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VOLTAGE-GATED POTASSIUM CHANNELS AT THE CROSSROADS OF NEURONAL FUNCTION, ISCHEMIC TOLERANCE, AND NEURODEGENERATION

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Abstract

Voltage-gated potassium (Kv) channels are widely expressed in the central and peripheral nervous system, and are crucial mediators of neuronal excitability. Importantly, these channels also actively participate in cellular and molecular signaling pathways that regulate the life and death of neurons. Injury-mediated increased K^+ efflux through Kv2.1 channels promotes neuronal apoptosis, contributing to widespread neuronal loss in neurodegenerative disorders such as Alzheimer's disease and stroke. In contrast, some forms of neuronal activity can dramatically alter Kv2.1 channel phosphorylation levels and influence their localization. These changes are normally accompanied by modifications in channel voltage-dependence, which may be neuroprotective within the context of ischemic injury. Kv1 and Kv7 channel dysfunction leads to neuronal hyperexcitability that critically contributes to the pathophysiology of human clinical disorders such as episodic ataxia and epilepsy. This review summarizes the neurotoxic, neuroprotective, and neuroregulatory roles of Kv channels, and highlights the consequences of Kv channel dysfunction on neuronal physiology. The studies described in this review thus underscore the importance of normal Kv channel function in neurons, and emphasize the therapeutic potential of targeting Kv channels in the treatment of a wide range of neurological diseases.

Keywords

voltage-gated potassium channels; Kv2.1; apoptosis; ischemia; ischemic preconditioning; neuronal hyperexcitability; epilepsy

I. Introduction

Voltage-gated potassium (Kv) channels are the largest gene family of potassium (K^+) channels, and are key regulators of neuronal excitability [1–4]. In humans, they are encoded by forty different genes and categorized into twelve sub-families, Kv1 through Kv12 [5]. Mammalian Kv channels are tetramers, composed of four α-subunits that surround an ion conduction pore. Each α-subunit contains six α-helical transmembrane domains (S1–S6), a membrane-reentering P loop between S5 and S6, and cytosolic N- and C-termini. Four S5-P-S6 segments line the ion conduction pore, while the S1–S4 sequences are critical for channel voltage-sensing and gating.

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Kv channels mediate outward K^+ currents that contribute to membrane repolarization and hyperpolarization, thus generally serving to limit neuronal excitability. Characterizing the precise molecular correlates of Kv-mediated K^+ currents in different cell types has been difficult, owing to the assortment of channels generated from α-subunit heteromerization within Kv families. This diverse channel subunit composition produces a wide spectrum of Kv channels with differing biophysical and pharmacologic profiles. Furthermore, Kv α-subunits can bind to regulatory Kv β-subunits, as well as with other Kv channel-interacting proteins, which can strongly modify channel properties [6–8]. Moreover, post-translational modifications such as phosphorylation, dephosphorylation, and sumoylation all have been shown to alter Kv channel properties significantly [9–11]. Despite these challenges, through electrophysiological studies utilizing pharmacologic agents and Kv channel subunit-specific genetic manipulation, the general functions of Kv channel sub-families in neurons have been relatively well characterized. As such, low-voltage-activated channels such as Kv1, Kv4, and Kv7 regulate the threshold potential for firing, and limit the number of action potentials generated in response to depolarization [12, 13]. In contrast, high-voltage-activated, slowly inactivating Kv2 channels play an important role in influencing action potential duration during periods of high frequency firing [14–17]. In addition to strongly shaping neuronal excitability, Kv channels also critically contribute to cell death and cell survival signaling pathways. In this review, the diverse neurotoxic, neuroprotective, and neuroregulatory roles of Kv channels will be discussed. Additionally, the implications of Kv channel dysfunction, particularly in the context of human neurological diseases, will also be addressed.

II. Neurotoxicity of Kv channels

A. K^+ efflux is a requisite component of apoptotic cell death

Apoptotic cell death contributes significantly to the neuronal loss observed in a number of neurological disorders, including Alzheimer's disease and stroke [18–22]. Therefore, understanding the mechanisms of apoptotic signaling pathways is of paramount importance in order to successfully develop therapeutic strategies for preventing or reducing neuronal damage. Apoptosis was first described as "shrinkage necrosis," due to the morphological features of shrunken cell size and fragmentation of nuclei, which distinguished apoptotic cells from the swollen appearance of necrotic cells [23]. The key biochemical features of apoptosis have since been characterized, and include DNA fragmentation, mitochondrial damage, and caspase activation. Several critical components of apoptotic cascades occur only in the presence of a reduction in cell volume, termed apoptotic volume decrease (AVD), and decreased intracellular ionic strength, both of which are observed regardless of apoptotic stimulus and cell type [23–32]. Because the net electrochemical gradient of the cell favors the exit of K^+, K^+ channel-mediated K^+ efflux was an early contender for promoting AVD and thus facilitating apoptotic signaling cascades. This idea is supported by several key findings:

1. **Physiological concentrations of K^+ inhibit, while lowered K^+ levels activate, apoptotic enzymes**: In 1997, Cidlowski and colleagues identified a critical relationship between potassium concentrations and apoptotic enzyme activity. They incubated thymocyte nuclei with calcium and magnesium to activate autodigestion, a process that recapitulates apoptotic DNA degradation *in vitro*. Potassium chloride (KCl) inhibited DNA fragmentation in a dose-dependent fashion, indicating blockade of pro-apoptotic nuclease activity. Importantly, normal physiological levels of intracellular K^+ effected near-complete inhibition of nuclease activity [33]. Using cytoplasmic extracts from rats treated with dexamethasone to induce apoptosis, they also showed that caspase-3 activation was reduced with increasing concentrations of KCl. In other *in vitro* systems of apoptosis, physiologic K^+ concentrations have been shown to mitigate DNA fragmentation and chromatin

condensation [34], as well as apoptosome formation [35]. In neurons exposed to serum deprivation, low intracellular K^+ concentrations enhance the DNA binding activity of pro-apoptotic transcription factors and the mRNA expression of their target genes, while depressing the DNA binding activity of anti-apoptotic factors and mRNA expression of their target genes [36]. This evidence strongly indicates that reduced intracellular K^+ concentrations provide a permissive environment for apoptotic signaling cascades.

2. **Apoptotic stimuli cause K^+ loss:** Reduced K^+ concentrations are observed in cortical neurons following serum deprivation [37], and in other cell types following an assortment of apoptotic insults [24, 28, 33, 34, 38]. Important early flow cytometry studies in thymocytes demonstrated that K^+ loss after exposure to an apoptotic stimulus is restricted to cells exhibiting apoptotic features such as cell volume reduction, DNA fragmentation, and loss of mitochondrial membrane potential [33, 34].

3. **K^+ efflux promotes apoptosis, while blocking K^+ efflux supports cell survival:** K^+ efflux promotes apoptotic signaling and cell death in a range of cell types [37, 39–44]. Ionophores that induce K^+ efflux, including nigericin and valinomycin, and the Na^+/K^+ ATPase inhibitor ouabain, activate LPS-stimulated, caspase-1-mediated maturation of IL-1β in phagocytes [41, 42]. Cortical neurons exposed to valinomycin undergo cell death, displaying the typical morphological and biochemical features of apoptosis [37].

