Is ion-channel a novel target for neuron disorder? Through study from mechanism to perspective

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Keywords: Ion channel, Alzheimer's disease, Multiple Sclerosis, Epilepsy, voltage-gated ion channel

Abstract: Through experiments, understanding the role of ion channels in the central nervous system and making ion channels become targeted therapies for central nervous system diseases from an electrophysiological perspective are potential topics in the future. There is still no effective systematic treatment for a large number of neurological diseases, so it is essential to find a new breakthrough for them. Through reading a large number of research papers and experimental reports, three of the most prevalent neurological diseases are selected to analyze their pathogenesis and mechanism, as well as how mutated ion channels cause them. These three diseases include Alzheimer's disease, multiple sclerosis, and epilepsy. A number of papers and reports show that when ion channels are mutated, different variations can cause different levels of damage to our health. Therefore, this paper calls on scientists to explore more ion channel targeted therapies for neurological diseases and figure out the unsolved mechanisms and causes of neurological diseases.

1. Introductory

Electrically charged atoms or molecules, also known as ions, that are dissolved in this water and have a net electrical charge, are responsible for the resting membrane potential, as well as the action potential. It is crucial to know that the electrical charge of an atom depends on the difference between its number of protons and electrons. The resting potential and action potentials are also dependent on particular proteins that span the phospholipid bilayer, which provides routes for ions to cross the neuronal membrane, and they are critical for neuronal excitability include ion channels and ion pumps.

An important property of most ion channels is ion selectivity. For example, potassium channels are selectively permeable to K^+; sodium channels are permeable almost exclusively to Na^+, and so on. Another important property of many channels is gated. Channels with this property can be open and closed or gated by changes in the local microenvironment around the membrane. These altered properties can significantly impact on the overall excitability of a neuron, in some cases leading to hyperexcitability or seizure-like activity. Specifically, ionic movement through channels is influenced by the concentration gradient and the voltage difference across the membrane. Because ions are electrically charged particles, opposite charges attract and like charges repel. As ion channel has the ability to decide how ion will move, if ion channels mutate or die, the movement of ions goes wrong, leading to cell death or even organ failure. Neurological diseases are one result of loss or mutation of ion channels.

Neurological disorders have been one of the most common diseases globally over decades. These include multiple sclerosis, Alzheimer's disease, epilepsy, stroke, Parkinson's disease, and more. The disease can be caused by genetics, infection, degeneration, and many other factors. It is imperative to establish the cognition of nervous system diseases, which can guide patients to actively seek medical assistance to be correctly diagnosed and effectively treated as soon as possible. This paper will introduce the use of ion channels as targeted therapy to inspire more scientists to develop new scientific treatment methods.

2. Alzheimer’s disease

2.1. Introduction of Alzheimer’s disease

Alzheimer’s disease(AD) is one of the common neurodegenerative diseases among older people. Amyloid-D(Aβ) peptide and tau protein are the primary plaques and tangles[1]. Tau is required to support the Kv4.2, a dendritic potassium channel important for regulating dendritic excitability and synaptic plasticity[2]. Knock-out Kv4.2 is essential for inducing dendritic excitability and synaptic plasticity, which is abnormal excitability that causes many neurological disorders[2]. However, Tau knock-out($Tau^{-/-}$) mice can prevent both Kv4.2 depletion and dendritic hyperexcitability[2]. Therefore, the drug that can block Kv4.2 depletion can be considered a target to treat Alzheimer’s disease.

