Microglial ion channels: Key players in non-cell autonomous neurodegeneration

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Abstract

Neuroinflammation is a critical pathophysiological hallmark of neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and traumatic brain injury (TBI). Microglia, the first responders of the brain, are the drivers of this neuroinflammation. Microglial activation, leading to induction of pro-inflammatory factors, like Interleukin 1-β (IL-1β), Tumor necrosis factor-α (TNFα), nitrites, and others, have been shown to induce neurodegeneration. Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce the risk of developing PD, but the mechanism underlying the microglial activation is still under active research. Recently, microglial ion channels have come to the forefront as potential drug targets in multiple neurodegenerative disorders, including AD and PD. Microglia expresses a variety of ion channels, including potassium channels, calcium channels, chloride channels, sodium channels, and proton channels. The diversity of channels present on microglia is responsible for the dynamic nature of these immune cells of the brain. These ion channels regulate microglial proliferation, chemotaxis, phagocytosis, antigen recognition and presentation, apoptosis, and cell signaling leading to inflammation, among other critical functions. Understanding the role of these ion channels and the signaling mechanism these channels regulate under pathological conditions is an active area of research. This review will be focusing on the roles of different microglial ion channels, and their potential role in regulating microglial functions in neurodegenerative disorders.

Keywords

Neuroinflammation; Channels; Microglia

1. Introduction

Microglia, the first responders of the brain, are critical players in shaping the neural circuit during development and maintaining neuronal health (Paolicelli et al., 2011). Hyperactivation of microglial cells has been linked to multiple diseases, including epilepsy (Sharma et al., 2017), Parkinson's disease (PD) (Panicker et al., 2015), Alzheimer's disease (AD) (Halle et al., 2008), and traumatic brain injury (TBI) (Turtzo et al., 2014). Furthermore, Glial-derived proinflammatory factors have been shown to be neurotoxic and can lead to neuronal loss (Harischandra et al., 2019; Sarkar et al., 2020a; Sarkar et al.,

2017; Sarkar et al., 2019). Hence, anti-inflammatory drugs targeting microglial activation and proliferation have gained importance in recent years. Of the many targets investigated, ion channels have been recognized as some of the most crucial. Indeed, microglial ion channels perform diverse functions that can lead to microglia-mediated inflammation and proliferation and migration of microglia (Feske et al., 2015). In neurodegenerative disorders, many of these ion channels have been shown to be upregulated, making them lucrative drug targets. In this review, we discuss the major ion channels involved in microglial function under specific contexts to provide a detailed overview of their mechanisms for the purposes of understanding druggable targets.

1.1. Potassium channels

1.1.1. Voltage-gated potassium channel (Kv1.3)—Kv1.3 is one of the 40 voltage-gated potassium channels in the human genome. Kv1.3 was identified first identified in T cells (DeCoursey et al., 1985; Grissmer et al., 1990; Matteson and Deutsch, 1984). It is composed of 4 α subunits, each containing 1 P loop and six transmembrane segments (S1-S6). 4 Arginine residues in the S4 segment are responsible for opening this channel because of polarization. T cell activation is associated with calcium influx into the cell, depolarizing the cell. This stimulates the Kv 1.3 channel to open and export potassium out of the cell, repolarizing it, thereby driving more calcium ions into the activated T cell (Beeton et al., 2006; Selvakumar et al., 2022). Other than T cells, Kv1.3 channels have also been identified in other lymphocytes, retinal ganglion cells, microglia, neurons, non-electrically excitable cells, and many others. Notably, this diverse tissue expression confers numerous functions of Kv1.3, and this has been best observed in complete knock-out mice, which are resistant to diet-induced obesity (Upadhyay et al., 2013; Xu et al., 2004), immune to experimental autoimmune encephalomyelitis (EAE) (Gocke et al., 2012), and also improved sense of smell (Fadool et al., 2004).