High extracellular K^+ concentrations, by decreasing the K^+ gradient and thus blocking K^+ efflux, oppose apoptotic signaling and promote cell survival. This observation has been well characterized particularly in cerebellar granule neurons (CGNs) [32, 45–51]. Neurons grown in 5 mM KCl exhibit indications of apoptotic cell death, as compared to neurons grown in 25 mM KCl, which are protected from DNA fragmentation and are resistant to TGF-β-induced apoptosis [48, 50, 51]. Accordingly, switching mature CGNs from 25 mM KCl to 5 mM KCl induces vacuole formation, condensing of nuclei, cellular and neurite shrinkage, and apoptotic cell death [46]. Cholesterol enhances apoptosis in CGNs cultured in low K^+ medium, but does not influence cell survival in CGNs incubated in high K^+ medium [52]. Similar results have been demonstrated in: *(i)* ciliary and dorsal root ganglion neurons, which display increased survival and differentiation in high extracellular K^+ media [53, 54]; *(ii)* cortical neurons, which are protected by high extracellular K^+ from apoptosis induced by oxidants, staurosporine, glutamate, ceramide, neurotoxic amyloid-β (Aβ) peptides, and serum deprivation [37, 55–58]; *(iii)* septal cholinergic cells, which in high K^+ media are resistant to Aβ-induced cell death [59]; and *(iv)* thymocytes, where high K^+ media limits pro-apoptotic caspase activation and DNA fragmentation [33]. Elevated extracellular K^+ also inhibits pro-apoptotic enzyme activity. IL-1β processing by caspase-1 is prevented by high K^+ growth media in human monocytes and mouse macrophages [41, 42]. In agreement with these findings, K^+ channel blockers attenuate apoptotic signaling cascades and cell death in numerous neuronal [37, 56, 57, 60–69] and non-neuronal systems [27, 70–72].

Some studies have suggested that elevated extracellular K^+ mitigates apoptotic cell death by increasing calcium (Ca^{2+}) entry through voltage-gated Ca^{2+} channels, rather than by eliminating pro-apoptotic K^+ efflux [38, 45, 48, 55, 73–78]. In rat embryonic sympathetic neurons, withdrawal of Ca^{2+} from the media or treatment with Ca^{2+} channel blockers precludes high extracellular K^+-induced rescue from NGF deprivation in some cases [73, 74, 77], while thapsigargin-induced Ca^{2+} influx restricts NGF deprivation-induced apoptosis [73]. Similarly, Ca^{2+} channel antagonists impede high K^+-mediated cell survival in CGNs [45, 48], and prevent rescue by increased extracellular K^+ of high oxygen-stimulated apoptotic toxicity in hippocampal neurons, and of staurosporine-mediated cell death in

cortical neurons [55, 78]. However, as noted by Yu and colleagues in a landmark paper [37], these studies do not rule out the possibility that reducing K^+ efflux inhibits apoptosis and promotes neuronal survival. In fact, increases in intracellular Ca^{2+} can promote neuronal apoptosis [79, 80], and heightened Ca^{2+} levels are not always required for high extracellular K^+-facilitated survival of NGF-deprived sympathetic neurons [81]. Importantly, in cortical neurons, Ca^{2+} channel blockers do not eliminate neuroprotection by high extracellular K^+ or tetraethylammonium (TEA, a blocker of delayed rectifying Kv channels) in response to serum deprivation, NMDA, Aβ peptide, or ceramide [37, 56, 57, 60]. Additionally, TEA analogs that ablate staurosporine-induced K^+ efflux, cell volume loss, caspase cleavage and activation, and neuronal apoptosis, also inhibit high threshold voltage-activated Ca^{2+} channels, supporting the idea that neuroprotection via K^+ channel inhibition does not occur by activation of Ca^{2+} channels [61]. The specificity for K^+ efflux, rather than inhibition of Ca^{2+} influx, in the promotion of apoptotic signaling cascades has also been demonstrated in monocytes [42], leukocytes [70], Chinese hamster ovary cells [43], and corneal epithelial cells [71, 72].

Chloride ion (Cl^-) efflux may accompany pro-apoptotic K^+ exit in order to maintain electroneutrality in the cell. In fact, Cl^- channel activation and Cl^- efflux are observed following an apoptotic stimulus in several cell types [82–86]. Furthermore, Cl^- channel blockers attenuate some features of apoptotic signaling and cell death in neurons and other cell types, although these blockers are not invariably as effective as K^+ channel inhibitors [83, 87–89]. Cl^- exit, while insufficient to facilitate the completion of apoptotic programs, may promote pro-apoptotic K^+ efflux and thus contribute to cell death. Although beyond the scope of this review, Cl^- efflux in apoptosis merits further investigation for possible therapeutic intervention.

Finally, while K^+ efflux is a requisite event for many forms of apoptosis, it is not, in and of itself, completely sufficient to stimulate apoptotic cell death in all injurious contexts. In Chinese hamster ovary cells, which do not express endogenous Kv channels and are resistant to apoptosis induced by hypoxia or serum deprivation, treatment with the K^+ ionophore valinomycin stimulates massive cell death characterized by mitochondrial damage and caspase activation [43]. In contrast, lymphocytes cultured under hypotonic conditions undergo a 50% drop in K^+ concentrations via a volume regulatory response, but this reduction alone is not sufficient to induce apoptosis [24]. Similarly, serum deprivation along with decreased extracellular K^+ is required to stimulate apoptosis in CGNs, while in cortical neurons, caspase activity inhibition blocks oxidant-induced apoptotic cell death, despite the presence of prominent increased outward K^+ currents [45–49, 51, 64, 90, 91].

B. Kv currents enable neuronal apoptosis

Delayed rectifier Kv channels are thought to be the principal conduits for the exit of K^+ in neuronal apoptosis [37, 51, 56–58, 60, 61, 65, 67, 68, 92–101], although other K^+ channels, including A-type K^+ channels [27, 42, 64, 69–72, 102], Ca^{2+}-activated K^+ channels [28, 62, 103, 104], K_{ATP} channels [63], and TASK leak K^+ channels [105], may also play an important role in this context. Yu and coworkers have shown that cortical neurons deprived of serum, or exposed to staurosporine, neurotoxic Aβ peptide, or ceramide, manifest a TEA-sensitive increase in delayed rectifying Kv currents, without exhibiting an increase in other major K^+ currents, including inwardly rectifying, A-type (with the exception of serum deprivation, which increases these currents slightly), M type, or BK currents [37, 56, 60]. TEA or TEA analogs render neurons resistant to the above-mentioned apoptotic insults, while 4-aminopyridine (4-AP), a Kv1 channel inhibitor that opposes apoptosis in some neuronal and non-neuronal systems [27, 42, 64, 70], does not attenuate the rise in K^+ currents or confer neuroprotection against apoptotic stimuli in these studies [37, 56, 60, 68, 87]. A study in septal cholinergic cells has similarly demonstrated Aβ-induced K^+ current

increase and apoptotic cell death, both of which are blocked by TEA. In a dopaminergic cell line that doesn't manifest Aβ-induced increased K^+ currents, TEA is not protective, while septal cholinergic cells that exhibit minimal basal K^+ currents are not susceptible to Aβ-mediated toxicity, consistent with the requirement for increased K^+ currents in the completion of apoptotic signaling [59]. In neurons, amplified apoptotic Kv channel currents that can be tempered by TEA, high extracellular K^+, Kv siRNA-mediated knockdown, and/or a dominant negative form of the Kv channel, have also been shown in response to peroxynitrite [99], the apoptosis inducer thiol oxidant 2,2′-dithiodipyridine (DTDP) [92, 93, 95, 96, 106–108], the nitric oxide donor S-nitrocysteine (SNOC) [99], low K^+/serum-free media [51, 101, 102], 6-hydroxydopamine [94], glutamate [109], and increased intracellular cholesterol [52]. These studies will be discussed in further detail below.

K^+ efflux and changes in K^+ current behavior have also been observed following ischemic injury *in vitro* and *in vivo* [110–119]. For instance, delayed rectifying K^+ currents are increased in CA1 pyramidal neurons after transient forebrain ischemia [120, 121]. Moreover, two Kv channel antagonists, tetraethylammonium (TEA) and clofilium, are neuroprotective against cerebral ischemia in mice [98]. In another study, TEA administered to rats post-forebrain ischemia significantly rescues neuronal density, shrunken cells, and nuclei condensation, while treatment with 4-AP does not prevent the apoptotic phenotype [97].

