, Chen J et al (2002) Crystal structure and mechanism of a calcium-gated potassium channel. Nature 417:515–522. doi:10.1038/417515a

Jiang Y, Pico A, Cadene M et al (2001) Structure of the RCK domain from the E. coli K^+channel and demonstration of its presence in the human BK channel. Neuron 29:593–601

Jovanović S, Crawford RM, Ranki HJ, Jovanović A (2003) Large conductance Ca^{2+}-activated K^+ channels sense acute changes in oxygen tension in alveolar epithelial cells. Am J Respir Cell Mol Biol 28:363–372

Julian D, Statile JL, Wohlgemuth SE, Arp AJ (2002) Enzymatic hydrogen sulfide production in marine invertebrate tissues. Comp Biochem Physiol, Part A Mol Integr Physiol 133:105–115

Kabil O, Banerjee R (2010) Redox biochemistry of hydrogen sulfide. J Biol Chem 285:21903–21907. doi:10.1074/jbc.R110.128363

Kajimura M, Fukuda R, Bateman RM et al (2010) Interactions of multiple gas-transducing systems: hallmarks and uncertainties of CO, NO, and H_2S gas biology. Antioxid Redox Signal 13:157–192. doi:10.1089/ars.2009.2657

Kameyama M, Kakei M, Sato R et al (1984) Intracellular Na^+ activates a K^+ channel in mammalian cardiac cells. Nature 309:354–356

Kanu A, Leffler CW (2007) Carbon monoxide and Ca^{2+}-activated K^+ channels in cerebral arteriolar responses to glutamate and hypoxia in newborn pigs. Am J Physiol Heart Circ Physiol 293:H3193–H3200. doi:10.1152/ajpheart.00274.2007

Kaufmann WA, Kasugai Y, Ferraguti F, Storm JF (2010) Two distinct pools of large-conductance calcium-activated potassium channels in the somatic plasma membrane of central principal neurons. Neuroscience 169:974–986. doi:10.1016/j.neuroscience.2010.05.070

Kawabata A, Ishiki T, Nagasawa K et al (2007) Hydrogen sulfide as a novel nociceptive messenger. Pain 132:74–81. doi:10.1016/j.pain.2007.01.026

Kawakubo T, Naruse K, Matsubara T et al (1999) Characterization of a newly found stretch-activated KCa,ATP channel in cultured chick ventricular myocytes. Am J Physiol 276:H1827–H1838

Kim HP, Ryter SW, Choi AMK (2006) CO as a cellular signaling molecule. Annu Rev Pharmacol Toxicol 46:411–449. doi:10.1146/annurev.pharmtox.46.120604.141053

Kimura H (2011) Hydrogen sulfide: its production and functions. Exp Physiol 96:833–835. doi:10.1113/expphysiol.2011.057455

Kimura Y, Kimura H (2004) Hydrogen sulfide protects neurons from oxidative stress. FASEB J 18:1165–1167. doi:10.1096/fj.04-1815fje

Knaus HG, Schwarzer C, Koch RO et al (1996) Distribution of high-conductance Ca(2+)-activated K^+ channels in rat brain: targeting to axons and nerve terminals. J Neurosci 16:955–963

Knecht KR, Milam S, Wilkinson DA et al (2010) Time-dependent action of carbon monoxide on the newborn cerebrovascular circulation. Am J Physiol Heart Circ Physiol 299:H70–H75. doi:10.1152/ajpheart.00258.2010

Komuro T, Borsody MK, Ono S et al (2001) The vasorelaxation of cerebral arteries by carbon monoxide. Exp Biol Med (Maywood) 226:860–865

Kullmann DM, Waxman SG (2010) Neurological channelopathies: new insights into disease mechanisms and ion channel function. J Physiol (Lond) 588:1823–1827. doi:10.1113/jphysiol.2010.190652

Lancaster B, Adams PR (1986) Calcium-dependent current generating the afterhyperpolarization of hippocampal neurons. J Neurophysiol 55:1268–1282

Lancaster B, Nicoll RA (1987) Properties of two calcium-activated hyperpolarizations in rat hippocampal neurones. J Physiol (Lond) 389:187–203