Despite most studies being on autoimmune disease, ischemia, and the development of retinal ganglion cells (RGCs), Kv1.3 shows a great importance in microglial physiology, which warrants further investigation into neurodegenerative disease models. First sequenced and cloned by Chandy in 1991 (Chandy, 1991), the transcript of Kv1.3 in microglial cells was soon discovered in 1993 by Norenberg et al. (Norenberg et al., 1993). Since then, the role of Kv1.3 in microglial function and activation has been implicated. A study by Schlichter et al. demonstrated that primary microglia in culture express functional Kv1.3 outward rectifier channels, but following prolonged culturing, these microglia lost channel activity over time, suggesting that Kv1.3 could be studied *in vitro* under specific time constraints (Schlichter et al., 1996). Later *in vitro* studies demonstrated that Kv1.3 is essential in driving lipopolysaccharide (LPS)-induced inflammation in microglial cells. Fordyce et al. observed that Kv1.3 channel activity in microglial cells is necessary to kill hippocampal neurons using a co-culture system.

Furthermore, Kv1.3 inhibitors reduced the respiratory burst and free radical production in microglial cells hence reducing the formation of peroxynitrite, a critical inflammatory molecule (Fordyce et al., 2005). Recently, Rangaraju et al. further elucidated the Kv1.3-dependent pathways in microglial cells post LPS treatment (Rangaraju et al., 2017). This

study used a Kv1.3 inhibitor, Shk, to inhibit the channel activity post LPS treatment and performed whole-cell proteomics to determine the Kv1.3 dependent pathways involved in an inflammogen insult. Interestingly, blocking Kv1.3 reduced phosphorylation of STAT1, an immediate downstream signaling protein of the LPS-TLR (Toll-like receptor) signaling cascade. Additionally, blocking Kv1.3 conferred many other effects, including reduced microglial phagocytic activity, induced microglial chemotaxis and migration, and altered the subunit alpha of GA binding protein (GABPA) that is involved in mitochondrial DNA replication and oxidative phosphorylation. Kv1.3 is known to be present on the mitochondrial membrane and has been linked to cytochrome c release and apoptosis in lymphocytes (Gulbins et al., 2010; Szabo et al., 2008). However, until recently, no studies have investigated the potential role of mitochondrial Kv1.3 and its role in microglial function. Our group and others have shown the importance of mitochondrial dynamics in driving inflammation in microglial cells (Lawana et al., 2017; Sarkar, 2021; Sarkar et al., 2020a; Sarkar and Feany, 2021; Sarkar, 2020; Sarkar et al., 2018; Sarkar et al., 2017). Hence, studies on mitochondrial Kv1.3 and its role in regulating mitochondrial health in microglial cells may provide critical mechanistic insights.

Currently, microglial Kv1.3 induction has been shown in some neurodegenerative models, including stroke, AD, HIV-induced dementia, radiation-induced brain injury, and status epilepticus. Menteyne et al. showed that Kv1.3 is the predominant potassium channel in the kainate mouse model of epilepsy in microglia. Post kainate treatment of CX3CR1(eGFP/+) mice, a whole-cell-patch clamp was performed on GFP-microglial cells, which demonstrated an increase of Kv1.3 current in the activated microglia. Treatment with Kv1.3 inhibitor, agitoxin-2, or margatoxin inhibited this current (Menteyne et al., 2009). In HIV, HIV-1 regulatory protein, Tat, induced microglial inflammation by inducing Kv1.3 and the classical activation of Nuclear factor kappa-light-chain-enhancer of activated B cells (NfκB) (Visentin et al., 2001). siRNA knockdown of Kv1.3 in microglial cells diminished the neurotoxicity induced by Tat by reducing the release of pro-inflammatory factors from the microglial cells. Additional evidence shows Kv1.3 inhibition may also decrease activation of extracellular signal-regulated protein kinase (ERK1/2) mitogen-activated protein kinase (MAPK) (Fig. 1) pathway induced by Tat (Liu et al., 2013). The gp-120 subunit itself of the HIV-1 virus has been shown to activate microglial cells through induction of Kv1.3 channel activity by activating the p38 MAPK pathway (Liu et al., 2012; Liu et al., 2017).

