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The Research Progress of CACNA1A in the Pathogenesis of Vestibular Migraine

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Abstract

Vestibular Migraine (VM) is a common neurological disorder characterized by recurrent episodes of vertigo and migraine symptoms. The pathogenesis of VM is complex and involves multiple genetic and environmental factors. Recent studies have suggested that the pathogenesis of vestibular migraine may be associated with variations in the CACNA1A gene, which is an important gene target for controlling calcium ion channels. Such variations may further affect the functions of the vestibular nervous system, thereby causing a series of vestibular nervous system-related symptoms. This article will summarize the genetic association studies of vestibular migraine, vestibular function studies, and research on how to establish relevant animal models to illustrate the possible association between CACNA1A variations and the pathogenesis of VM, providing new ideas for clarifying the pathogenesis of VM.

Keywords

Vestibular Migraine, CACNA1A, Genetic Variants, Calcium Channel, Pathogenesis, Systematic Review

1. Introduction

Vestibular Migraine (VM) is a kind of recurrent vertigo disease. During the attack of vertigo, there may be clinical manifestations such as spontaneous vertigo, dizziness caused by head movement with nystagmus and nausea, visual vertigo and blurred vision, and other migraine symptoms such as headache, photophobia, phonophobia, and visual aura. Most of them have a history of migraine in the past and have similar diseases in their families. Vestibular symptoms and migraine symptoms are often not synchronized, and headache symptoms may occur before, during, or after the onset of vertigo symptoms. At present, the pathogenesis of vestibular migraine is not clear, so the clinical diagnosis and treatment are poorly targeted. To clarify the pathogenesis of vestibular migraine is of great significance for the establishment of personalized treatment of vestibular migraine.

2. Epidemiology and Diagnostic Criteria

Vestibular migraine is an underdiagnosed but increasingly recognized disorder. Today, about 15% to 20% of adults are affected by dizziness (including vertigo) each year. Vestibular vertigo accounts for about a quarter of dizziness, with a 12-month prevalence of 5% and an annual incidence of 1.4%. [1] 44.3 (±13.7) years, the prevalence of women is about two to three times higher than that of men, and there is a certain degree of familial inheritance, and most patients with VM have a personal and family history of migraine. And nearly a third of VM patients have family members with paroxysmal vestibular symptoms. Nowadays, many studies are emphasizing the emotional disorders caused by VM. It has been shown that VM patients are prone to and often accompanied by mental disorders such as anxiety. With the increase in population aging and the common epidemiological characteristics of the disease in the elderly, the group of patients with VM is gradually expanding. A series of symptoms caused by vestibular dysfunction have attracted more and more people's attention due to various comprehensive factors. [2] [3]

The clinical manifestations of vestibular migraine are usually diverse. In general, the clinical manifestations of vestibular migraine are migraine accompanied by vertigo, and the vertigo attack usually lasts from 5 minutes to 72 hours. [4] attacks are usually accompanied by other symptoms of migraine, including vertigo, photophobia, misophonia, and visual aura. 60.3% of the patients reported tinnitus symptoms, 21.4% of the patients reported ear distension or perceived ear pressure elevation symptoms, and most of them were binaural symptoms, and the neurological examination was generally not obvious. [5] found that there are mild abnormalities of semicircular canal function and inter-ocular movement in patients with acute attacks, which are spontaneous nystagmus or positional nystagmus in most patients. [6] International Committee on the Classification of Vestibular Disorders (ICVD) of the Barany Society requires a history of migraine and an overlap in the timing of vestibular and migraine symptoms in at least 50% of attacks and allows for the possibility of possible vestibular migraine. [7] criteria have been shown to be reliable in repeated assessments over a 9-year period. [8]

Vestibular migraine is a complex genetic condition, with many genes ultimately contributing to disease susceptibility and the development of periodic neurological disorders. Current studies have found a strong genetic component to the pathophysiology of the disorder, with a fourfold increased risk of developing the disorder in first-degree relatives. [1] Although advances in technology have enabled these large-scale, high-throughput genetic studies to be done, the precise genetic basis of migraine has remained elusive.