Latorre R, Oberhauser A, Labarca P, Alvarez O (1989) Varieties of calcium-activated potassium channels. Annu Rev Physiol 51:385–399. doi:10.1146/annurev.ph.51.030189.002125
Laumonnier F, Roger S, Guérin P et al (2006) Association of a functional deficit of the BKCa channel, a synaptic regulator of neuronal excitability, with autism and mental retardation. Am J Psychiatry 163:1622–1629. doi:10.1176/appi.ajp.163.9.1622
Lee JE, Kwak J, Suh CK, Shin JH (2006) Dual effects of nitric oxide on the large conductance calcium-activated potassium channels of rat brain. J Biochem Mol Biol 39:91–96
Lee US, Cui J (2010) BK channel activation: structural and functional insights. Trends Neurosci 33:415–423. doi:10.1016/j.tins.2010.06.004
Leffler CW, Nasjletti A, Yu C et al (1999) Carbon monoxide and cerebral microvascular tone in newborn pigs. Am J Physiol 276:H1641–H1646
Leffler CW, Parfenova H, Jaggar JH (2011) Carbon monoxide as an endogenous vascular modulator. Am J Physiol Heart Circ Physiol 301:H1–H11. doi:10.1152/ajpheart.00230.2011
Levitan IB (1999) Modulation of ion channels by protein phosphorylation. How the brain works. Adv Second Messenger Phosphoprotein Res 33:3–22
Levitan IB (1994) Modulation of ion channels by protein phosphorylation and dephosphorylation. Annu Rev Physiol 56:193–212. doi:10.1146/annurev.ph.56.030194.001205
Li L, Hisamoto K, Kim KH et al (2007) Variant estrogen receptor-c-Src molecular interdependence and c-Src structural requirements for endothelial NO synthase activation. Proc Natl Acad Sci USA 104:16468–16473. doi:10.1073/pnas.0704315104
Li M, Sun Y, Simard JM et al (2009) Augmented bladder urothelial polyamine signaling and block of BK channel in the pathophysiology of overactive bladder syndrome. Am J Physiol Cell Physiol 297:C1445–C1451. doi:10.1152/ajpcell.00259.2009
Li Q, Sun B, Wang X et al (2010) A crucial role for hydrogen sulfide in oxygen sensing via modulating large conductance calcium-activated potassium channels. Antioxid Redox Signal 12:1179–1189. doi:10.1089/ars.2009.2926
Li S, Deng Z, Wei L et al (2011) Reduction of large-conductance Ca2(+) -activated K(+) channel with compensatory increase of nitric oxide in insulin resistant rats. Diabetes Metab Res Rev 27:461–469. doi:10.1002/dmrr.1196
Lin M-W, Wu AZ, Ting W-H et al (2006) Changes in membrane cholesterol of pituitary tumor (GH3) cells regulate the activity of large-conductance $Ca2^{+}$-activated K^{+} channels. Chin J Physiol 49:1–13
Lingle CJ, Solaro CR, Prakriya M, Ding JP (1996) Calcium-activated potassium channels in adrenal chromaffin cells. Ion Channels 4:261–301
Lorenz S, Heils A, Kasper JM, Sander T (2007) Allelic association of a truncation mutation of the KCNMB3 gene with idiopathic generalized epilepsy. Am J Med Genet B Neuropsychiatr Genet 144B:10–13. doi:10.1002/ajmg.b.30369
Łowicka E, Bełtowski J (2007) Hydrogen sulfide (H2S)—the third gas of interest for pharmacologists. Pharmacol Rep 59:4–24
Ma Y-G, Dong L, Ye X-L et al (2010) Activation of cloned BK(Ca) channels in nitric oxide-induced apoptosis of HEK293 cells. Apoptosis 15:426–438. doi:10.1007/s10495-009-0423-x
Ma Z, Lou XJ, Horrigan FT (2006) Role of charged residues in the S1–S4 voltage sensor of BK channels. J Gen Physiol 127:309–328. doi:10.1085/jgp.200509421
Maeda Y, Aoki Y, Sekiguchi F et al (2009) Hyperalgesia induced by spinal and peripheral hydrogen sulfide: evidence for involvement of Cav3.2 T-type calcium channels. Pain 142:127–132. doi:10.1016/j.pain.2008.12.021
Malen PL, Chapman PF (1997) Nitric oxide facilitates long-term potentiation, but not long-term depression. J Neurosci 17:2645–2651
Mancardi D, Penna C, Merlino A et al (2009) Physiological and pharmacological features of the novel gasotransmitter: hydrogen sulfide. Biochim Biophys Acta 1787:864–872. doi:10.1016/j.bbabio.2009.03.005
Mandalà M, Heppner TJ, Bonev AD, Nelson MT (2007) Effect of endogenous and exogenous nitric oxide on calcium sparks as targets for vasodilation in rat cerebral artery. Nitric Oxide 16:104–109. doi:10.1016/j.niox.2006.06.007

