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The Role of Calcium in the Pathophysiology of Vertigo and its Treatment with Flunarizine

Jianxia Yang[1#], Zhao Dong[2#], Mingxin Li[3], Ge Tan[4], Miaomiao Jia[1], and Shengyuan Yu[2*]

1 Medical Affairs, Xian Janssen Pharmaceutical Ltd, Beijing, P.R. China
2 Department of Neurology, Chinese PLA General Hospital, Beijing, P.R. China
3 Department of Neurology, Qilu Hospital of Shandong University, Jinan, Shandong Province, P.R. China
4 Department of Neurology, the First Affiliated Hospital of Chongqing Medical University, Chongqing, P.R. China

***Corresponding author:** Yu S

yusy1963@126.com

Department of Neurology, Chinese PLA General Hospital, Beijing, P.R. China.

Tel: +8618311081809

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Abstract

Vertigo is a complicated symptom caused mainly by a dysfunctional vestibular system, either central or peripheral. Benign paroxysmal positional vertigo (BPPV), vestibular migraine (VM) and posterior circulation ischemia (PCI) are the three common causes of vertigo, all of which are related to abnormal calcium function. As a calcium antagonist, flunarizine has a multitude of mechanisms of action in vertigo treatment. The drug exerts neuroprotective effects on brain, endothelial and hair cells of the inner ear; reduces angiospasm, normalizes blood viscosity, improves the circulation of blood flow to the brain and inner ear; protects and restores injured neuronal or vascular cells from hypoxic-ischaemic damage; accelerates vestibular function recovery and inhibits cortical spreading depression (CSD). Many studies showed flunarizine to be effective especially against vertiginous attacks resulting from BPPV, VM and PCI with few serious side effects, probably due to its multiple mechanisms of action.

Keywords: BPPV; VM; PCI; Calcium; Vestibular; CSD; Flunarizine

Abbreviations: BPPV: Benign Paroxysmal Positional Vertigo; VM: Vestibular Migraine; PCI: Posterior Circulation Ischemia; CSD: Cortical Spreading Depression; VBI: Vertebrobasilar Insufficiency; BMD: Bone Mineral Density; SH/SS: Native Thiol/Disulphide; TT: Total Thiol; VA: Vertebral Artery; VAD: Vertebral Artery Diameter; CGRP: Calcitonin Gene-Related Peptide; FHM: Familial Hemiplegic Migraine (FHM); EA-2: Episodic Ataxia Type 2 (EA-2); IAA: Internal Auditory Artery; PICA: Posterior-Inferior Cerebellar Artery; NCX: Sodium-Calcium Exchanger; L-VDCC: L-Type Voltage Dependent Calcium Channel; IP3R: Inositol Triphosphate Receptors; MPT: Mitochondrial Permeability Transition; CBF: Cerebral Blood Flow; BR: Blink Reflex; BAEP: Brain Stem Auditory Evoked Potential; TCD: Transcranial Doppler.

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Introduction

Vertigo is a common symptom which involves the sensation that either one's own body, or the environment around the body, is moving or spinning, or both [1]. In the general population, the lifetime prevalence of vertigo is estimated at 7% [2]. Vertigo impairs the quality of life and reduces self-confidence in many forms of physical activity. Persistence may lead to anxiety and then depression. Diagnosing vertigo is complex because it may occur as the main or as an accompanying symptom of many related-diseases. Central conditions that cause vertigo include vestibular migraine (VM), posterior circulation ischemia (PCI), tumours and multiple sclerosis, etc; and the potential causes of peripheral vertigo are BPPV, Meniere's disease, vestibular neuronitis, etc. [3-5]. Moreover, there are also psychogenic factors involved.3 In general, the common causes of vertigo are believed to be BPPV, VM and PCI [6]. PCI is also previously known as vertebrobasilar insufficiency (VBI) [7].

The sensorimotor control mechanism consists of the visual, proprioceptive and vestibular systems that help us to achieve and maintain balance [8,9]. Damage to any of these three interconnected components would lead to vertigo, and the common damage is that to the vestibular system. Although the mechanisms of BPPV, VM and PCI remain unclear, they are all related to a dysfunctional vestibular system, where calcium

homeostasis is disrupted.