3. Genetic Links to Pathogenesis

3.1. Pathogenesis

3.1.1. Cortical Diffusion Inhibits Diffusion Theory

The cortical spreading inhibition hypothesis has been used to explain the transient vestibular symptoms of migraine. Extracellular K+ levels are locally elevated, promoting glutamate release and activation of NMDA receptors and voltage-gated calcium channels from the apical dendrites of cortico-cortical pyramidal cells [9] triggers cortical spreading depression, in which a neuron experiences a sudden depolarization, a transient "flip" of the microvoltage present on the cell membrane of all neurons, which leads to increased levels of intracellular Ca^{2+}, extracellular H^{+}, K^{+}, glutamate, arachidonic acid, and nitric oxide in the synaptic cleft. [10] Subsequently, a large number of neurons undergo depolarization, and the resulting waves slowly spread from the occipital region to the cortex, which eventually leads to long-term inhibition of electrical activity in the cortex because all neurons are interconnected and all of their activity ultimately comes down to changes in chemical concentrations within and around them. And this unexpected depolarization "propagates" to neighboring neurons and continues in this manner. [11] Molecules such as K^{+}, glutamate, and arachidonic acid produced by this process also activate pain receptors in the trigeminal vasculature and neurons in the trigeminal nucleus, and because this process is so slow, it also increases the duration of pain in migraine sufferers. [12] In addition, during the onset of VM, some patients report the appearance of a "halo" in front of their eyes, which may be related to the activation of the bilateral cerebellum and frontal cortex, as well as the inactivation of bilateral posterior parietal and occipital regions, which leads to the activation of the vestibule thalamocortical pathway and the mutual inhibition of the visual and vestibular systems, which also prove this mechanism. [13]

3.1.2. Ion Channel Theory

Ion channels play a key role in the dysfunction of vestibular neurons. Specifically, ion channels are mainly used by vestibular neurons to regulate the intracellular and extracellular ion balance, which affects the excitability and conduction ability of cells. [13] Abnormal activity of some ion channels may lead to abnormal discharge activity of vestibular neurons, including abnormal action potential production and excessive discharge. [14] These abnormal discharges may misconvey information about body balance and sense of orientation, ultimately leading to the onset of headache and other vestibular symptoms. [15] Current studies have found that the voltage-dependent P/Q calcium channel subunit α1 can regulate the release of calcitonin gene-related peptide from the dura mater, trigeminal ganglion neuronal processes, and trigeminal spinal tract. [16] Gene mutation of this ion channel leads to the involvement of the trigeminal nerve, vestibular nerve, and auditory nerve. At the same time, calcium channel blockers can effectively relieve vertigo and other symptoms of VM, and objective vestibular function tests such as caloric tests and vestibular myogenic evoked potential can also be improved.

The abnormality of ion channels may also affect the interaction between neurons, resulting in excessive neuronal excitability and aggravating the symptoms of vestibular migraine. [17] Therefore, ion channels are considered to be an important regulatory factor in the pathogenesis of vestibular migraine. In-depth studies on the mechanism of ion channels in vestibular migraine will help to reveal the pathogenesis of the disease and provide an important theoretical basis for related treatment strategies and drug development.

3.2. Genetic Factors

Vestibular migraine is a polygenic disorder in which there is the accumulation of many genetic variants, each with a small effect, leading to the occurrence of migraine. Some studies have proved that vestibular migraine has a familial inheritance and may be related to chromosome 22q12. Most female patients with VM usually have a VM susceptibility allele on chromosome 11q. In Behmad's whole-group gene study of selected families with a history of VM, the pathogenic gene was located between rs244895 and d5s2073 on chromosome 5q35, and VM was considered to be an autosomal dominant inheritance. [18] Genetic mutations are associated with migraine by affecting the regulation of neurotransmitters and the excitatory/inhibitory balance of the brain. In familial migraine, several genetic mutations have been identified, including CACNA1A, ATP1A2, and SCN1A. [19] Associations with migraine, episodic vertigo, and MD often cluster in families that include monozygotic twins, supporting the heritability of VM. Epidemiological studies have reported that about 56% of patients with MD also have migraine, and in both conditions, there is a familial predisposition. [20] New studies suggest that the pathogenesis of VM, which is expressed around the auditory vestibulum and is associated with migraine-related CGRP, is largely involved, but there are several theories related to sensory hypersensitivity, altered multisensory processing, trigeminal neurovascular, and calcitonin gene-related peptide (CGRP) effects on the vestibular system. [21] At present, there are many theories about the pathogenesis of vestibular migraine, in which the initiation and propagation of CSD require the influx2+ of Ca ions through the presynaptic P/ q-type Ca^{2+} channels. [22] These channels play a crucial role in regulating the level of Ca^{2+} ions and are encoded by genes belonging to the CACNA family. [23]

