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MINIREVIEWS

Involvement of leak K^+ channels in neurological disorders

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Abstract

TWIK-related acid-sensitive K^+ (TASK) channels give rise to leak K^+ currents which influence the resting membrane potential and input resistance. The wide expression of TASK1 and TASK3 channels in the central nervous system suggests that these channels are critically involved in neurological disorders. It has become apparent in the past decade that TASK channels play critical roles for the development of various neurological disorders. In this review, I describe evidence for their roles in ischemia, epilepsy, learning/memory/cognition and apoptosis.

Key words: Leak K^+ channel; TWIK-related acid-sensitive K^+ channel; Neurological disorder

Core tip: The leak K^+ conductance generated by TWIK-related acid-sensitive K^+ (TASK) channels is crucial for neuronal excitability. Because of the substantial expression of TASK channels in the brain, it is possible that these channels are responsible for numerous neurological disorders. However, little is known about the roles of TASK channels in the development of neurological disorders. In this review, I introduce the molecular basis of leak K^+ channels and describe the possible roles for TASK channels in several neurological disorders.

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INTRODUCTION

The neurological disorders are diseases of the brain, spinal cord, and nerves that make up the nervous system. There are a large number of neurological disorders such as epilepsy, Parkinson's disease and stroke. To date, many studies have been demonstrated that various ion channels expressed in the nervous system are involved in the development of neurological diseases[1,2]. The ion channels are classified into voltage-gated, ligand-gated, mechanosensitive and leak channels based on the control mechanism, while being classified into Na^+, K^+, Ca^{2+} and Cl^- channels based on the ion selectivity[3]. In recent years, the molecular basis of ion channels has been elucidated through the development of the molecular cell biology and genetic engineering method. However, much of the roles of ion channels in pathophysiological conditions including neurological

disorders remains unclear[4]. In this review, I will discuss the roles of leak K^+ channels in neurological disorders. In particular, I will focus on the TWIK-related acid-sensitive K^+ (TASK); TWIK, for tandem P domains in a weak inwardly rectifying K^+) channels (*e.g.,* TASK1 and TASK3) due to the high expressions in the central nervous system.

LEAK K^+ CHANNELS

Based on the structural features, K^+ channels are classified into three major families[5]. Members of the first family of K^+ channels include the voltage-gated K^+ channels (the delayed rectifier and transient voltage-dependent K^+ channels)[6] and Ca^{2+}-dependent K^+ channels[7] and form tetramers with each subunit containing six transmembrane domains and one pore domain. Members of the second family of K^+ channels include the inwardly-rectifying K^+ channels such as ATP-sensitive K^+ channels[8] and form tetramers with each subunit containing two transmembrane domains and one pore domain. Members of the third family of K^+ channels include the leak K^+ (two-pore-domain K^+) channels[5,9] and form dimers with each subunit containing four transmembrane domains and two pore domains. In excitable cells such as neurons, a negative membrane potential is critical for electrical signaling, and it has long been considered that this key mechanism is largely mediated by leak K^+ currents. However, the molecular basis for characterizing functional properties of leak K^+ currents remained unknown until recently. In the 1990s, the discovery of the *KCNK* gene family has been described whose members generate the hallmark properties of leak K^+ currents[9]. In mammalians, fifteen subunits have been identified and divided into six subfamilies (TWIK, TREK, TASK, TALK, THIK, and TRESK) on the basis of sequence similarity and functional resemblance[4,9]. The TWIK group includes the weakly inwardly rectifying channels (TWIK1, TWIK2, and the nonfunctional KCNK7); the THIK group includes halothane-inhibited THIK1 channel and related non-functional THIK2; the TREK group includes the arachidonic acid and mechanosensitive channels (TREK1, TREK2, and TRAAK); the TALK group includes the alkaline-activated channels (TASK2, TALK1, and TALK2/TASK4); the TASK group includes acid-sensitive channels (TASK1, TASK3, and the nonfunctional TASK5); the TRESK group includes Ca^{2+}-activated channels (TRESK1). Among fifteen subunits of leak K^+ channels described above, TASK1 and TASK3 are widely expressed in the central nervous system[10].

TASK CHANNELS

TASK channels are two-pore–domain channels that generate pH-sensitive K^+ currents with little time-dependence and weak rectification[5]. In heterologous expression systems, TASK5 was found to be inactive while TASK1 and TASK3 were able to form functional homomeric channels[9]. In addition, there is evidence that TASK1 and TASK3 might form functional heterodimers *in vitro* and *in vivo*[11,12]. The unitary conductance of TASK3 channel (approximately 28 pS) is about two times larger than that of TASK1 channel (approximately 14 pS)[13]. Although the macroscopic currents arising from these two channels are similar, the sensitivity to extracellular pH is different. The pK for TASK1 inhibition is approximately 7.4 while that for TASK3 is approximately 6.7[13]. TASK channels are inhibited by extracellular acidification, local anesthetics and G-protein-coupled receptors[5]. In contrast, TASK channels are activated by phospholipids and volatile anesthetics such as halothane and isoflurane[5].