Microgliosis and neuroinflammation are important factors contributing to neuronal loss in AD (Halle et al., 2008). Kv1.3 is highly expressed in microglial cells in AD brains. Moreover, these Kv1.3 positive glial cells were shown to be associated with amyloid β (Aβ) tangles in the frontal cortex of AD patients, suggesting a potential role of this channel in phagocytosis (Rangaraju et al., 2015). Further, *in vivo* transcriptomic analysis has shown that Kv1.3 is one of the key hallmarks of pro-inflammatory disease associated microglia (DAM), while inhibiting Kv1.3 pushes the microglia towards an anti-inflammatory phenotype (Ramesha et al., 2021; Rangaraju et al., 2018). Aβ also induced microglial activation and Kv1.3 upregulation in microglial cells, and even in the transgenic mouse model APP/PS1 of AD, Kv1.3 was upregulated. Pharmacological inhibition of Kv1.3 *in vivo* in APP/PS1 model resulted in reduced inflammation and rescuing the disease

phenotype. Specifically, treatment with Kv 1.3 inhibitor, PAP-1, reduced Aβ-induced Nfκ-b activation, TNF-α, Nitrite, and IL-1β mRNA levels. Importantly, Kv1.3 inhibition resulted in higher uptake of Aβ and reduced cerebral amyloid load. PAP1, the Kv1.3 inhibitor, improved hippocampal neuronal plasticity and behavioral and cognitive deficits APP/PS1 model of AD (Maezawa et al., 2017). Though the importance of microglial Kv1.3 in AD has been elucidated, further studies looking into the downstream signaling mechanism of Kv1.3 in microglia and even the upstream signaling resulting in its activation, may identify novel pathways in regulating microglial function associated with this disease pathology. Furthermore, studies looking into the role of Kv1.3 in tau models and frontal temporal dementia with parkinsonism-17 (FTDP-17) is warranted.

The role of Kv1.3 was not well known in PD, and because of its natural similarity in pathology to Alzheimer's, we investigated Kv.13 expression in PD models. We demonstrated that Kv1.3 is highly induced by aggregated α-synuclein. Additionally, post-mortem PD patients had higher microglial Kv1.3 expression (Sarkar et al., 2020b). As in AD, inhibition of Kv1.3 reduced microglial activation and neurodegeneration in multiple PD models *in vitro* and *in vivo.* The N-terminal end of Kv1.3 contains a proline-rich sequence, and the proline-rich sequence has been shown to bind to the src-homology domain of src-family kinases (SFK). Of these SFKs, Fyn was shown to interact and modulate the function of Kv1.3 *via* phosphorylation directly (Sarkar et al., 2020b). Furthermore, Fyn regulates the p38 and NF-kB pathways (Panicker et al., 2015), supporting that Kv1.3 can be regulated transcriptionally and post-translationally in this signaling axis. *In silico* promoter analysis has shown that Kv1.3 is transcriptionally regulated by p38 MPAK (Sarkar et al., 2020b). Further, we have demonstrated that inhibition of p38 using MAPK inhibitors can reduce α-synuclein-induced Kv1.3 levels transcriptionally. The significant number of studies implicating the role of this channel in disease pathology and inflammation and its diverse role in specifically regulating microglial signaling cascades makes it an exciting target for a drug in many of these diseases mentioned above (Sarkar et al., 2020b). Subcellular localization further warrants Kv1.3 research, as we have discussed in the case of mitochondrial Kv1.3 expression, and should be a sought-after avenue in diversifying potential drug targets in the given diseases, which could also provide insight into how organelles alter in pathological contexts.

1.1.2.   Calcium-activated potassium channel ($K_{ca}3.1$)—First identified by György Gárdos in 1958 (Gardos, 1958), $K_{ca}3.1$ is a voltage-independent potassium channel activated by intracellular calcium. This is an intermediate channel that exists as a tetramer consisting of six transmembrane domains and calcium-binding calmodulin-binding domains on the C-terminal end of these voltage-independent channels (Brown et al., 2017). The activation of this channel leads to hyperpolarization of the membrane leading to calcium influx (Joiner et al., 1997; Wei et al., 2005). Kaushal et al. demonstrated that $K_{ca}3.1$ inhibition reduced microglial activation and pro-inflammatory cytokine release (Fig. 2) by regulating the p38 MAPK pathway (Fig. 1) but not the Nfκb signaling cascade. Moreover, TRAM-34, a Kca3.1 blocker, reduced the degeneration of retinal ganglion cells in an optic nerve transection mouse model (Kaushal et al., 2007). A study by Maezawa and colleagues demonstrated that oligomeric Aβ-induced microglial activation and proliferation *in vitro* activated this voltage-