Marijic J, Li Q, Song M et al (2001) Decreased expression of voltage- and Ca(2+)-activated K(+) channels in coronary smooth muscle during aging. Circ Res 88:210–216
Marsh N, Marsh A (2000) A short history of nitroglycerine and nitric oxide in pharmacology and physiology. Clin Exp Pharmacol Physiol 27:313–319
Martínez-Ruiz A, Cadenas S, Lamas S (2011) Nitric oxide signaling: classical, less classical, and nonclassical mechanisms. Free Radic Biol Med 51:17–29. doi:10.1016/j.freeradbiomed.2011.04.010
Marty A (1981) Ca-dependent K channels with large unitary conductance in chromaffin cell membranes. Nature 291:497–500
Mason RP, Cockcroft JR (2006) Targeting nitric oxide with drug therapy. J Clin Hypertens (Greenwich) 8:40–52
Matsunami M, Tarui T, Mitani K et al (2009) Luminal hydrogen sulfide plays a pronociceptive role in mouse colon. Gut 58:751–761. doi:10.1136/gut.2007.144543
McCartney CE, McClafferty H, Huibant J-M et al (2005) A cysteine-rich motif confers hypoxia sensitivity to mammalian large conductance voltage- and Ca-activated K (BK) channel alpha-subunits. Proc Natl Acad Sci USA 102:17870–17876. doi:10.1073/pnas.0505270102
Meera P, Wallner M, Jiang Z, Toro L (1996) A calcium switch for the functional coupling between alpha (hslo) and beta subunits (KV,Ca beta) of maxi K channels. FEBS Lett 382:84–88
Meera P, Wallner M, Song M, Toro L (1997) Large conductance voltage- and calcium-dependent K^+ channel, a distinct member of voltage-dependent ion channels with seven N-terminal transmembrane segments (S0–S6), an extracellular N terminus, and an intracellular (S9–S10) C terminus. Proc Natl Acad Sci USA 94:14066–14071
Meera P, Wallner M, Toro L (2000) A neuronal beta subunit (KCNMB4) makes the large conductance, voltage- and Ca^{2+}-activated K^+ channel resistant to charybdotoxin and iberiotoxin. Proc Natl Acad Sci USA 97:5562–5567. doi:10.1073/pnas.100118597
Melman A, Bar-Chama N, McCullough A et al (2006) hMaxi-K gene transfer in males with erectile dysfunction: results of the first human trial. Hum Gene Ther 17:1165–1176. doi:10.1089/hum.2006.17.1165
Mistry DK, Garland CJ (1998) Nitric oxide (NO)-induced activation of large conductance Ca^{2+}-dependent K^+ channels (BK(Ca)) in smooth muscle cells isolated from the rat mesenteric artery. Br J Pharmacol 124:1131–1140. doi:10.1038/sj.bjp.0701940
Moczydlowski E, Alvarez O, Vergara C, Latorre R (1985) Effect of phospholipid surface charge on the conductance and gating of a Ca^{2+}-activated K^+ channel in planar lipid bilayers. J Membr Biol 83:273–282
Moody BF, Calvert JW (2011) Emergent role of gasotransmitters in ischemia-reperfusion injury. Med Gas Res 1:3. doi:10.1186/2045-9912-1-3
Mori A, Suzuki S, Sakamoto K et al (2011) BMS-191011, an opener of large-conductance Ca^{2+}-activated potassium channels, dilates rat retinal arterioles in vivo. Biol Pharm Bull 34:150–152
Münch D, Ott SR, Pflüger H-J (2010) Three-dimensional distribution of NO sources in a primary mechanosensory integration center in the locust and its implications for volume signaling. J Comp Neurol 518:2903–2916. doi:10.1002/cne.22396
Murata Y, Iwasaki H, Sasaki M et al (2005) Phosphoinositide phosphatase activity coupled to an intrinsic voltage sensor. Nature 435:1239–1243. doi:10.1038/nature03650
Mustafa AK, Gadalla MM, Sen N et al. (2009a) H2S signals through protein S-sulfhydration. Sci Signal 2:ra72. doi: 10.1126/scisignal.2000464
Mustafa AK, Gadalla MM, Snyder SH (2009b) Signaling by gasotransmitters. Sci Signal 2:re2. doi: 10.1126/scisignal.268re2
Nagai Y, Tsugane M, Oka J-I, Kimura H (2004) Hydrogen sulfide induces calcium waves in astrocytes. FASEB J 18:557–559. doi:10.1096/fj.03-1052fje
Nagaoka T, Hein TW, Yoshida A, Kuo L (2007) Resveratrol, a component of red wine, elicits dilation of isolated porcine retinal arterioles: role of nitric oxide and potassium channels. Invest Ophthalmol Vis Sci 48:4232–4239. doi:10.1167/iovs.07-0094
Nardi A, Olesen S-P (2008) BK channel modulators: a comprehensive overview. Curr Med Chem 15:1126–1146

Navaratnam DS, Bell TJ, Tu TD et al (1997) Differential distribution of Ca^{2+}-activated K^+ channel splice variants among hair cells along the tonotopic axis of the chick cochlea. Neuron 19:1077–1085

Nishimura S, Fukushima O, Ishikura H et al (2009) Hydrogen sulfide as a novel mediator for pancreatic pain in rodents. Gut 58:762–770. doi:10.1136/gut.2008.151910

Niu X, Qian X, Magleby KL (2004) Linker-gating ring complex as passive spring and Ca(2+)-dependent machine for a voltage- and Ca(2+)-activated potassium channel. Neuron 42:745–756. doi:10.1016/j.neuron.2004.05.001

Niu XW, Meech RW (2000) Potassium inhibition of sodium-activated potassium (K(Na)) channels in guinea-pig ventricular myocytes. J Physiol (Lond) 526(Pt 1):81–90

Node K, Kitakaze M, Kosaka H et al (1997) Roles of NO and Ca^{2+}-activated K^+ channels in coronary vasodilation induced by 17beta-estradiol in ischemic heart failure. FASEB J 11:793–799

Olson KR, Healy MJ, Qin Z et al (2008) Hydrogen sulfide as an oxygen sensor in trout gill chemoreceptors. Am J Physiol Regul Integr Comp Physiol 295:R669–R680. doi:10.1152/ajpregu.00807.2007

Olson KR, Whitfield NL (2010) Hydrogen sulfide and oxygen sensing in the cardiovascular system. Antioxid Redox Signal 12:1219–1234. doi:10.1089/ars.2009.2921

Orio P, Rojas P, Ferreira G, Latorre R (2002) New disguises for an old channel: MaxiK channel beta-subunits. News Physiol Sci 17:156–161

Ortega-Sáenz P, Pascual A, Gómez-Díaz R, López-Barneo J (2006) Acute oxygen sensing in heme oxygenase-2 null mice. J Gen Physiol 128:405–411. doi:10.1085/jgp.200609591

Park YB (1994) Ion selectivity and gating of small conductance Ca(2+)-activated K^+ channels in cultured rat adrenal chromaffin cells. J Physiol (Lond) 481(Pt 3):555–570

Paul V, Ekambaram P (2011) Involvement of nitric oxide in learning and memory processes. Indian J Med Res 133:471–478