INVOLVEMENT OF TASK CHANNELS IN NEUROLOGICAL DISORDERS

Ischemia

Neuronal damage caused by ischemic stroke is a major health care problem for persistent disability and death in clinical practice[14]. When ischemic state occurs, the transient membrane depolarization is induced in neurons. Consequently, the release of neurotransmitters such as glutamate, neuropeptide and Zn^{2+} is enhanced[15]. It is well known that the excessive glutamate causes neurotoxicity including neuronal dysfunction and degeneration. When the ischemic events continue to occur, cell death is induced[16]. On the other hand, mild hypoxia can induce neuroprotective signaling cascades that prevent neuronal death[17,18]. The activation of K^+ channels causes membrane hyperpolarization, which increases cell survival during cellular stress conditions. The decreased neuronal activity and the resultant lower metabolic demands could enhance neuronal survival under stress conditions. Thus, the protective effect of K^+ channels would reduce the development of ischemic stroke.

TASK1 and TASK3 channels are sensitive to acidic pH and hypoxic conditions. In addition, TASK3 homomeric channels are selectively suppressed by Zn^{2+}[19]. Considering that acidic pH and hypoxia are observed and the release of Zn^+ is enhanced during ischemic conditions, it is likely that TASK1 and TASK3 channels are involved in the development of ischemic stroke. Indeed, the roles of these channels in the ischemic stroke development have been revealed by pharmacological inhibitors and genetic knockout (KO) mice. In a study using a mouse model of cerebral ischemia, transient middle cerebral artery occlusion (MCAO), the infarct volume in TASK1 KO mice was significantly larger than that in its control mice while there was no significant difference in the infarct volume between TASK3 KO and its control mice[20]. The increased infarct volume could be mimicked by the TASK1 inhibitor anandamide[20]. Furthermore, in a study using a mouse model of permanent MCAO, the expression of TASK1 channel gene reduced the infarct volume, most likely

by a general influence on blood pressure[21]. These finding suggest TASK1 expressed in the brain decreases neuronal damage when stroke occurs.

Epilepsy

Epilepsy is a brain disorder that is characterized by the presence of spontaneous episodes of neuronal discharges[22]. Excessive and/or synchronous discharges in the brain cause the disruption of consciousness and disturbance of sensation and movement[22]. K^+ channels contribute to nearly all aspects of cellular electrical signaling and are important determinants of seizure susceptibility[23]. Therefore, K^+ channels have been considered as practical targets for anti-epileptic drug development.

In pathological conditions such as ischemia and epilepsy, it has been demonstrated that the extracellular pH was changed in the brain[24,25]. In the CA1 hippocampal areas, recurrent epileptiform activity caused biphasic pH shifts, consisting of an initial extracellular alkalinization followed by a slower acidification[25]. The authors indicated that the different extracellular pH shifts between CA1 and dentate gyrus might have caused the regional difference in seizure susceptibility between these two areas[25]. Because TASK channels are highly sensitive to changes in extracellular pH, several studies implicated the involvements of these channels in the generation of epilepsy. The changes in neuronal excitability within the hippocampus are one of the hallmarks of temporal lobe epilepsy[26]. Therefore, it is conceivable that TASK channels expressed in the hippocampus play essential roles in the generation of epilepsy. First, the role of TASK1 channels in epilepsy was investigated in the hippocampus of gerbils[27]. Between the hippocampi of young seizure-resistant (SR) and seizure-sensitive (SS) gerbils (1 to 2 mo old), there was no difference in the TASK1 and TASK2 immunoreactivites. In adult SS gerbil hippocampus, TASK1 immunoreactivity in astrocytes was higher compared to the adult SR gerbil hippocampus. After seizure events, TASK1 immunoreactivity was significantly downregulated in astrocytes of the SS gerbil hippocampus. Furthermore, several anti-epileptic drugs selectively reduced the TASK1 immunoreactivity in astrocytes of the SS gerbil hippocampus[27]. These findings indicated that upregulation of TASK1 channels in astrocytes may be responsible for the seizure activity of adult SS gerbils and that downregulation of TASK1 channels in astrocytes may suppress the seizure activity. In addition to TASK1 channels, the role of TASK2 channels in epilepsy was examined by using a rat model of experimental temporal lobe epilepsy[28]. Following status epilepticus, TASK2 expression in the CA1 pyramidal cell layer was downregulated, probably due to damage or loss of CA1 pyramidal cells. On the other hand, the TASK2 expression was significantly upregulated in the dentate granuler and CA3 pyramidal cell layers and endfeet of perivascular astrocytes[28]. These findings suggest that upregulation of TASK2 channels may make a contribution to adaptive responses by inducing hyperpolarization and reducing seizure activity.