independent potassium channel. TRAM-34 treatment inhibited the activation of microglia and oligomeric Aβ-induced neurotoxicity, further suggesting a role of $K_{ca}3.1$ in regulating neuroinflammation and neurodegeneration (Maezawa et al., 2011). The expression of Kca3.1 was shown to be induced in microglial cells surrounding infarction areas in a stroke mouse model. TRAM-34 was able to abrogate the microglial activation and infarction area (Chen et al., 2011). Likewise, $K_{ca}3.1$ expression was highly induced in microglial cells in a spinal cord injury mouse model. Inhibition of this channel not only reduced the production of inflammatory cytokines TNFα and IL-1β but also improved locomotor deficits and provided tissue protection by enhancing neuronal and axonal sparing (Bouhy et al., 2011). $K_{ca}3.1$ also displays importance by regulating glioblastoma invasiveness and activation and propagation of microglia (D'Alessandro et al., 2013). Surprisingly, however, LPS, which can promote activation and propagation, did not elicit $K_{ca}3.1$ channel activity, but ATP and IFNγ elicited moderate amounts of $K_{ca}3.1$ channel activity (Nguyen et al., 2017). These findings highlight the physiological role Kca3.1 plays in cellular inflammation, but deviations from the classical manners of proinflammation exist and remain to be studied.

1.1.3. ATP sensitive potassium channels (KATP)—ATP-sensitive-K_{ATP} channels were first identified in cardiac myocytes (Noma, 1983) and composed of eight protein subunits, four subunits of the inward rectifier, Kir6.1 or Kir6.2, and four subunits of sulfonylurea receptors (Inagaki et al., 1995). These channels act as metabolic sensors and have a variety of physiological functions, including insulin secretion and inflammation (Quan et al., 2011). Microglial K_{ATP} channels have been implicated in various disorders, including stroke, multiple sclerosis, and PD. Iptakalim, a K_{ATP} channel opener, reduced microglial activation and production of pro-inflammatory factors like TNFα and p38 MAPK activation (Fig. 1) in the MPP+ model of PD. These protective effects were reversed when a K_{ATP} channel blocker, hydroxy decanoate, was used (Yang et al., 2009). Opening of K_{ATP} channel reduced neuroinflammation induced by rotenone in BV2 microglial cell line by reducing p38/JNK MAPK pathway (Zhou et al., 2008). This ATP sensitive potassium channel is further involved in NOS2 production from microglial cells in response to LPS (Kurland et al., 2016). Taken together, most of the current literature suggest that opening of this class of potassium channel has an anti-inflammatory role in regulating microglial activation in neurodegenerative disorders (Fig. 2). Further studies, looking into the potential signaling cascades involved in regulating K_{ATP} will give leads to potential anti-inflammatory strategies in disease condition.

1.1.4. Other microglial potassium channels—Various potassium channels, including those discussed above, play essential roles in regulating microglial functions by modulating signaling cascades. Kir2.1, an inward rectifier channel, has been shown to be induced upon treatment with IL-4 which can induce an M2-like microglial phenotype (Lam et al., 2017). Kir2.1 inhibition reduces microglial proliferation upon an inflammatory stimulus (Lam et al., 2017), suggesting Kir2.1 modulates microglial chemotaxis, migration, and intracellular calcium signaling at resting and M2-like alternative activation states (Lam and Schlichter, 2015) through unknown signaling mechanism. Conversely, Kv1.5 has been shown to be induced in classically activated microglial cells (Jou et al., 1998), as in the case of amyloid β treated microglial cells. The knock-out of Kv1.5 in microglia

reduces the production of NO and proliferation post-inflammatory insult (Pannasch et al., 2006) through ERK/MAPK pathway, suggesting the proinflammatory role of this outward potassium channel in multiple microglial functions. Together, the role of potassium channels in microglia is diverse in physiological and disease conditions (Fig. 1). Modulation of these ion channels may lead to the discovery of key drug targets for neurodegenerative disorders, but further mechanistic study to understand the downstream signaling of these channels are necessary.

