The Role of Slack (KCNT1) Channels in the Pathogenesis of Temporal Lobe Epilepsy

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Abstract: Current therapeutic strategies for epilepsy predominantly focus on seizure frequency control and symptom alleviation. However, approximately 30% of patients progress to drug-resistant epilepsy, particularly temporal lobe epilepsy (TLE), due to the absence of specific therapeutic targets, etiological complexity, and interindividual heterogeneity. Delineating the pathogenic mechanisms of TLE and identifying novel regulatory factors hold critical clinical significance for developing targeted therapies. Notably, in vivo studies have demonstrated that gain-of-function mutations in KCNT1 selectively suppress the excitability of inhibitory interneurons, disrupting excitatory/inhibitory (E/I) balance and promoting epileptogenesis. This evidence suggests a pathological association between KCNT1 dysfunction and epilepsy. A hypothesis arises whether upregulated KCNT1 expression during TLE episodes may predominately localize in inhibitory neurons, exacerbating epileptic progression through functional suppression of these cells. Furthermore, neuroglial cell activation during epileptogenesis triggers massive release of inflammatory mediators (e.g., interleukins, tumor necrosis factors). The NF-κB signaling cascade, activated by seizure-induced oxidative stress and elevated proinflammatory mediators associated with neuronal damage, has been shown to bind specific cis-elements in the KCNT2 promoter to regulate its transcription — a mechanism implicated in neurological pathogenesis. At the same time, some studies have found that mouse NF-κB can specifically bind to the KCNT2 promoter regulatory sequence and up-regulate KCNT2 transcription. Since KCNT1 and KCNT2 have similar structure and function, they interact to form functional channels and cause similar related diseases. So can KCNT1 expression change in response to the occurrence and development of temporal lobe epilepsy and is the mechanism of change related to the NF-κB pathway? This raises a pivotal question: Could inflammatory mediators modulate KCNT1 expression via NF-κB pathway activation during TLE progression? Through systematic investigation, this study aims to address these scientific inquiries, providing mechanistic insights into epileptogenic processes and potential therapeutic targets.

***Keywords*:** Slack channel; Epilepsy; KCNT1; inflammatory mediators; NF-κB pathway.

1. Introduction

Epilepsy, a prevalent chronic neurological disorder characterized by recurrent and stereotypic seizures, arises from multifactorial etiologies [1]. These include traumatic brain injury, central nervous system infections, cerebrovascular pathologies, neurodegenerative disorders, neurodevelopmental anomalies, and genetic predispositions linked to specific gene mutations or inherited defects [2]. Epidemiologically, epilepsy affects over 70 million individuals worldwide [1], with approximately 10 million cases in China alone — a figure exhibiting a steady upward trend [3]. The disorder demonstrates a bimodal age distribution, with higher incidence rates in pediatric and elderly populations due to developmental vulnerabilities and age-related neurophysiological decline [4]. Clinically, epileptic manifestations vary across age groups but commonly involve motor, sensory, and psychiatric disturbances, often accompanied by profound consciousness impairment and behavioral retardation [5], imposing severe physical and psychological burdens. Alarmingly, epilepsy patients face a threefold increased risk of premature mortality compared to the general population.

Despite advancements in epilepsy research, current therapeutic paradigms remain largely confined to seizure suppression and symptomatic management. Anti-seizure medications (ASMs), targeting the rebalancing of excitatory (glutamate) and inhibitory (GABA) neurotransmission, fail to achieve adequate efficacy in approximately 30% of patients due to multidrug resistance, etiological complexity, and interindividual heterogeneity, ultimately leading to refractory epilepsy — most frequently temporal lobe epilepsy (TLE) [6]. This therapeutic impasse underscores the urgent need to elucidate the pathogenic mechanisms of TLE and identify novel regulatory targets. Such efforts hold transformative potential for developing precision therapies, addressing unmet clinical needs, and improving patient outcomes.

2. Pathophysiological Mechanisms

Although the precise epileptogenic mechanisms remain incompletely elucidated, a scientific consensus recognizes that

the disruption of excitatory-inhibitory (E/I) neurotransmission homeostasis serves as the fundamental trigger for epileptic seizures. This homeostatic imbalance induces pathological neuronal hypersynchronization—a hallmark of epileptiform discharges [7]. Neurons, the pivotal cellular units of the central nervous system (CNS), mediate signal reception, integration, and propagation through electrochemical transmission, enabling coordinated physiological functions[8]. Aberrant neuronal hyperexcitability manifests as epileptic seizures when synchronized electrical activities overwhelm intrinsic regulatory mechanisms.

