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REVIEW

The versatile Kv channels in the nervous system: actions beyond action potentials

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Abstract

Voltage-gated K^+ (Kv) channel opening repolarizes excitable cells by allowing K^+ efflux. Over the last two decades, multiple Kv functions in the nervous system have been found to be unrelated to or beyond the immediate control of excitability, such as shaping action potential contours or regulation of inter-spike frequency. These functions include neuronal exocytosis and neurite formation, neuronal cell death, regulation of astrocyte Ca^{2+}, glial cell and glioma proliferation. Some of these functions have been shown to be independent of K^+ conduction, that is, they suggest the non-canonical functions of Kv channels. In this review, we focus on neuronal or glial plasmalemmal Kv channel functions which are unrelated to shaping action potentials or immediate control of excitability. Similar functions in other cell types will be discussed to some extent in appropriate contexts.

Keywords Voltage-gated K^+ channel · Neuron · Glia · Ca^{2+} · Nervous system · Non-canonical

Introduction

During an action potential, voltage-gated K^+ (Kv) channel opening repolarizes excitable cells by allowing K^+ efflux [1]. The ion-conducting α-subunit of Kv channel is composed of four polypeptide (tetramer) clustering around a central pore [2]. Each polypeptide contains six transmembrane helices (S1–S6), with the S5–S6 linker being a pore-forming P-loop, and the P-loops from the four polypeptides constitute the K^+ selectivity filter [3, 4]. Kv channel α-subunits usually form complexes with auxiliary subunits which serve to modulate channel trafficking and gating [3–5].

Depending on sequence homology, Kv channels are classified into Kv1 to Kv12 subfamilies. Each Kv subfamily has a number of subtype members, and Kv subfamily members display distinct gating modes. Delayed rectifiers, such as Kv1.2, Kv2.1 and Kv3.1, exhibit very slow inactivation [1, 4]. They are, in general, blockable by millimolar levels of tetramethylammonium ions (TEA). A-type K^+ channels, exemplified by members such as Kv1.4, Kv3.4 and Kv4.2, are fast-inactivating Kv channels [1, 4]. These are preferentially blocked by 4-aminopyridine (4-AP). In addition to their functions as repolarizing channels, A-type K^+ channels, because of their gating characteristics, regulate inter-spike frequency during neuronal firing [1]. Also modulating neuronal firing frequency are Kv7 channels (Kv7.2 and 7.3, the so-called M-currents) [6]. Different neuron types express their own sets of Kv channels to fulfill their roles, allowing the neuron to regulate their patterns of excitability.

Over the last two decades or so, multiple Kv functions in the nervous system have been found to be unrelated to or beyond the immediate control of excitability (shaping action potential contours or regulation of inter-spike frequency). These functions include exocytosis, neurite formation, regulation of astrocyte Ca^{2+}, glial cell or glioma proliferation and neuron death. In this review, we focus on neuronal or glial Kv channel functions which are unrelated to shaping action potentials or immediate control of excitability. Similar functions in other cell types will be discussed to some extent where appropriate. Kv channels are also expressed in the mitochondrial inner membrane, and they control

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mitochondrial potential. We will restrict our review only to plasma membrane Kv channels, and readers interested in mitochondrial Kv channels are referred to several reviews [7–10].

Role of Kv channels in exocytosis

Depolarization at the synapse triggers neuronal exocytosis of neurotransmitters. While traditional views hold that Kv channel activities regulate (suppress) neuronal vesical release by causing repolarization or hyperpolarization, Kv channels were first shown to be important in facilitating exocytosis in a manner independent of their function of conducting K^+ ions [11, 12]. Using PC12 cells as a neuroendocrine model and release system, Lotan's group has shown that a Kv2.1 mutant (Kv2.1 W365C/Y380T), which has non-conducting pores, could facilitate depolarization-evoked exocytosis as equally well as wild-type Kv2.1. This mutant binds syntaxin, a component of the exocytotic SNARE complex, as equally well as the wild type does. Exocytosis is inhibited when Kv2.1 fails to interact with syntaxin, either by introducing competing peptide or deletion of a Kv2.1 domain (C1a domain of the cytoplasmic C terminus aa 411–522) responsible for binding syntaxin. These observations suggest that Kv channels promote exocytosis not because of its ion conduction, but via interaction with syntaxin. It is postulated that Kv2.1 binds preferentially to and stabilizes the open configuration of syntaxin, which facilitates docking and priming of vesicles [for a review see ref. 12]. The same group later reported that such K^+ flux-independent Kv2.1 facilitation of exocytosis also occurs in rat dorsal root ganglion neurons and bovine adrenal chromaffin cells [13]. This facilitation, also requiring syntaxin binding, was shown to augment the rate of vesicle recruitment without altering the readily releasable vesicle pool size.