Calcium Mechanisms in the Pathophysiology of Vertigo

Calcium ion in the pathophysiology of BPPV and vertigo-related symptoms

BPPV, commonly known as otolithiasis, is the most common cause of peripheral vertigo that mainly presents with recurrent and transient vertigo, and positional nystagmus [10-13]. BPPV can occur at any age but is more prevalent in women aged over 40 years [14]. BPPV affects 2.4% of the general population in life, and the 1-year prevalence rate is 1.6% [15].

Canalithiasis and cupulolithiasis are currently recognized as the underlying pathogenetic mechanisms of BPPV [11,14,16-19]. According to the mechanism of canalolithiasis, otoconia (or calcium carbonate crystals) relocate from the utricle into the semicircular canal where they move freely within the endolymph [11,20]. The movement of otoliths causes an abnormal endolymphatic flow that stimulates or inhibits the vestibular afferent signals and leads to positional vertigo [12]. This may occur in any of the three semicircular canals, but more often in the posterior semicircular canal [18]. However, if the otoconia adhere to the cupula, this is the mechanism that can explain cupulolithiasis [16].

Otoconia are made of inorganic calcium carbonate which accumulates onto an organic matrix core composed of glycoproteins. Calcium is required for otoconia mineralization and turnover. Moreover, the magnitude of mechano-electrical transduction in the vestibular receptors is mainly dependent on the endolymph calcium concentration and the permeability of the calcium conducting channels [21]. Therefore, calcium metabolism is an essential etiological factor in BPPV development.

In the inner ear, thanks to the expression of the epithelial calcium channel transport system, sodium-calcium exchangers, and plasma membrane calcium pumps, a normal calcium level is maintained by transepithelial absorption of calcium ions from the endolymph [22]. Vitamin D plays an important role in keeping calcium ions at a normal level by regulating the expression of some calcium binding proteins; and its deficiency can change the structure of otoconia and disrupt calcium metabolism, resulting in BPPV attacks due to calcium deficiency-related degradation and fragmentation of otoconia [22]. Recently, multiple studies have investigated BPPV patients and the results showed these patients had significantly lower BMD (bone mineral density) or serum 25-hydroxyvitamin D levels, vitamin D deficiency or oxidative stress status [10,12,18,19,23-26].

Beyond that, an interesting study using native thiol/disulfide (SH/SS) homeostasis as a novel marker of oxidative stress for the first time showed oxidative stress played a significant role in the disorder of calcium metabolism and the development of BPPV [18]. Free oxygen radicals are naturally generated in every reaction of the body and they can be eliminated by the body's natural antioxidant defence systems. Oxygen stress occurs when there is insufficient response to the formation of free radicals and this is related to calcium metabolism at the cellular level. During this period, the endoplasmic reticulum may initiate an increase in calcium levels, causing the rupture of the mitochondrial membrane and triggering apoptosis. In the cell, sulfhydryl groups (-SH) containing SH's remove oxidative stress. The cysteine residues of circulating albumin proteins bind SH groups to form reversible SS bonds that reduce the toxicity of reactive oxygen species. The total thiol (TT) levels in cells remain constant to maintain SH/SS homeostasis. It has been shown that BPPV patients have significantly higher SS/SH and SS/TT ratios and lower SH/TT ratios, which is consistent with the increase in oxidative stress in BPPV patients through calcium metabolism and the direct toxic effects of free oxygen radicals, including the triggering of apoptosis [18].

Furthermore, a high percentage of BPPV patients display one or more atherosclerotic risk factors [27]. One of the explanations which link BPPV with these factors is that atherosclerosis of the vertebral artery (VA) may initially cause labyrinthine ischemia, since vestibular structures of the internal ear receive blood supply from the labyrinthine artery, which is a branch of VA. During this period oxidative radicals are produced, facilitating detachment of otoconia from the otolith membrane of the utricle [27]. Yazici and Inanc used extracranial-colour-coded duplex sonography, a useful screening tool for the evaluation of posterior cerebral circulation. This was the first study to show that BPPV patients had a lower vertebral artery diameter (VAD) and vertebral artery (VA) flow rate on the side where BPPV was diagnosed, suggesting that BPPV could be a precursor for future atherosclerosis development [27].

Several studies have supported the genetic predisposition in BPPV occurrence because many patients with BPPV have family histories of BPPV [13]. The *CACNA1A* gene at locus 19P13 encodes a component of the Cav2.1 (P/Q type) voltage-dependent calcium channel and this channel is distributed across the brain and neuromuscular junctions [13]. Mutations in *CACNA1A* weaken Cav2.1 function, resulting in abnormal channel function and triggering neurological diseases. The *CACNA1A* gene analysis in BPPV patients showed increased risk of BPPV occurrence correlated with TT mutation of rs2074880 in the *CACNA1A* gene, indicating that *CACNA1A* was involved in the occurrence and pathogenesis of BPPV through calcium channel regulation, but the exact molecular mechanisms remain unknown and require further investigation [13].