4. Structure and Function of CACNA1A Gene

4.1. CACNA Gene Family

The CACNA gene family encodes the α subunit of the VGCC complex, which is essential for the formation of functional calcium channels. These genes are located on different chromosomes and exhibit tissue-specific expression, particularly in the nervous system. VGCC is controlled by the CACNA gene family and plays a key role in neuronal excitability, synaptic transmission, and plasticity. [24]

Different members of the CACNA gene family contribute to the complexity of calcium signaling throughout physiological processes, from neuronal excitability to muscle contraction and hormone secretion. After membrane depolarization, these channels are activated, allowing Ca^{2+} to flood into the cell. This triggers downstream signaling, which is critical for neuronal communication and synaptic transmission. [25] VGCC regulates neurotransmitter release in presynaptic endings, is essential for synaptic transmission and plasticity, and is essential for learning and memory mechanisms. [26]

The activity of the CACNA gene and its protein product is stringently regulated at multiple levels to ensure precise control of calcium influx and neuronal excitability. Regulation can occur through various mechanisms, including post-translational modification, alternative splicing, and protein-protein interactions. The regulation of the CACNA gene is further complicated by post-transcriptional mechanisms. The alternative splicing of CACNA transcripts can generate numerous subtypes with distinct functional properties, thereby facilitating the biosynthesis of protein variants with modified voltage sensitivity or activation and inactivation kinetics. Additionally, microRNAs (miRNAs) play a role in post-transcriptional regulation by binding to the 3' untranslated region (UTR) of target mRNAs, thereby modulating the expression and activity of calcium channels. [27] Beyond transcription and post-transcriptional processes, post-translational mechanisms also govern the expression and function of the CACNA gene. Phosphorylation of CACNA channel subunits by protein kinases, such as protein kinase A (PKA) and protein kinase C (PKC), can modify channel activity and synaptic transmission. Moreover, protein-protein interactions with accessory subunits or regulatory proteins, such as beta subunits and alpha2delta subunits, can influence channel dynamics, voltage sensitivity, and plasma membrane trafficking. [28] Furthermore, activity-dependent processes, such as calcium-dependent inactivation (CDI) and calcium-dependent facilitation (CDF), dynamically regulate the gating characteristics of CACNA channels in response to variations in intracellular calcium levels. [29]

These regulatory mechanisms jointly fine-tune the expression and function of the CACNA gene, ensuring precise control of calcium influx and neuronal excitability. Dysregulation of these regulatory pathways can disrupt calcium homeostasis and contribute to the pathogenesis of neurological disorders. [29]

CACNA genes play a key role in various neurological disorders, revealing their importance in maintaining normal brain function. In migraine, genetic alterations in CACNA1A are associated with familial hemiplegic migraine, which is characterized by premonitory symptoms and temporary paralysis. Calcium channel dysfunction may contribute to abnormalities in neuronal excitability and cortical spreading inhibition implicated in migraine pathogenesis.