Recent findings in pancreatic β-cells have revealed yet another interesting feature of Kv2.1 in promoting exocytosis. Clustering of Kv2.1 channels, but not ion flux or syntaxin binding, is important in facilitating depolarization-evoked insulin release in INS 832/13 cells and human β-cells [14]. A truncated Kv2.1 channel (Kv2.1-ΔC318), which loses its ability to form channel clusters but still retains ion-conducting function and syntaxin 1A binding, could not facilitate granule recruitment or exocytosis. Further, a more recent study showed clusters of Kv2.1 on the β-cell plasma membrane, by binding Syn-3 through its C-terminal C1b domain, facilitate recruitment of newcomer insulin secretory granules [15]. C1b-deleted mutant (Kv2.1ΔC1b), while still keeping ion conducting function albeit having smaller current amplitude, lost its ability to facilitate recruitment of newcomer granules. Whether such Kv2.1-mediated facilitation mechanisms also take place in neurons is yet to be examined.

Role of Kv channels in neurite formation

Neuritogenesis is essential in forming the neuronal circuitry during development, neurogenesis in adulthood, and neuronal repair after injury. Several ion channels are implicated in neuritogenesis, namely, TRPC5, voltage-gated Na^+ channels (VGSC) and voltage-gated Ca^{2+} channels (VGCC) [16–18]. McFarlane and Pollock [19] were the first to report the involvement of Kv channels in axon development. Blocking Kv channels of *Xenopus* retinal ganglion cells (RGC) and their growth cones with 4-aminopyridine (4-AP) applied to the developing *Xenopus* optic projection inhibited RGC axon extension. McFarlane's group has also found that *Xenopus* RGC somata, axons, and growth cones express Kv1.3-, Kv1.5-, Kv3.4-, and Kv4.2-like subunits [20]. The same group later on showed that, intriguingly, 4-AP and tetraethylammonium (TEA) inhibited and stimulated *Xenopus* RGC neurite growth, respectively [21]. To understand whether these differential effects are related to cytosolic Ca^{2+} concentration, they demonstrated while 4-AP stimulated spontaneous Ca^{2+} transients in *Xenopus* RGC, TEA suppressed them. It is therefore suggested that 4-AP- and TEA-sensitive Kv currents have differential effects (inhibition and stimulation, respectively) on spontaneous Ca^{2+} transient generation, the frequency of which is inversely related to neurite extension.

A similar finding was obtained in chick embryonic spinal neurons, where blockade of Kv3.4 channels augments the amplitude and frequency of Ca^{2+} influx via VGCC, with a consequent reduction in axon growth [22]. These findings suggest that Kv channel opening suppresses growth cone membrane excitability, curbing $[Ca^{2+}]_i$ at a concentration most optimal for axon growth.

However, the above mechanism, that is, Kv channel-membrane excitability-Ca^{2+} signaling, may not be a universal model. In our previous report, mouse neuroblastoma N2A cells were used to examine how the cAMP signaling pathway stimulates neuritogenesis [23]. N2A cells are frequently used model in the study of neuronal differentiation [24–26]. Pharmacological block of Kv channels or knockdown of Kv1.1, Kv1.4 and Kv2.1 gene expression using siRNA in N2A cells reduced Kv currents and inhibited neuritogenesis. N2A cells do not have spontaneous Ca^{2+} transients, but only display cilnidipine-blockable high KCl-triggered Ca^{2+} signals. cAMP-induced neurite formation was not affected by cilnidipine or tetrodotoxin, suggesting that neurite formation does not require VGCC and VGSC activities. Since K^+ concentration inside the neurite was lower than that inside the cell body, and valinomycin, a K^+ ionophore, alone could induce neurite formation, Kv channel-mediated K^+ efflux could be an

underlying mechanism for neuritogenesis. Lowered cytosolic K^+ concentration might favor molecules promoting neurite formation.