Calcium mechanism in the pathophysiology of VM and vertigo-related symptoms

VM is the second most common cause of episodic vertigo, characterized by vestibular symptoms, such as vertigo, dizziness, or imbalance in at least 50% of migrainous symptoms [28,29]. It affects about 1% of the general population, with a female predominance [30]. Despite a well-defined diagnostic criteria developed by the Barany Society and the Subcommittee of the International Headache Society [31] the pathophysiology of VM is poorly understood. It is considered that the occurrence of VM symptoms is an overlap between vestibular pathways and the

migraine pathway. The current hypotheses of "cortical spreading depression (CSD)", "trigeminovascular pathway" and "ion channel defect", especially calcium ion channel defect, maybe the underlying aetiology of VM.

CSD is defined as the slow and propagating wave (2-6 mm/min) of depolarising neuronal and glial cells, followed by a prolonged inhibition (15-30 min) of cortical activity and long-lasting decrease in cerebral blood flow in the brain [32]. In migraine, cerebral ischemia or traumatic brain injury, CSD is thought to be caused by the rise of extracellular potassium or other ions [33]. One study showed that the flow of calcium ions into cells is enhanced by the use of the calcium carrier A23187, which increases the transmission rate of CSD in a dose-dependent manner, and higher concentrations of the compound trigger CSD [33]. During CSD, neocortical and extracellular release of signals, such as K+, H+, Ca^{2+}, arachidonic acid, calcitonin gene-related peptide (CGRP) and nitric oxide, activate trigeminal afferents on cranial blood vessels that elicit a trigeminovascular reflex-mediated vasodilatation in the meninges, resulting in pain perception with central processing of trigeminal afferent activation in ascending thalamocortical pathways [32,34]. This trigeminovascular reflex system also innervates the blood supply of the inner ear and modulates rapid vasodilation [34]. Information transmitted from peripheral vestibular sensory organs and the vestibular nerve to the medulla and pons is an external trigger within the migraine circuit constructs [34]. Thus, CSD may explain the onset of transient vertigo.

There is some evidence regarding the genetic susceptibility of VM. Firstly, VM usually affects women in their 40s with a personal and family history of migraine [35]. Secondly, the characteristics of VM share some clinical similarities with familial hemiplegic migraine (FHM) and episodic ataxia type 2 (EA-2). Mutations in the gene *CACNA1A*, which encodes a neuronal calcium channel α subunit, may cause FHM and EA-2 [36]. Cav2.1 (P/Q type) voltage-dependent calcium channels were proven to be mediators of the trigeminovascular reflex, which can modulate transmission of spinal dural trigeminal afferent relays [34]. In addition, these channels regulate CGRP release from neuronal processes in the dura, trigeminal ganglion, the spinal trigeminal nucleus, and the inner ear. 34 CGRP, as a neurotransmitter, may be involved in the pathogenesis of vestibular migraine [37].

Calcium mechanism in the pathophysiology of PCI and vertigo-related symptoms

Posterior circulation, which is also known as vertebrobasilar system, is comprised of the vertebral arteries, basilar artery and posterior cerebral artery, that mainly supplies oxygen-rich blood and nutrients to the brainstem, thalamus, cerebellum, vestibular system, occipital and medial temporal lobes [7,38,39]. PCI occurs when there is insufficient blood flow through the posterior circulation of the brain [7,38-40]. For the vestibular system, it is mainly supplied by: (1) very small penetrating vessels originating from the basilar artery that supply the vestibular nuclei; and (2) the internal auditory artery (IAA), that irrigates the cochleovestibular nerve, the cochlea, and the posterior labyrinth [38]. The IAA originated either from the anterior-inferior cerebellar artery (80–85%), or a vascular loop from the posterior-inferior cerebellar artery (PICA), which is a branch of the VA (15%). The PICA is a terminal vessel with very few collateral branches. Since the labyrinthine branches are smaller and receive less collateral irrigation, the labyrinth should be more affected and sensitive to ischemia [38]. This may explain that more than one symptom of PCI as a result of ischemia is usually presented which include vertigo, dizziness, unilateral limb weakness, dysarthria, headache and nausea or vomiting, but the most common symptom maybe vertigo [41,42].