The dynamic equilibrium of neuronal network activity relies on precise counterbalancing between excitatory and inhibitory processes. Ion channels — the molecular gatekeepers of neuronal excitability — play a central role in CNS electrophysiology by regulating action potential generation, synaptic transmission, and interneuronal communication [9]. Perturbations in ion channel structure, functional anomalies, or pathological interactions with endogenous modulators can profoundly dysregulate channel activity [10]. Such disturbances cascade into systemic neurophysiological dysfunction, particularly within the CNS, where ion channel abnormalities destabilize neuronal firing patterns, promote hypersynchrony, and perpetuate epileptogenesis [11]. Notably, genetic mutations in ion channel-encoding genes or acquired channelopathies generate either loss- or gain-of-function phenotypes, disrupting the delicate E/I balance and culminating in recurrent seizures that severely compromise patient health and quality of life.

3. The Relationship Between Slack Channels and Epilepsy

Slack channels (KNa channels encoded by KCNT1) are ubiquitously expressed in central neurons [12]. During action potential generation, massive Na+ influx induces membrane depolarization, triggering Slack channel activation [13]. These activated channels mediate KNa currents that critically regulate neuronal excitability by modulating post-spike afterhyperpolarization (AHP) — specifically influencing AHP amplitude and duration [13,14]. Enhanced Slack channel activity amplifies AHP effects, prolonging the post-discharge hyperpolarized state and optimizing neuronal readiness for subsequent stimuli [15]. Notably, Slack channels shape neuronal firing adaptation via KNa current-mediated modulation of firing frequency—a vital mechanism for maintaining stable discharge patterns during high-frequency or sustained synaptic inputs, thereby ensuring reliable neural coding [16]. Their regulatory effects on neuronal excitability are achieved through dynamic K+ efflux and membrane potential modulation [17]. During action potentials, Slack activation accelerates K+ extrusion to drive membrane repolarization, thereby terminating depolarizing states and preventing hyperexcitability-induced network instability [18]. In resting conditions, low Slack channel activity minimizes K+ leakage, preserving membrane potential stability [19].Slack channels do not operate in isolation but engage in intricate crosstalk with voltage-gated sodium/channels, calcium channels, and other modulators to form an integrated regulatory network for precise neuronal excitability control [20]. This multi-channel interaction enables context-dependent neural responsiveness and maintains CNS homeostasis [17].

Pathological dysregulation of Slack channels due to KCNT1 mutations is strongly implicated in epileptogenesis. Genotype-phenotype correlations reveal KCNT1 variants in multiple epilepsy syndromes, including epilepsy of infancy with migrating focal seizures (EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), and early-onset epileptic encephalopathies (EOEEs) [21]. Ion channelopathies constitute approximately one-third of monogenic epilepsy etiologies [22], with KCNT1 mutations inducing either gain-of-function or loss-of-function channel alterations. These defects disrupt physiological K+ gradients, destabilize neuronal membrane potentials, and promote hyperexcitability cascades. Among voltage-gated channels, potassium channels represent the most diverse family, critically regulating cardiac repolarization, smooth muscle relaxation, insulin secretion, and neuronal excitability [23]. The KCNT1 encoded Slack channel plays a non-redundant role in neuronal membrane dynamics, cementing its importance as both a physiological regulator and a therapeutic target in epilepsy pathogenesis.

4. Structural and Functional Characteristics of Slack Channels

Gene mapping studies reveal species-dependent chromosomal localization of the KCNT1 gene: human KCNT1 resides at chromosome 9q34.3, murine KCNT1 on chromosome 2, and rat KCNT1 on chromosome 3 [24]. The α subunit of Slack channels, the largest known potassium channel subunit, belongs to the Slo subfamily of potassium channels [25]. In mammals, Slack channels exhibit an exceptionally high unitary conductance (~180 pS) and are encoded by KCNT1 [26]. Structurally and functionally related to voltage-gated potassium channels, Slack channels display a complex architecture comprising six hydrophobic transmembrane segments (S1–S6), with S5 and S6 forming the pore-lining helix [27]. They possess a short intracellular N-terminal domain (NTD) and an extended cytoplasmic C-terminal domain (CTD) [28]. Notably, the CTD harbors two regulator of K+ conductance (RCK) domains and a nicotinamide adenine dinucleotide (NAD+)-binding site