It is still unknown how exactly Kv channels interact with molecules directly involved in neurite formation. AMIGO-1 is a single-pass transmembrane protein which acts as a homophilic cell adhesion molecule to promote neurite generation during development [27, 28]. Interestingly, AMIGO-1 has recently been shown to be an auxiliary subunit of adult brain Kv2.1 channels. AMIGO-1 is co-expressed and co-localized with Kv2.1 and Kv2.2 in diverse neuronal populations throughout the mouse brain and in diverse mammalian species; in adult brain, there is no AMIGO-1 expression other than that co-localized with Kv2α subunits [29]. At which Kv channel domain AMIGO-1 interacts and how this interaction promotes neuritogenesis are yet to be determined.

Regulation of Ca^{2+} entry in astrocytes

In addition to the roles of nourishing and providing mechanical support for the neurons, astrocytes also serve to clear neurotransmitters and maintain extracellular K^+ homeostasis [30, 31]. Astrocytes are considered non-excitable cells, as they do not generate action potentials. Astrocytes nevertheless exhibit "excitation" as cytosolic Ca^{2+} signaling, which is generated by stimulation of neurotransmitter receptors, some of which are ionotropic (Ca^{2+}-permeable) or metabotropic (generation of inositol-1,4,5-trisphosphate) receptors [32]. Stimulated astrocytes may release gliotransmitters such as ATP, glutamate and d-serine, which could in turn modulate synaptic transmission [33, 34]. Thus, astrocytes are not simply supportive cells, but actually play active roles in regulating neural processes. Intriguingly, astrocytes have robust Kv channel expression [31]; however, the latter's functions in astrocytes are only poorly understood.

Current injection into spinal cord astrocytes elicits an "action potential-mimicking voltage overshoot" [35]. Subsequent repolarization is suppressed by 4-AP, suggesting that Kv channels may play a role in regulating membrane potential. As membrane potential changes presumably modulate Ca^{2+} entry (depolarization and hyperpolarization decreases and increases, respectively, the electrical driving force for Ca^{2+} influx in non-excitable cells), it is possible that Kv channel activities could regulate Ca^{2+} influx in astrocytes.

We examined whether Kv channel activities regulated Ca^{2+} signals in neonatal rat cortical astrocytes [36]. Voltage-clamp experiments showed that neonatal rat cortical astrocytes expressed both delayed rectifiers and A-type Kv channels. The block of delayed rectifier Kv channels by TEA and A-type Kv channels by quinidine profoundly inhibited store-operated Ca^{2+} influx triggered by cyclopiazonic acid (CPA, inhibitor of sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase). TEA and quinidine in combination, but not alone, substantially enhanced current injection-triggered membrane potential overshoot (depolarization). These results suggest that both delayed rectifier and A-type Kv channels are needed to regulate astrocyte Ca^{2+} signaling via controlling the membrane potential. Our working hypothesis is that Ca^{2+} influx causes depolarization, which would trigger Kv channel opening. The latter allows K^+ efflux, thus curbing depolarization; and since

