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REVIEW

Oxidation of KCNB1 K^+ channels in central nervous system and beyond

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Abstract

KCNB1, a voltage-gated potassium (K^+) channel that conducts a major delayed rectifier current in the brain, pancreas and cardiovascular system is a key player in apoptotic programs associated with oxidative stress. As a result, this protein represents a *bona fide* drug target for limiting the toxic effects of oxygen radicals. Until recently the consensus view was that reactive oxygen species trigger a pro-apoptotic surge in KCNB1 current *via* phosphorylation and SNARE-dependent incorporation of KCNB1 channels into the plasma membrane. However, new evidence shows that KCNB1 can be modified by oxidants and that oxidized KCNB1 channels can directly activate pro-apoptotic signaling pathways. Hence, a more articulated picture of the pro-apoptotic role of KCNB1 is emerging in which the protein induces cell's death through distinct molecular mechanisms and activation of multiple pathways. In this review article we discuss the diverse functional, toxic and protective roles that KCNB1 channels play in the major organs where they are expressed.

Key words: Apoptosis; Kv2.1; Aging; Reactive oxygen species; Alzheimer's disease

Core tip: KCNB1 is a K^+ channel that plays a key role in the brain, pancreas and cardiovascular system. KCNB1 is unique in that it induces apoptosis in association with oxidative stress. In this review article we discuss the diverse roles of this channel in the organs where it is expressed including recent advances in the molecular mechanisms through which KCNB1 causes cytotoxicity.

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KCNB1 IS A PROMINENT MEMBER OF THE SHAB-RELATED FAMILY OF VOLTAGE-GATED K^+ CHANNELS

KCNB1 (HUGO nomenclature), formerly DRK1 and Kv2.1, is a *Shab* delayed rectifier voltage-gated K^+ channel which was cloned by Frech *et al*[1] using size-fractionated mRNA extracted from rat brain. KCNB1 is expressed in the central nervous system, pancreas, pulmonary arteries, heart, auditory outer hair cells, stem cells and retina[2-21]. As in other voltage-gated K^+ channels, KCNB1 spatial and temporal expressions are both developmentally regulated. For example, three distinct (4.4, 9.0, 11.5 kb) mRNA transcripts are expressed in the rat brain, with the 4.4 kb transcript being predominant in embryos and the 11.5 kb transcript being predominant in adults[15]. Accordingly, multiple KCNB1 isoforms are detected which differ in

their developmental expression. Functional KCNB1 channels can result from the assembly of four identical pore-forming subunits along a symmetry axis[22]. However, this simple stoichiometry is not likely to be observed in nature. In order to serve the specific requisites of the tissues in which the channel is expressed, heterogeneity of KCNB1 current can be achieved by formation of heterometric complexes containing non-conducting, pore-forming subunits of the KCNG and KCNS families as well as by assembly with accessory subunits of the KCNAB and KCNE families[16,17,23-28]. KCNB1 exhibits an unusual large number of consensus sites for phosphorylation. Accordingly, the channel is a substrate for protein kinases of different families and is constitutively phosphorylated in native cells[29-32]. KCNB1 can also be SUMOylated and acetylated in nervous system and pancreas even though the physiological role of these regulations awaits elucidation[33-35]. Finally, mature KCNB1 channels are not glycosylated despite the presence of consensus sites in the N-terminus[36].