Ion channels are essential for the regulation of excitability in the central nervous system[3]. It is believed that various inherited diseases associated with abnormal excitability of the affected neurons are caused as a result of mutations in ion channel encoding genes[2]. Several studies reported the discovery of epilepsy-related mutations in genes encoding TASK channel proteins. Childhood absence epilepsy is an idiopathic, generalized, nonconvulsive epilepsy that occurs in otherwise normal children. The *KCNK9* gene coding for the TASK3 channel is present on chromosome 8 in a locus that shows positive genetic linkage to the human absence epilepsy phenotype[29]. Furthermore, in the genetic absence epilepsy rats from Strasbourg (GAERS), an additional alanine residue in a polyalanine tract within the C-terminal intracellular domain was detected in the *KCNK* gene. For this reason, *TASK3* channels were regarded as a promising candidate gene for absence epilepsy. However, there were no significant differences in the physiological properties between the wild-type and mutant *TASK3* channels[30]. In addition, leak K^+ currents were almost similar between thalamocortical neuros in GAERS and nonepileptic animals[30]. These observations suggest that *TASK3* gene was not associated with absence epilepsy. On the other hand, a mutation analysis of the *TASK3* gene was performed in patients with children and juvenile absence epilepsy[31]. Only one silent polymorphism was detected in exon 2 of the TASK-3 coding region. However, since there was no relationship between the exon 2 polymorphism and absence epilepsy[31], the human TASK-3 appears not to be involved in the absence epilepsy.

Apoptosis

During brain development, the cell excitability is an important determinant for neuronal survival and proliferation[32]. K^+ channels are responsible for the resting membrane potential and action potential duration. Activation of K^+ channels results in membrane hyperpolarization, which significantly influences neuronal death or survival. It has been demonstated that activation of K^+ channels induced neuronal apoptotic cell death[33,34] whereas it protected neurons from ischemia[35] and glutamate-induced cell death[36]. Previous studies revealed that the expression of TASK channels may substantially affect cell viability in either direction[37]. It has been demonstrated that TASK3 channels are responsible for K^+-dependent apoptosis in cultured cerebellar granule neurons. Neuronal death was caused by apoptosis when cerebellar granule neurons were cultured *in vitro* in physiological K^+ concentration, but was prevented when they were cultured in high K^+ concentration. The cell death of granule neurons was also suppressed by pharmacological inhibition

of TASK3 channels with extracellular acidosis and ruthenium red. The cell death was in parallel with the expression level of TASK3 channels[37]. These results indicate a direct relationship between the activity of TASK3 channels and programmed cell death that is necessary for shaping the appropriate cerebellar structure. The authors have also shown that genetic transfection of TASK channel subunits into cultured hippocampal neurons induced apoptotic effect. On the other hand, viral overexpression of TASK3 in cultured hippocampal slices increased cell survival during cellular stress conditions such as an oxygen-glucose deprivation injury[38]. These results suggested that the activation of TASK3 channels can also be protective in neurons under cellular stress conditions.

Learning, memory and cognition

TASK1 and TASK3 channels are widely expressed in the central nervous system. Therefore, it is suggested that the deletion of TASK1 and/or TASK3 channels affects learning and memory. However, in TASK1 KO mice, the higher brain functions were almost similar to the wild-type mice[39]. For example, there were no appreciable differences in anxiety-related behavior and stress-induced hyperthermia between the wild-type and TASK1 KO mice, although the deletion of TASK1 enhanced the sensitivity to thermal nociceptive stimuli[39]. By contrast, TASK3 KO mice exhibited pronounced behavioral changes in relation to memory functions compared with the TASK1 KO mice[40]. In T-maze spontaneous alternation test, the performance in the TASK3 KO mice was poorer compared to the wild-type mice, indicating that working memory was impaired. In addition, during training for the Morris water-maze spatial memory task, the TASK3 KO mice were slower to find the hidden platform, suggesting the impairment of learning[40]. In TASK3 KO mice, the action potential generation and sustained repetitive firing to suprathreshold depolarization were impaired in the granule neurons[41]. Since long term synaptic changes induced by spike activity are believed to underlie learning and memory[42], it is possible that the reduced working memory is ascribed to the impaired spike activity caused by the deletion of TASK3.

CONCLUSION

TASK channels produce background K^+ currents that are time- and voltage- independent, and play crucial roles in setting the resting membrane potential and controlling the K^+ homeostasis. These channels are distributed abundantly in the central nervous system and involved in neurological disorders. Therefore, TASK channel subunits can serve as the molecular targets for treatment of neurological disorders. However, the roles of TASK channels in neurological disorders are just beginning to be investigated. Future studies on the TASK channels will be able to provide even more revealing insights into the neurological disorders.

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