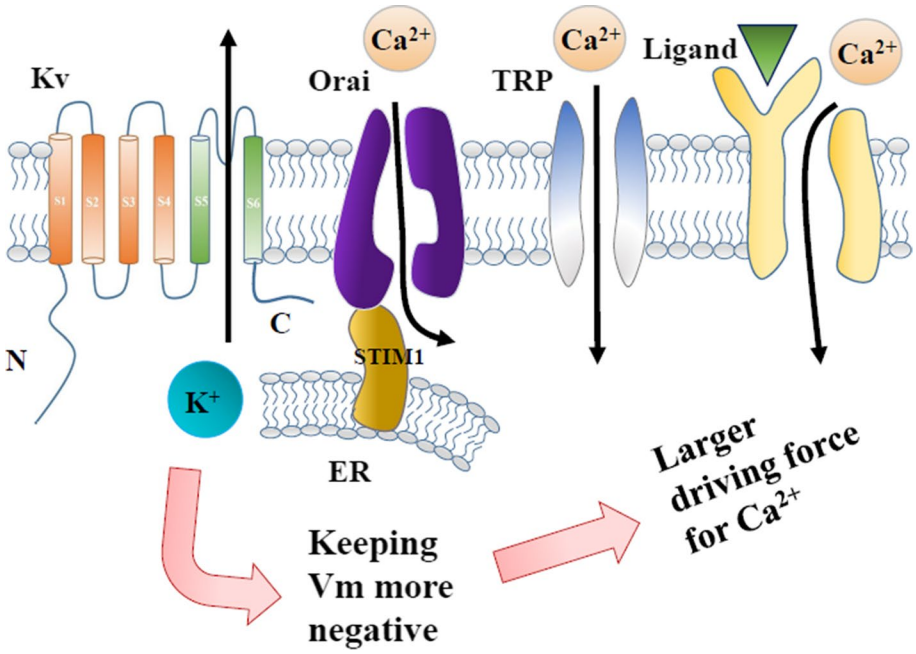

Fig. 1 Regulation of Ca^{2+} influx by Kv channels in non-excitable cells. Opening of Kv channels allows K^+ efflux, which keeps the membrane potential low. The latter condition provides favorable electrical driving force for influx of Ca^{2+}. In this diagram, the Ca^{2+} channels shown belong to non-voltage-gated types which are present in non-excitable cells such as astrocytes. These channels include Orai (allows store-operated Ca^{2+} entry when coupled with STIM1 from endoplasmic reticulum), various TRP channels and ligand-gated channels

depolarization decreases the electrochemical driving force for Ca^{2+} influx in the non-excitable astrocyte, curbing of depolarization by Kv channels favors Ca^{2+} influx (Fig. 1).

How Kv channels regulate Ca^{2+} influx in non-excitable cells is also exemplified in embryonic chicken limb bud chondrogenic cells, where both frequency and amplitude of spontaneous Ca^{2+} oscillations are repressed by 10 mM TEA, the latter causing suppression of chondrocyte Kv currents by 73% [37]. The same work also shows that TEA could inhibit chondrocyte proliferation and cartilage production. Another example is human platelet [38]. Real-time PCR revealed the presence of Kv1.3 as the only Kv α-subunit. Consistently, electrophysiological examination of human megakaryocytes (from which platelets are derived) showed the presence of outward currents, which were completely inhibited by margatoxin, a selective inhibitor of Kv1.3. Margatoxin also caused a slow depolarization of megakaryocytes. In human platelets, margatoxin suppressed ionotropic $P2X_1$ receptor-triggered Ca^{2+} influx and delayed the onset of thapsigargin-induced store-operated Ca^{2+} entry [38]. These data suggest that Kv channels regulate Ca^{2+} influx via modulation of the membrane potential.

Proliferation in glia

Kotecha and Schlichter [39] have studied microglia tissue printed directly from the hippocampus of brain slices of 5- to 14-day-old rats. The microglia, expressing a large Kv1.5-like current, were non-proliferative. The microglia only became highly proliferative after a few days of culture and, interestingly, these cells expressed prominently Kv1.3. In agreement, agitoxin-2 (AgTx-2, a specific and potent Kv1.3 blocker) and 4-AP strongly inhibited proliferation. These data suggest that hippocampal microglia proliferation requires a switch from Kv1.5 to Kv1.3.

In another study [40], it was shown that Kv1.4 was absent in axons, but present in astrocytes, oligodendrocytes, and oligodendrocyte progenitor cells in normal and injured rat spinal cord white matter. Kv1.4 protein was significantly increased 6 weeks after spinal cord injury (SCI) in spinal cord white matter. Consistently, in situ hybridization showed that Kv1.4 mRNA increased in spinal cord white matter after SCI. Upregulation of Kv1.4 channels may enhance glial proliferation after SCI. However, in 1-day-old mouse brain microglia, opposite results have been obtained, showing that suppressing Kv1.3 expression by applying anti-sense oligonucleotides enhanced proliferation by twofold [41].

Pérez-García's laboratory has studied the effects of heterologous expression of Kv1.3 and Kv1.5 channels in HEK cells [42]. Interestingly, the expression of Kv1.3 promotes while that of Kv1.5 suppresses proliferation. Remarkably, the promotion of proliferation is achieved by expressing mutant, non-conducting, Kv1.3 channels. However, Kv1.3 mutants, whose voltage dependence of gating was inhibited, do not stimulate growth. These data imply that Kv1.3 promotes cell growth not by permitting K^+ flux, but by providing a voltage-dependent conformational change mechanism. In a later work, the same laboratory reported that two residues (Tyr-447 and Ser-459) at the C terminus are critical for proliferation [43]. They have delineated the mechanism: conformation change of the Kv1.3 from the closed to open form causes a MEK-ERK1/2-dependent Tyr-447 phosphorylation, which may open up docking sites necessary for proliferation.

