Available online at www.sciencedirect.com
SCIENCE DIRECT
Pharmacology & Therapeutics 110 (2006) 103 – 116
Pharmacology & Therapeutics
www.elsevier.com/locate/pharmthera

Large-conductance, calcium-activated potassium channels: Structural and functional implications

Srinivas Ghatta [a,*,1], Deepthi Nimmagadda [a,1], Xiaoping Xu [b], Stephen T. O'Rourke [a]

[a] Department of Pharmaceutical Sciences, College of Pharmacy, North Dakota State University, Fargo, ND 58105, USA
[b] CVU-CEDD, GlaxoSmithKline, King of Prussia, PA 19406, USA

Abstract

The large-conductance, calcium-activated potassium channels (BK, also termed BK_{Ca}, Slo, or MaxiK) distributed in both excitable and non-excitable cells are involved in many cellular functions such as action potential repolarization; neuronal excitability; neurotransmitter release; hormone secretion; tuning of cochlear hair cells; innate immunity; and modulation of the tone of vascular, airway, uterine, gastrointestinal, and urinary bladder smooth muscle tissues. Because of their high conductance, activation of BK channels has a strong effect on membrane potential. BK channels differ from all other potassium (K^+) channels due to their high sensitivity to both intracellular calcium (Ca^{2+}) concentrations and voltage. These features make BK channels ideal negative feedback regulators in many cell types by decreasing voltage-dependent Ca^{2+} entry through membrane potential hyperpolarization. The current review aims to give a comprehensive understanding of the structure and molecular biology of BK channels and their relevance to various pathophysiological conditions. The review will also focus on the therapeutic potential and pharmacology of the various BK channel activators and blockers.
© 2005 Elsevier Inc. All rights reserved.

Keywords: BK; Calcium; Voltage sensitivity; BK openers; BK blockers

Abbreviations: BK, large-conductance, calcium-activated potassium channel; Ca^{2+}, calcium; ChTX, charybdotoxin; CICR, Ca^{2+}-induced Ca^{2+} release; CO, carbon monoxide; DHS-1, dehydrosoyasaponin-1; EETs, epoxyeicosatrienoic acids; G_{PTX}, pertussis toxin-sensitive G-proteins; IbTX, iberiotoxin; K^+, potassium; KATP, ATP-sensitive potassium channel; MAP, mean arterial pressure; Mg^{2+}, magnesium; NO, nitric oxide; OHC, outer hair cell; RCK, regulator of conductance for potassium; RyRs, ryanodine receptors; SR, sarcoplasmic reticulum; STOC, spontaneous transient outward current; TBA, tetrabutyl ammonium; TEA, tetraethyl ammonium.

Contents

1. Introduction . . . 104
2. Structure of BK channels . . . 104
3. Phenotypical characteristics of BK channel knockout mice . . . 106
4. BK openers . . . 106
5. BK blockers . . . 109
6. BK as a drug target . . . 110
   6.1. Cardiovascular system . . . 110
   6.2. Urinary system . . . 111
   6.3. Nervous system . . . 111
7. Concluding remarks . . . 112
Acknowledgments . . . 112
References . . . 112

* Corresponding author. Tel.: 701 231 7776; fax: 701 231 8333.
E-mail address: Srinivas.Ghatta@ndsu.edu (S. Ghatta).
[1] These authors contributed equally to this review.

0163-7258/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2005.10.007

1. Introduction

Calcium (Ca^{2+}) flow into the cells triggers a cascade of events such as release of calcium from the intracellular depots, activation of secondary messenger systems, and opening of ion channels. One such phenomenon is the opening of potassium (K^+)-selective ion channels, which are triggered by an increase in intracellular calcium levels. It was in 1958 that minor changes in intracellular Ca^{2+} levels that can alter potassium diffusion across the plasma membrane was first observed by Gardos, who studied potassium permeability through human erythrocytes in presence of elevated calcium concentrations (Gardos, 1958), and the first identification of an ionic current activated by a rise in intracellular calcium was made by Meech in 1970 (Meech & Strumwasser, 1970). Currently, it is known that such ionic currents originate in different types of cells and are mediated mainly by the opening of potassium-selective channels.

Potassium channels belong to a diverse family of membrane proteins that play important roles in various physiological processes such as neurotransmitter release, cell excitability, hormone secretion, heart rate, vascular reactivity, and smooth muscle tone. They can be activated by several factors such as voltage, intracellular calcium release and entry, G-proteins, and ATP. One such class of potassium channels is Ca^{2+}-activated potassium channels, whose gating is mediated by the rise of intracellular concentration of the free calcium ions. Three broad categories of Ca^{2+}-activated potassium channels have been identified and classified according to their conductance and are called large-conductance, 100–300 pS (BK_{Ca}) (Marty, 1981), intermediate-conductance, 25–100 pS (IK_{Ca}) (Gardos, 1958; Ishii et al., 1997; Logsdon et al., 1997), and small-conductance, 2–25 pS (SK_{Ca}) calcium-activated potassium channels (Blatz & Magleby, 1986; Park, 1994).