Pedarzani P, Kulik A, Muller M et al (2000) Molecular determinants of Ca^{2+}-dependent K^+ channel function in rat dorsal vagal neurones. J Physiol (Lond) 527(Pt 2):283–290

Peers C, Wyatt CN, Evans AM (2010) Mechanisms for acute oxygen sensing in the carotid body. Respir Physiol Neurobiol 174:292–298. doi:10.1016/j.resp.2010.08.010

Peng Y-J, Nanduri J, Raghuraman G et al (2010) H_2S mediates O_2 sensing in the carotid body. Proc Natl Acad Sci USA 107:10719–10724

Pérez GJ, Bonev AD, Nelson MT (2001) Micromolar Ca(2+) from sparks activates Ca(2+)-sensitive K(+) channels in rat cerebral artery smooth muscle. Am J Physiol Cell Physiol 281:C1769–C1775

Perry MD, Sandle GI (2009) Regulation of colonic apical potassium (BK) channels by cAMP and somatostatin. Am J Physiol Gastrointest Liver Physiol 297:G159–G167. doi:10.1152/ajpgi.00132.2009

Quertemont E, Tambour S, Tirelli E (2005) The role of acetaldehyde in the neurobehavioral effects of ethanol: a comprehensive review of animal studies. Prog Neurobiol 75:247–274. doi:10.1016/j.pneurobio.2005.03.003

Raffaelli G, Saviane C, Mohajerani MH et al (2004) BK potassium channels control transmitter release at CA3-CA3 synapses in the rat hippocampus. J Physiol (Lond) 557:147–157. doi:10.1113/jphysiol.2004.062661

Ragsdale SW, Yi L (2011) Thiol/Disulfide redox switches in the regulation of heme binding to proteins. Antioxid Redox Signal 14:1039–1047. doi:10.1089/ars.2010.3436

Reiffenstein RJ, Hulbert WC, Roth SH (1992) Toxicology of hydrogen sulfide. Annu Rev Pharmacol Toxicol 32:109–134. doi:10.1146/annurev.pa.32.040192.000545

Reinhart PH, Chung S, Levitan IB (1989) A family of calcium-dependent potassium channels from rat brain. Neuron 2:1031–1041

Renga B (2011) Hydrogen sulfide generation in mammals: the molecular biology of cystathionine-β- synthase (CBS) and cystathionine-γ-lyase (CSE). Inflamm Allergy Drug Targets 10:85–91

Riesco-Fagundo AM, Pérez-García MT, González C, López-López JR (2001) O(2) modulates large-conductance Ca(2+)-dependent K(+) channels of rat chemoreceptor cells by a membrane-restricted and CO-sensitive mechanism. Circ Res 89:430–436

Roberts GP, Youn H, Kerby RL (2004) CO-sensing mechanisms. Microbiol Mol Biol Rev 68:453–473. doi:10.1128/MMBR.68.3.453-473.2004

Robertson BE, Schubert R, Hescheler J, Nelson MT (1993) cGMP-dependent protein kinase activates Ca-activated K channels in cerebral artery smooth muscle cells. Am J Physiol 265:C299–C303

Robitaille R, Charlton MP (1992) Presynaptic calcium signals and transmitter release are modulated by calcium-activated potassium channels. J Neurosci 12:297–305

Rolim ALR, Lindsey SC, Kunii IS et al (2010) Ion channelopathies in endocrinology: recent genetic findings and pathophysiological insights. Arq Bras Endocrinol Metabol 54:673–681

Rosenegger D, Roth S, Lukowiak K (2004) Learning and memory in Lymnaea are negatively altered by acute low-level concentrations of hydrogen sulphide. J Exp Biol 207:2621–2630. doi:10.1242/jeb.01073

Roth M, Rupp M, Hofmann S et al (2009) Heme oxygenase-2 and large-conductance Ca^{2+}-activated K^+ channels: lung vascular effects of hypoxia. Am J Respir Crit Care Med 180:353–364. doi:10.1164/rccm.200806-848OC

Rüttiger L, Sausbier M, Zimmermann U et al (2004) Deletion of the Ca^{2+}-activated potassium (BK) alpha-subunit but not the BKbeta1-subunit leads to progressive hearing loss. Proc Natl Acad Sci USA 101:12922–12927. doi:10.1073/pnas.0402660101

Ryan MJ, Jernigan NL, Drummond HA et al (2006) Renal vascular responses to CORM-A1 in the mouse. Pharmacol Res 54:24–29. doi:10.1016/j.phrs.2006.01.012

Ryter SW, Choi AMK (2010) Heme oxygenase-1/carbon monoxide: novel therapeutic strategies in critical care medicine. Curr Drug Targets 11:1485–1494

Ryter SW, Otterbein LE (2004) Carbon monoxide in biology and medicine. BioEssays 26:270–280. doi:10.1002/bies.20005

Sacerdoti D, Bolognesi M, Di Pascoli M et al (2006) Rat mesenteric arterial dilator response to 11,12-epoxyeicosatrienoic acid is mediated by activating heme oxygenase. Am J Physiol Heart Circ Physiol 291:H1999–H2002. doi:10.1152/ajpheart.00082.2006

Sailer CA, Kaufmann WA, Kogler M et al (2006) Immunolocalization of BK channels in hippocampal pyramidal neurons. Eur J Neurosci 24:442–454. doi:10.1111/j.1460-9568.2006.04936.x

