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Inwardly Rectifying Potassium Channels in Neurological Diseases in Last Decade

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Review Article

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Abstract

Along the last decade, the central role of ion channels in neurological diseases has been carefully studying. Especially, inwardly-rectifying potassium (Kir) channels controlling the cell excitability by acting towards the hyperpolarization phase of neuronal action potential are vital in the neurological disease mechanism.

Recent functional studies have shown that the Kir channels associating with various neurological disorders, primarily epilepsy cannot carry K^+ ions into the cell due to dysfunction. Investigations into the role of Kir channels with 7 subfamilies in the mechanism of neurological disorders (epilepsy, multiple sclerosis, Alzheimer's disease, Parkinson's disease, autism, etc.) have shown that the Kir channels functionally may change. After the key role of Kir channels in the pathophysiology is shown, novel drug studies targeting these channels have begun to be developed. Mutations in genes encoding ion channel protein dysfunction have also been included in this review. This is the review to our knowledge in neurological disorders showing the functional expression of Kir channels. Our review shows that Kir channels may play a role in pathophysiology associated with neurologic diseases. In review, the role of Kir channels in various common neurological diseases will be classified and a resource will be created for the researchers.

Keywords: Epilepsy; Kir Channels; Alzheimer; Multiple Sclerosis

Introduction

Inwardly rectifying potassium channels (Kir channels), which play an essential role in excitable cells such as neuron and cardiac myocyte, work into the end of the action potential and carry the K^+ ion into the cell. The main task of the Kir channels is to control the cell excitability by transforming the action potential into membrane resting potential. In order to bring the hyperpolarized cell to the normal resting potential at the end of the action potential, Kir channels carrying the K^+ ion into the cell to accelerate the repolarization and to make the action potential a reproducible process.

Kir channels (Kir1-Kir7) consisting of seven different subunits are of tetramer structure and consist of two transmembrane domains. These channels perform their physiological functions by acting as a diode carrying K^+

ion in the cells, which have more negative potentials than the potassium equilibrium potential (E_K). In addition, Kir channels gain their straightening properties due to the voltage-gated blocking of the channel pores with Mg^{2+} ion and cytoplasmic polyamines. Accordingly, the K^+ ion flow to extracellular is inhibited depending on the value of intracellular Mg^{2+} concentration and the influx is released to alter the membrane potential.

It has been determined in recent studies that Kir channel has important role in the formation of various neurological diseases. For this purpose, we have prepared a review to show the role of Kir channels in epilepsy, Alzheimer's disease, multiple sclerosis, Parkinson disease, autism, Huntington disease and amyotrophic lateral sclerosis (ALS) for last decade.

Epilepsy

Epilepsy is a chronic neurological disorder characterized by neuronal discharges resulting from impairment of excitatory and inhibitory balance, caused by functional and structural changes in the brain. It is known that astrocytes help neuronal activity, and these cells are thought to be essential players in brain signaling. A change in Kir channels and gap junction suggesting altered astroglial junction is reported to be in the epileptic tissue. In addition, it was found that high extracellular potassium and glutamate were resistant to hyperactivity by facilitating clearance. In 2012, the temporal lobe epilepsy study showed astrocyte dysfunction in terms of potassium channels. It was reported that K^+ channels are associated with gap junctions and combine astrocytes with gapjunction, a precondition for redistributing high potassium from areas of excess neuronal activity to regions with low extracellular potassium concentration. In the study, refractory epilepsy modeled astroglial Kir4.1 channels deterioration has been detected and accordingly it has been shown to cause changes in localization and function [1].

G-protein activated, inward rectifying potassium channels, GIRK, is a family of ion channels that has concentrated on intensive research interest for nearly two decades (Kir3.1-Kir3.4). In 2013, the antiepileptic properties of the first potent and selective activator ML297 (VU0456810) in GIRK channels were investigated in mice. ML297 has been shown to be active in two in vivo epilepsy models, with 40% of patients characterized by symptoms resistant to current therapies. In addition to selectively investigating the role of ML297 in the physiology of GIRK, it has been reported to be an essential development beginning to understand its potential for the diversity of therapeutic indications [2].

In a 2013 study, it was shown that Kir4.1 level increased especially in hypothalamus of astrocytic Kir4.1 channel in the temporal lobe epilepsy model. Kir5.1 and Kir2.1 channel were not changed. The role of the astroglial Kir4.1 channel in the pathogenesis and treatment of epilepsy were reported to mediate the spatial K^+ buffering function of the astrocytes in which the astrocytes were specifically expressed in the brain. Kir4.1 channels, especially in the amygdaloidal nuclei, have been implicated in the production of generalized tonic-clonic seizures by increasing the extracellular levels of K^+ and/or glutamate [3].