The most frequent cause of PCI is atherosclerosis, which can occur in the proximal portion of the VA in the neck, intracranial vertebral arteries, basilar artery and posterior cerebral arteries [38,39]. The significant build-up of atherosclerotic plaques over time leads to ischemia. About 20% of ischemic events in the brain involve posterior circulation (vertebrobasilar) structures [43-45]. The other common etiologies include: (1) cardioembolic conditions: such as atrial fibrillation, infective endocarditis, vertebral artery dissection, and systemic hypercoagulable states; (2) embolism, atherosclerosis of great vessels, and arterial dissection; (3) and less frequently, migraine, fibromuscular dysplasia, coagulopathies, and drug abuse [38,39].

Brain ischemia rapidly leads to the loss of glucose and oxygen and thus energy depletion in the affected core tissue [46-49]. This leads to loss of ionic gradients resulting in marked losses of intracellular potassium and a large influx of calcium ions into the cells, and loss of membrane potential depolarization in neurons and astrocytes. Then, this process induces the release and accumulation of glutamate and other neurotransmitters to the extracellular space. Energy depletion causes glutamate transporters to fail in clearing the excessive glutamate and the sodium-calcium ATP pump that is normally used to eliminate calcium ions also fail. The excess glutamate then over stimulates ionotropic and metabotropic glutamate receptors resulting in the overloading of intracellular calcium ions into neurons, which then triggers further downstream proteases, lipases, phosphatases and endonucleases. Their over-activation results in lethal reactions such as nitrosative and oxidative stress, lipid peroxidation, and mitochondrial dysfunction that damage structural cell integrity and cell injury leading eventually to necrotic cell death. This mechanism of glutamate excitotoxicity is the primary mediator of acute neuronal death, and is largely caused by calcium overload [46,50].

An occlusion of the vertebral or basilar artery, an embolus that may be trapped in the arteries closer to the brain or arterial dissection may cause stroke. Hypoxia is a common occurrence after stroke, and may cause changes to multiple calcium channels such as the sodium-calcium exchanger (NCX), L-type voltage dependent calcium channel (L-VDCC), and inositol triphosphate receptors (IP3R) which contribute to calcium overload, eventually triggering cell apoptosis that precipitates the onset of diseases [51,52]. Under hypoxic stress, calcium overload may initiate different apoptotic pathways in the cell using different calcium channels [52]. Activation of different calcium channel isoforms will result in different outcomes of the cell under hypoxia [52].

Mechanisms of Action of Flunarizine

Inhibition of calcium overload as a calcium channel blocker

Flunarizine, as a calcium channel blocker, works by causing the sustained inhibition of extracellular calcium ions entering tissue cells when activated by high potassium ion levels, vasoactive substances or hypoxia, thereby preventing calcium overload that is cytotoxic to cells as excessive calcium leads to the over-activation of deleterious enzymes and signalling processes that impair neuronal function or lead to cell death [53]. Flunarizine exhibits gradual onset and long duration of action, and the way it works on calcium ions is dose-dependent [54]. Since the induction of vasoconstriction by endogenous vasoactive substances depends on the contribution of calcium ions from different sources, the effects of flunarizine vary in different blood vessels, which are particularly marked in isolated cerebral arteries and in the cerebral circulation, that may help to explain its beneficial effects in cerebrovascular disorders [53].

Protective effects of flunarizine on brain cells, endothelial cells and hair cells

In pathological conditions, massive glutamate would be released to the extracellular space, resulting in excessive stimulation of glutamate receptors and neuronal injury, thus inducing calcium influx. Calcium signalling pathways play a vital role in the survival of neurons. Further studies showed pre-treatment with flunarizine protected rat hippocampal neural cells from glutamate-induced injury as a calcium blocker [55].

Endothelial cell damage may trigger inflammation, edema and thrombosis, leading to cell dysfunctionality that eventually causes atherosclerosis. However, pre-treatment of animals with flunarizine provided prolonged protection against induced endothelial cell damage. Flunarizine also inhibits edema formation, platelet activation and thrombosis that should subsequently occur after endothelial cell damage [53,56].