1.2. Sodium channels

First identified in jellyfish, sodium channels play a major role in diverse physiological functions, including cognition, locomotion, and depolarization (Marban et al., 1998). Sodium channels were the first voltage-gated channels to be cloned in 1984 (Noda et al., 1984), but the role of sodium channels in microglial channels is not well studied. Primary rat microglia isolated from prenatal pups expressed different isoforms of sodium channels, including Nav1.1, Nav1.5, and Nav1.6 (Black et al., 2009). These channels can control a range of microglial functions. Non-specific sodium channel inhibition leads to reduced phagocytosis in LPS-activated microglial cells and can regulate the proinflammatory cytokine release from microglial cells. This was observed by phenytoin treatment, a sodium channel inhibitor capable of reducing the production of IL-1α, IL-1β, and TNFα, induced by LPS but has minimal effect on the other secretory cytokines and chemokines. Lastly, the inhibition could reduce ATP-induced microglial chemotaxis and migration (Black et al., 2009). Deng et al. identified the critical role of sodium channels in microglial cells in a hypoxic environment. This study showed that under hypoxia, microglia express higher levels of sodium channels. Under hypoxia, the microglial cells elicited the production of pro-inflammatory factors, including TNFα and IL-1β, which resulted in the loss of neurons and was also linked to periventricular white matter damage associated with the hypoxic environment in the brain (Deng et al., 2011). In the case of ATP release in the extracellular space, which can damage neurons and spur inflammation in multiple neurodegenerative disorders, sodium channels were also observed to be heavily involved (Gan et al., 2015; Jun et al., 2007; Rodrigues et al., 2015; Shin et al., 2016). Persson et al. demonstrated that inhibition of Nav1.6 modulates the ERK1/2 MAPK pathway, thereby regulating the accumulation of Rac1 in response to extracellular ATP in microglial cells. This study further showed that Nav1.6 directly regulates the cellular polarization, spatial arrangement, and microglial movement in response to ATP (Persson et al., 2014). These findings indicate that the sodium channels play an important role in the normal physiological functions of microglial cells. Microglial sodium channels have been shown to be upregulated in multiple disease models including spinal cord injury and multiple sclerosis. Sodium channel blockage lead to a decreased microglial activation and production of proinflammatory cytokines in spinal cord injury model by reduced activation of classical Nfκb, pro-inflammatory pathway, and p38 MAPK pathway but did not alter the activation of JNK pathway (Jung et al., 2013). In animal model of experimental autoimmune encephalopathy, Nav1.6 was found to be highly upregulated in activated microglial cells (Craner et al., 2005). But recent studies looking into specific inhibition of sodium channels have shown that Nv1.2, Na1.4, and Nav1.6 blockage exacerbates experimental autoimmune encephalomyelitis (Stevens et al., 2013). These studies suggest that sodium channel plays a complex role in regulating

microglial function. Further studies, understanding the modulation of these diverse channels in disease condition and the signaling pathway is necessary.

1.3. Proton channels

Another critical channel affecting microglial function in disease models is the unique voltage-gated proton channel, Hv1. Microglia, but not astrocytes and neurons, have been shown to express Hv1 current. Hv1 knock-out mice have reduced neuronal loss in an ischemic stroke mouse model. Hv1 was shown to play an important role in NADPH oxidase mediated ROS generation in glial cells, in the context of neurodegeneration in stroke (Wu et al., 2012). This voltage-gated proton channel compensates the cellular loss of electrons with protons, activating NADPH oxidase (Wu, 2014) (Fig. 2). Dextromethorphan that has anti-inflammatory properties was shown to reduce proton channels in BV2s (Song and Yeh, 2012) and primary rat microglia. Yang et al. demonstrated that dextromethorphan reduced LPS-induced TNF-α production and caspase-3 activation (Yang et al., 2020).

Moreover, Hv1 knock-out microglia had lower NOX activation in a cell culture model of periventricular leukomalacia (Yu et al., 2017). Tian et al. demonstrated that this unique proton channel could be a potential target for modulating microglial activation profile in photothrombotic ischemic stroke as well. Hv1 deficient microglia are shifted towards an alternative anti-inflammatory M2-like phenotype in stroke models (Tian et al., 2016). ROS generation and NADPH oxidase activation in microglial cells are the major inflammatory pathways in multiple neurodegenerative disorders, including PD (Langley et al., 2017) and AD (Hernandes and Britto, 2012; Zekry et al., 2003). NOX inhibition has been implicated as therapeutic targets in these neurodegenerative disorders (Cifuentes-Pagano et al., 2015). Although the potential role of Hv1 has not been studied in the most prevalent neurodegenerative disorders, AD and PD, the existing models such as stroke suggest inhibition of Hv1 in microglia could alleviate neuronal death in AD and PD if its inhibition leads to anti-inflammatory properties.