Kv2.1-mediated neuronal apoptosis—Kv2.1, the predominant mediator of delayed rectifying K^+ currents in neurons [15, 122, 123], has been identified as the channel responsible for the pro-apoptotic K^+ current increase in cortical, hippocampal, and cerebellar granule neurons. Importantly, the increase in K^+ current amplitude occurs without changes in the voltage-gated activation or inactivation kinetics of the Kv2.1 channels [37, 52, 93–96, 100, 101, 106, 108].

A Kv2.1-mediated neuronal apoptotic pathway stimulated by oxidant treatment has been well characterized (Fig. 1a and Fig. 2, right). Oxidants, such as DTDP, induce an intracellular release of zinc (Zn^{2+}) from metal-binding proteins, which is required to activate two kinase signaling pathways that converge upon increased phosphorylation of Kv2.1 channels, enhanced plasma membrane delivery of Kv2.1 channels, and amplified Kv2.1 K^+ currents, producing an intracellular environment that enables DNA fragmentation, caspase activation, and apoptosis [92, 93, 95, 96, 99, 106, 107, 124]. The increased Kv2.1-mediated K^+ currents are observed approximately three hours following a brief exposure to the apoptogenic stimulus.

Apoptotic enhancement of K^+ currents via Kv2.1 channels occurs upstream of caspase activation and requires coordinate channel phosphorylation at two amino acid residues, C-terminal S800 and N-terminal Y124, by p38 kinase and Src kinase, respectively [92, 107]. The oxidant-stimulated Zn^{2+} release is a necessary early event for p38 kinase activation, via either apoptosis signal-regulating kinase 1 (ASK-1) [96] or mixed-lineage kinase (MLK) [125], and for consequent, p38 kinase-mediated S800 phosphorylation [95, 96, 107]. Inhibiting p38 kinase activity blocks oxidant-induced S800 phosphorylation, increased Kv2.1 currents, caspase activation, and toxicity [92]. Zn^{2+} also permits the second, Src kinase-mediated phosphorylation step by inhibiting the activity of cytoplasmic protein tyrosine phosphatase ε (Cyt-PTPε), which is normally responsible for dephosphorylating Kv2.1 channels at the Src kinase-phosphorylated site Y124 [107, 126, 127]. In fact, over-expression of Cyt-PTPε blocks the increase in K^+ currents and is neuroprotective, while Src kinase activity inhibition blocks the apoptotic K^+ current surge [107]. The coordinate, oxidant-induced phosphorylation of Kv2.1 channels at the S800 and Y124 residues permits Kv2.1 channels to interact with soluble N-ethylmaleimide-sensitive factor attachment

protein receptor (SNARE) proteins via a proximal C-terminal region of the channel [106, 126, 128]. This SNARE-Kv2.1 channel interaction, which requires Ca^{2+}-activated Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activation, facilitates Kv2.1 channel delivery to the cell surface, enabling pro-apoptotic K^+ currents through Kv2.1 channels [129]. Accordingly, oxidant-stimulated Kv2.1 trafficking to the plasma membrane is blocked by co-expression of botulinum toxin fragments, expression of an S800A mutant, or treatment with p38 kinase inhibitor [95, 106]. In summary, interfering with any one of multiple steps of this apoptotic pathway, including ROS production, intracellular Zn^{2+} release, CAMKII activation, Src- and p38-mediated Kv2.1 phosphorylation, or SNARE-dependent membrane insertion of new Kv2.1 channels, precludes the pro-apoptotic K^+ current rise and rescues neurons from oxidant-mediated toxicity. This injurious pathway has also been validated in neurons exposed to activated microglia, which generate peroxynitrite, a well-established Zn^{2+}-liberating agent [100, 130].

Neuronal cell death facilitated by a range of other apoptotic stimuli share several features of DTDP-mediated neurotoxicity, particularly the Kv2.1-mediated current increase, providing a compelling argument for the convergence of apoptotic signaling pathways on a requisite, Kv2.1-facilitated rise in K^+ currents in neurons. In CGNs, increased K^+ currents and apoptosis follow incubation in low K^+, serum-free media, while silencing Kv2.1 gene expression via siRNA knockdown reduces K^+ current amplitudes and increases cell viability [51]. Increased intracellular cholesterol potentiates the low K^+/serum deprivation-stimulated Kv2.1 current rise, DNA fragmentation, and consequent apoptosis in CGNs, all of which are blocked by TEA or MβCD, a cholesterol-binding agent [52]. The elevated K^+ currents are attenuated by inhibition of endoplasmic reticulum/Golgi transport [52], indicating a role for *de novo* Kv channel plasma membrane insertion in propagating pro-apoptotic K^+ efflux, similar to that seen in DTDP-treated neurons [106]. Treatment of cerebrocortical neurons with the nitric oxide donor SNOC facilitates apoptosis characterized by K^+ efflux, cell shrinkage, and activation of TEA-sensitive K^+ channels. In agreement with the cell death pathway observed in DTDP-treated cortical neurons, this process involves nitric oxide-mediated Zn^{2+} release, leading to further oxidative injury, mitochondrial function impairment, and p38 kinase activation-mediated enhanced Kv currents, all of which are required for neurotoxicity [99]. p38 kinase activation, and Kv2.1 K^+ current-mediated apoptosis is also observed in hippocampal neurons following sustained treatment with the chemokine stromal cell-derived factor-1α (SDF-1α) or exposure to HIV-1 glycoprotein gp120 [131], in dopamine transporter-expressing non-dopaminergic neurons after incubation with 6-hydroxydopamine (6-OHDA), and in 6-OHDA-treated dopaminergic neurons [94]. In another report, serum deprivation in cortical neurons was shown to provoke Kv2.1 K^+ current surge-mediated apoptosis that is dependent on SNARE-facilitated channel membrane insertion: the apoptotic stimulus enhances interaction of Kv2.1 and SNARE protein SNAP-25, while blocking this interaction with botulinum toxin completely blocks the serum deprivation-associated enhancement of K^+ currents [101].

Additionally, most features of this Kv2.1-facilitated apoptotic pathway have been recapitulated in recombinant cell systems, strongly implicating Kv2.1 channels in an apoptogen-stimulated, requisite K^+ current surge that is sufficient for caspase activation and completion of apoptosis [92, 93, 95, 96, 106, 107, 131–133]. Transfection of Kv2.1 in Chinese hamster ovary or HEK293 cells, for example, renders them newly susceptible to apoptosis induced by DTDP or oxygen-glucose deprivation, respectively [93, 132]. Further, these studies have confirmed the involvement of pro-apoptotic p38- and Src-mediated Kv2.1 phosphorylation, as well as *de novo* Kv2.1 channel membrane insertion [106, 131].

Other signaling components that may participate in Kv2.1-mediated neuronal apoptosis have been identified, but have not yet been thoroughly investigated. For example, the cyclic

adenosine monophosphate (cAMP)/protein kinase A (PKA)/cAMP response element-binding protein (CREB) pathway has been implicated in K^+ channel-mediated apoptosis. In CGNs, cAMP-promoting agents reduce Kv channel-facilitated apoptosis induced by low extracellular K^+ or ethanol treatment [46, 48, 51, 66, 91]. In contrast, cAMP/PKA/CREB activation promotes the Kv2.1-mediated rise in K^+ currents and subsequent cell death in cholesterol-enhanced, low K^+-mediated apoptosis [52]. Kv2.1-facilitated K^+ efflux and consequent neuronal apoptosis following exposure to SDF-1α or HIV-1 glycoprotein gp120 depend on calcineurin signaling, and are accompanied by a shift in Kv2.1 voltage-gated kinetics that is not normally observed in oxidant-mediated neurotoxicity [131].