2.2. Voltage-gated potassium channel

Kv4.2 knockout mice increase dendritic APs, which impair learning and memory. Scientists crossbreed hAPPJ20 mice with $Tau^{-/-}$ mice in a recent study to detemine if Tau is required to cause hyperexcitability and ultimately aggravate the progression of Alzheimer’s disease. The study shows haPPJ20/$Tau^{-/-}$ mice have normal dendritic Action Potentials(APs), whereas hAPPJ20/$Tau^{+/+}$ mice have an increased level of dendritic excitability, which means tau is required for the increase in dendritic excitability shown in Figure 1B. What is more, by using the patch-clamp recording to find that haPPJ20/$Tau^{+/+}$ mice also show a significant decrease of Kv4.2 compared to haPPJ20/$Tau^{-/-}$ mice in both CA1 region of the hippocampus are shown in Figure 1C and D. Therefore, misregulation of Kv4.2 will easily cause dendritic hyperexcitability which leads to incorrect synaptic signal. Indeed, the loss of the Kv4.2 channel is harmful to neuron heath and will increase the deficiency of neuron disorder. Overall, Tau is required for Aβ-induced dendritic hyperexcitability and loss of Kv4.2. Furthermore, Kv4.2 and dendritic hyperexcitability can be target treatments for curing Alzheimer’s disease.

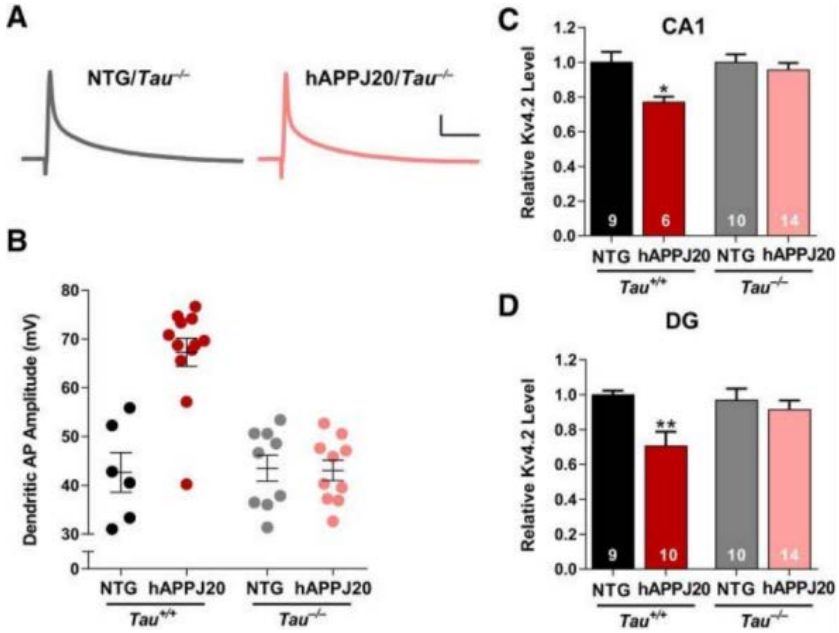

Figure 1. Tau is required for Aβ-induced dendritic hyperexcitability and loss of Kv4.2 in hAPPJ20 mice[2].

2.3. Calcium channel

Senile plaque is one of the typical case features of Alzheimer's disease, and studies have shown that senile plaque has a certain degree of toxicity to neurons. The main component of senile plaques is the Amyloid β peptide(Aβ). There is evidence that Aβ can disrupt calcium balance in neurons and thus increase intracellular calcium concentration[3]. Therefore, in addition to potassium channels, another ion channel that has been implicated in Alzheimer's disease is abnormal calcium channels.

Ca^{2+} plays a vital role in the brain. Calcium homeostasis controls the various activities of neurons by regulating their function, thus contributing to long-term memory in the brain. Voltage-gated Ca^{2+} channels can be activated by changes in the electrical membrane potential, thus changing the trajectory of Ca^{2+} and leading to signal release from presynapse. Under normal circumstances, specific voltage changes or ligand-receptor interactions will change the dynamic state of Ca^{2+} channels[3]. In patients with Alzheimer's disease, the flow of Ca^{2+} can be difficult to control under abnormal conditions. As shown in Figure 2, membrane-associated oxidative stress (MAOS) can make neurons more likely to receive excitotoxicity of Ca^{2+} easier than normal by damaging ion-motive ATPase, thus increasing [Ca^{2+}] and disrupting Ca^{2+} homeostasis, and ultimately killing neurons[4]. Therefore, maintaining calcium homeostasis can help improve or reduce the risk of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, stroke, etc. Moreover, targeting Ca^{2+} channel regulation can be another method to treat neurodegenerative disease, especially in Alzheimer's disease.