4.2. CACNA1A Gene

The CACNA1A gene is located on chromosome 19p13.1 and encodes the α-1A subunit of VGCC. This element is mainly expressed in neurons, particularly in the cerebellum, where it plays an important role in synaptic transmission, neuronal excitability, and motor coordination. Pathogenic variants in the CACNA1A gene cause a range of neurological, neuropsychiatric, and neuromuscular disorders. [30]

The CACNA1A gene encodes the calcium voltage-gated channel subunit α1A, also known as subunit Cav2.1, which is mainly located in the presynaptic regions of the cerebral cortex, thalamus, hypothalamus, hippocampus, and cerebellum. This subunit is involved in muscle contraction, hormone or neurotransmitter release, and gene expression by forming conductive pores. [31]

At present, the commonly employed animal model for gene variability in migraine is developed by introducing the human CACNA1A S218L mutation into the homologous Cacna1a gene through methods such as gene targeting and homologous Recombination, thereby generating Cacna1aS218L mice. This model has been well verified in the study of animal models for familial periodic migraine. Currently, this gene-mutated mouse has also been well-validated in the research of vestibular nerve-related diseases. Previously, whole-cell patch clamp recordings of cerebellar granule neurons were conducted in the animal model of chronic migraine, and the results indicated that neurons expressing the S218L channel demonstrated a significant increase in whole-cell CaV2.1 current density at negative voltages. In contrast, the current density remained unchanged at positive voltages. This suggests that the number of functional Cav2.1 channels on the somatodendritic plasma membrane is similar among different genotypes. In mice expressing S218L, it can be observed that 1) the CaV2.1-mediated calcium$^+$ current density shows a more substantial increase during weak depolarization; 2) there is a greater increase in spontaneous neurotransmitter release at the NMJ; 3) The NMJ is a model synapse that is entirely dependent on CaV2.1 channels and can be electrophysiologically analyzed relatively easily; and CSD is more prone to occur, characterized by a lower trigger threshold, higher propagation speed, and a higher possibility of consecutive CSD events with a single stimulus. [32]-[34]

Currently, the modeling methods for chronic migraines are also typically applied to the related modeling of vestibular migraines. Meanwhile, in the current predominant hypotheses, it is considered that the vestibular symptoms of vestibular migraine are attributed to the central sensitization of the vestibular nervous system. The animal model with gene mutations has demonstrated that mutations in the CACNA1A gene make nerve cells more prone to depolarization. Whether these mutations also enhance the sensitization of the vestibular system, thereby resulting in a series of vestibular symptoms when patients have migraines, still requires a series of animal behavioral tests and specific patch clamp experiments related to vestibular nucleus cells for further verification. [35]

5. Conclusions

Although no specific gene locus has been confirmed in VM so far, experiments studying the pathogenesis of VM have shown that the absence of CGRP in transgenic mice is associated with a reduction in suprathreshold cochlear nerve activity and a decrease in vestibular reflex (VOR) gain. CGRP-deficient mice also exhibit impaired otolith activity and balance impairment; in the CM rat model, CGRP can reduce VN neuron activation and alleviate vestibular dysfunction, and these beneficial effects may be mediated by the PKC/ERK/CREB signaling pathway. Exploring the therapeutic effect of CGRP1 receptor antagonists in the CM model as a preclinical approach for potential clinical translation in patients with vestibular symptoms of migraine is currently ongoing. For migraine patients, the CGRP receptor antagonist Erenumab has been widely used in clinical practice. According to relevant clinical data feedback, this biologic agent has shown good efficacy in preventing the frequency and severity of migraine attacks. However, whether this monoclonal antibody also has a good inhibitory effect on vestibular symptoms in patients with vestibular migraine still needs further clinical trials to observe. [36] Currently, according to the latest Chinese clinical treatment guidelines for vestibular migraine, flunarizine hydrochloride, a calcium channel antagonist, has a relatively clear clinical effect in preventing the frequency of attacks and relieving vestibular nerve symptoms in patients with vestibular migraine. However, how to conduct more precise and effective clinical drug treatment still requires a large number of animal experiments and clinical trials for verification. [37]

Vestibular disorders are complex disorders with heterogeneous presentations and overlapping symptoms, making a purely clinical diagnosis extremely challenging. The combination of deep phenotype with complete family history and NGS can better analyze the rare variants and genes associated with vestibular migraine, thus allowing a more accurate classification of the disease process. Research on the pathogenesis and genetic-related genes of vestibular migraine can continue to open up the direction of treatment for vestibular migraine, including gene and stem cells.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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