Apoptosis in neurons

Yu et al. [44] was the first group to report the loss of cytosolic K^+ via Kv channels during neuronal apoptosis. They reported K^+ efflux was enhanced via Kv channels in mouse neocortical neurons undergoing apoptosis induced by staurosporine and serum deprivation [44]. Suppressing loss of cytosolic K^+ to the extracellular milieu by 5 mM TEA alleviated cell death. In addition, raising extracellular $[K^+]$ to 25 mM (thus decreasing the K^+ gradient and reducing K^+ efflux) also effectively attenuated apoptosis. On the contrary, valinomycin (K^+ ionophore) or cromakalim (K^+ channel opener) inflicted apoptosis. Enhanced Kv currents and apoptosis were similarly observed in beta-amyloid-challenged cortical neurons in a later work [45]. Again, TEA treatment or raising extracellular $[K^+]$ attenuated beta-amyloid-induced cell death.

Later works have substantiated that neuronal apoptosis is accompanied with increased Kv channel expression at the plasma membrane [46–48]. Increased Kv expression facilitates K^+ efflux, loss of cytosolic K^+, Cl^- outflow and water efflux, eventually leading to cell shrinkage and initiation of apoptosis [49], manifested later as mitochondrial swelling and depolarization, generation of reactive oxygen species, reduced ATP production and compromised Na^+, K^+-ATPase activity; the latter situation aggravates the drop in $[K^+]_i$ [50].

A sharp drop in $[K^+]_i$ is fatal and triggers apoptosis. Inside the cell, K^+ regulates a number of processes such as DNA and protein synthesis [51] and second messenger production [52]. $[K^+]_i$ affects pro-apoptotic enzymes such as nucleases and caspases [53]. K^+ inhibits these enzymes with a K_i of around 40 mM [54]. Healthy cells maintain $[K^+]_i$ at around 140 mM; however, $[K^+]_i$ could decrease to as low as 70–80 mM as a result of apoptosis [54]. While 140 mM K^+ fully inhibits caspases, $[K^+]_i$ at 80 mM or lower relieves such inhibition (Fig. 2). It has been demonstrated that staurosporine, an inducer of apoptosis, caused a drastic reduction in $[K^+]_i$ (measured using PBFI as a fluorescent