In 2018, it was reported that antiepileptic drugs increased the astrocyte Kir4.1 expression in rat limbic region and Kir4.1 were specifically expressed in astrocytes and regulated neuronal susceptibility by mediating spatial potassium buffering. Accordingly, antiepileptic drugs that are effective for convulsive seizures have been shown to increase astrocytic Kir4.1 channel expression in limbic regions which may be associated with antiepileptic effects [4].

Kir4.1 channel was investigated in the expression of brain-derived neurotrophic factor (BDNF) in astrocytes. Recent evidence suggests that Kir4.1 channel play an important role in modulating the effects of antidepressant drugs and BDNF expression in astrocytes. Inhibition of astrocytic Kir4.1 channel (downregulation or blockage) seems to weaken K^+ buffering, increase extracellular K^+ and glutamate, enhance neuronal excitability and facilitate expression of BDNF. Conversely, activation (upregulation or opening) of the Kir4.1 channel decreases extracellular K^+ and glutamate, reducing neuronal excitability and alleviating BDNF expression. In particular, old pathophysiological changes appear to be crucial in the pathogenesis of depressive disorders in epileptogenesis and pain sensitivity [5].

Because sudden unexpected death in epilepsy (SUDEP) is unknown, cardiac Kir channels were targeted to clarify. In 2018, it was shown that epilepsy and cardiac Kir channel expression change in rats. The results show that Kir channels might play role in epilepsy-related cardiac pathology [6].

Alzheimer's Diseases

Alzheimer's disease (AD) is a chronic neurodegenerative disease that involves a buildup of

amyloid beta plaques and neurofibrillary tangles in the brain. Memory loss is among the first clinical symptoms complained by patients suffering from AD because 60–70% of dementia cases are due to AD.

In a 2009 study, the effect of vascular amyloid on astrocytic water and potassium channels in mouse models and people with AD was investigated. Transgenic mice with elevated cerebral amyloid angiopathy levels have been shown to have significant reductions in AQP4 and Kir4.1 positive staining associated with blood vessels. A possible explanation for the loss of AQP4 and Kir4.1 channel is that they share a common binding protein affected by vascular amyloid deposition. As a result of the study, the expression of Kir4.1 was found to be significantly decreased in AD brain diagnosed after mortem [7].

In 2016, it is thought that the blocking of K_{ATP} channel (Kir6.2) by memantine represents a new mechanism for the treatment of AD. As a result, memantine has changed Kir6.2 activity and Kir6.2 channel has been shown to be a new target to improve memory impairment in Alzheimer's patients [8]. The relationship between Kir3 and hippocampal function in a mouse model of early AD pathology was aimed. As a result, a synaptic mechanism has been found by Kir3 channel modulation in order to prevent hypertension causing synaptic network and cognitive disorders in the pathogenesis of early AD [9].

Multiple Sclerosis

Multiple sclerosis (MS) is a neurological disorder that involves the destruction of myelin (demyelination) in the central nervous system and may also affect the peripheral nervous system. It was examined whether increased anti-Kir4.1 antibody in MS have a marker role in disease relapsing. Screening of the default autoimmune targets MS revealed some of the patients carrying antibodies against Kir4.1, a potassium channel sharing functional properties with AQP4. Anti-Kir4.1 antibodies were significantly higher in MS patients; however, anti-Kir4.1 antibody levels showed differences in recurrence and remission in MS patients; therefore, anti-Kir4.1 antibodies may be indicative of a disease exacerbation [10].

In a study conducted in 2016, Kir4.1 potassium channel expression and its relationship with MS pathogenesis were investigated. In approximately half of the MS patients examined, autoantibodies against Kir4.1 were detected. In addition, it is stated that the identification of Kir4.1 autoantibodies may have high therapeutic values in the treatment of MS [11]. In 2018, Kir4.1 channel was investigated in MS model of mice. Accordingly, these channels have been shown to be overexpressed in astrocytes. The results show that there is an increase in K^+ internal flow in glial cells of mice treated with MS model, which can reduce neuronal depolarization and contribute to cell flexibility mechanisms [12].

