Clinical Neuroscience Research, 2024, Volume 2, Issue 3
http://ojs.bbwpublisher.com/index.php/CNR
Online ISSN: 2981-8133

Slack Channels as Key Regulators of Neuronal Excitability: Implications for Neural Function and the Link to Epilepsy Pathogenesis

Qiao Peng*, Miao Tong

School of Chemistry, Chemical Engineering and Life Sciences, Wuhan University of Technology, Wuhan 430070, Hubei Province, China

Corresponding author: Qiao Peng, 3449878622@qq.com

Abstract: The Slack channel encoded by the KCNT1 gene is a sodium-activated potassium channel. By regulating the flow of potassium ions, the Slack channel affects the membrane potential and discharge activity of neurons, thus participating in regulating neuronal excitability. Therefore, it plays a crucial role in maintaining the normal function of the nervous system. Consequently, abnormal Slack channel function is closely linked to various neurological diseases, such as epilepsy. Currently, quinidine-based medication therapy and neuroregulatory therapy are key components of the treatment of epilepsy resulting from Slack channel dysfunction. This article aims to outline the fundamental features of the Slack channel while providing a thorough analysis of the main distinctions and possible connections between Slick and Slack channels. Furthermore, this study focuses on the function of controlling the neuronal excitability of Slack channels while delving deeper into the potential correlation between Slack channels and epilepsy and their treatment strategies.

Keywords: Slack channel; Neuronal excitability; Epilepsy; Therapeutic strategies

Online publication: September 30, 2024

1. Introduction

The Slack channel, encoded by the KCNT1 gene, is a distinctive potassium(K^+) ion channel that is among the biggest subunits in the potassium channel family. The importance of it in the neurological system is of utmost importance, playing a vital part in neuronal activity. As an outwardly rectifying potassium channel, it helps K^+ ions flow out of the cell when the cell membrane is depolarized, which is crucial for regulating neuronal excitability and firing activity [1–3]. This regulatory function is essential for ensuring normal signal transmission in the nervous system and helps maintain its balance and stability [4–5].

Slack channel malfunctions can have a significant impact on the nervous system, potentially causing neuronal hyperexcitability or inhibition. This disruption can contribute to the development of various neurological diseases, including epilepsy [4–8]. In epilepsy, dysfunction of Slack channels may result in neuronal hyperexcitability, triggering abnormal discharges and seizures [9–11]. Therefore, conducting in-depth research on

the structure and function of Slack channels, as well as their relationship with neurological diseases, will not only help researchers obtain a deeper understanding of the basic working principles of the nervous system but may also provide new ideas and methods for the diagnosis and treatment of related diseases. This paper aims to provide a thorough overview of the most recent developments in the Slack channel, investigate its fundamental properties in more detail, and examine its crucial function in the nervous system. This article also addresses the Slack channel abnormalities linked to seizures to offer novel approaches to the treatment of epilepsy.

2. Basic characteristics of Slack channels

Research has shown that the sodium-activated potassium (K_{Na}) channel is encoded by two genes belonging to the SLO family: KCNT1 (also known as Slack, Slo2.2) and KCNT2 (Slick, Slo2.1), which play a crucial role in regulating neuronal excitability and discharge activities [1, 3–4]. Regarding K_{Na} channels, the activation of the K_{Na} channel is closely related to the intracellular concentration of sodium (Na^+) ions. When neurons are stimulated, the accumulation of intracellular Na^+ ions can activate the Slack channel, triggering its opening and thereby regulating the flow of K^+ ions [1, 4].

Slack channel is an important member of the K_{Na} channel family, and the molecular structure of the Slack channel is primarily composed of four major α-subunits, which exhibit a high degree of structural consistency [11–13]. Each α-subunit contains a small intracellular amino-terminal domain, six transmembrane domains (S1–S6), and a large intracellular carboxy-terminal domain (**Figure 1**). Among these domains, S1 to S4 are primarily responsible for voltage sensing, with their charge distribution making them highly sensitive to changes in membrane potential [14–15]. Additionally, the Slack channel possesses a longer C-terminal domain and contains regulatory domains for K^+ conductance (RCK) and an NAD^+ binding domain [16–17]. The RCK domain regulates K^+ ion conduction through specific mechanisms, ensuring that ions can pass through the channel smoothly when needed, while the NAD^+ binding domain affects the activity of the channel through binding to NAD^+ [12]. Apart from these functional domains, the C-terminal domain of the Slack channel may also interact with various proteins such as FMRP, phosphatases, Phactr1 (a regulator of actin dynamics), and Cyfip1 (cytoplasmic FMR1-interacting protein 1), forming a complex protein network [15, 18–19].