Because of the potential therapeutic implications, the pharmacology of KCNB1 to a variety of toxins and drugs has been extensively investigated. Thus, KCNB1 is blocked by tarantula toxins that belong to the same structural family of inhibitor cystine knot spider peptides reticulated by disulfide bridges. Hanatoxin from *G. spatulata*, was the first toxin to be shown to interact with KCNB1, followed in more recent years by heteroscordratoxin and stromatoxin 1 from *H. maculata* and *S. calceata* and jingzhaotoxin (JZTX- Ⅰ, -Ⅲ, and -Ⅴ) and guangxitoxin (GxTx-1E), isolated from the venoms of the Chinese tarantulas *C. jingzhao* and *P. guangxiensis*[37-40]. All these structurally related toxins exhibit variable affinities for the channel in the nanomolar to micromolar range and act to alter its gating by interacting with the voltage sensor[41,42]. KCNB1 is susceptible to inhibition by a number of compounds of different classes including classic K^+ channel blockers tetraethylammonium (TEA) and 4-aminopyridine and antipsychotic, anesthetic and antiarrhythmic compounds[43-53]. Of particular relevance to the topic of this review is the fact that acetylcholinesterase inhibitor Donepezil, a drug used in the treatment of Alzheimer's disease and vascular dementia, protects neurons from apoptosis by inhibiting KCNB1[54]. The exact mechanism awaits elucidation but recent findings showing that KCNB1 is subject to direct oxidative modification may suggest that the protective effect of the drug may stem from its ability to prevent the oxidation of KCNB1[55].

In summary, toxins and synthetic drugs have significantly contributed to the effort of dissecting native KCNB1 currents in various tissues and probing channel's structure and functional mechanisms of gating.

KCNB1 IS A CRITICAL MEDIATOR OF HIPPOCAMPAL AND CORTICAL EXCITABILITY

KCNB1 is broadly expressed in the brain and is a major contributor to the delayed rectifier somatodendritic K^+ current in hippocampal and cortical neurons[14,56]. In electrically quiescent neurons, KCNB1 is mostly localized in microdomains in the membranes of dendrites and cell bodies where it is constitutively phosphorylated and poorly conducting[20,21,29-32,57-60]. Upon the onset of neuronal activity, a series of cellular events are initiated that lead to de-phosphorylation of the channel. This transition is associated with two major changes in channel's status: (1) its threshold for voltage activation is lowered; and (2) KCNB1 is released from the microdomains and begins to diffuse in the membrane[30]. The net effect of these changes is that KCNB1 conducts a delayed rectifier K^+ current that acts to slow down and/or terminate periods of high frequency firing. Activity-dependent phosphorylation/de-phosphorylation of KCNB1 is partly mediated by cyclin-dependent kinase 5 and the phosphatase calcineurin. The latter is activated by a calcium influx driven by the electrical activity of the neuron[29-32]. Using mass spectrometry, Trimmer and colleagues identified 16 phosphorylation sites in KCNB1, of which roughly half provided a substrate for calcineurin[32]. This indicates that modulation of KCNB1 by protein kinases is graded to reflect dynamic regulation of neuron firing properties. However, KCNB1 can also terminate periods of neuronal activity by being directly phosphorylated. For example, AMP-activated protein kinase (AMPK, which is activated by ATP depletion) can phosphorylate KCNB1 at residue S440 and induce hyperpolarizing shifts in the current-voltage relationship for activation, shifts that make the channel more conductive at negative voltages[61].

KCNB1 PROMOTES APOPTOSIS IN RESPONSE TO OXIDATIVE STRESS

KCNB1 is a specific mediator of apoptosis in a variety of neuronal cell types including hippocampal, cortical and granule neurons[62-65]. For example, a study investigating the molecular correlate of the apoptotic K^+ current in hippocampal neurons found that among nine alpha and 3 beta Kv subunits screened, KCNB1 was the primary correlate[63]. Several groups have demonstrated that the key event triggering KCNB1-induced apoptosis is an increase in reactive oxygen species (ROS), either following acute oxidation, or as a consequence of cellular stresses such as serum deprivation and excitotoxicity[55,62-65]. It is currently accepted that dysregulated K^+ homeostasis causes apoptosis by inducing mitochondrial swelling and depolarization, ROS generation, deficient energy production and cell volume decrease[66]. Accordingly, augmented insertion of KCNB1 channels into the plasma membrane is observed in neurons subjected to oxidative challenges[67]. The accompanying increase in KCNB1 current is thought to be a key step in the apoptotic program. The execution of the latter requires phosphorylation of KCNB1 by multiple types of protein kinases a fact that should not surprise considering the primary role that phosphorylation plays for the function of KCNB1. Zhou *et al*[68] investigated apoptosis induced by lack of serum