An alternate mechanism of Kv2.1-mediated neuronal apoptosis has been proposed. In this model, oxidant-mediated oligomerization of Kv2.1 channels leads to a rapid decrease, rather than an increase, of Kv2.1 K^+ currents that is absent in cells expressing an oxidation-resistant Kv2.1 cysteine mutant. Neurons expressing the mutant are protected from neurotoxic Aβ peptide-stimulated apoptosis, and, interestingly, increased oxidation of Kv2.1 channels is observed in an Alzheimer's disease mouse model brain [134]. Oxidant-induced toxicity is postulated to proceed via defective Kv2.1 internalization and consequent Kv2.1 oligomer formation, leading to activation of the Src/JNK signaling pathway, although the data does not unequivocally place Kv2.1 oligomerization upstream of Src/JNK activation [135]. Further, while decreased K^+ currents are observed acutely following DTDP treatment in this study, the previously described, pro-apoptotic, Kv2.1 K^+ current increase is detected approximately three hours after oxidant treatment [58, 92, 93, 95, 96, 107]. The results from these studies, therefore, are not irreconcilable; in fact, there may be oxidation of Kv2.1 channels and reduction of currents immediately following oxidative insult [134, 135], followed by SNARE-dependent trafficking of Kv2.1 channels to the plasma membrane, resulting in K^+ current enhancement, caspase activation, and apoptotic cell death [52, 58, 92–95, 99–101, 106, 107, 109].

Evidence collected thus far from numerous studies certainly points to the existence of disparate cell death signaling events in neurons, potentially depending on the nature of apoptotic stimulus and neuronal cell type. However, the fact that several early (e.g. Zn^{2+} release) and late pro-apoptotic processes are elicited by such a diverse range of toxic stimuli, converging on Kv2.1-mediated K^+ current enhancement, strongly suggests that this step represents a key mechanism in neuronal apoptosis that could be therapeutically targeted. In this vein, the hepatitis C virus nonstructural protein 5A (NS5A) was recently discovered to attenuate pro-apoptotic Kv2.1 K^+ current enhancement in hepatocytes and cortical neurons [125, 136, 137]. This K^+ current blockade has been suggested to occur through NS5A-mediated inhibition of mixed lineage kinase 3 (MLK3), a MAP kinase kinase kinase which promotes the activation of p38 kinase [125]. As described above, p38 kinase is required for Kv2.1 S800 phosphorylation, enabling the pro-apoptotic K^+ current increase. However, in another study, NS5A was shown to block Src kinase-facilitated phosphorylation of the Y124 residue, without affecting channel phosphorylation of S800 by p38 kinase. In fact, pseudo-phosphorylation of Kv2.1 channels at S800 does not eliminate NS5A-induced inhibition of K^+ currents, whereas Kv2.1 channels expressing a phospho-mimetic substitution at Y124F are no longer susceptible to K^+ current attenuation by NS5A, strongly indicating that NS5A exerts its inhibition of Kv2.1 currents and neuroprotective effects through preventing Src kinase-mediated Y124 phosphorylation rather than by blocking p38 kinase-induced S800 phosphorylation [137]. This mechanism warrants further exploration, as NS5A could serve as a model for new neuroprotective agents specifically targeting pro-apoptotic Kv2.1-mediated K^+ currents.

Other Kv channels involved in neuronal damage and cell death—In addition to Kv2.1 channels, Kv1.5 channels, which also mediate delayed rectifying K^+ currents, have

been implicated in playing a role in neuronal cell death, particularly in the context of ischemia. Cell viability following ischemia is increased in rat cortical neurons lacking Kv1.5 and the auxiliary β-subunit Kvβ2 [138]. Ischemic preconditioning *in vivo*, which limits infarct size following lethal ischemia, produces a decrease in Kv1.5 and Kvβ2 mRNA and protein expression in rat cortex, while preconditioning in rat cortical neurons reduces delayed rectifying K^+ currents, suggesting that inhibition of Kv1.5 channel-mediated K^+ currents is neuroprotective, and may be a viable therapeutic strategy for reducing neuronal damage and cell death in ischemic stroke [139].

Apoptotic stimuli that enhance delayed rectifier Kv currents have also been shown to increase rapidly inactivating, A-type Kv channel-mediated K^+ currents (I_a), implicating these currents in promoting apoptosis, although the molecular mechanisms underlying these processes have not yet been thoroughly characterized [27, 42, 64, 70, 102, 140–145]. Activated macrophages and conditioned media from these inflammatory cells induce an increase in I_a and in apoptotic cell death in hippocampal neurons [143]. Similarly, the HIV-1 glycoprotein gp120 causes a rise in I_a and protein kinase C-mediated apoptotic cell death [69]. In both studies, the I_a increase and toxicity are attenuated by 4-AP. 4-AP also reduces low K^+/serum deprivation-mediated I_a current increase and augments viability in CGNs [64, 102, 145], and in UV-treated epithelial cells [71, 72]. However, 4-AP inhibits a relatively broad spectrum of Kv channels that mediate currents which include but are not limited to rapidly inactivating, A-type K^+ currents [5], underscoring the need for further exploration of the role of A-type K^+ currents in apoptotic cell death pathways.

A-type Kv currents may be particularly relevant in Alzheimer's disease (AD) as neurotoxic Aβ peptides have been shown to provoke an increase in I_a [140–142]. A specific inhibitor of Kv3.4 channels, which mediate I_a, reduces Aβ peptide-stimulated I_a enhancement and apoptotic nuclear morphology in hippocampal neurons [140]. Kv3.4 co-localizes with Aβ plaques, and its mRNA and protein expression is increased in AD mouse model brain, neurotoxic Aβ-treated PC-12 cells and rat hippocampal neurons, and in post-mortem frontal cortex tissue from patients with early and late AD [140, 141, 146]. mRNA and protein expression of Kv4.2, another channel responsible for A-type K^+ currents, is also enhanced in the cortex of rats whose spatial memory is compromised due to an intracerebroventricular injection of Aβ peptide [147]. Of note, increased Kv1.4 and Kv2.1 channel expression is also observed in the hippocampus of these Aβ-injected animals, and in CGNs, the neuroprotective peptide substance P blocks Aβ-induced increases in both delayed rectifier and rapidly inactivating K^+ currents, suggesting that both types of K^+ currents may be involved in Aβ-mediated neurotoxicity [56, 65, 142]. In contrast to these observations, several groups have suggested a normal physiological role for Aβ in modulating K^+ currents in a neuronal cell type-specific manner. One study has shown that aggregated, neurotoxic Aβ peptide has no effect on K^+ currents in cortical neurons or cerebellar granule neurons. Non-toxic, unaggregated Aβ peptide, however, increases Kv4.2 protein expression, and A-type and calcium-activated delayed rectifier K^+ currents in cerebellar granule neurons, while inhibition of endogenous Aβ production decreases Kv4.2 expression and inhibits K^+ currents [148, 149].

Kv1.1 channels have also been implicated in I_a-mediated neuronal apoptosis [150–152]. siRNA knockdown of Kv1.1 blocks I_a in CGNs, and prevents rises in I_a and rescues cell viability in low K^+/serum-deprived CGNs [150]. This apoptotic pathway is promoted by protein kinase C signaling, which is sufficient to activate I_a and apoptosis, effects that are mitigated by decreasing Kv1.1 expression. Further, Kv1-specific blockers reduce retinal ganglion cell degeneration after axotomy, while siRNA knockdown of Kv1.1 or Kv1.3 channels augments cell survival [151, 152].

III. Neuroprotective and neuroregulatory roles for Kv channels

A. Kv channels in ischemic neuroprotection

As described above, Kv2.1 channels critically contribute to oxidant injury-induced neuronal apoptosis. As the major mediators of delayed rectifying, outward K^+ currents in neurons, Kv2.1 channels also play a key role in maintaining intrinsic neuronal excitability, primarily by promoting slow after-hyperpolarization and by regulating action potential repolarization during high frequency stimulation [3, 14, 15, 93, 122, 123, 153–158]. Excitatory stimuli, such as glutamate treatment, exposure to convulsants, or ischemia, trigger dramatic changes in Kv2.1 voltage-gated activation, in addition to affecting their cellular localization (Fig. 1b). Emerging evidence indicates that these modifications aid in reducing neuronal excitotoxicity in the context of an injurious stimulus (Fig. 2, left).