BK_{Ca} channels are present in many members of the animal kingdom such as nematodes (*Caenorhabditis*), insects (*Drosophila*), and mammals. These channels are also known as large-conductance, BK, Slo, and MaxiK channels and were the first ones in the family to be identified (Marty, 1981). They are activated both by elevated cytosolic Ca^{2+} levels and by membrane depolarization. Quite surprisingly, these channels can open even in the absence of calcium, and it is thought that the calcium and membrane potential dependence of the channels are independent of each other, both of which can enhance the channels' open probability (Pallotta, 1985). BK channels were first studied in smooth muscle cells where they are the key players in setting the contractile tone. However, they are also abundant in other tissues such as the brain, pancreas, and urinary bladder.

BK channels are important integrators in many biological systems and their activity can be modulated by multiple mechanisms. This review discusses a few selected examples of such modulatory molecules and mechanisms and also the physiological outcomes of channel modulation.

2. Structure of BK channels

Similar to other type of ion channels, BK channels consist of 2 distinct subunits: α and β, which are arranged in a 1:1 stoichiometry (Knaus et al., 1994a, 1994b; Toro et al., 1998). Each channel exists as a tetramer, composed of 4 α-subunits either alone or in association with β-subunit pairs (Shen et al., 1994; Garcia-Calvo et al., 1994; McManus et al., 1995). The α-subunit of the BK channel was first cloned and characterized from the slowpoke locus of *Drosophila* and mutations of the locus eliminate the Ca^{2+}-activated potassium current in the muscles and neurons (Atkinson et al., 1991). Hence, these channels were also called *dSlo*. Multiple transcriptional promoters (Bohm et al., 2000) of the gene and alternative splicing of the slowpoke mRNA (Atkinson et al., 1991; Adelman et al., 1992) give rise to diverse electrophysiological phenotypes of the channel. Human homologue (*hSlo*) of the *dSlo* gene was cloned from the brain (Dworetzky et al., 1994), and the mouse counterpart (*mSlo*) was isolated from its brain and skeletal muscle (Butler et al., 1993). The human BK gene is designated as KCNM and the BK-α is encoded by KCNMA1 gene and BK-ß encoded by KCNMB1.

The α-subunit is the pore-forming unit whereas the β-subunit is the regulatory unit. The α-subunit consists of 7 transmembrane spanning domains (S0–S6) at the N-terminus, the P-loop (or the pore-forming loop) between the S5 and S6 domains, and the four hydrophobic segments (S7–S10) at the large intracellular carboxyl (C) terminus. Unlike SK_{Ca} and IK_{Ca} channels, the α-subunit of the BK channels has an extra hydrophobic domain (S0) that leads to the extracellular N-terminus (Wallner et al., 1996). The N-terminus acts as a binding domain for ß-subunits. The potassium-selective pore is located at the center of the four α-subunits. The narrowest part of the pore is called the selectivity filter, which determines the high potassium flux rate of these channels as compared to other cations. The S6 domain is thought to be the gate for the potassium-selective pore (Jiang et al., 2002). In each α-subunit, the pore-forming motif consists of the P-loop and the S5 and S6 domains. The P-loop also bears the receptor for the binding of the pore blockers: iberiotoxin (IbTX) and charybdotoxin (ChTX). Acidic residues in the S2 domain (Seoh et al., 1996) and S3 domain (Papazian et al., 1995) along with basic residues (Arg) at every third position in the S4 domain (Papazian et al., 1991) confer voltage sensitivity to the channel ('act as voltage sensor'). Depolarization causes movement of these charged residues, known as 'gating currents', which results in conformational changes in the channel, causing the pore to open (Bezanilla et al., 1991; Stefani et al., 1997). This conformational change occurs when the inner helix lining the intracellular side of the pore bends at the conserved glycine gating hinge point (Magidovich & Yifrach, 2004).

The C-terminal (carboxy, COOH) region consists of a regulator of conductance for potassium (RCK) domain (Jiang et al., 2001), connected by a non-conserved linker to the tail domain (Wei et al., 1994). The COOH terminus contains multiple regulatory sites, e.g., a tetramerization region, the "Ca^{2+} bowl" motif, several leucine zipper domains for protein–protein interactions (Tian et al., 2003), and multiple phosphorylation sites for cAMP- and cGMP-dependent protein kinases (Zhou et al., 2001), and for protein kinase C and tyrosine kinase (Wang et al., 1999). The tail domain

Download English Version:

https://daneshyari.com/en/article/2564345

Download Persian Version:

https://daneshyari.com/article/2564345

Daneshyari.com