1.4. Other channels

Multiple calcium channels and purinergic receptors have been reported to modulate various physiological functions of microglia in disease conditions (Echeverry et al., 2016; Espinosa-Parrilla et al., 2015; Sperlagh and Illes, 2014). L-type voltage-gated calcium channels have been implicated in microglial activation in AD and prion disease. Misfolded prion protein, a classical hallmark of the prion-associated disease, increased the expression of L-type calcium channels and induced microglial activation. Treatment with inhibitors of L-type voltage-sensitive calcium channels reduced the microglial activation, suggesting this type of channel's role in the classical activation of glial cells (Silei et al., 1999). Cav1.2 subunit of voltage-gated calcium channel was shown to be upregulated in glial cells in a mouse model of AD and was related to an increase in amyloid β load (Daschil et al., 2013). Moreover, Cav1.2 and Cav1.3 have been shown to be upregulated in microglial cells in a rodent model of *N*-methyl-D-aspartate-induced hippocampal neurodegeneration (Espinosa-Parrilla et al., 2015). Furthermore, blocking of these calcium channels reduced the production of proinflammatory factors, TNFα and NO, in BV2 microglial cell line post LPS

treatment further elucidating the role of these channels in regulating microglial inflammation (Espinosa-Parrilla et al., 2015).

Transient receptor potential (TRP) channels, which are non-selective cation channels, further regulate microglial functions under physiological and disease conditions (Echeverry et al., 2016). Out of the TRPV subfamily of channels, TRPV1, TRPV2, and TRPV4 have been shown to regulate major microglial functions. TRPV1 has been associated with microglial inflammation as the induction of TRPV1 leads to increased ROS production and NOX activity (Schilling and Eder, 2009). The induction of TRPV1 channels has been shown to produce other proinflammatory factors, like IL-6 and Nitric oxide (NO), and activate the pro-inflammatory signaling cascade Nf-κB (Sappington and Calkins, 2008; Talbot et al., 2012) and MAPK (Miyake et al., 2015). TRPV1 has also been linked to microglial chemotaxis, in which induction of TRPV1 increases chemotaxis, while TRPV1-selective blockers reversed the effect (Miyake et al., 2015). TRPV2 is predominantly present in the endoplasmic reticulum and translocates to the plasma membrane post-stress. Though the role of glial TRPV2 is not well established, this channel may be regulating intracellular calcium signaling leading to microglial activation (Hassan et al., 2014). TRPV4 is a mechanosensitive channel shown to play an important role in infrasound-induced glial activation and production of proinflammatory factors (Shi et al., 2013), whose blockage reduced LPS-induced TNFα release and microglial activation (Konno et al., 2012) as such TRP channels may be exploitable targets for the purposes of anti-inflammatory drugs.

TRPM family of non-selective calcium channels also plays a role in regulating inflammation in microglial cells. TRPM2 has been shown to act as a regulator of H_2O_2-induced microglial activation by modulating calcium influx. TRPM2 knock-out mice have reduced inflammatory responses post-treatment of LPS/ IFN-γ and reduced activation of MAPK and JNK signaling cascades (Miyake et al., 2014). Additionally, TRPM4 channel activity has been shown to be induced under inflammatory insults and may play a critical role in monitoring microglial cytokine release (Beck et al., 2008; Haraguchi et al., 2012). TRPM7, a calcium-permeable channel, has been shown to modulate microglial migration and invasion during alternative activation (Siddiqui et al., 2014). Microglial ATP-sensitive purinergic receptor P2X7 has been recently implicated in playing an essential role in the activation of NLRP3 inflammasome (Burm et al., 2016). NLRP3 inflammasome is one of the major functional inflammasomes in microglial, which has been implicated in neurodegenerative disorders including AD (Halle et al., 2008; Heneka et al., 2013). Collectively, the microglial functions modulated by these channels are observably diverse. Regulation of ion movement and how it could impact signaling mechanisms and their associated gene expression changes could reveal numerous insights into druggable targets for neuroinflammatory disorders such as PD.