Trimmer and coworkers first showed that Kv2.1 channels are maintained in highly phosphorylated, somatodendritic clusters in neurons [11, 122, 159, 160]. An excitatory stimulus induces bulk Kv2.1 dephosphorylation *in vivo*, in rats subjected to kainate-induced seizures or CO_2 exposure, for example, and *in vitro*, in cultured hippocampal or cortical neurons treated with glutamate, NMDA, or chemical ischemia. This dephosphorylation is thought to be critical in promoting two concomitant changes in the channels: dispersal of Kv2.1 channel clusters, and a hyperpolarizing shift in voltage-gated activation of the channel [9, 11, 16, 17, 131, 161–166]. Several lines of evidence support this concept. Phosphorylation of Kv channels promotes depolarizing shifts in voltage dependence, possibly due to an increase in the density of negative surface charges near the voltage sensor, explaining why dephosphorylation may induce a hyperpolarizing shift in the activation voltage [166]. Phospho-mimetic substitutions of seven, normally phosphorylated serine residues on the cytosolic Kv2.1 C-terminus eliminate the hyperpolarizing effects of excitatory stimuli, while serine-to-alanine mutations, which render the residues non-phosphorylatable, result in hyperpolarized voltage-gated activation. Similarly, blocking phosphorylation or inducing dephosphorylation of Kv2.1 channels results in channel declustering as well as hyperpolarizing voltage-gated activation [9, 167].

What signaling mechanisms govern these neuronal activity-induced changes in Kv2.1 channels? Several studies have demonstrated an early requirement for intracellular Zn^{2+} release and the Ca^{2+}/calmodulin-dependent phosphatase calcineurin. Chelating Zn^{2+} blocks the channel dephosphorylation and cluster dispersal, but not the hyperpolarizing shift in cortical neurons [163]. Ca^{2+} influx via a Ca^{2+} ionophore is sufficient to induce Kv2.1 dephosphorylation, declustering, and the hyperpolarizing activation shift, while inhibiting either Ca^{2+} influx or calcineurin activity blocks these changes in Kv2.1 in response to an excitatory stimulus in hippocampal and cortical neurons [9, 16, 161, 163–165]. One C-terminal serine residue in particular, Ser603, is highly sensitive to excitatory stimuli-induced, calcineurin-mediated dephosphorylation [165]. Recently, cyclin-dependent kinase 5 (Cdk5) was shown to phosphorylate this residue. Pharmacologic inhibition of Cdk5 kinase activity blocks Kv2.1 Ser603 phosphorylation and stimulates dispersal of channel clusters [167]. Further, neuronal activity blockade promotes precipitous increases in Ser603 phosphorylation, whereas activity-inducing stimuli trigger its dephosphorylation. As the phosphorylation status of Ser603 critically regulates voltage-dependent gating of the channel [9], this residue may serve as a bidirectional sensor of neuronal activity, mediating changes in Kv2.1 channel gating kinetics, and thus regulating neuronal excitability in response to excitatory or inhibitory stimuli.

A few groups have proposed that ischemia-induced changes in Kv2.1 channel properties may be dependent on specific neuronal-glial interactions. In the rat cerebral cortex, Kv2.1 channel clusters are located in the extra-synaptic zone, adjacent to astrocytic processes that

contain a high concentration of glutamate transporters [162, 168]. During ischemia, excessive glutamate accumulation in the extracellular space due to compromised glutamate uptake in damaged astrocytes may be responsible for promoting Kv2.1 channel dephosphorylation, cluster dispersal, and hyperpolarizing shifts in voltage-gated activation following NMDA receptor activation [17, 162, 169, 170]. Indeed, NMDA exposure or selective inhibition of astrocytic glutamate uptake in cortical or hippocampal slices is sufficient to promote neuronal Kv2.1 dephosphorylation. Accordingly, NMDA receptor antagonists block the dephosphorylation and hyperpolarizing gating shift activated by exogenous glutamate treatment or inhibition of astrocytic glutamate uptake [17, 162, 169, 170].

The hyperpolarizing shift in Kv2.1 channel voltage-gated activation is thought to reduce excitability and, consequently, excitotoxicity in neurons facing an ischemic or epileptic challenge. Sub-lethal chemical ischemia, which renders rat cortical neurons tolerant to subsequent NMDA receptor-mediated excitotoxicity [171, 172], induces Kv2.1 channel dephosphorylation and declustering, and produces a hyperpolarized shift in voltage-gated activation, implicating these channel modifications in promoting neuroprotection [163]. In hippocampal neurons, ischemia or glutamate treatment reduces spontaneous calcium transients, and spontaneous and current-evoked firing. Combining Kv2.1 channel block with either of these treatments promotes an increase in calcium overload and in firing frequency, demonstrating the requirement for Kv2.1 channel-mediated K^+ currents in reducing neuronal hyperexcitability within the context of ischemia [14, 16, 17].

As described above, the changes in Kv2.1 localization, phosphorylation status, and voltage gating have been observed in response to a range of excitatory stimuli *in vitro* and *in vivo*. Further, the dephosphorylation and hyperpolarization of voltage-gated activation have been linked to reduction of intrinsic excitability, and neuronal tolerance to otherwise-lethal injury. However, little is known about the mechanism and significance of Kv2.1 channel clustering, and the specific contribution of Kv2.1 declustering towards mediating neuronal hyperactivity. Four C-terminal residues, Ser583, Ser586, Phe587, and Ser589, are critical for Kv2.1 channel clustering. A C-terminal portion of Kv2.1 channels possessing all four of these residues confers Kv2.1-like clustered localization on other Kv channels subtypes, such as Kv2.2 and Kv1.5 [164, 173, 174]. Additionally, a cytoplasmic N-terminal/C-terminal interaction is required for proper channel surface expression and phosphorylation-driven modulation of activation kinetics [175]. As mentioned above, it has been postulated that channels in clusters located at extra-synaptic locations and adjacent to astrocytic processes may be important in sensing ischemia-induced glial dysfunction through glutamate signaling, while the channel declustering following calcineurin activity-dependent dephosphorylation would remove the Kv2.1 channels from the site of calcium release, initiating recovery and precluding a potentially detrimental, prolonged response. This cluster dispersal may occur through excess glutamatergic stimulation of extrasynaptic rather than synaptic NMDA receptors, prompting relocation of Kv2.1 channels to synaptic zones [162, 169, 170]. However, the cellular and molecular mechanisms involved in these processes require further exploration.

Tamkun and colleagues have proposed a somewhat different role for Kv2.1 channel clusters. They have reported that clustered Kv2.1 channels are non-conducting, but retain gating currents that display a hyperpolarized activation profile when compared to that of Kv2.1 ionic currents [176]. Because the channels would detect membrane depolarization at a lower threshold, these studies suggest that Kv2.1 channel clusters may serve as voltage sensors of neuronal activity that convey changes in membrane potential to cytosolic signaling pathways. Supporting this hypothesis is the demonstration that Kv2.1 channel clusters are insertion platforms for trafficking of Kv2.1 and other channels to the plasma membrane,

indicating that clustered Kv2.1 channels could be sites of depolarization-driven vesicle trafficking and neurotransmitter release [177–179]. In fact, Lotan and coworkers have shown that in neuroendocrine cells, Kv2.1 channels play an important role in depolarization-induced exocytosis that is independent of their ion conducting properties [180, 181]. However, these investigations have been conducted in recombinant cell expression systems and future studies examining these properties in neurons are necessary. Importantly, it was demonstrated recently that the majority of Kv2.1 channels in hippocampal neurons are non-conducting, lending further credence to the theory that Kv2.1 channel clusters may regulate key neuronal functions unrelated to their ion conducting properties [182].