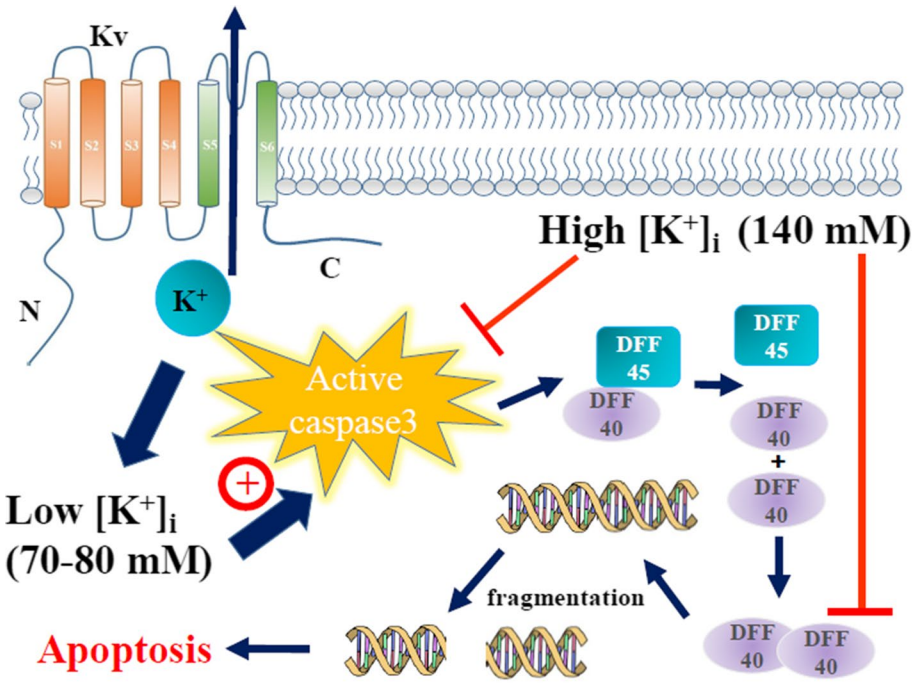

Fig.2 Participation of Kv channels in apoptosis. Overexpression of Kv channels in apoptotic cells results in excessive K^+ efflux and large reduction in cytosolic K^+ concentration. Low cytosolic K^+ relieves inhibition of caspases and results in caspase-dependent apoptosis: active caspase-3 activates the endonuclease DNA fragmentation factor 40 (DFF40) by cleaving off the nuclease's inhibitor DFF45; DFF40 then dimerizes and causes DNA fragmentation. Normal concentration of cytosolic K^+ (around 140 mM) completely inhibits the caspases and nucleases

probe) in rat hippocampal neurons to a level close to the K_i of K^+ inhibition of apoptotic enzymes [55].

More published works have identified individual Kv members involved in neuronal apoptosis and, in some reports, the mechanisms leading to their increased expression at the plasma membrane. Pal et al. [46] showed de novo insertion of Kv2.1 channels at the plasma membrane in cortical neurons undergoing apoptosis. The trafficking of Kv2.1 channels is supported by soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins (syntaxin and SNAP-25). Kv2.1 trafficking to the plasma membrane during apoptosis requires p38 MAPK-mediated phosphorylation of the channel at Ser800 [48]. Later evidence indicates that phosphorylation at Tyr124 of Kv2.1 is also important in apoptotic surfacing of the channel to the plasmalemma [56].

Kv1.1 is involved in mediating apoptosis of cerebellar granular neurons incubated in low extracellular [K^+] or in the absence of serum [57]. Dendrotoxin-K block or siRNA silencing of Kv1.1 suppressed Kv currents and enhanced cell viability. Optic nerve transection in vivo induces apoptosis in rat retinal ganglion cells [58]. The authors, using specific toxin blockers and siRNA techniques, identified Kv1.1 and Kv1.3 channels to be major culprits for retinal ganglion cell apoptosis. Remarkably, Kv1.1 knockdown enhances the expression of the anti-apoptotic gene, Bcl-X(L), while Kv1.3 knockdown decreases expression of pro-apoptotic genes, caspase-3, caspase-9 and Bad [58].

In hippocampal neurons, beta-amyloid-induced apoptosis was accompanied by upregulation of Kv3.4 and KCNE3 (MinK-related peptide 2, an auxiliary subunit of Kv channels) and increased Kv3.4-encoded A-type K^+ currents [59]. Blood depressing substance-I and peptide SN-50 inhibit beta-amyloid-induced increase in Kv3.4 currents and prevent beta-amyloid-induced cell death. Beta-amyloid could also inflict cerebellar granule cell apoptosis by upregulating Kv4.2 and Kv4.4 channels, resulting in increased A-type K^+ currents; substance P prevents this upregulation and offers neuroprotective effects [60].

To understand how human immunodeficiency virus (HIV) could damage the brain white matter, it has been shown in vitro that exposure of oligodendrocyte in primary culture to HIV-1 viral trans-activator of transcription (Tat) could cause apoptosis and upregulation of K1.3 expression [61]. Pharmacological block or siRNA knockdown of Kv1.3 inhibited Kv1.3 currents and apoptosis. Similar results were obtained in cultured rat brain slices. In addition, direct interaction between Tat and Kv1.3 has been demonstrated by protein pulldown assay.

Increased expression of Kv channels in microglia has not been implicated in their own death, but interestingly in the killing of neurons. In an early work, Fordyce et al. [62] reported that lipopolysaccharide-activated microglia, in a mechanism depending on Kv1.3 channel activities, produce peroxynitrite as a neurotoxic molecule to kill postnatal hippocampal neurons. Rat microglia challenged with HIV-1 glycoprotein 120 (gp120) showed enhanced Kv1.3 gene expression, protein expression, K^+ currents and cytotoxicity against co-cultured neurons [63]. Pharmacological block and knockdown of Kv1.3 substantially alleviated gp120-inflicted neurotoxicity. Evidence also suggests p38 MAPK is involved in gp120-induced Kv1.3 upregulation

and consequent neurotoxicity. The same group showed similar findings in another report when rat microglia were challenged with HIV-1 Tat protein [64]. Thus, rat microglia treated with Tat exhibited augmented Kv1.3 currents, and increased production of TNF-α, IL-1β, reactive oxygen species, and nitric oxide. Pharmacological inhibition or siRNA knockdown of Kv1.3 expression significantly suppressed microglia-mediated neurotoxicity.