2. Conclusion, limitations and future directions

As discussed in this review, the current literature has a wealth of information suggesting the potential role of microglial ion channels in regulating diverse physiological and disease-associated microglial functions (Table 1). The potential of microglial ion channels as drug targets is immense, keeping into consideration the diverse function of these channels. But

it has to also acknowledged that since most of the channels are expressed in multiple cell types, there can also be non-targeted effect of these drugs. Hence research on drug delivery system that can deliver these drugs is warranted. As mentioned in Fig. 2, these channels have been shown to regulate both classical and alternative microglial activation. Hence proper modulation of microglial ion channels may lead to reduced inflammation or anti-inflammatory microglial phenotype in neurodegenerative conditions. These ion channels may regulate multiple key inflammatory or anti-inflammatory signaling cascades in glial cells and modulate neuroinflammation in disease conditions. Using one or more of these ion channels as drug targets may be beneficial in the case of neurodegenerative disorders, considering the role of inflammation in these diseases. Although we have a lot of evidence regarding these channels' probable role in glial cells, the signaling pathways involved are not clearly understood. Future studies concentrating on the exact pathways these ion channels affect and its role in microglial physiological functions needs to be studied. Further, the cellular and molecular mechanism through which these microglial ion channels regulate neuronal health is not well understood. Co-culture studies looking into the role of these key channels regulating the crosstalk is warranted. Future studies, looking into the channel-dependent pathways in these glial cells may open a new avenue for a new class of drug targets for neurodegenerative disease.

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Data availability

No data was used for the research described in the article.

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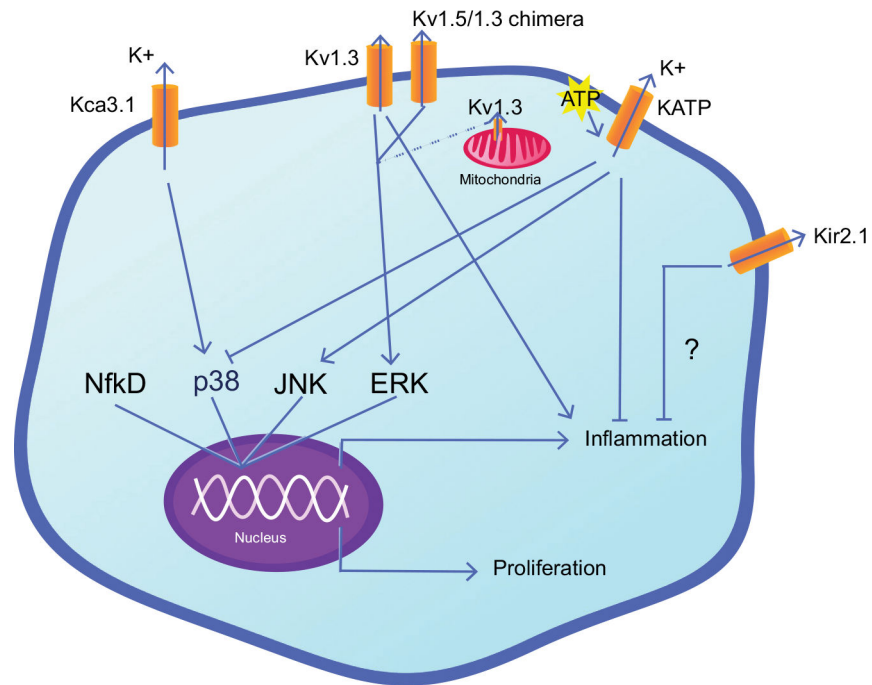
Fig. 1.
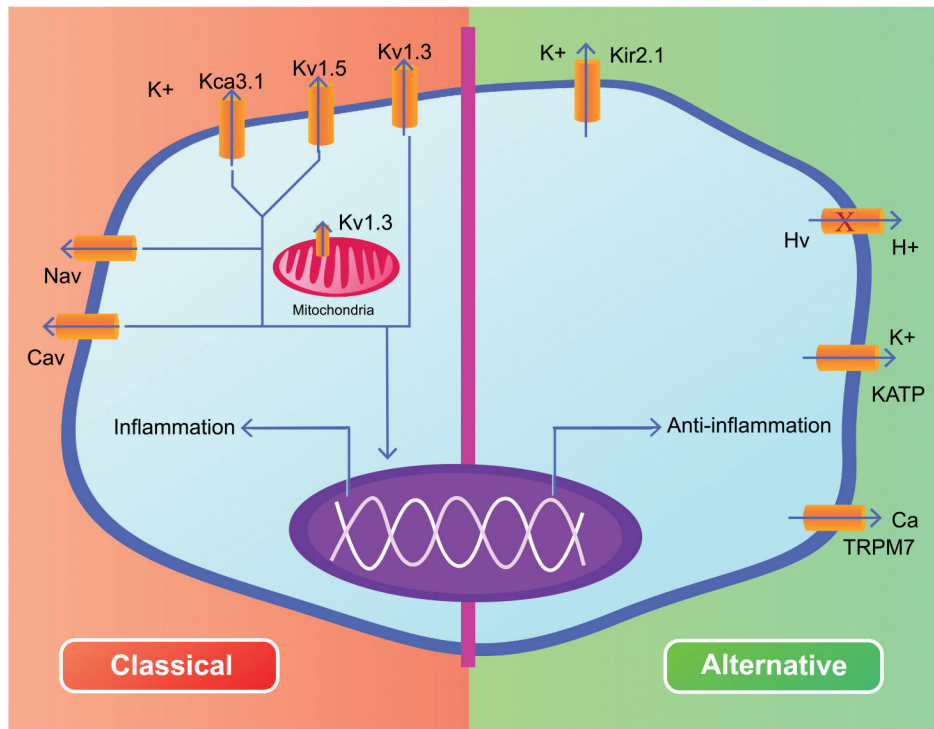Signaling pathways regulated by potassium channels in microglial cells leading to inflammation.