[29] (Fig. 1). Unlike Kv channels, Slack channels lack voltage-sensing domains (VSDs), with no charged residues on the S4 segment, rendering them voltage-insensitive — an intrinsic mechanism still under investigation [30]. Slack channels exhibit high sodium (Na^+)-dependent activation but minimal chloride (Cl^-) sensitivity. Under Na^+-free intracellular conditions, whole-cell patch-clamp recordings of Slack channels in wild-type mice demonstrate negligible activity [31]. Their Na^+ sensitivity has been mechanistically linked to the RCK domains: elevated intracellular Na^+ induces conformational changes in the RCK loop at the cytoplasmic face, thereby exposing the electrostatic pore gate; however, the precise molecular mechanism remains unresolved [32]. The NAD+ binding domain is proposed to enhance channel activation. Within the central nervous system (CNS), Slack channels are ubiquitously expressed in the cerebral cortex, brainstem, cerebellum, and olfactory bulb, where they critically regulate neuronal excitability. During normal neurophysiological activity, Slack channels encoded by KCNT1 mediate slow afterhyperpolarization (sAHP) following single or burst action potentials [33], while also modulating resting membrane potential, threshold currents, neurotransmitter release, and synaptic transmission [34]. Although the functional roles of Slack channels have been partially elucidated, detailed operational mechanisms require further exploration.

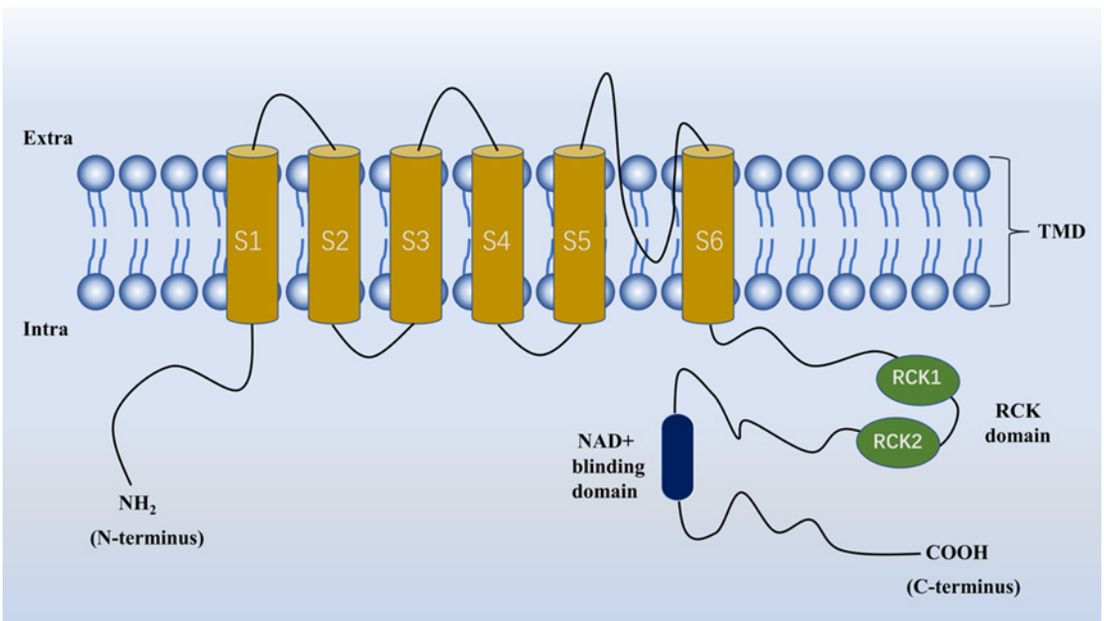

Figure 1. Slack channel topology

Figure 1 shows an S1-S4 transmembrane domain and no voltage-sensing domain (VSD). A hole-lining ring formed by S5 and S6; long C-terminal containing two K^+ conductance regulatory (RCK) domains and a niacinamide adenine dinucleotide (NAD+) binding domain.

5. Excitation-Inhibition Balance in Neural Networks

Normal brain function relies on precisely coordinated interactions between excitatory and inhibitory neurons within complex neural networks to maintain dynamic excitation-inhibition (E/I) equilibrium, which not only establishes an optimized microenvironment for neural circuit maturation but also governs neuronal excitability [35,36]. Glutamate (Glu), the primary excitatory neurotransmitter, is released via presynaptic vesicle exocytosis upon action potential-induced depolarization, binding to postsynaptic AMPA and NMDA receptors to mediate cation influx and generate excitatory postsynaptic potentials (EPSPs) for synaptic signal transmission [37]. Conversely, γ-aminobutyric acid (GABA), synthesized and secreted by inhibitory neurons, activates GABAA receptors to induce Cl^- influx and triggers GABAB receptor-mediated K^+ channel modulation through G protein-coupled mechanisms, thereby driving hyperpolarization and inhibitory postsynaptic potentials (IPSPs) to offset excessive excitation [38,39]. Disruption of this E/I balance is implicated in neurological pathologies: excessive extracellular Glu and/or diminished GABA levels in epilepsy lead to excitotoxicity, seizures, and neuronal death, while altered GABA/Glu ratios in cortico-limbic regions characterize major depressive disorder [40,41]. Chronic E/I dysregulation further contributes to neurodegenerative cascades in Alzheimer's disease [42]. Notably, Slack channels encoded by KCNT1 , expressed in both glutamatergic and GABAergic neurons, critically regulate E/I homeostasis [43]. Murine models with KCNT1 gain-of-function mutations exhibit suppressed GABAergic neuron excitability and distorted

E/I ratios, directly promoting epileptogenesis, highlighting Slack channels as pivotal regulators of network excitability and potential therapeutic targets [44].

