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Nuance of inward rectifying potassium (Kir) channel dysfunctions in neurodegenerative diseases

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Neurodegenerative disorders are highly prevalent and diverse in nature. Their manifestation largely depends on the cell types involved, with aberrant inflammatory episodes progressively inducing a constellation of phenotypes that are classified into specific diseases based on their neuropathological traits. The two most prevalent neurodegenerative diseases worldwide, Alzheimer's disease (AD) and Parkinson's disease (PD), for example, share notable similarities, yet they differ in terms of the specific cell types lost within the central nervous system (CNS). The significant and progressive loss of cortical and certain subcortical neurons in various regions is a major defining trait of AD. In contrast, the specific loss of dopaminergic neurons (DA) within the substantial nigra pars compacta (SNpc) is sufficient to cause motor symptoms associated with PD. Another devastating condition arising from neurodegeneration within the CNS, amyotrophic lateral sclerosis (ALS), results in the progressive death of upper and lower motor neurons. This degeneration originates in oligodendrocytes, whose defective myelination abilities lead to the denervation of the anterior horn, aggravating motor neuron death. In the case of Huntington's disease (HD), early motor symptoms are generally attributed to the selective loss of D2-medium spiny neurons. These multifactorial diseases involve diverse risk factors and complex pathobiological mechanisms that are intertwined and convoluted. Intriguingly, a growing body of research in recent years has associated inward-rectifying potassium (Kir) channels with several neurodegenerative diseases such as AD (Akyuz et al., 2020), ALS (Peric et al., 2021), HD (Tong et al., 2014) and PD (Liu et al., 2022).

Kir channels are a distinctive class of transmembrane proteins with an increased propensity to selectively transport K^+ inwardly compared to outwardly when subjected to the equivalent driving force in the opposite direction. There are four sub-classes of Kir channels consisting of classical Kir channels (Kir2.1-Kir2.4), G protein-coupled Kir channels (GIRKs/Kir3.1-Kir3.4), K^+ transport Kir channels (Kir1.1, Kir4.1, Kir4.2, Kir5.1, Kir7.1) and adenosine triphosphate (ATP)-sensitive Kir channels (K_{ATP}/Kir6.1 and Kir6.2 and their regulatory subunits SUR1/2A/2B; **Figure 1a**).

K_{ATP} channels and neurodegeneration: Various Kir channels have different levels of proficiency in inward rectification, which enables fine-tuning of the resting membrane potential, the duration of action potentials, K^+ homeostasis, and signal transduction in a multitude of cell types. Interestingly, Kir channels exhibit both neuroprotective and degenerative effects in different experimental models. For instance, K_{ATP} channels, which are sensitive to cellular metabolism, can suppress neuronal excitation by enabling K^+ efflux and hyperpolarization during hypoxic episodes or conditions marked by low ATP/adenosine diphosphate ratios. This action aids in decreasing cellular energy consumption and subsequently triggers neuroprotective effects during conditions like cerebral ischemia (**Figure 1b**). In fact, the knockout of both Kir6.1 and Kir6.2 exacerbates neurodegeneration under such circumstances (Szeto et al., 2018).

However, an opposite effect of K_{ATP} channels was observed in PD models. In a rotenone-induced PD model, for example, the activation of mitoK_{ATP} (Kir6.1/Sur2B) channels on the inner membrane of mitochondria led to excessive DA neuron degeneration due to imbalances in mitochondrial dynamics (Peng et al., 2018; **Figure 1c**). Furthermore, in PD, the selective degeneration of DA neurons is primarily observed in the SNpc region, whereas DA neurons in the adjacent ventral tegmental area (VTA) are largely spared. This distinct vulnerability of DA neurons in SNpc has long been perplexing, but it seems to involve greater expression and enhanced selective activation of Kir6.2-containing K_{ATP} channels in SNpc DA neurons compared to those in the VTA (Liss et al., 2005; **Figure 1d**). Therefore, an increased K_{ATP} channel activity might be beneficial during short-term metabolically demanding conditions but could promote chronic neurodegeneration in the long term. Indeed, type 2 diabetes patients with insufficient closure of β cell K_{ATP} channels, which control insulin secretion, have a higher predisposition for PD (Santiago and Potashkin, 2014).