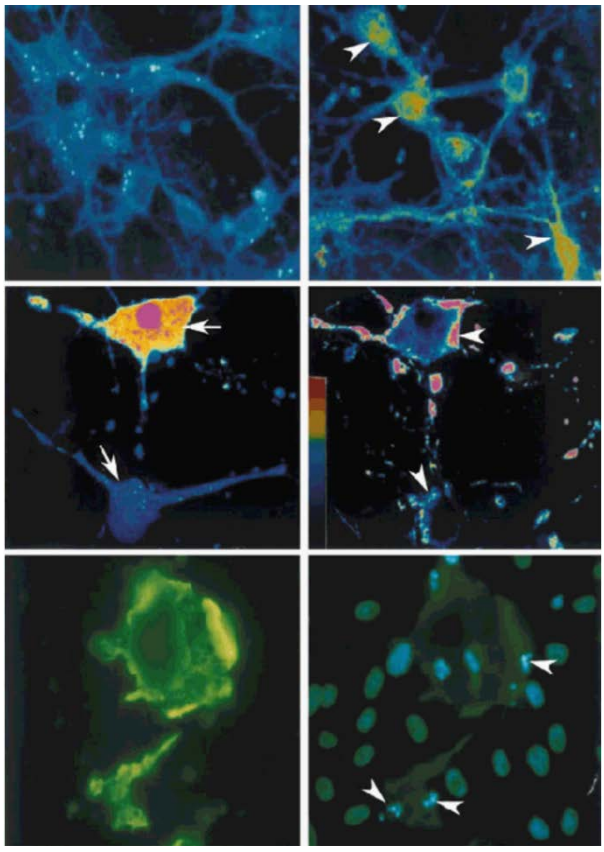

Figure 2. Amyloid β-peptide induces membrane-associated oxidative stress, cellular Ca^{2+} overload and apoptosis[4].

3. Multiple Sclerosis:

3.1. Introduction of Multiple Sclerosis

Another central nervous system-related disease of concern is multiple sclerosis (MS). Although the pathogenesis of the disease is still unknown, it is believed to have a genetic component. In addition, environmental factors can also cause immune system disorders related to MS, such as Epstein-Barr virus (EBV) infection, vitamin D deficiency, smoking, high-sodium diet, etc.[5]. The more severe the loss of long nerve fibers in MS patients, the probability of patients are disabilities are higher. Nerve fiber defects result from excess intracellular calcium ions($Ca^{2+}{}_i$) flowing into the neuron through ruptured cell membranes, resulting in fiber death. Therefore, understanding the mechanism of Ca^{2+} in MS patients can become a targeted therapy for multiple sclerosis by regulating the Ca^{2+} signaling pathway [6]. In addition, as mentioned above, high sodium diets also increase the risk of multiple

sclerosis, so sodium ion(Na^+) is one of the targeted therapies for the treatment of this disease.

3.2. Voltage-gated Calcium Channel(VGCC)

By establishing a mouse model of multiple sclerosis, mice were induced central nervous disorder by impaired motor and sensory neurons[7]. From the study in 2004, when the influx of extracellular Ca^{2+} through VGCC increases, the white matter damage will increase, and the risk of experimental autoimmune encephalomyelitis (EAE, an animal model of MS) will increase as well[7]. From Figure 3, a common type of calcium channel blocker called Bepridil is used on the mice model to inhibit Na^+-Ca^{2+} exchange[7]. When the calcium channel is blocked, the disease score of the Bepridil MS group mice is lower than the control MS group after 11 days[7]. Therefore, Bepridil as a calcium antagonist has positive effects on MS mice. This drug can reduce the neuronal damage caused by the blocked calcium channel in the MS model, and this mechanism can be a potential target treatment in future studies.