6. Interplay Between Inflammatory Cytokines, NF-κB Pathway, and KCNT Channels

During epileptic seizures, abnormal high-frequency neuronal discharges activate neuroglial cells, including microglia and astrocytes [45]. Activated glial cells robustly secrete proinflammatory mediators such as interleukins (ILs) and tumor necrosis factor (TNF) [46]. Concurrently, seizure-induced ischemic/hypoxic brain injury stimulates immune cells to release inflammatory factors, amplifying neuroinflammatory cascades [47]. In status epilepticus, neuroinflammation escalates dramatically with explosive cytokine release, triggering self-reinforcing chain reactions that exacerbate cerebral damage and impair neurological function [48]. Epileptogenic processes are characterized by activation of multiple neuroinflammatory signaling pathways, including NF-κB, MAPK, ERK, RIPK, JNK, and JAK-STAT systems [48]. The neuroimmune response generates cytotoxic substances (e.g., cytokines, chemokines) that serve as biomarkers for epileptogenesis [49]. For instance, interleukin-1β (IL-1β) activates the PI3K/mTOR/Akt pathway in hippocampal circuits, driving cognitive impairment in temporal lobe epilepsy or status epilepticus [50]. This signaling axis further interacts with caspase-3 and BH3 proteins to mediate aberrant hippocampal neuronal death during epileptogenesis [51]. Sustained seizures also activate oxidative stress and downstream proinflammatory pathways (e.g., NF-κB, MAPK, ERK), elevating levels of TNF-α, IL-1β, and IL-6 — hallmarks of seizure-induced neuronal injury [49].

Nuclear factor kappa-B (NF-κB), a master transcriptional regulator, critically governs diverse physiological and pathological processes by modulating genes encoding cytokines, chemokines, immune/non-immune receptors, antigen-presenting proteins, and enzymes [52]. The NF-κB family comprises five members: p50 (NF-κB1), p52 (NF-κB2), p65 (RelA), c-Rel, and RelB [53]. All share a conserved N-terminal Rel homology domain (RHD) mediating dimerization, DNA binding, and interaction with inhibitory proteins (IκBs) [54]. Approximately 12-15 functional NF-κB dimer combinations regulate gene transcription through distinct DNA-binding affinities [53]. NF-κB is distinguished by its pleiotropic effects, inducible expression patterns, unique regulatory mechanisms, and extensive crosstalk with signaling cascades [55]. Mechanistically, NF-κB acts as a positive regulator of KCNT2 gene expression—a finding supported by suppressed KCNT2 transcription upon NF-κB inhibition in primary neurons [56]. KCNT2 encodes Slick channels, sodium-activated potassium channels within the same family as Slack [21]. Under physiological conditions, baseline NF-κB activity maintains homeostatic KCNT2 expression; however, pathological stimuli (e.g., inflammation, oxidative stress) induce NF-κB translocation into the nucleus [57]. Nuclear NF-κB binds specific promoter elements of the KCNT2 gene, recruits transcriptional coactivators, and enhances RNA polymerase II recruitment to drive transcription [56], thereby linking neuroinflammatory signaling to ion channel regulation in epilepsy pathophysiology.

7. Conclusions

This article has analyzed the possible role of Slack channel in the process of temporal lobe epilepsy in detail, and animal experiments and cell experiments can be used to further study. The research content includes two aspects: whether Slack channel can respond to the occurrence and development of epilepsy and produce changes in expression; Whether the change of Slack channel expression is related to the activation of NF-κB pathway by inflammatory factors.

(1) Animal experiments: HE staining and Nissl staining were used to observe the morphological and pathological changes of hippocampus. PCR was used to detect the expression of inflammatory factors after seizures. Western blot and immunofluorescence were used to detect the expression of KCNT1, VGLUT1 and GAD67. The expression of KCNT1 in different neuron types was observed by immunofluorescence staining. Wild type C57BL/6J and KCNT1 knockout mice were used to observe the susceptibility to epilepsy in different groups. The above experiments were used to confirm whether KCNT1 gene expression changes in response to the occurrence and development of epilepsy.

(2) Cell experiments: primary neurons were extracted and cultured for 7-10 days for subsequent experiments. The NF-κB activation-nuclear translocation assay kit was used to detect the effect of TNF-α on NF-κB activity. The effect of NF-κB on KCNT1 expression was detected by PCR.

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