Fig. 2.
Ion channels involved in classical and alternative activation of microglial cells.

Table 1

Ion channel dependent microglial function in disease conditions.

Channel Name	Disease Associated	Microglial function	References
Kv1.3	AD, PD, HIV induced dementia, epilepsy, and radiation-induced brain injury	Proinflammation, Phagocytosis, Antigen Presentation, Migration and Proliferation	Schlichter et al., 1996; Fordyce et al., 2005; Rangaraju et al., 2017; Visentin et al., 2001; Reeves et al. 2016; Liu et al., 2017; Liu et al., 2013; Sarkar, 2020;
Kca3.1	optic nerve transection mouse model, AD, stroke	Proinflammation, Migration, and Proliferation	Maezawa et al., 2011; Chen et al., 2011; Bouhy et al., 2011; D'Alessandro et al., 2013; Nguyen et al., 2017;
Kv1.5	AD	Inflammation	Jou et al., 1998; Pannasch et al., 2006; Chung et al. 2001;
K$_{ATP}$	MS, Stroke, PD	Anti-inflammation	Yang et al., 2009; Zhou et al., 2008; Kurland et al., 2016;
Kir2.1	IL–4 and IL–10 treatment	Anti-inflammation; Migration, and proliferation	Lam et al., 2017; Lam and Schlichter, 2015;
Nav	Hypoxia, spinal cord injury, multiple sclerosis, stroke	Inflammation, phagocytosis, cellular polarization, spatial arrangement and microglial movement	Black et al., 2009; Deng et al., 2011; Gan et al., 2015; Jun et al., 2007; Rodrigues et al., 2015; Shin et al., 2016; Jung et al., 2013; Craner et al., 2005; Stevens et al., 2013;
Hv	Stroke, PD, AD	Anti-inflammation	Hernandes and Britto, 2012; Zekry et al., 2003; Cifuentes-Pagano et al., 2015; Tian et al., 2016;
L-type calcium channels	AD, Hippocampal neurodegeneration	Proinflammation	Silei et al., 1999; Daschil et al., 2013; Espinosa-Parrilla et al., 2015;
TRPV	Inflammatory stress condition	Proinflammation, Chemotaxis	Echeverry et al., 2016; Schilling and Eder, 2009; Sappington and Calkins, 2008; Talbot et al., 2012; Miyake et al., 2015; Hassan et al., 2014; Shi et al., 2013; Konno et al., 2012;
TRPM	Inflammatory stress condition	Proinflammation, chemotaxis, migration, Anti-inflammation.[*]	Miyake et al., 2014; Beck et al., 2008; Haraguchi et al., 2012; Siddiqui et al., 2014;

[*]TRPM7 has an anti-inflammatory function leading to alternative activation of glial cells. Other know TRPM induces classical activation of microglia.