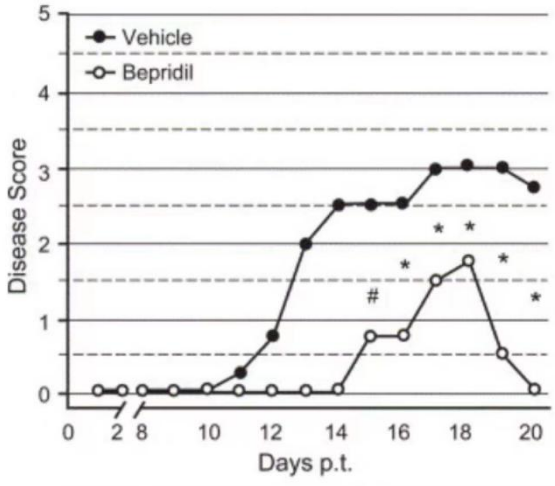

Figure 3. Bepridil treatment on MS mice shows a significant decrease of neurological disability after day 11[7].

3.3. Sodium Channel

A high-salt diet increases the risk of multiple sclerosis and a variety of other neurological diseases. In MS patients, voltage-gated sodium channels (VGSC) are mainly responsible for action potential initiation and propagation [8]. Abnormalities of VGSC in different subunits also lead to different degrees of cardiovascular disease and central nervous disease. MS occurs when Nav1.8 is abnormal. Experiments have proved that Tetrodotoxin(TTX) is a common voltage-gated sodium channel blocker, which stops the hypoxia of white matter axons by blocking the flow of sodium ions [9]. In another experiment, phenytoin, also used as a sodium channel blocker, significantly reduced degeneration and clinical score in C57BI mice with MS model (EAE+phenytoin) compared to the control, as shown in Figure 4[9]. It has been proved that blocking sodium channels can play a neuroprotective role in the MS model. Therefore, it is essential to study the long-term effects of sodium channels on the treatment of this disease. In addition, a low-salt diet is important for patients with autoimmune diseases.

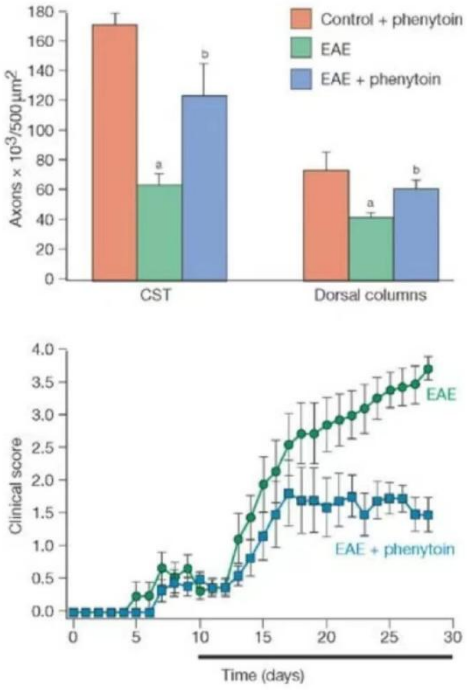

Figure 4. Protective effect of treatment with phenytoin compared with untreated mice in MS model[9].

4. Epilepsy

4.1. Introduction of epilepsy

The last neurological disorder mentioned in this article is epilepsy. Seizures are caused by excessive or synchronized electrical activity in the brain[10]. An *action potential* is a signal generated by neurons that conveys information over distances between neurons and the nervous system. Critical to the generation of an action potential is the voltage-gated sodium channel. Voltage-gated sodium channels have a unique pattern of behavior. They stay open for about one millisecond and then close inactivate. Another important player in action potential generation is the delayed rectifier potassium ion channel, which generates a transient increase in K^+ conductance, that function speed the restoration of a negative membrane potential out of the spike. So it is essential to look into epilepsy from an electrophysiological perspective because the status of the ion channel can affect the membrane potential.