Salkoff L, Butler A, Ferreira G et al (2006) High-conductance potassium channels of the SLO family. Nat Rev Neurosci 7:921–931. doi:10.1038/nrn1992

Sausbier M, Arntz C, Bucurenciu I et al (2005) Elevated blood pressure linked to primary hyperaldosteronism and impaired vasodilation in BK channel-deficient mice. Circulation 112:60–68. doi:10.1161/01.CIR.0000156448.74296.FE

Sausbier M, Hu H, Arntz C et al (2004) Cerebellar ataxia and Purkinje cell dysfunction caused by Ca^{2+}-activated K^+ channel deficiency. Proc Natl Acad Sci USA 101:9474–9478. doi:10.1073/pnas.0401702101

Schopperle WM, Holmqvist MH, Zhou Y et al (1998) Slob, a novel protein that interacts with the Slowpoke calcium-dependent potassium channel. Neuron 20:565–573

Schreiber M, Salkoff L (1997) A novel calcium-sensing domain in the BK channel. Biophys J 73:1355–1363. doi:10.1016/S0006-3495(97)78168-2

Schubert R, Nelson MT (2001) Protein kinases: tuners of the BKCa channel in smooth muscle. Trends Pharmacol Sci 22:505–512

Shao LR, Halvorsrud R, Borg-Graham L, Storm JF (1999) The role of BK-type Ca^{2+}-dependent K^+ channels in spike broadening during repetitive firing in rat hippocampal pyramidal cells. J Physiol (Lond) 521(Pt 1):135–146

Shibuya N, Mikami Y, Kimura Y et al (2009) Vascular endothelium expresses 3-mercaptopyruvate sulfurtransferase and produces hydrogen sulfide. J Biochem 146:623–626. doi:10.1093/jb/mvp111

Shieh CC, Coghlan M, Sullivan JP, Gopalakrishnan M (2000) Potassium channels: molecular defects, diseases, and therapeutic opportunities. Pharmacol Rev 52:557–594

Shin JH, Chung S, Park EJ et al (1997) Nitric oxide directly activates calcium-activated potassium channels from rat brain reconstituted into planar lipid bilayer. FEBS Lett 415:299–302

Shipston MJ, Armstrong DL (1996) Activation of protein kinase C inhibits calcium-activated potassium channels in rat pituitary tumour cells. J Physiol (Lond) 493(Pt 3):665–672
Shipston MJ, Duncan RR, Clark AG et al (1999) Molecular components of large conductance calcium-activated potassium (BK) channels in mouse pituitary corticotropes. Mol Endocrinol 13:1728–1737
Shipston MJ, Kelly JS, Antoni FA (1996) Glucocorticoids block protein kinase A inhibition of calcium-activated potassium channels. J Biol Chem 271:9197–9200
Silva JM, Lewis DL (2002) Nitric oxide enhances Ca(2 +)-dependent K(+) channel activity in rat carotid body cells. Pflugers Arch 443:671–675. doi:10.1007/s00424-001-0745-1
Sitdikova GF, Weiger TM, Hermann A (2010) Hydrogen sulfide increases calcium-activated potassium (BK) channel activity of rat pituitary tumor cells. Pflugers Arch 459:389–397. doi:10.1007/s00424-009-0737-0
Sokolowski B, Orchard S, Harvey M et al (2011) Conserved BK channel-protein interactions reveal signals relevant to cell death and survival. PLoS ONE 6:e28532. doi:10.1371/journal.pone.0028532
Stec DE, Drummond HA, Vera T (2008) Role of carbon monoxide in blood pressure regulation. Hypertension 51:597–604. doi:10.1161/HYPERTENSIONAHA.107.097154
Stockand JD, Sansom SC (1996) Role of large Ca(2 +)-activated K^+channels in regulation of mesangial contraction by nitroprusside and ANP. Am J Physiol 270:C1773–C1779
Storm JF (1987) Action potential repolarization and a fast after-hyperpolarization in rat hippocampal pyramidal cells. J Physiol (Lond) 385:733–759
Sun X-H, Ding J-P, Li H et al (2007) Activation of large-conductance calcium-activated potassium channels by puerarin: the underlying mechanism of puerarin-mediated vasodilation. J Pharmacol Exp Ther 323:391–397. doi:10.1124/jpet.107.125567
Sun Y-G, Cao Y-X, Wang W-W et al (2008) Hydrogen sulphide is an inhibitor of L-type calcium channels and mechanical contraction in rat cardiomyocytes. Cardiovasc Res 79:632–641. doi:10.1093/cvr/cvn140
Szabadits E, Cserép C, Szonyi A et al (2011) NMDA receptors in hippocampal GABAergic synapses and their role in nitric oxide signaling. J Neurosci 31:5893–5904. doi:10.1523/JNEUROSCI.5938-10.2011
Tan BH, Wong PT-H, Bian J-S (2010) Hydrogen sulfide: a novel signaling molecule in the central nervous system. Neurochem Int 56:3–10. doi:10.1016/j.neuint.2009.08.008
Tanaka Y, Koike K, Toro L (2004) MaxiK channel roles in blood vessel relaxations induced by endothelium-derived relaxing factors and their molecular mechanisms. J Smooth Muscle Res 40:125–153
Tang QY, Qi Z, Naruse K, Sokabe M (2003a) Characterization of a functionally expressed stretch-activated BKca channel cloned from chick ventricular myocytes. J Membr Biol 196:185–200. doi:10.1007/s00232-003-0637-8
Tang XD, Daggett H, Hanner M et al (2001) Oxidative regulation of large conductance calcium-activated potassium channels. J Gen Physiol 117:253–274
Tang XD, Garcia ML, Heinemann SH, Hoshi T (2004) Reactive oxygen species impair Slo1 BK channel function by altering cysteine-mediated calcium sensing. Nat Struct Mol Biol 11:171–178. doi:10.1038/nsmb725
Tang XD, Xu R, Reynolds MF et al (2003b) Haem can bind to and inhibit mammalian calcium-dependent Slo1 BK channels. Nature 425:531–535. doi:10.1038/nature02003
Telezhkin V, Brazier SP, Cayzac S, Müller CT, Riccardi D, Kemp PJ (2009) Hydrogen sulfide inhibits human BK(Ca) channels. Adv Exp Med Biol 648:65–72
Telezhkin V, Brazier SP, Mears R et al (2011) Cysteine residue 911 in C-terminal tail of human BK(Ca)α channel subunit is crucial for its activation by carbon monoxide. Pflugers Arch 461:665–675. doi:10.1007/s00424-011-0924-7
Thompson J, Begenisich T (2009) Mechanistic details of BK channel inhibition by the intermediate conductance, Ca^{2+}-activated K channel. Channels (Austin) 3:194–204
Thorup C, Jones CL, Gross SS et al (1999) Carbon monoxide induces vasodilation and nitric oxide release but suppresses endothelial NOS. Am J Physiol 277:F882–F889