Other Kv channels may be involved in reducing neuronal excitability and cell death in the context of ischemic injury. Following ischemia, Kv1-mediated delayed rectifying K^+ currents increase in large aspiny neurons, which are highly resistant to anoxic cell death [183]. Ischemic injury shortens spike duration in these neurons, which could limit Ca^{2+} influx and thus mitigate excitotoxicity. Importantly, blocking Kv1 channel function restores action potentials to normal duration in anoxia-treated cells, suggesting a role for Kv1-facilitated K^+ currents in regulating neuronal excitability in ischemia. Further, increased Kv1.2 subunit expression is observed in rat brain following transient focal ischemia [184]. An ischemic injury-promoted rise in A-type K^+ currents may also be responsible for decreasing excitability and thus limiting excitotoxic cell death in large aspiny neurons [185]. Medium spiny neurons, which are more vulnerable to ischemic neuronal damage, do not manifest an increase in I_a. Importantly, over-expression of I_a-mediating Kv1.4 or Kv4.2 channels in medium spiny neurons reduces oxygen-glucose deprivation-induced toxicity, while neurons lacking Kv1.4 or Kv4.2 channel expression are more sensitive to ischemic cell death [185]. Increased I_a is also observed in CA1 hippocampal neurons after transient forebrain ischemia [121].

B. Loss of Kv1 or Kv7 channel function mediates neuronal hyperexcitability disorders

Kv1 and Kv7 encode K^+ channels that are also important contributors to neuronal excitability, with functions including maintenance of resting membrane potential, action potential repolarization and after-hyperpolarization, and regulation of neurotransmitter release [2, 12, 13, 186–204]. Accordingly, loss of proper function of these channels is generally associated with hyperexcitability phenotypes such as episodic ataxia type 1 (EA-1) and epilepsy.

Kv1 channels and EA-1—EA-1 is a rare, autosomal dominant disorder characterized by generalized ataxia attacks and spontaneous muscle quivering [205]. In 1994, Browne and colleagues discovered four mutations in Kv1.1 in each of four families that had multiple members affected by EA-1[206]. Since then, more than a dozen Kv1.1 mutations have been identified in EA-1 patients with variable symptomatic presentations [206–222]. Most of these are point mutations in highly conserved channel residues that generate Kv1.1 loss-of-function phenotypes of varying degrees. For several EA-1 Kv1.1 mutations, the extent of disease in patients correlates to the magnitude of altered channel properties in *Xenopus* oocyte expression experiments, strongly implicating Kv1.1 channel dysfunction in the pathogenesis of EA-1 [210, 211, 223, 224].

When expressed in oocytes or mammalian cells, the majority of EA-1 Kv1.1 channel mutants exhibit undetectable or reduced K^+ currents, compared to expression of wild-type Kv1.1 channels [207–211, 214, 217]. Dysfunctional post-translational modifications and improper plasma membrane trafficking may mediate the reduced currents [217, 223–226]. R417stop Kv1.1 channels, for example, lack a C-terminal targeting determinant, and

undergo inefficient phosphorylation and N-glycosylation, forming large intracellular membranous aggregates in COS cells and mammalian neurons [225].

Other modifications that are observed in several EA-1 Kv1.1 mutant channels expressed in oocytes, such as slowed activation kinetics and a depolarizing shift in voltage-gated activation, implicate gating defects as the source of Kv1.1 dysfunction [7, 208–210, 214, 224, 227–230]. Given the importance of Kv1 channels in limiting neuronal excitability, these alterations in Kv1.1 channel kinetics would be expected to increase neuronal activity, providing a possible explanation for the hyperexcitable EA-1 phenotype. Indeed, expressing Kv1.1 R417stop or T226R mutant channels in hippocampal neurons elicits a lower current threshold for action potential firing, and increased neurotransmitter release compared to expression of wild-type Kv1.1 channels [196]. Another EA-1 Kv1.1 mutation, V408A, confers a range of channel gating defects in recombinant cell systems [7, 206, 208, 209, 226, 227, 229, 230]. V408A heterozygous mice show increased frequency and amplitude of cerebellar Purkinje cell inhibitory post-synaptic currents, spontaneous neuromuscular activity, and importantly, stress-induced motor deficits, similar to EA-1 patients [212, 231]. Two other Kv1.1 mutant mouse models that demonstrate variable EA-1 phenotypes have also been reported [232, 233]. However, as most EA-1 Kv1.1 mutational analysis has been conducted in oocyte expression systems, a thorough investigation into the biophysical properties of neurons expressing EA-1 Kv1.1 channel mutations is warranted, given the key role Kv1.1 dysfunction likely plays in this disorder.

Kv1 channels and epilepsy—A subset of patients with familial EA-1 is affected with epileptic seizures, suggesting that Kv1 channel dysfunction may play a role in the pathophysiology of epilepsy [210, 211, 224]. Several reports have also identified patients who are heterozygous for Kv1.1 mutations, and suffer epileptic seizures concomitant with other neurologic abnormalities such as cognitive delay [234, 235]. Injection of dendrotoxin, a Kv1 channel antagonist, into rat hippocampus induces neuronal hyperexcitability, seizures, and cell death [236, 237]. Importantly, Kv1.1-null mice exhibit an epileptic phenotype, undergoing spontaneous behavioral seizures once or twice every hour, which are consistently accompanied by ictal electroencephalographic (EEG) patterns. The threshold for seizure initiation is determined by Kv1.1 gene dosage. Homozygous Kv1.1-null mice are more rapidly susceptible to convulsant-induced seizures than heterozygous Kv1.1-null mice, which are in turn more sensitive than their wild-type littermates [238, 239]. On the cellular level, loss of Kv1.1 channel function in Kv1.1-null mice produces a neuronal hyperexcitability phenotype that is commonly observed in epilepsy models, in the hippocampus, a brain region highly susceptible to epileptogenic activity [13, 196, 238, 240–247]. Neuronal hyperexcitability in Kv1.1-null mice has also been observed in myelinated nerves [242, 243], cerebellar basket neurons [244, 248], and medial nucleus of the trapezoid body neurons in the brainstem [13, 245]. Decreasing network excitability by impairing P/Q-type Ca^{2+} channel function, or providing inhibitory synaptic input by grafting medial ganglionic GABAergic neuron precursors into the cortex of Kv1.1-null mice, lowers the duration and frequency of spontaneous seizures [246, 249]. In agreement with these findings, in a rodent model of tetanus toxin-induced neocortical epilepsy, lentiviral-mediated delivery of Kv1.1 channels to motor cortex pyramidal neurons along with, or one week after, tetanus toxin injection, attenuates neuronal hyperexcitability and prevents EEG-measured epileptic activity [247].

Kv1.2 channel dysfunction in neuronal hyperexcitability has also been reported. Early studies revealed that Kv1.1 α-subunits co-localize and likely form heteromers with Kv1.2 channel subunits in most parts of the brain where both channels are expressed [186, 250–254]. When co-expressed in fibroblast cells, trafficking of EA-1 R417stop Kv1.1 mutant channels and wild-type Kv1.2 channels is impaired, implying heteromerization and

suggesting that loss of Kv1.2 channel function, as a result of Kv1.1 mutations, may play a role in familial EA-1 [225]. Further, most pharmacologic agents that block Kv1.1 channels and induce neuronal hyperexcitability, inhibit Kv1.2 channels as well [189, 197, 236]. Several studies indicate that loss of Kv1.2 channel function alone is sufficient to promote neuronal hyperexcitability, and may mediate epileptic pathology. For example, Kv1.2-specific inhibitors instigate hyperexcitability in cerebellar and brainstem neurons [186, 192]. Additionally, decreased Kv1.2 protein expression, which can be rescued by anti-convulsant agents, is detected in the hippocampus of seizure-prone or convulsant-treated mice [232, 255]. Although no Kv1.2 mutations have been detected in patients with epilepsy, Kv1.2-null mice display increased susceptibility to seizures and decreased life span [256]. In contrast to studies demonstrating impairment of Kv1.2 channel function due to Kv1.1 dysfunction in EA-1 [225], some investigators have suggested that Kv1.2 subunits may play a compensatory role in neurons when Kv1.1 function is compromised [13].