Parkinson's Disease

Parkinson's disease (PD) is caused by the loss of dopamine-producing neurons belonging to a group called motor system diseases. PD is a progressive disease that gradually worsens as the hands, arms, legs, chin and face tremble. In a 2008 study, overexpression of Kir2.3 channels and use of dopamine-1 receptor promoter in striatal neurons were investigated. Kir2.3 channel is naturally expressed in basal ganglia in dysfunction-related pathways in PD; therefore, to distinguish the potassium channel protein produced from the vectors, Kir2.3 gene was modified as a fusion protein comprising the strep-tag epitope in the N-terminal region [13].

In 2011, Kir2 expressions could be considered as potential peripheral biomarkers in lymphocytes from patients with PD. In this study, dopamine receptor (D2, D3), Kir2 (Kir2.1, Kir2.2, Kir2.3, Kir2.4) and Kir6.2 gene expression levels were determined. The results showed that D2 and D3 mRNA expression in peripheral blood lymphocytes of PD was significantly reduced compared to controls. Kir2, Kir2, Kir2, Kir2, 4 and Kir2.4 mRNA expression was found to be down regulated in PD. However, no significant difference was observed in mRNA expression of Kir6.2 between PD patients and controls [14].

Huntington's Disease

Huntington's disease (HD) is a genetic neurological disease. Patients have some movement disorders as well as mental retardation. In 1872, he first observed that the disease was hereditary. It is an autosomal dominant disease and affects the brain and nervous system. Mutations in the Kir2.1 channel gene are known to cause this disease. In a study conducted in 2014, astrocytic Kir4.1 channel was reported to contribute to neuronal dysfunction in HD model of mice. Accordingly, it was determined that the extracellular potassium was elevated. These findings suggest that astrocyte-mediated K^+ homeostasis, which causes Kir4.1 channel in HD as therapeutic targets, may be caused by unknown disorders [15].

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a medical term describing muscle loss and damage to the spinal cord. It is also a progressive muscle weakness. The main reason is the death of nerve cells called motor neurons that control the muscles. Kir4.1, AQP4 channels and the microspheres of the spinal cord are located together with clusters; these two proteins lead K^+ buffer and water away from the extracellular space to remove blood vessels in the spinal cord. In a 2010 study, loss of Kir4.1 and an increase in AQP4 protein were observed in ALS mouse model [16]. However, this observation, which is associated with the disturbance of Kir4.1 channel loss and K^+ buffering, was reported to explain the understanding of paracrine toxicity in motor neurons typical of ALS [17]. In 2012, changes in astrocytic aquaporin-4 and Kir4.1 expression in the brain were examined in the brainstem and cortex in ALS model of rats. Accordingly, the expression of AQP4 was increased and Kir4.1 expression was shown to be decreased. In addition, whole-cell patch-clamp recordings from cultured ALS cortical astrocytes showed markedly lower Kir flow density [18].

Autism

Autism is a disorder that begins before the age of three and lasts a lifetime, preventing the development of the brain, which leads to limited and repetitive behaviors that damage social interaction and communication. In a study conducted in 2011, possible causes in gain of function for Kir4.1 were investigated in autism related to seizures and mental disability. The KCNJ10 gene encoding Kir4.1 has recently been associated with seizure sensitivity in humans and mice, and has been identified as a possible candidate gene for Autism Spectrum Disorders (ASD). The study showed that the molecular mechanism contributing to the disorder was due to an increase in surface expression or conductivity of the Kir4.1 channel [19].

In 2014, the effects of genetically induced functions of Kir2.1 channel on short QT3 syndrome and autism-epilepsy phenotype were investigated. Electrocardiographic recordings and monozygotic twins showing short QT interval in autism-epilepsy phenotype have been reported. A new KCNJ2 variant was identified in Kir2.1 by genetic screening. The KCNJ2 variant increased the surface expression and stability of the channel in the plasma membrane [20].

In 2016, dysfunction of astrocytic Kir4.1 channel was investigated in children with epilepsy accompanying to ADS. In order to identify the role of Kir4.1 variant in the disease, genotype-phenotype correlations were performed in one of the affected individuals in KCNJ10. As investigated on astrocyte-like cells, the p.R18Q mutation resulted in a gain of function by increasing Kir4.1 membrane expression and current density. It was stated that the results confirming the variables in KCNJ10 deserve attention in autism and epilepsy and that they have an understanding of the molecular mechanisms of autism and seizures [21].

Conclusion

It can easily be said that Kir channels play a role in diseases such as epilepsy, Alzheimer's disease, multiple sclerosis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and autism. Particularly the function of the astrocytic Kir4.1 channel, its relation with AQP4, and the management of extracellular K^+ concentration are the key reasons for its involvement in these neurological diseases.

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