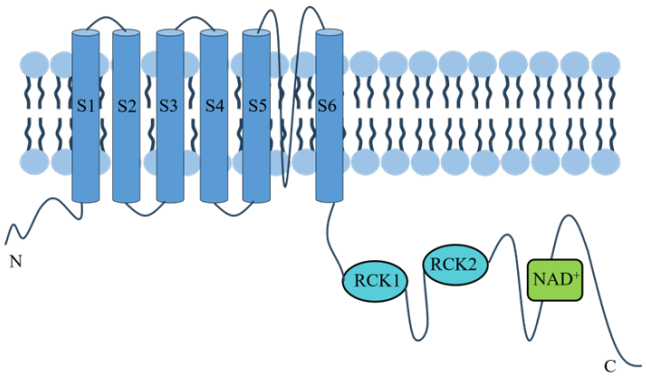

Figure 1. Schematic diagram of the Slack channel subunit

3. Comparisons between Slack and Slick

Similar to the Slack channel, the Slick channel encoded by the KCNT2 gene also plays a crucial role in the nervous system [11, 20–21]. Their primary function is to regulate the flow of K^+ ions across the cell membrane in maintaining the transmembrane potential difference and regulating cell excitability [3, 22–24]. Therefore, both Slack

and Slick channels have significant impacts on the electrophysiological properties of cells [11]. Furthermore, Slack and Slick channels are both K_{Na} channels, meaning that their open state is regulated by the concentration of Na^+ ions, which makes them essential in responding to external stimuli and maintaining cellular homeostasis [3, 24–26]. Additionally, Slack and Slick channels exhibit certain structural similarities. As potassium channels, they possess similar channel protein structures, including transmembrane regions, ion-selective filters, and regulatory domains [11]. These structural similarities contribute to their functional commonalities, such as their ability to selectively permeate K^+ ions and respond to external stimuli [3, 22, 27].

However, compared to the Slack channel, the Slick channel exhibits some differences. Firstly, despite their structural similarities, the Slick protein is slightly smaller than the Slack protein, with its N-terminal size being half of that of Slack (**Figure 2**). Furthermore, there is an ATP binding site in the C-terminal region of the Slick channel, and the application of adenosine triphosphate directly reduces Slick channel activity [23, 28]. In contrast, Slack channels do not exhibit such inhibitory effects. Additionally, Slick channels exhibit a more widespread distribution, existing not only in the central nervous system but also extensively in the peripheral nervous system, encompassing both sensory and motor neurons [25]. The distribution pattern of Slick channels in the brain nearly overlaps with that of Slack channels [29]. Apart from the brain, Slick channels are also expressed in organs such as the heart, skeletal muscles, lungs, and liver, further broadening their potential roles in physiological and pathological processes [25]. Additionally, the overall electrochemical properties of the Slick channel differ from those of the Slack channel. The opening of the Slack channel absolutely requires Na^+ ions, whereas the Slick channel exhibits a basic level of activity in the absence of Na^+ ions and has a higher half-maximal effective concentration (EC50) for Na^+ ions [3, 28]. Meanwhile, the activity of Slick channels can be enhanced by intracellular Cl^- ions concentration, and this effect is more pronounced in Slick channels compared to Slack channels [30]. Moreover, Slick and Slack channels exhibit distinct activation characteristics in response to cell depolarization. When a neuron is stimulated and generates an action potential, causing a rapid depolarization of the membrane potential, the Slick channel can rapidly open, allowing for a swift outflow of K^+ ions from the cell [28]. In contrast, the activation process of the Slack channel is relatively slow. Although it is also activated during cell depolarization, its opening rate is slower, resulting in a relatively slower outflow of K^+ ions [26, 31]. The rapid activation of the Slick channel enables it to quickly function during the generation of action potentials and restore the resting state of the membrane potential, ensuring rapid regulation of neuronal excitability [21, 28, 32]. The slow activation of the Slack channel, however, allows it to provide a sustained and stable outflow of K^+ ions during neuronal excitation, contributing to the maintenance of membrane potential stability and the prolongation of depolarization, thus enabling fine-tuned regulation of neuronal excitability [11, 33].