As described above, neuronal hyperexcitability due to Kv1 channel loss-of-function is associated with the pathogenesis of some forms of epilepsy. However, epilepsy is a complex disorder that encompasses network excitability abnormalities arising from dysfunction of a wide range of molecular components in various cell types and in different brain regions. The effects of reduced Kv1 K^+ currents on epileptic pathology, therefore, may be varied depending on the location of the epileptogenic focus, and the affected neuronal cell type. Kv1.1 channel loss-of-function is associated with promotion of epileptic activity in the hippocampus, whereas in an animal model of absence epilepsy associated with defects in thalamocortical circuitry, eliminating Kv1.1 channel function rescues the seizure phenotype [249]. Moreover, in cortical, fast-spiking inhibitory neurons, decreased intrinsic excitability via up-regulation of Kv1.1 channel activity may promote seizure susceptibility [257].

Spinal cord injury and multiple sclerosis are additional examples of clinical disorders in which increased neuronal signaling via blockade of Kv1 channel activity may be beneficial. In these diseases, outward K^+ currents through exposed Kv1 channels along damaged, demyelinated axons may impair action potential propagation. In fact, fampridine, a slow-release formulation of the Kv channel blocker 4-AP, was recently approved by the Food and Drug Administration (FDA) to improve walking in patients with multiple sclerosis [258].

A success story: Kv7 channel activators in the treatment of epilepsy—

Heteromeric Kv7.2/Kv7.3 channels mediate the low-voltage-activated, slowly activating, non-inactivating M currents in central and peripheral neurons [12, 259, 260]. These channels critically contribute to the after-hyperpolarizing potential, aid in maintaining resting membrane potential and firing thresholds, and importantly, reduce intrinsic burst firing and repetitive action potential firing in response to excitatory stimuli [12, 198, 200, 201, 203, 259, 261–265]. Increasing Kv7 channel function decreases excitability, while suppressing Kv7 channel K^+ currents enhances excitability in hippocampal pyramidal, and superior cervical and dorsal root ganglionic neurons, and promotes epileptiform activity in hippocampal neurons [202, 264–271]. Mice expressing dominant negative mutant Kv7.2 channels display spontaneous seizures, behavioral hyperactivity, and increased hippocampal neuronal excitability and cell death [202].

Mutations in Kv7.2 and Kv7.3 channels are associated with sporadic neonatal seizures, and benign familial neonatal convulsions (BFNC), an autosomal dominant disease of frequent generalized epileptic seizures beginning in the first week of life and generally disappearing within a few months [272–279]. However, several neonatal seizure-associated Kv7.2 mutations are linked to more severe abnormalities in patients, such as increased risk of seizures and therapy-refractory epilepsy later in life, epileptic encephalopathy, myokymia, and slowed psychomotor development [280–287]. These studies further confirm the

involvement of Kv7 channel dysfunction in some forms of epilepsy, and implicate central and peripheral neuronal Kv7 channel dysfunction in diverse clinical phenotypes generally correlating with neuronal hyperexcitability.

Most Kv7.2 and Kv7.3 mutations associated with BFNC and more severe disorders occur in the cytosolic C-terminus, voltage-sensing domain, or pore-forming region. Expression of mutant channels in oocytes or hippocampal neurons reveals a range of channel defects. Several mutations, particularly those in the voltage-sensing domain of the channel, confer slower activation kinetics and depolarizing shifts in voltage-gated activation [274, 285, 286, 288–290], while C-terminal frameshift, insertion, or truncation mutant Kv7 channels exhibit reduced current amplitudes due to intracellular trafficking defects, inefficient membrane targeting, or increased degradation [274, 290–294]. Two transgenic BFNC mouse models, expressing Kv7.2 A306T or Kv7.3 G311V channels, present with generalized seizures likely of hippocampal origin, but display minimal synaptic reorganization or permanent neuronal damage in the hippocampus, recapitulating the major features of human BFNC. Additionally, Kv7 current density in homozygous mutant hippocampal slices is decreased, while deactivation kinetics are accelerated [271, 295]. Heterozygous adult mice show reduced threshold to electroconvulsant-induced seizures and similar, albeit less severe, Kv7 current alterations to homozygous mice.

Retigabine, also known as ezogabine, is a Kv7 channel activator that was approved by the FDA in 2011 for adjuvant treatment of partial-onset seizures in adults [277, 296–299], following demonstration of seizure reduction in animal models of epilepsy [300, 301] and in human clinical trials [302–304]. Retigabine enhances Kv7 channel activation by inducing a hyperpolarizing effect on voltage-gated channel activation. This mechanism of action limits neuronal excitability, as evidenced by the reduction of depolarization-induced action potential firing in neurons treated with retigabine [305, 306]. Since the discovery of retigabine's anticonvulsant properties, numerous novel Kv7 activators are being explored for their therapeutic potential in treating epilepsy [277, 307–311]. Notably, in addition to epilepsy, Kv7 channel activators may also be effective in treating other diseases in which neuronal hyperexcitability represents a primary pathological component, including inflammatory or neuropathic pain [312–314], tinnitus [315], as well as neuropsychiatric disorders [316, 317].

D. A role for Kv channels in neuro-cardiac regulation

Recently, Kv channels have been associated with sudden unexplained death in epilepsy (SUDEP), an event which occurs in two to eighteen percent of chronic, idiopathic epileptic patients, and is thought to arise from neurologically-driven cardiac dysfunction [318–321]. Kv1.1-null mice display a range of cardiac abnormalities, some of which are ameliorated by inhibiting parasympathetic innervation from the vagus nerve (where Kv1.1 is normally expressed) to the heart [322]. Additionally, about half of Kv1.1-null mice die suddenly between the third and fourth week of life, with several of these mice exhibiting severe generalized seizures prior to death [238, 239], suggesting that they may be experiencing SUDEP. In another study, mice carrying a human long QT syndrome mutation in Kv7.1 channels exhibit cardiac arrhythmias and epileptiform activity, with a mouse in this report experiencing seizures that developed into status epilepticus accompanied by severe cardiac abnormalities, culminating in cardiac arrest [319]. These studies implicate Kv channels in the pathophysiology of a disastrous complication of epilepsy, highlighting the importance of Kv channels in neurological regulation of cardiac function.

IV. Conclusion

The Kv channel family is a diverse group of channels mediating outward K^+ currents that play important roles in normal and pathological processes in neurons. Increased efflux of currents through Kv2.1 channels promotes apoptotic signaling (Fig. 1a and Fig. 2, right), while neuronal activity-regulated alterations in channel localization, phosphorylation, and voltage-gated activation reduce neuronal excitability, suggesting a role for these modifications in neuroprotection against ischemic or epileptic injury (Fig. 1b and Fig. 2, left). Loss of Kv1 or Kv7 promotes neuronal hyperexcitability, which manifests pathological consequences in disorders such as epilepsy or EA-1. Further, Kv channelopathy is likely to contribute to the pathophysiology of several other neurological diseases, including spinal cord injury, multiple sclerosis, inflammatory and neuropathic pain, and neuropsychiatric disorders. Significant challenges, however, exist for developing Kv channel-directed therapeutic agents. Kv channels are widely expressed in most organs, including the brain, heart, liver, lungs, pancreas, and kidney [5, 310]. As such, drugs targeting these channels in neuronal diseases may cause potentially harmful, off-target effects. Additionally, the precise molecular composition of Kv channels mediating specific K^+ currents in different neuronal cell types is often difficult to pinpoint, given the diversity of α-subunit heteromerization patterns and the presence of modulatory binding partners. However, as evidenced by the successful clinical use of retigabine to activate Kv7 channels in the treatment of epilepsy, targeting Kv channels is likely to be a viable therapeutic strategy for a wide range of neurological diseases in the near future.