in granular neurons and found that this was associated with upregulation of KCNB1 *via* the activation of a signaling pathway involving cAMP, protein kinase A and cAMP response element-binding protein (CREB). Aras *et al*[69] have identified several kinases including apoptosis signal-regulating kinase 1 (ASK1), p38 MAPK-dependent kinase, c-Src tyrosine kinase, and $Ca(2^+)$/calmodulin-dependent protein kinase Ⅱ (CaMKII) that interact with KCNB1 in response to oxidative stress[70-73]. Their studies have provided a model that predicts that oxygen radicals induce simultaneous increases in cytosolic levels of Zn^{2+} and Ca^{2+}. These increases activate the previously listed kinases and accelerate KCNB1 forward trafficking by modulating and facilitating its interaction with SNARE family protein syntaxin. This apoptotic program is tightly regulated: knock down of just a single phosphorylation site (S800 for p-38, Y124 for c-Src) is sufficient to suppress the pro-apoptotic influence of KCNB1[70]. However, Src tyrosine kinases and protein tyrosine phosphatase epsilon (PTP epsilon) also play a role in the physiological modulation of KCNB1. In the Schwann cells of mice, Src-mediated phosphorylation of Y124, (the same residue responsible for Zn^{2+}/Ca^{2+} induced apoptosis), causes specific augmentation of KCNB1 current which appears to be critical for Schwann cell proliferation and myelination[74,75]. In fact, de-phosphorylation of KCNB1 at Y124 by PTP epsilon reduces KCNB1 activity and stops KCNB1-induced myelination[76,77]. Accordingly, mice lacking PTP epsilon exhibit hypomyelination of sciatic nerve axons at an early post-natal age, an effect due to constitutive activation of KCNB1 by Src tyrosine kinases[78]. Moreover, a number of K^+ channels can cause apoptosis *via* dysregulated K^+ homeostasis in a variety of cell types[66]. Therefore, increased K^+ current may not be the key feature responsible for the specific ability of KCNB1 to promote apoptosis, but rather a consequence of it. Recent work from our laboratory may shed light on this issue. Cotella *et al*[55] showed that oxygen radicals directly modify KCNB1 channels, leading to the formation of oligomers held together by disulfide bridges[55]. A KCNB1 variant which does not form oligomers, obtained by mutating an N-terminal cysteine (C73A), fails to increase apoptosis in mammalian cells. Cotella *et al*[55] further showed that in inside-out patches, oxidants inhibit KCNB1 current. These findings imply that the formation of oligomers, rather than KCNB1 current, is the event that triggers an initial pro-apoptotic stimulus. To answer this question, Wu *et al*[79] have investigated the fate of the KCNB1 oligomers. They found that they accumulate in the plasma membrane as a result of defective internalization. Notably, accumulation is transient, and normal endocytosis/surface expression are mostly restored within one hour post-oxidation. The transient accumulation of KCNB1 oligomers is associated with activation of c-Src and JNK kinases coupled to a steady increase in the levels of free radicals. Thus, oligomer-induced activation of a "death pathway" appears to trigger the initial pro-apoptotic stimulus. As apoptosis progresses and ROS levels increase in the cell, the surge of KCNB1 current follows to further execute the apoptotic program (Figure 1).