Tian L, Coghill LS, MacDonald SH-F et al (2003) Leucine zipper domain targets cAMP-dependent protein kinase to mammalian BK channels. J Biol Chem 278:8669–8677. doi:10.1074/jbc.M211661200

Tian L, Coghill LS, McClafferty H et al (2004) Distinct stoichiometry of BKCa channel tetramer phosphorylation specifies channel activation and inhibition by cAMP-dependent protein kinase. Proc Natl Acad Sci USA 101:11897–11902. doi:10.1073/pnas.0402590101

Tjong Y-W, Li M, Hung M-W et al (2008a) Nitric oxide deficit in chronic intermittent hypoxia impairs large conductance calcium-activated potassium channel activity in rat hippocampal neurons. Free Radic Biol Med 44:547–557. doi:10.1016/j.freeradbiomed.2007.10.033

Tjong YW, Li MF, Hung MW, Fung ML (2008b) Melatonin ameliorates hippocampal nitric oxide production and large conductance calcium-activated potassium channel activity in chronic intermittent hypoxia. J Pineal Res 44:234–243. doi:10.1111/j.1600-079X.2007.00515.x

Toro L, Ramos-Franco J, Stefani E (1990) GTP-dependent regulation of myometrial KCa channels incorporated into lipid bilayers. J Gen Physiol 96:373–394

Tseng-Crank J, Foster CD, Krause JD et al (1994) Cloning, expression, and distribution of functionally distinct Ca(2 +)-activated K^+channel isoforms from human brain. Neuron 13:1315–1330

Tseng-Crank J, Godinot N, Johansen TE et al (1996) Cloning, expression, and distribution of a Ca(2 +)-activated K^+channel beta-subunit from human brain. Proc Natl Acad Sci USA 93:9200–9205

Verma A, Hirsch DJ, Glatt CE et al (1993) Carbon monoxide: a putative neural messenger. Science 259:381–384

Wallace JL (2010) Physiological and pathophysiological roles of hydrogen sulfide in the gastrointestinal tract. Antioxid Redox Signal 12:1125–1133. doi:10.1089/ars.2009.2900

Wallner M, Meera P, Toro L (1999) Molecular basis of fast inactivation in voltage and Ca^{2+}-activated K^+channels: a transmembrane beta-subunit homolog. Proc Natl Acad Sci USA 96:4137–4142

Wallner M, Meera P, Toro L (1996) Determinant for beta-subunit regulation in high-conductance voltage-activated and Ca(2 +)-sensitive K^+channels: an additional transmembrane region at the N terminus. Proc Natl Acad Sci USA 93:14922–14927

Wang L, Sigworth FJ (2009) Structure of the BK potassium channel in a lipid membrane from electron cryomicroscopy. Nature 461:292–295. doi:10.1038/nature08291

Wang R (2011) Signaling pathways for the vascular effects of hydrogen sulfide. Curr Opin Nephrol Hypertens 20:107–112. doi:10.1097/MNH.0b013e3283430651

Wang R (2010) Hydrogen sulfide: the third gasotransmitter in biology and medicine. Antioxid Redox Signal 12:1061–1064. doi:10.1089/ars.2009.2938

Wang R, Wang Z, Wu L (1997a) Carbon monoxide-induced vasorelaxation and the underlying mechanisms. Br J Pharmacol 121:927–934. doi:10.1038/sj.bjp.0701222

Wang R, Wu L (1997) The chemical modification of KCa channels by carbon monoxide in vascular smooth muscle cells. J Biol Chem 272:8222–8226

Wang R, Wu L (2003) Interaction of selective amino acid residues of K(ca) channels with carbon monoxide. Exp Biol Med (Maywood) 228:474–480

Wang R, Wu L, Wang Z (1997b) The direct effect of carbon monoxide on KCa channels in vascular smooth muscle cells. Pflugers Arch 434:285–291