4.2. Voltage-gated sodium channel

Mutations in specific voltage-gated sodium channel genes have also been discovered in patients affected by several inherited epilepsy syndromes. The voltage-gated sodium 1.1($Na_V1.1$) channel are the primary sodium channels in the central nervous system. These channels control the flow of Na^+ into neurons during action potential initiation and propagation. The SCN1A gene is one part of the $NA_v1.1$ channels. A recent study have found that this channel is significant for the excitability of GABAergic inhibitory neurons[11]. An animal model with a targeted deletion or mutation of the SCN1A in mice has been constructed to understand better the primary mechanism for hyperexcitability and severe myoclonic epilepsy in infancy[11]. As a result, they explained how the loss of function of $Na_v1.1$ could cause hyper-excitability that leads to epilepsy in patients.

The experiment starts with preparing for targeting construct and embryonic stem cell lines. Neurons are dissociated from the mouse hippocampus. In the heterozygous(+/-) and homozygous group(-/-), the scientists knockout the SCN1A gene with either one or both alleles. After the patch-clamp recording, the postnatal weeks and the percentage alive of these three groups are shown in Figure 5A. Almost all wild-type mice survive through 15 days. Heterozygous(+/-) mice survive rate

decrease since day 1. And all of the homozygous(-/-) group died on day 2, and these mice did not survive beyond day 15. Moreover, time in seconds for recovering from a spine to prone position for these three groups is also recorded. Figure 5B shows the righting reflex of these mutant mice determined as latency in seconds to recover from a supine to prone position. Both wild type(+/+) and heterozygous(+/-) mice recover from a supine to prone position last in less than 1 second. Nevertheless, homozygous(-/-) mice spend about 10 seconds recovering from supine to prone position, which displayed a pronounced lack of coordination[11].

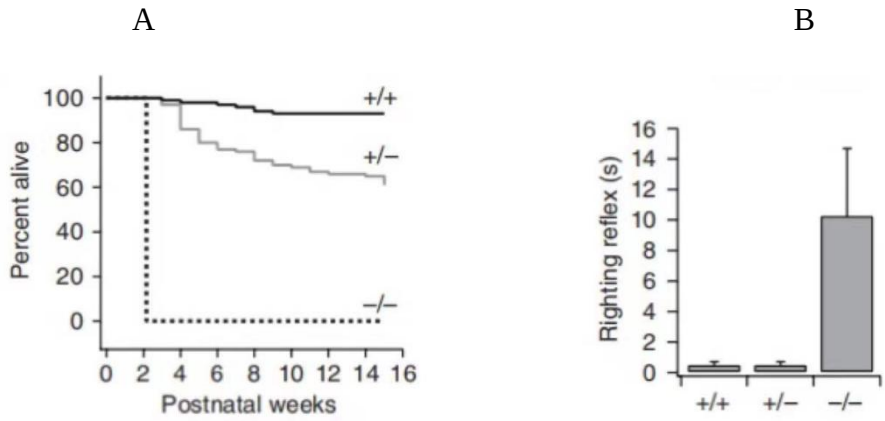

Figure 5. Premature deaths of $Na_V1.1$ mutant mice[11].

Another important figure from this experiment is recording the sets of action potential traces from +/+, +/-, -/- interneurons by using whole-cell patch-clamp recording at room temperature in voltage or current-clamp configuration. This technique is a modern electrophysiology method involving using a single microelectrode to monitor membrane voltage and to pass current into the cell. A significantly large reduction of sodium currents in interneurons from knockout mice can be observed in figure 6a. Figure 6b shows an input-output relationship between the number of action potentials elicited and the injected current. The number of action potentials increased linearly with increasing depolarizing current in +/+ mice. The number of action potentials in interneurons form +/- and -/- knockout mice reached a peak and declined with increasing injected current.