Notably, a gain-of-function mutation in the G-protein activated Kir channel, Kir3.2 (GIRK2), naturally occurring in the *Weaver* mouse, results in a loss of the K^+ selectivity of GIRK2. This alteration permits constitutive activation of Kir3.2 and increased Na^+ influx, consequently augmenting neuronal hyperexcitability and degeneration (**Figure 1e**). This spontaneous mutation generates a PD-like phenotype due to the degeneration of DA and cerebellar granule cells. Interestingly, the knockout of Kir6.2-containing K_{ATP} channels in the *Weaver* mouse specifically rescues SNpc DA neurons, presumably due to the absence of selective K_{ATP} activation in response to mitochondrial complex I inhibition. This lends credence to the hypothesis that the lower susceptibility of VTA DA neurons is because of their mild basal mitochondrial uncoupling, which prevents the activation of K_{ATP} channel when challenged with significant complex I inhibition (Liss et al., 2005; **Figure 1d**). Further supporting the pathogenetic role of selective activation of K_{ATP} channels, sulfonylurea receptor 1 (SUR1), a regulatory subunit forming K_{ATP} channels with Kir6.2 in SNpc DA neurons, was shown to be upregulated in PD patients, contributing to an increased burst firing and neuronal excitation in DA neurons (Liu et al., 2022). The distinct roles that K_{ATP} channels play in the context of different types of neurodegeneration highlight the intricate nature and significance of Kir channels as potential targets in comprehending neurodegenerative disorders.

Kir channels and glial functions in neurodegenerative diseases: Neuroinflammation is a crucial component in the pathogenesis and progression of neurodegenerative diseases. Microglia, the primary mediators of neuroinflammation, play an indispensable role in preserving a healthy CNS environment, and aberrant microglial activation has long been associated with neurodegeneration by virtue of overproduction of pro-inflammatory cytokines, resulting in oxidative stress and apoptosis of neurons. There has been compelling evidence associating Kir channel dysfunctions with microglia-mediated neuroinflammation.

In contrast to the detrimental function of Kir6.2-containing K_{ATP} channels in neurodegeneration, as discussed above, Kir6.1-containing K_{ATP} channels can switch microglia from the destructive pro-inflammatory M1 phenotype toward the beneficial anti-inflammatory M2 phenotype. This is demonstrated by the promotion of M2 polarization and inhibition of M1 inflammatory responses by Kir6.1 overexpression, which suppresses the p38 MAPK-NF-κB signaling pathway and alleviates DA neurodegeneration in PD mouse models; while Kir6.1 knockdown has the opposite effects (Du et al., 2018; **Figure 1f**).

Beyond K_{ATP} channels, Kir2.1 has also been suggested to mediate the IL-4-induced M2 phenotype of microglia (Nguyen et al., 2017; **Figure 1f**). Furthermore, its expression can be stimulated in microglia by AβO, a highly toxic amyloid-β species and principal instigator of AD phenotypes (Maezawa et al., 2018). This AβO-induced overexpression of Kir2.1 is likely a protective response, as the knockout of Kv1.3, which skews microglial activation from M1 to M2 phenotype, also leads to Kir2.1 activation following LPS treatment (Maezawa et al., 2018; **Figure 1f**). The exact manner in which the overexpression of Kir2.1 influences microglia-mediated AD pathobiology remains unclear. However, these fascinating findings inspire further investigation into the role of Kir channels in microglial polarization and their functions in neurodegenerative disorders.

Not only microglia, but other glial cells, such as astrocytes and oligodendrocytes, also play instrumental roles in the progression of neurodegenerative disorders, with Kir channels significantly affecting several causative mechanisms. Similar to microglia, Kir6.1 is abundantly expressed in astrocytes and exerts anti-inflammatory effects. Mice with astrocytic Kir6.1 knockout demonstrated a substantially higher ratio of reactive astrocytes and increased DA neurodegeneration (**Figure 1g**). This neuroprotective function of astrocytic Kir6.1 in PD was ascribed to the interplay between astrocyte and neuron via NF-κB/C3/C3aR signaling-mediated communication (Chen et al., 2021).