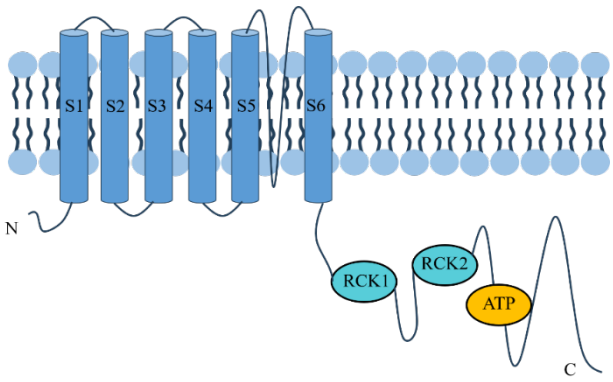

Figure 2. Schematic diagram of the Slick channel subunit

4. Slack channels regulate neuronal excitability

The Slack channel controls K^+ ion flow and membrane potential to modulate neuron excitability [12, 34–36]. When neurons are stimulated and generate action potentials, the influx of Na^+ ions causes membrane depolarization, which subsequently activates the Slack channels [33, 37]. Once activated, these channels mediate the outflow of K^+ ions, contributing to the repolarization of the membrane potential and returning it to the resting level [38]. This outflow of K^+ ions helps terminate the excitatory state of neurons, thus preventing neuronal hyper-excitability [38]. In addition, specific variants in Slack channels may lead to their enhanced function, increasing the rate of potassium influx or outflow, which in turn affects neuronal excitability. On the other hand, when neurons are in a resting state, Slack channels may maintain a relatively low level of openness, minimizing the outflow of K^+ ions and thus stabilizing the membrane potential [39–40]. Maintaining this balanced state is crucial for the normal functioning of neurons [15].

The cell membrane potential experiences slow afterhyperpolarization (sAHP), which is a state of prolonged, significant hyperpolarization, following the completion of an action potential [41]. This physiological phenomenon is a crucial component in the control of neuronal activity because it lowers the firing threshold of neurons, that is, the frequency at which neurons fire, by allowing the neuron to again cross the stimulus intensity threshold necessary for the release of action potentials [42]. After excitation, this inhibition aids neurons in swiftly returning to a resting state, preventing excessive discharge and energy consumption. Slack channels are essential to the sAHP process because they enable K^+ ions to move from inside the cell to the outside in a selective manner [41]. Since K^+ ions have a positive charge, their outflow causes the inner side of the cell membrane to become relatively more negatively charged, which exacerbates the hyperpolarized state of the cell. Thus, one of the key ways that the Slack channel controls neuronal excitability is by mediating K^+ ions outflow, which is necessary for the creation and maintenance of sAHP.

5. Slack channels in neurological diseases

5.1. Association of abnormal Slack channel function with epilepsy

Epilepsy, a chronic brain disease triggered by abnormal discharge of neurons in the brain, is closely related to abnormalities in neuronal excitability [43]. Studies have demonstrated that mutations in the gene encoding Slack channels are one of the important factors leading to certain focal epilepsies, commonly including epilepsy with migratory focal seizures (EIMFS) and autosomal dominant nocturnal frontal lobe epilepsy (ADNFE) [9, 32, 44–47].