INHIBITION OF KCNB1 MAY REPRESENT A VALID ANTI-APOPTOTIC STRATEGY

Pharmacological inhibition of KCNB1 current may represent a valid approach to preventing apoptosis. Accordingly, Peers and colleagues have shown that carbon monoxide (CO) can provide neuronal protection against an increase in KCNB1 current *via* regulating ROS and protein kinase G activity[80]. The same group has further proposed that the anti-apoptotic effect of CO may also be partially responsible for the etiology of cancer, as many oncogenic cells constitutively express heme oxygenase-1 (HO-1), which generates CO as a by product of its catalytic activity[81]. Chronic viruses, which establish a state of persistent infection by rendering infected cells resistant to apoptosis also appear to exploit inhibition of KCNB1 current. In human hepatocytes infected with hepatitis C virus (HCV), oxidative insults fail to initiate apoptosis because the HCV NS5A protein inhibits phosphorylation of KCNB1 by p38 MAPK and thus suppresses the current surge[82,83]. Furthermore, a neuronal NS5A isoform from HCV genotype 1b, NS5A1b, protects rat neurons against apoptosis by inhibiting KCNB1[73]. However, while NS5A acts on tyrosine kinase phosphorylation at residue Y124, NS5A1b inhibits p38-MAPK at residue S800 suggesting that the actions of these viral proteins are genotype-selective probably reflecting the characteristic of these viruses to target specific tissues.

VASOCONSTRICTION OF SMALL PULMONARY ARTERIES MAY PROCEED THROUGH DIRECT INHIBITION OF KCNB1 CURRENT BY ROS

Hypoxic pulmonary vasoconstriction is a physiological response to alveolar hypoxia, in which blood flow is redirected to better ventilated lobes *via* constriction of small pulmonary arteries. The mechanical force leading to vasoconstriction is exerted by pulmonary arteries smooth muscle cells (PASMCs). Hypoxia initially promotes PASMCs depolarization *via* inhibition of an oxygen-sensitive K^+ current. This leads to the activation of L-type Ca^{2+} channels, which elevate cytosolic calcium thereby triggering PASMCs contraction. Biochemical, pharmacological, electrophysiological and genetic evidence designates KCNB1 - alone or mixed with KCNS3 silent subunits-as one of the major molecular correlates of the oxygen-sensitive K^+ current in PASMCs[16-18,84,85]. Studies using the human ductus arteriosus as model system have provided a detailed picture of the cellular and molecular events leading to vasoconstriction during hypoxia[86-88]. Changes in O_2 levels are translated to the mitochondrial electron transport chain (KCNB1 is insensitive to O_2[89])