Astrocytes also serve an important function by uptaking K^+ ions discharged into the brain's extracellular spaces during neuronal activity, thereby maintaining K^+ homeostasis. This is crucial for ensuring the neurons function properly. This task largely depends on the Kir4.1 channel, which is abundantly expressed in astrocytes. It contributes not only to the spatial buffering of effluxed K^+ ions, but also to maintaining the resting membrane potential of astrocytes, regulating cell volume, and reuptaking glutamate, which influences action potentials and neuronal excitability. Accordingly, reduced astrocytic Kir currents are observed during cerebral trauma, ischemia, inflammation, and neurodegenerative diseases (**Figure 1g**). In the context of ALS, localized progressive reductions in Kir4.1 channel expression have been observed in the ventral spinal cord, facial and trigeminal nuclei, brainstem and motor cortex in animal models. Furthermore, ALS cell models showed a loss of Kir currents, along with diminished K^+ uptake and depolarized membrane potentials. In addition, Kir channel expression and activity in oligodendrocytes are significantly reduced in a $SOD1^{G93A}$ mutation-induced ALS animal model, indicating the participation of this channel in the mechanisms leading to anterior horn denervation and motor neuron degeneration (Peric et al., 2021; **Figure 1h**). Similarly, there is significant downregulation in astrocytic Kir4.1 expression associated with AD and HD (**Figure 1i**). Intriguingly, specifically restoring the expression of astrocytic Kir4.1 in the striatum appeared sufficient to correct altered astrocytic membrane properties, re-establish K^+ homeostasis, and improve both morbidity and mortality in HD mouse models (Tong et al., 2014). Consequently, astrocytic Kir4.1 presents itself as a highly promising therapeutic target for these neurodegenerative disorders.

Kir channels and abnormal protein aggregation in neurodegenerative diseases: Abnormal protein aggregation is a hallmark of numerous neurogenerative disorders. For instance, β-amyloid (Aβ) and Tau proteins form amyloid plaques and Tau tangles respectively in AD, while α-synuclein proteins aggregate into Lewy bodies in PD. Misfolded huntingtin proteins are associated with HD, and protein aggregates formed by superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43, and fused in sarcoma are linked with ALS.

The progressive aggregation of these proteins results in neuroinflammation and the degeneration of cortical and subcortical neurons, severely exacerbating symptoms such as cognitive impairment, personality changes, and motor symptoms associated with these diseases. Despite this understanding, the precise mechanisms by which these aggregates contribute to the pathogenesis of these neurodegenerative disorders remain unclear. Current research continues to explore these mechanisms and develop potential therapies aimed at preventing protein aggregation, enhancing the clearance of aggregates, or protecting neurons from the toxic effects of these aggregates

by modulating their downstream targets. Intriguingly, one class of these downstream targets appears to be the Kir channels.

For example, Aβ has been shown to directly impact the expression of Kir channels in animal models of AD. A study by Akyuz et al. (2020) found that in an amyloid-β (Aβ)(1–42)-infused rat model of AD, the progressive aggregation and spread of Aβ resulted in reduced expression of Kir2.1 and Kir6.1 at both RNA and protein levels within the hippocampus (Akyuz et al., 2020). In addition, a reduction of Kir4.1 expression was observed in both transgenic amyloid deposition-mediated AD mouse models and post-mortem analyses of AD patients with moderate to severe Aβ aggregation (**Figure 1j**). Importantly, this diminished channel expression correlated with the level of vascular amyloid deposits and disease progression, implying a mechanistic role of Kir4.1 in Aβ aggregation-induced AD pathology (Wilcock et al., 2009).

In contrast to the deficiency of Kir channels observed in AD, over-functionality of Kir channels is suggested to contribute to α-synuclein pathology in PD. For instance, an upregulation of the SUR1 regulatory subunit of the K_{ATP} channel was noted in A53T α-synuclein transgenic (α-synA53T$^{+/+}$) mice, which coincided with an increased occurrence of burst firing in DA neurons. Interestingly, when the abnormally elevated SUR1 level was reduced, the DA neuron degeneration was delayed (Liu et al., 2022; **Figure 1k**). While multiple Kir channels have been linked to aberrant protein aggregation across various forms of neurodegeneration, the precise mechanisms remain elusive, and numerous questions persist. For example, what causes the expression of certain Kir channels to change in response to specific protein aggregation? Which signaling pathways are involved in these regulatory processes? Are there any compensatory mechanisms activated when a particular channel is abnormally regulated? What would be the most effective strategy to restore K^+ homeostasis in order to mitigate these pathological events? These and other questions highlight the complexity of the issue and the need for continued exploration in this field.

In summary, although there are some conflicting findings regarding the effects of Kir channels, as observed with K_{ATP} channels in different models, the majority of studies suggest that deficiencies in Kir channels exacerbate neurodegeneration. The modulation of K^+ homeostasis during periods of neuronal stress plays a pivotal role in influencing both neurons and glial cells, with clear implications for neurodegeneration. When considered together, the nuances of Kir channel dysfunctions and their downstream effects hold significant relevance to the mechanisms of neurodegeneration observed across several diseases. By gaining a deeper understanding of the intricacies of K^+ homeostasis in various CNS-residing cells, the prospect of developing novel neuroprotective drugs that target upstream neurodegenerative mechanisms resulting from these dysfunctions becomes highly promising.