Proliferation and migration of glioma

Ru et al. [65] have demonstrated that selective blockers of Kv and K_{ATP} channels suppress the proliferation of U87-MG human glioma cells, arrested cells at G0/G1 phase, and caused apoptosis. Using U87-MG xenograft model in nude mice, Kv or K_{ATP} channel blockers substantially alleviated tumor growth in vivo. Importantly, the link between channel block and anticancer activity is substantiated by the observation that Kv or K_{ATP} channel blockers suppress channel currents and cell proliferation/tumor growth with comparable concentration–response relations.

The role of Kv channels in glioma growth in humans is less clear. With semi-quantitative analysis of immunohistochemistry of patients [66], the expression of Kv1.5 was statistically higher in low-grade astrocytoma (WHO II) than in higher grades. However, glioblastoma patients with higher Kv1.5 expression did not have a significantly better survival.

Other studies have shown that Kv channels in general promote cancer cell growth. For instance, knockdown of hERG1 gene expression and the resultant decreased NF-κB signaling inhibit proliferation and cause apoptosis in human osteosarcoma cells [67]. Knockdown of expression of the electrically silent Kv9.1 caused G0/G1 cell cycle arrest in HCT15 and A549 cells without inducing apoptosis [68]. Further, tumor growth in an SCID mouse xenograft model was suppressed by knockdown of Kv9.3 expression by short-hairpin RNA. Readers interested in the role of Kv channels in cancer cell growth are referred to a recent review article by Serrano-Novillo et al. [69].

There is hitherto no report of Kv channel involved in glioma migration. However, in view of the numerous reports showing Kv channels are involved in migration in other cancer cell types, it would not be surprising that future research would reveal Kv channel involvement in migration of glioma cells. Knockdown of hERG1 gene expression and the resultant decreased NF-κB signaling inhibit migration of human osteosarcoma cells [67]. Kv1.3 and Kv1.5 channel expression was found to be positively correlated with leiomyosarcoma (LMS) tumor aggressiveness [70]. Expression of Kv3.1 and Kv3.4, which have been known to be oxygen sensors, in A549 and MDA-MB-231 cells has been found to increase as cells proliferate and density hence increases [71]. The manner of increase was comparable to the expression patterns of hypoxia-inducible factor-1α (HIF-1α) as cell density increased. Blood depressing substance, a neurotoxin from snake venom which blocks Kv3.1 and Kv3.4, did not affect cell growth but inhibited cell migration and invasion.

In the search of the mechanism of how Kv channels are linked to migration, Hammadi et al. [72] obtained data showing that blocking or silencing hEag1 (Kv10.1) depolarized breast cancer MDA-MB-231 cells, reducing Ca^{2+} entry (via Orai1-associated channel) and eventually inhibiting cell migration without affecting cell proliferation. Thus, hEag1 is essential in maintaining a negative membrane potential to be favorable for Ca^{2+} entry, which is important in cell motility. However, using BT474 cells, our data do not support such a hyperpolarizing role of Kv channels [73]. We found that migratory cells had much higher Kv current densities than non-migratory cells. Kv currents and cell migration were substantially inhibited by TEA, a delayed rectifier Kv channel blocker, but not by 4-AP, an A-type Kv channel blocker. Intriguingly, migratory cells had more depolarized membrane potential and reduced Ca^{2+} influx than non-migratory cells. The results hence suggest increased Kv channel expression played a role in BT474 cell migration, but the mechanism(s) by which Kv channels enhanced migration appeared to be unrelated to membrane hyperpolarization and augmented Ca^{2+} influx.