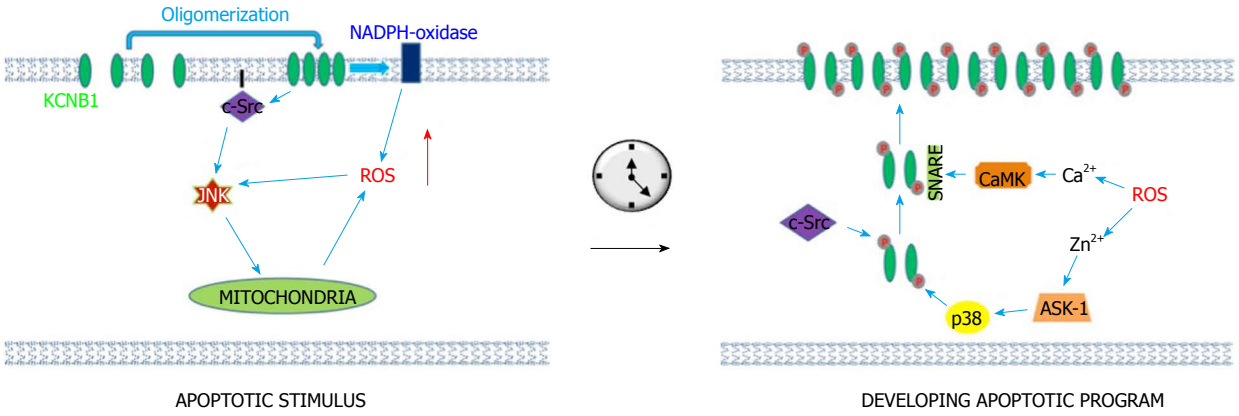

Figure 1 A two-step model for the pro-apoptotic actions of KCNB1. Upon exposure to oxidants, KCNB1 oligomers are formed. They accumulate in the plasma membrane thereby perturbing the organization of lipid rafts. This results in activation of an apoptotic stimulus mediated by c-Src and downstream, JNK kinases. As result of activation of c-Src and JNK kinases and in part of NADPH-oxidase (Xilong Wu, private communication) which is localized in the plasma membrane, ROS levels increase in the cell. ROS induce a raise in cytosolic Ca^{2+} and Zn^{2+} that initiate a phosphorylation-mediated surge of KCNB1 channels that further drives apoptosis. The signaling pathway activated by Zn^{2+} proceeds through activation of p38 by ASK-1 and independently, of c-Src tyrosine kinases (Zn^{2+} inhibits the activity of the tyrosine phosphatase PTP epsilon) which phosphorylate KCNB1 at S800 and Y124 thereby allowing interaction with SNARE family protein syntaxin. The Ca^{2+} signaling pathway results in activation of CaMKII kinase which in turn acts to modulate the interaction of KCNB1 with syntaxin. It is not known whether Src and p38 phosphorylation directly act to increase KCNB1 current. ROS: Reactive oxygen species.

which responds by speeding the synthesis of diffusible hydrogen peroxide (H_2O_2). H_2O_2 causes smooth muscle cell depolarization, *via* inhibition of K^+ current which further results in influx of calcium through L-type channels. The molecular details of the mechanism that links H_2O_2 to K^+ current inhibition were not known previously but the fact that KCNB1 can be directly oxidized by H_2O_2 and most importantly, that its current is suppressed by oxidants may now provide a natural explanation for this mechanism of inhibition. It is worth noticing that chronic hypoxia is characterized by depolarized resting potential and elevated cytosolic Ca^{2+}. Chronic depolarization is achieved by downregulation of KCNB1 protein[90-93] through mechanisms not completely understood, even though studies have implicated 15-lipoxygenase catalysis of arachidonic acid and hypoxia-inducible factor 1 in the mechanism[94,95]. Thus, different regulations of KCNB1 appear to mediate acute versus chronic conditions of hypoxia.

CONCLUSION

KCNB1 is a channel with a double-hedged sword nature: it is essential to the physiology of multiple organs, including the brain, pancreas and cardiovascular system and further acts as a mediator of apoptosis in response to oxidative stresses[2-21]. Dysregulated K^+ homeostasis is a well established mechanism through which K^+ channels contribute to an apoptotic program with a great deal of evidence implicating that KCNB1 do indeed work in this mechanism[55,62-65,67]. However recent findings have unveiled new ways through which KCNB1 mediates cell death: by giving rise to cytotoxic protein aggregates that result from direct oxidation of the protein[79]. The accumulation of these KCNB1 oligomers in the plasma membrane is transient but sufficient to trigger a pro-apoptotic signal *via* activation of a c-Src/JNK kinases pathway. As the apoptotic program progresses, a surge of KCNB1 current follows to induce mitochondrial destabilization, ROS generation, deficient energy production and cell volume decrease. Hence, KCNB1 plays a double role as both initiator and later executor of the apoptotic program.

Aging pathologies pose new challenges to health care, because even as advances in medicine are increasing lifespan, health problems become more prevalent as people age. A recent survey done by Harvard University School of Public Health and the Alzheimer's Europe Consortium suggests that senile dementia is the second leading health concern after cancer[96]. Aging is also the most important risk factor in neurodegenerative conditions such as Alzheimer's disease, the third most costly disease in the United Sates[97]. It is projected that the number of Western elders suffering from dementia and related neurodegenerative disease will increase by 350% by the midcentury[98,99]. Therefore, because of the impact of increasing lifespan on global human health issues, it is important to elucidate the cellular and molecular processes involved in aging. Oxidative modifications of KCNB1 are pervasive in the aging nervous system[55]. Hence, KCNB1 oxidation has the potential to impact all those conditions characterized by an imbalance in the redox status of the cell, from normal senescence to neuropathies such as Alzheimer's disease. Understanding how oxidation of KCNB1 influences the function of the brain during aging may provide the insight necessary to design better pharmacological strategies; these include targeting KCNB1 for the potential therapeutic use of antioxidants in neurological treatments or targeting other components of the signaling pathways activated by oxidation of KCNB1.

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