Wang W, Huang H, Hou D et al (2010) Mechanosensitivity of STREX-lacking BKCa channels in the colonic smooth muscle of the mouse. Am J Physiol Gastrointest Liver Physiol 299:G1231–G1240. doi:10.1152/ajpgi.00268.2010

Wang ZW, Nara M, Wang YX, Kotlikoff MI (1997c) Redox regulation of large conductance Ca(2 +)-activated K^+channels in smooth muscle cells. J Gen Physiol 110:35–44

Wanner SG, Koch RO, Koschak A et al (1999) High-conductance calcium-activated potassium channels in rat brain: pharmacology, distribution, and subunit composition. Biochemistry 38:5392–5400. doi:10.1021/bi983040c

Watanabe T, Kikuchi M, Hatakeyama D et al (2007) Gaseous neuromodulator-related genes expressed in the brain of honeybee Apis mellifera. Dev Neurobiol 67:456–473. doi:10.1002/dneu.20359

Wei AD, Gutman GA, Aldrich R et al (2005) International Union of Pharmacology. LII. Nomenclature and molecular relationships of calcium-activated potassium channels. Pharmacol Rev 57:463–472. doi:10.1124/pr.57.4.9

Weiger T, Hermann A (1994) Polyamines block Ca(2 +)-activated K^+channels in pituitary tumor cells (GH3). J Membr Biol 140:133–142

Weiger TM, Hermann A (2009) Modulation of potassium channels by polyamines. In: Dandrifosse G (ed) Biological aspects of biogenic amines, polyamines and conjugates. Transworld Research Network, Kerala, India, pp 185–199

Weiger TM, Hermann A, Levitan IB (2002) Modulation of calcium-activated potassium channels. J Comp Physiol A Neuroethol Sens Neural Behav Physiol 188:79–87. doi:10.1007/s00359-002-0281-2

Weiger TM, Holmqvist MH, Levitan IB et al (2000) A novel nervous system beta subunit that downregulates human large conductance calcium-dependent potassium channels. J Neurosci 20:3563–3570

Weiger TM, Langer T, Hermann A (1998) External action of di- and polyamines on maxi calcium-activated potassium channels: an electrophysiological and molecular modeling study. Biophys J 74:722–730. doi:10.1016/S0006-3495(98)73997-9

Wellman GC, Bonev AD, Nelson MT, Brayden JE (1996) Gender differences in coronary artery diameter involve estrogen, nitric oxide, and Ca(2 +)-dependent K^+ channels. Circ Res 79:1024–1030

Werner ME, Zvara P, Meredith AL et al (2005) Erectile dysfunction in mice lacking the large-conductance calcium-activated potassium (BK) channel. J Physiol (Lond) 567:545–556. doi:10.1113/jphysiol.2005.093823

White RE, Darkow DJ, Lang JL (1995) Estrogen relaxes coronary arteries by opening BKCa channels through a cGMP-dependent mechanism. Circ Res 77:936–942

White RE, Kryman JP, El-Mowafy AM et al (2000) cAMP-dependent vasodilators cross-activate the cGMP-dependent protein kinase to stimulate BK(Ca) channel activity in coronary artery smooth muscle cells. Circ Res 86:897–905

White RE, Lee AB, Shcherbatko AD et al (1993) Potassium channel stimulation by natriuretic peptides through cGMP-dependent dephosphorylation. Nature 361:263–266. doi:10.1038/361263a0

White RE, Schonbrunn A, Armstrong DL (1991) Somatostatin stimulates Ca(2 +)-activated K^+ channels through protein dephosphorylation. Nature 351:570–573. doi:10.1038/351570a0

Widmer HA, Rowe ICM, Shipston MJ (2003) Conditional protein phosphorylation regulates BK channel activity in rat cerebellar Purkinje neurons. J Physiol (Lond) 552:379–391. doi:10.1113/jphysiol.2003.046441

Williams DL Jr, Katz GM, Roy-Contancin L, Reuben JP (1988) Guanosine 5'-monophosphate modulates gating of high-conductance Ca^{2+}-activated K^+ channels in vascular smooth muscle cells. Proc Natl Acad Sci USA 85:9360–9364

Williams SE, Brazier SP, Baban N et al (2008) A structural motif in the C-terminal tail of slo1 confers carbon monoxide sensitivity to human BK Ca channels. Pflugers Arch 456:561–572. doi:10.1007/s00424-007-0439-4

Williams SEJ, Wootton P, Mason HS et al (2004) Hemoxygenase-2 is an oxygen sensor for a calcium-sensitive potassium channel. Science 306:2093–2097. doi:10.1126/science.1105010

Wu L, Cao K, Lu Y, Wang R (2002) Different mechanisms underlying the stimulation of K(Ca) channels by nitric oxide and carbon monoxide. J Clin Invest 110:691–700. doi:10.1172/JCI15316

Wu L, Wang R (2005) Carbon monoxide: endogenous production, physiological functions, and pharmacological applications. Pharmacol Rev 57:585–630. doi:10.1124/pr.57.4.3

Wu Y, Yang Y, Ye S, Jiang Y (2010) Structure of the gating ring from the human large-conductance Ca(2 +)-gated K(+) channel. Nature 466:393–397. doi:10.1038/nature09252

Wyatt CN, Wright C, Bee D, Peers C (1995) O_2-sensitive K+ currents in carotid body chemoreceptor cells from normoxic and chronically hypoxic rats and their roles in hypoxic chemotransduction. Proc Natl Acad Sci USA 92:295–299