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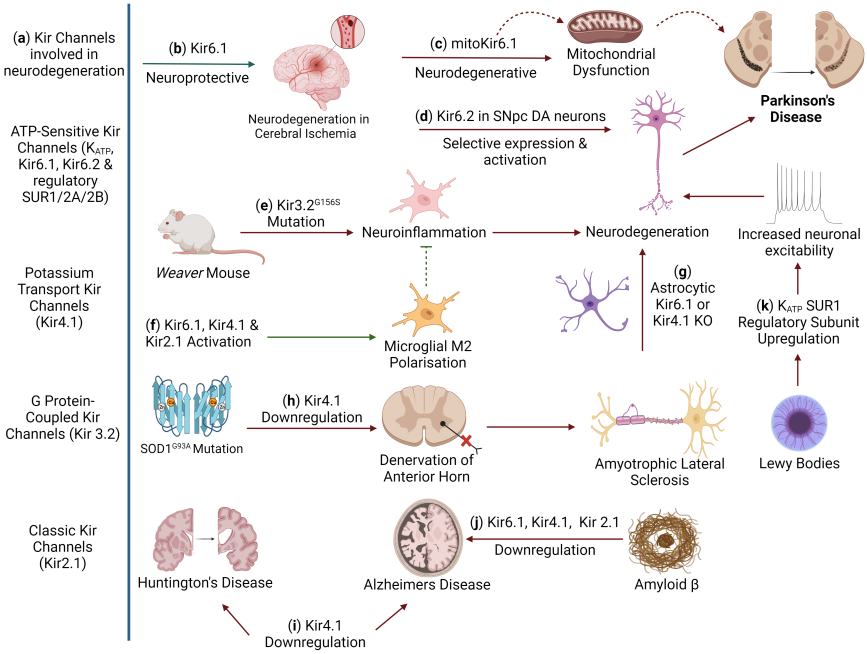

Figure 1 | **Current evidence of the role of Kir channelopathies in the pathogenesis of neurodegenerative disorders.** (a) The four classes of Kir channels, ATP-sensitive Kir channels, potassium transport Kir channels, G protein-coupled Kir channels, and Classic Kir channels, all play roles in neurodegeneration. (b) Kir6.1 exhibits neuroprotective properties during cerebral ischemia-related neurodegeneration, which starkly contrasts with the detrimental effects of mitoKir6.1 observed in the rotenone-induced Parkinson's disease (PD) model (c). This neurodegenerative role of Kir6.1 was also underscored by the rescue of dopaminergic (DA) neurons upon its deletion in the MPTP-induced PD model. (d) The high expression and selective activation of Kir6.2-containing K_{ATP} channels in the substantia nigra pars compacta (SNpc) DA neurons contribute to these neurons' specific vulnerability compared to DA neurons in the neighboring ventral tegmental area (VTA). (e) A genetic Kir3.2 mutation (Kir3.2^{G156S}) triggers neuroinflammation and the subsequent degeneration of DA neurons and cerebellar granule cells, resulting in PD symptoms in a murine model known as the *Weaver* mouse. (f) Three classes of Kir channels have demonstrated a mechanistic impact on the M2 activation of microglia, potentially mitigating neuroinflammatory episodes. (g) The deletion of astrocytic Kir6.1 or Kir4.1 impairs functional aspects of astrocytes, leading to neurodegeneration. (h) In the genetic mutation SOD1^{G93A}-induced Amyotrophic Lateral Sclerosis (ALS) animal models, Kir4.1 is downregulated, causing anterior horn denervation and disruption of motor neuron myelination by oligodendrocytes. (i) A decrease in Kir 4.1 expression in astrocytes is observed in both AD and Huntington's Disease (HD). Notably, the latter exhibited substantially less neurodegeneration when Kir4.1 was upregulated. (j) Reduced expression of Kir6.1, Kir4.1, and Kir2.1 has been observed in both transgenic amyloid deposition (Aβ)-mediated Alzheimer's disease (AD) animal models and in AD patients with moderate to severe Aβ aggregation. (k) In an α-synuclein transgenic murine model, an upregulation of the regulatory subunit of K_{ATP} channels, SUR1, leads to increased burst firing of DA neurons, causing neurodegeneration. Created with BioRender.com.

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