Potassium Channels and CNS Diseases

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In central nervous system (CNS), ion channels, especially potassium channels play important regulatory roles in physiological processes. Potassium (K⁺) channels (e.g., voltage-gated K⁺ channel, calcium-activated K⁺ channel) can be activated by membrane potential shift as well as various ligands [1]. K⁺ channels have widely relationship with CNS diseases. Although many studies have tried to reveal the effect of K⁺ channels in CNS diseases [2-5], the underlying mechanisms are not clearly elucidated, because of the various subfamilies and subtypes of K⁺ channels.

In physiological condition, K⁺ channels mainly elicit an inhibitory modulation in central nervous system. Functional deficiency or expressionional down-regulation of K⁺ channels may enhance neuronal excitability, induce pathological condition, and thus leads to CNS diseases, such as epilepsy [3]. The suppression of G protein-gated K⁺ (GIRK) channels are related to the pathogenesis of Parkinson’s disease, drug addiction, cerebellar ataxia, pain and analgesia [4]. Some K⁺ channels can also control the local microenvironment by regulating the extracellular K⁺ concentration.

This thematic issue has reviewed those research works describing the experimental discoveries, as well as the pathological effect of K⁺ channels. In addition, some reviews in this thematic issue also summarized other ion channels, such as Na⁺ channels, Ca²⁺ channels, Cl⁻ channels, transient receptor potential cation (TRP) channels and synaptic receptors (AMPA, NMDA, GABA receptors), concentrating on their correlationship with K⁺ channels and CNS diseases.

First of all, Zang K. et al. [6] and Zhu Y. et al. [7] focused on the large conductance calcium-activated K⁺ (BK) channels, and retrospected the most recent scientific literature on the structure, subunits and locations of BK channels, broadly describing the functional effects of different BK types on neurons, astrocytes, microglias, oligodendrocytes and smooth muscle cells. After that, two reviews both concentrated on the modulation of BK channels on the epilepsy, and discussed the possibility of developing potential antiepileptics targeted on different BK subunits. In the conclusion, the authors optimistically prospected that the SNPs (single nucleotide polymorphisms) of KCNMA1 and KCNBMs might be the future investigation targets of BK channel dysfunction, and optogenetic technique could be helpful to suppress the epileptic seizures [6-7].

Gao F. et al. [8] and Feng X. et al. [9] more specifically evaluated recent research papers on particular K⁺ channels. Gao et al. reviewed those K⁺ channels in Müller glial cells, which located on the retina and related to the retinal disorders, including retinal ischemia-reperfusion, diabetic retinopathy, inherited retinal dystrophy, retinal detachment, proliferative vitreoretinopathy and glaucoma. These retinal K⁺ channels, such as BK channel, delayed rectifier K⁺ channel (KDR) and A-type K⁺ channel, keep the hyperpolarized potential and contribute to retinal neuronal damage in pathological conditions, which may serve as potential targets to develop new therapeutic approaches in the future [8].

Feng et al. reviewed the functions and pathological relations of lysosomal K⁺ channels with neurodegenerative diseases, which were also called lysosomal storage diseases (LSDs). Lysosomal BK channel and transmembrane protein 175 (TMEM175), a novel lysosomal K⁺ channel, have been reviewed in this paper, describing their structure, expression on lysosomal plasma membrane, modulation effects on Ca²⁺ signaling and lipid metabolism. Dysfunction of lysosomal BK channels and TMEM175 elicits LSD-related Fabry disease and Hunter syndrome, which can be rescued by specific K⁺ channel agonists [9].

Yang J. et al. [10] reviewed the oxidation of K⁺ channels in neurodegenerative diseases, such as Alzheimer’s disease (AD) and Parkinson’s disease (PD). This short review elucidated the damages of different K⁺ channels caused by reactive oxygen species (ROS). Oxidation of Kv2.1, Kv3.4, Kv4.3, BK, KATP and organellar K⁺ channel causes the abnormal features such as mitochondrial dysfunction, oxidative stress and autophagy compromise, which will result in collapse of intracellular homeostasis and eventually leads to cell death [10].
In this thematic issue, Wu X. et al. [11] and Yan R. et al. [12] reported their experimental findings on inwardly rectifying K⁺ (Kir) channels, both through patch clamp electrophysiological recordings. Wu et al. affirmed that tenidap, an inhibitor of cyclooxygenase / arachidonate 5-lipoxygenase (COX/5-LOX), served as the opener of Kir2.3 channel and possessed antiepileptic effect in cyclothiazide induced epileptiform seizures [11]. Meanwhile, Yan et al. reported that Jingshu Keli, a herbal formula of traditional Chinese medicine (TCM), alleviated the mechanical and thermal symptoms of cervical spondylotic myelopathy by increasing the phosphorylation level of Kir3.1 [12]. These two works are the only original researches in this thematic issue, which may enhance the value and significance of this thematic issue, on contributing the advancement of knowledge in K⁺ channels.

Here we mention the TCMs, which represent a large group of medicinal compounds derived from plants and other natural sources. Those studies of the effects of TCMs on different K⁺ channels provide new insights on the pharmacognostic aspects to research K⁺ channels and CNS diseases. Recent studies have detected several compounds from TCMs that serve as novel K⁺ channel modulators, for example, curcumin (from Curcuma longa) as blocker to Kv1.3, Kv1.4, Kv2.1 channels [13-15], puerarin (from Pueraria lobata) as inhibitor to Kir2.1, Kir2.3, Kv7.1 channels [16]. In the study from Yan et al., two saponins, ginsenoside Rb1 (GRb1) and notoginsenoside R1 (NGR1), were also found that acted as an antagonist to Kir currents [12].

To further investigate the modulation of TCMs on K⁺ channels and other ion channels, Huang Y. et al. was then provided a review elucidating the recent studies of TCMs and ion channel [17]. In this review, several TCM herbs and their containing active ingredients were introduced, including Salvia miltiorrhiza Radix et Rhizoma, Ligusticum chuanxiong Rhizoma, Angelica sinensis Radix, Panax ginseng Radix et Rhizoma, Panax notoginseng Radix et Rhizoma, Uncaria rhynchophylla Ramulus Cum Uncis, Scutellaria baicalensis Radix and so on [17].

Finally, Zhou Y. et al. [18] and Feng Y. et al. [19] focused on the voltage-gated Na⁺ channels (VGSCs) and reviewed their functional relationship to CNS diseases from recent scientific literature. Zhou et al. discussed the roles of VGSCs in the processing of sensory information, including auditory sense, visual sense, olfactory sense, tactile sense and taste sense, as well as related disorders caused by the dysfunction of VGSCs [18]. Meanwhile, Feng et al. retrospected the mutations of VGSC subunits both on the aspects of genotypes and phenotypes, and introduced specific CNS diseases elicited by VGSC mutations, especially the epilepsy. In this review, those mutations located on SCN1A (Nav1.1), SCN2A (Nav1.2), SCN3A (Nav1.3), SCN8A (Nav1.6) and SCN9A (Nav1.7) were described [19]. These two reviews were included into this thematic issue to exhibit the similarities and differences between Na⁺ channels and K⁺ channels, as well as their correlations, in the pathology of CNS diseases.

We hope that this special issue represents a valuable contribution to understand the roles of different K⁺ channels, as well as other ion channels, in the pathogenesis of CNS diseases like epilepsy.

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REFERENCES


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