Xi Q, Tcheranova D, Parfenova H et al (2004) Carbon monoxide activates KCa channels in newborn arteriole smooth muscle cells by increasing apparent Ca^{2+}sensitivity of alpha-subunits. Am J Physiol Heart Circ Physiol 286:H610–H618. doi:10.1152/ajpheart.00782.2003

Xia X-M, Ding JP, Lingle CJ (2003) Inactivation of BK channels by the NH_2 terminus of the beta2 auxiliary subunit: an essential role of a terminal peptide segment of three hydrophobic residues. J Gen Physiol 121:125–148

Xie J, McCobb DP (1998) Control of alternative splicing of potassium channels by stress hormones. Science 280:443–446

Xie M-J, Ma Y-G, Gao F et al (2010) Activation of BKCa channel is associated with increased apoptosis of cerebrovascular smooth muscle cells in simulated microgravity rats. Am J Physiol Cell Physiol 298:C1489–C1500. doi:10.1152/ajpcell.00474.2009

Yang W, Yang G, Jia X et al (2005) Activation of KATP channels by H_2S in rat insulin-secreting cells and the underlying mechanisms. J Physiol (Lond) 569:519–531. doi:10.1113/jphysiol.2005.097642

Ye S, Li Y, Chen L, Jiang Y (2006) Crystal structures of a ligand-free MthK gating ring: insights into the ligand gating mechanism of K^+ channels. Cell 126:1161–1173. doi:10.1016/j.cell.2006.08.029

Yu JY, Upadhyaya AB, Atkinson NS (2006) Tissue-specific alternative splicing of BK channel transcripts in Drosophila. Genes Brain Behav 5:329–339. doi:10.1111/j.1601-183X.2005.00164.x

Yuan A, Santi CM, Wei A et al (2003) The sodium-activated potassium channel is encoded by a member of the Slo gene family. Neuron 37:765–773

Yuan C, O'Connell RJ, Feinberg-Zadek PL et al (2004) Bilayer thickness modulates the conductance of the BK channel in model membranes. Biophys J 86:3620–3633. doi:10.1529/biophysj.103.029678

Yuan P, Leonetti MD, Pico AR et al (2010) Structure of the human BK channel Ca^{2+}-activation apparatus at 3.0 A resolution. Science 329:182–186. doi:10.1126/science.1190414

Yusifov T, Savalli N, Gandhi CS et al (2008) The RCK2 domain of the human BKCa channel is a calcium sensor. Proc Natl Acad Sci USA 105:376–381. doi:10.1073/pnas.0705261105

Zeng H, Weiger TM, Fei H et al (2005) The amino terminus of Slob, Slowpoke channel binding protein, critically influences its modulation of the channel. J Gen Physiol 125:631–640. doi:10.1085/jgp.200509252

Zeng H, Weiger TM, Fei H, Levitan IB (2006) Mechanisms of two modulatory actions of the channel-binding protein Slob on the Drosophila Slowpoke calcium-dependent potassium channel. J Gen Physiol 128:583–591. doi:10.1085/jgp.200609653

Zhang L, Li X, Zhou R, Xing G (2006a) Possible role of potassium channel, big K in etiology of schizophrenia. Med Hypotheses 67:41–43. doi:10.1016/j.mehy.2005.09.055

Zhang Y, Niu X, Brelidze TI, Magleby KL (2006b) Ring of negative charge in BK channels facilitates block by intracellular $Mg^{2+}$and polyamines through electrostatics. J Gen Physiol 128:185–202. doi:10.1085/jgp.200609493

Zhao G, Neeb ZP, Leo MD et al (2010) Type 1 IP3 receptors activate BKCa channels via local molecular coupling in arterial smooth muscle cells. J Gen Physiol 136:283–291. doi:10.1085/jgp.201010453

Zhao G, Zhao Y, Pan B et al (2007) Hypersensitivity of BKCa to Ca^{2+}sparks underlies hyporeactivity of arterial smooth muscle in shock. Circ Res 101:493–502. doi:10.1161/CIRCRESAHA.107.157271

Zhao W, Zhang J, Lu Y, Wang R (2001) The vasorelaxant effect of H(2)S as a novel endogenous gaseous K(ATP) channel opener. EMBO J 20:6008–6016. doi:10.1093/emboj/20.21.6008

Zhou X-B, Wulfsen I, Utku E et al (2010) Dual role of protein kinase C on BK channel regulation. Proc Natl Acad Sci USA 107:8005–8010. doi:10.1073/pnas.0912029107

Zhou Y, Fei H, Levitan IB (2003) An interaction domain in Slob necessary for its binding to the slowpoke calcium-dependent potassium channel. Neuropharmacology 45:714–719

Zhou Y, Schopperle WM, Murrey H et al (1999) A dynamically regulated 14-3-3, Slob, and Slowpoke potassium channel complex in Drosophila presynaptic nerve terminals. Neuron 22:809–818

Zhu S, Han G, White RE (2002) PGE2 action in human coronary artery smooth muscle: role of potassium channels and signaling cross-talk. J Vasc Res 39:477–488. doi:10.1159/000067201

Zuidema MY, Yang Y, Wang M et al (2010) Antecedent hydrogen sulfide elicits an anti-inflammatory phenotype in postischemic murine small intestine: role of BK channels. Am J Physiol Heart Circ Physiol 299:H1554–H1567. doi:10.1152/ajpheart.01229.2009