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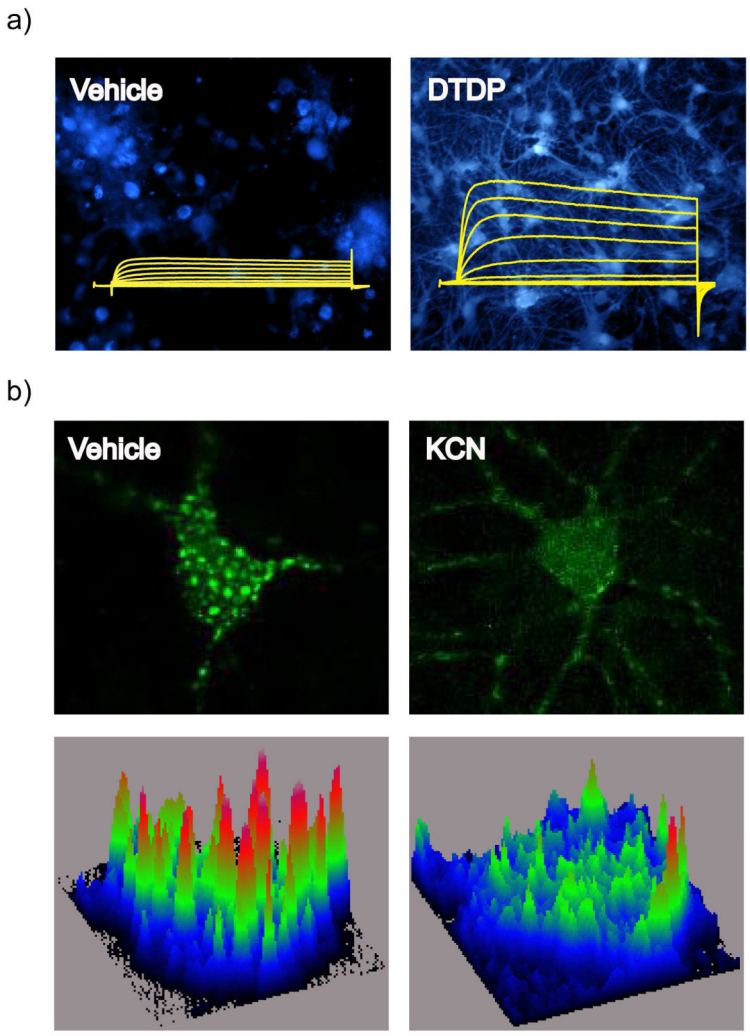

Fig. 1.

Kv2.1 channel-mediated pathways of neuronal apoptosis **(right)** and neuronal tolerance **(left). (Right)** An oxidant stimulus induces the release of Zn^{2+} from mitochondrial stores and metal-binding proteins, such as metallothionein (MT). Zn^{2+} activates ASK-1, leading to the phosphorylation and activation of p38 kinase. Zn^{2+} also inhibits PTPε and activates Src kinase. The combined action of both kinase systems results in increased phosphorylation of Kv2.1 channel residues S800 (by p38 kinase activation) and Y124 (by Src kinase activation and PTPε inhibition). Oxidant injury additionally stimulates release of Ca^{2+} from endoplasmic reticulum (ER) stores, which activates CaMKII. Coordinate phosphorylation of Kv2.1 channels at S800 and Y124, and the interaction of CaMKII with syntaxin, facilitate Kv2.1 channel-syntaxin binding, and subsequent channel delivery to the plasma membrane. Increased K^+ currents through these newly inserted Kv2.1 channels permit the completion of the apoptotic signaling pathway by mediating cytoplasmic K^+ loss. **(Left)** Neuronal activity or sub-lethal ischemia induces Ca^{2+} influx through glutamate receptors or intracellular Ca^{2+} release from the ER, and release of free Zn^{2+} from metal-binding proteins. Ca^{2+} increases calcineurin activity, leading to dephosphorylation and declustering of Kv2.1 channels. These changes are accompanied by a hyperpolarizing shift in the channel's voltage-gated activation profile. Zn^{2+} is required for channel de-clustering and the voltage-gated activation shift, but not for Kv2.1 channel dephosphorylation. These changes in Kv2.1 channels reduce

neuronal excitability in the context of an ischemic or epileptic insult, and render neurons tolerant to excitotoxic or other forms of injury

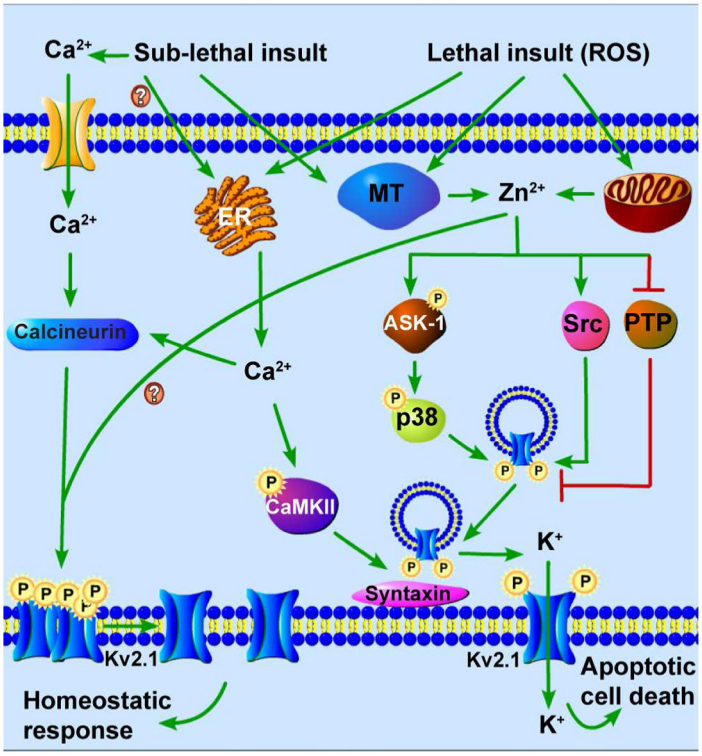

Fig. 2.

a) Oxidant exposure in neurons liberates Zn^{2+} from intracellular metal binding proteins (as detected by an increase in fluorescence using a Zn^{2+}-sensitive indicator such as FluoZin-3), which produces a pro-apoptotic enhancement of Kv2.1 K^+ currents. Reprinted with permission and adapted from [124] b) In contrast, neuronal activity or sub-lethal ischemia stimulates Kv2.1 channel dephosphorylation-dependent declustering, which, along with hyperpolarizing voltage-gated activation, induces neuronal tolerance to ischemic or epileptic challenge. Shown are confocal micrographs of rat cortical neurons transfected with plasmid vectors encoding GFP-labeled Kv2.1 channels. Below are fluorescence surface intensity maps, used to quantify the number of clusters present in neurons [163]

Table 1

Kv channels implicated in neuronal pathology and human neurological disease

Subtype	K^+ current type	Associated pathology	Sources
Kv1	Delayed rectifying (Kv1.1–1.3, Kv1.5–1.8), A-type (Kv1.4)	Episodic ataxia, epilepsy (Kv1.1, Kv1.2, Kv1.4) Neuronal apoptosis (Kv1.1, Kv1.3) Ischemic cell death (Kv1.5)	7,13,192,196,197,206–257,322,323 150–152 138,139
Kv2	Delayed rectifying	Neuronal apoptosis (Kv2.1)	37,46,48,51,52,58, 66,91–96,99–101,106–109,125–137
Kv3	Delayed rectifying (Kv3.1, Kv3.2), A-type (Kv3.3, Kv3.4)	Alzheimer's disease (Kv3.4) Epilepsy (Kv3.2)	140,141,146 324
Kv4	A-type	Alzheimer's disease (Kv4.2) Epilepsy (Kv4.2, Kv4.3)	147–149 323, 325–330
Kv7	Delayed rectifying, M-type	Epilepsy, tinnitus, pain, neuropsychiatric disorders (Kv7.1–7.5)	202,264–317,319