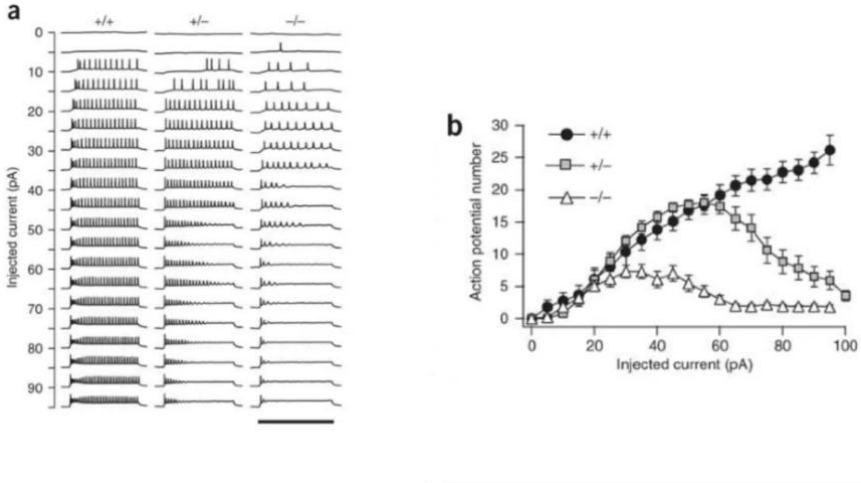

Figure 6. Depolarization-evoked firing activity of hippocampal interneurons from $Na_V1.1$ mutant mice[11].

Overall, SCN1A gene knockout-induced disorder of the $Na_V1.1$ channel will lower lifespan and balance, which shows how important the function of the NaV1.1 channel will affect motor function. Also, Nav1.1 channels are partly in response to the sodium channel; mutant of this channel can disrupt the current and action potential, which lead to the hyperexcitability in epilepsy. Therefore, the Nav1.1 channel can be a potential target to treat epilepsy.

4.3. Voltage-gated K+ channel

KCNA1, one of the subunits encoding Kv1.1 voltage-gated potassium channels, is associated with a sudden unexpected death in epilepsy(SUDEP) in human epilepsy. Experiments have shown that when this gene is knockout (cKO), mice without Kv1.1 will show abnormal action potential and lead to arrhythmias, respiratory disorders, epilepsy, and even death [13]. As shown in Figure 7A, the survival rate of cKO mice after day 20 was significantly higher than that of the control group [13]. Furthermore, Figure 7B shows that most cKO mice developed spontaneous epilepsy [13]. Therefore, it is important to have a functional potassium channel. This ion channel, like sodium channels, deserves to be a targeted therapy for epilepsy and other neurological disorders in the future.

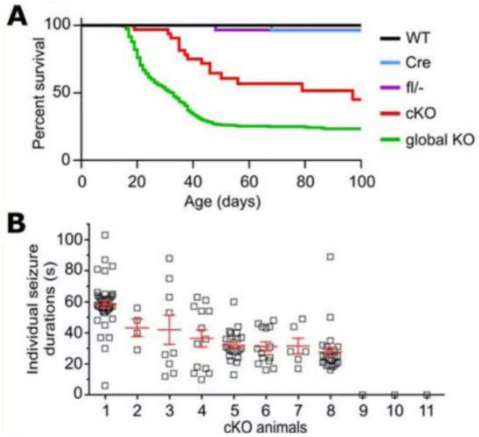

Figure 7. percent survival rate and indivudual seizure duration of KCNA1 knockout mice[13].

5. Conclusions

Abnormal ion channels are only one part of the problem among all CNS diseases, but they still play an essential role in our nervous system. The importance of sodium, potassium, and calcium ion channel loss in the pathogenesis of three neurological disorders is described in detail. This article inspired more scientists and medical staff to further study ion channels as a breakthrough in treating various diseases. By summarizing the different variations or deletions of ion channels, which have a significant risk of exacerbating central nervous system diseases, the discovery of ion channels will become one of the futures and potential targeted therapies.

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