Slack channels can modulate neuronal excitability and play a crucial role in the nervous system. Seizure-related mutation sites are found in various parts of Slack channels, such as the N-terminal domain, RCK1 domain, RCK2 domain, and C-terminal domain [32, 47]. These mutation sites can impact the functioning of Slack channels, including their opening, closing, and conductance properties, thus affecting the excitability of neurons. Gain-of-function (GOF) mutations in Slack channels lead to increased K^+ ions efflux, thereby shortening the action potential duration and increasing the excitability of neurons [40]. This excitability abnormality can disrupt the balance of the neuronal network and lead to excessive firing of the neuronal network, which in turn increases the risk of seizures [35, 48]. Additionally, Slack channels play a significant role in neural plasticity processes, and epileptic patients often exhibit changes in neural plasticity [4, 49]. By regulating neuronal excitability and synaptic transmission, Slack channels further influence the dynamic adjustment of neural network connections, thereby affecting the course of epileptic episodes and disease progression [50–51]. Consequently, the Slack channel plays a crucial role in the pathophysiology of epilepsy as a regulator of neuronal excitability. Its regular operation directly influences the frequency and mode of neuronal firing, which in turn influences the likelihood and duration of seizures [52–53].

5.2. Treatment strategies for abnormal Slack channel function

Being a crucial modulator of neuronal excitability, the Slack channel's malfunction is intimately linked to the development of numerous nervous system disorders, most notably epilepsy [8]. Therefore, improving patients' quality of life greatly depends on the development of efficient treatment plans to address Slack channel dysfunction. Certain epileptic patients with Slack channel abnormalities may benefit from the use of traditional antiepileptic medications such as quinidine, phenytoin sodium, and carbamazepine [40, 54]. Quinidine's clinical use must still be used with caution, though, as any potential side effects, such as cardiotoxicity, need to be properly monitored. It should be highlighted, furthermore, that not all patients with abnormalities of the Slack channel respond well to traditional antiepileptic medications, since these medications may not target Slack channels directly [54]. Consequently, the development of novel antiepileptic medications that target Slack channels is required.

For some epilepsy patients who are refractory to treatment or who do not respond to medical intervention, surgery may be a viable option. Deep brain stimulation (DBS), focus excision for epilepsy, and other surgical techniques are available. Surgical treatment can significantly reduce or completely eradicate seizures by either directly removing the epileptic focus or by modifying the electrical activity of the neural network. For instance, pulsed magnetic fields are used in transcranial magnetic stimulation (TMS), a therapy that modifies the excitability of neurons in the cerebral cortex [55]. In patients with Slack channel abnormalities, TMS may reduce the number of seizures or improve other neurological symptoms by regulating the balance of neuronal networks. This treatment method has the advantages of non-invasive and high safety, but the durability of efficacy and individual differences still need to be further studied. Furthermore, the pathogenic variants of the KCNT1 gene can be precisely repaired or replaced using gene editing technologies like CRISPR-Cas9, which will return potassium channels to their normal function [56]. Although this treatment is drastic, more research and verification are still needed to fully understand its technical complexity and safety.

6. Conclusion and prospect

In conclusion, the dynamics of the nervous system depend on the Slack channel, also known as the K_{Na} channel, which is an essential component of the potassium ion channel. It achieves precise control over the excitability of neurons, the nervous system's ability to react rapidly to both internal and external stimuli and sustain normal function, by carefully regulating the flow of K^+ ions across their membranes. But if Slack channel function is compromised, the nervous system's capacity for adaptation and learning may be severely compromised, which could lead to the development of several nervous system disorders, including epilepsy. Furthermore, it has been demonstrated that modern anti-epileptic medications like quinidine and phenytoin sodium are crucial in the treatment of epilepsy brought on by Slack channel dysfunction. The frequency and intensity of seizures are effectively reduced and controlled by them by stabilizing and modifying the function of Slack channels.

Despite the established significance of Slack channels in the modulation of neural systems, the precise biochemical pathways and regulatory structures behind them remain incompletely understood. More research is required to understand how Slack channels interact with other ion channels, receptors, and signaling molecules. Moreover, further research is still needed to determine how Slack channel expression and function are impacted by mutations in the KCNT1 gene, and how these modifications contribute to the development of epilepsy. Currently, the primary treatment for epilepsy related to KCNT1 is medication therapy. But there are drawbacks as well, like patchy effectiveness and glaring negative effects. Therefore, to maximize treatment outcomes and enhance patient quality of life, future research should concentrate on the development of antiepileptic medications with high specificity and low side effects. These investigations will contribute to the growing

understanding of the function of Slack channels in neurological disorders and offer fresh perspectives on the identification and management of associated illnesses.

Disclosure statement

The authors declare no conflict of interest.

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