Blocking intermediate- and large-conductance Ca^{2+}-activated K^+ (Kca) channels inhibits glioma migration and tumor infiltration [74, 75]. A model integrating the functions of Kv, Kca and inward rectifier K^+ (Kir) channels in migrating cancer cells has been proposed by Huang and Jan [76]. In the moving cells, mobile lamellipodia are at the leading edge and the contracting cell body is at the trailing edge. At the moving cell's posterior, Kca channels and Kv channels provide efflux of K^+ and water then flows out osmotically via water channels, resulting in local volume decrease and retraction at the cell posterior. Kir channels allow K^+ influx at the cell anterior, osmotically drawing water in through water channels, resulting in local volume increase and protrusion at the cell front. There is evidence that this mechanism could provide sufficient motile force for the cell without the involvement of actin polymerization [77].

Conclusion and perspectives

Kv channels regulate many cellular processes unrelated to action potential generation in the nervous system. These include exocytosis, neuritogenesis, and cell death in neurons, Ca^{2+} regulation in astrocytes, glial cell growth, and glioma proliferation (Table 1). As already explained above, some of these processes do not require K^+ flux through the Kv

Table 1 Kv channels and their functions (unrelated to action potential) in neurons and glia

Kv members	Functions	Cell types [ref]
Kv2.1	Exocytosis	PC12 cells [11]
Kv2.1	Exocytosis	Rat dorsal root ganglion neurons [13]
4-AP-sensitive Kv channels	Neurite growth	*Xenopus* retinal ganglion cells [21]
Kv3.4	Axon growth	Chick embryonic spinal neurons [22]
Kv1.1, 1.4, 2.1	Neurite growth	Mouse neuroblastoma N2A cells [23]
4-AP- and TEA-sensitive Kv channels	Regulation of Ca^{2+} Entry	Rat cortical astrocytes [36]
Kv1.3	Cell proliferation	Rat brain microglia [39]
Kv1.4	Cell proliferation	Rat spinal cord glial cells [40]
4-AP- and TEA-sensitive Kv channels	Cell proliferation	U87-MG human glioma cells [65]
Kv1.1	Apoptosis	Rat cerebellar granular neurons [57]
Kv1.1,1.3	Apoptosis	Rat retinal ganglion cells [58]
Kv2.1	Apoptosis	Rat cortical neurons [46]
Kv3.4	Apoptosis	Rat hippocampal neurons [59]
Kv4.2, 4.4	Apoptosis	Rat cerebellar granular neurons [60]

channel pore (non-canonical function), as Kv channels interact with other proteins via particular intracellular domains.

Reports in the past few years have demonstrated an intimate relation between Kv channels and transporters. Heterologous co-expression showed Kv7.1 channels form physical complexes with a sodium-myo-inositol cotransporter (SMIT1) and enhance SMIT1 activities; SMIT1 reciprocally augments Kv7.1 currents [78]. A very recent report demonstrated that Kv7.2/7.3 forms physical complexes with DAT (sodium-dopamine cotransporter) and GLT1 (sodium-glutamate cotransporter), and enhances these transporter activities as Kv-mediated K^+ efflux dampens depolarization caused by Na^+ influx [79]. This interaction provides a rapid and local control of membrane potential. In addition, a co-expression study demonstrated that SLC7A5, a neutral amino acid transporter, profoundly alters Kv1.2 gating [80]. Such channel–transporter interaction was coined "chansporter" by Manville and Abbott [81], who also reviewed interactions between various transporters and channels other than Kv channels. Whether transporters interact with Kv channels other than Kv7 and Kv1 members is yet to be explored.

Kv channels form clusters, and clustering of Kv channels may act as a platform to promote other biological functions. Hence, a cluster of non-conducting Kv2.1 in HEK cells and hippocampal neurons has been shown to provide a platform for channel trafficking, not only for Kv2.1 but also Kv1.4 [82]. The recent finding that Kv channel clustering facilitates beta-cell exocytosis strengthens this platform concept [14]. Further works may demonstrate that Kv channel clustering has "more to offer".

Non-canonical functions of VGSC, such as promotion of phagocytosis and migration of non-excitable cells, have been well documented and reviewed [83]. Here in this review, we have discussed that Kv channels are equally versatile molecules. Future efforts may reveal more about the multi-tasking of these protein molecules.

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Compliance with ethical standard

Conflict of interest The authors declare no conflict of interests.

Humans and/or animals participants This is a review article; no animals or humans were experimented in this work.

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