Cisplatin primarily damages the outer hair cells in the basal and middle turns of the cochlea with sporadic loss of inner hair cells, inducing cell apoptosis or death [57]. Flunarizine could protect auditory cells from cisplatin-induced cytotoxicity through direct inhibition of lipid peroxidation and mitochondrial permeability transition (MPT), but interestingly not through calcium-dependent mechanisms, though changes in intracellular calcium level are known to trigger apoptosis and under normal conditions, the increase in intracellular calcium regulates hair cell functions.57 Other studies have also demonstrated that flunarizine may be able to protect hair cells [58,59].

Improving blood circulation in the brain and inner ear, and improving blood/oxygen supply

In animals at the macroscopic level, flunarizine inhibits calcium influx into red blood cells and by functioning as such, alleviates angiospasm, normalises blood viscosity, increases blood flow to the brain and inner ear thereby improving blood and oxygen supply, improving circulation in the brain and inner ear, and protecting and/or restoring them from hypoxic-ischemic damage [53, 56,60-71]. This is on top of exerting neuroprotective effects on brain, endothelial and hair cells of the inner ear.

Acceleration of vestibular compensation

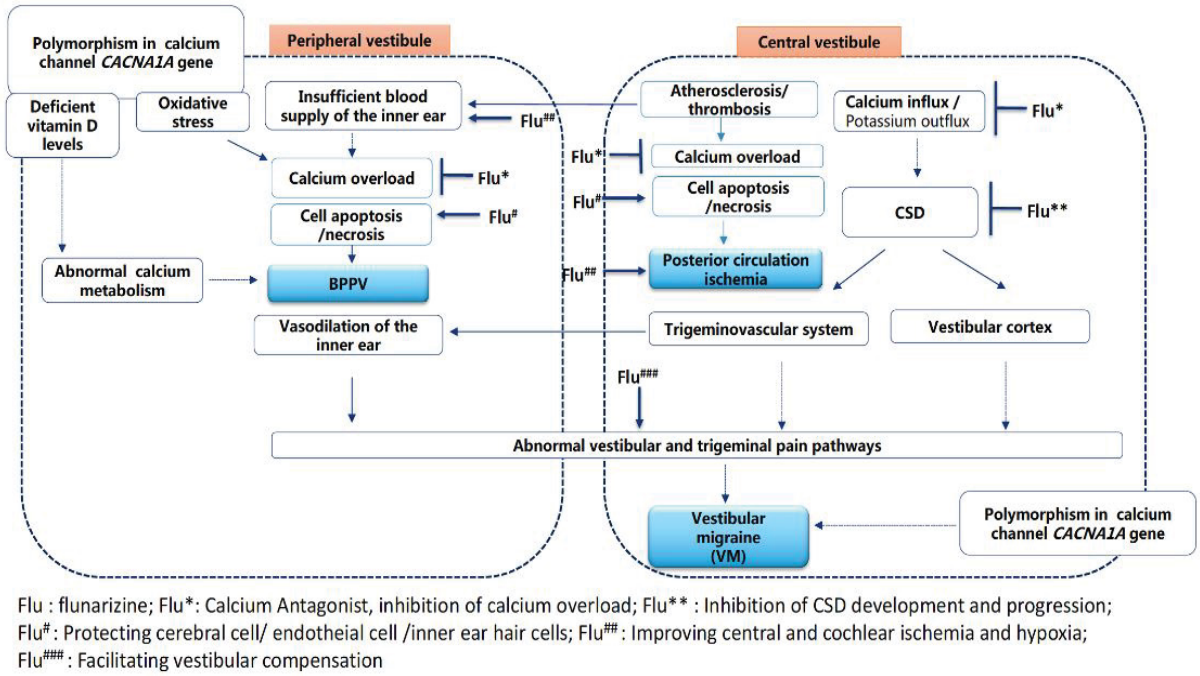
Damage to the vestibular system affects the control of eye movements and posture, and vestibular compensation refers to the behavioural recovery after the permanent loss of the peripheral semicircular canal and macular receptors of one inner ear that result in loss of vestibular function. The process involves extensive synaptic and neuronal plasticity in the brainstem vestibular nuclei, cerebellum and related areas of the brain but not all patients that suffer from this loss may recover completely. Many methods can be used to restore vestibular function such as pharmacologic therapy, physical measures, surgery and procedures to unilaterally disable the function of the labyrinth, but the method used should depend on the individual's capacity for vestibular compensation [72].

Three studies on the treatment of labyrinthectomized-cerebellectomized and (or) labyrinthectomized guinea pigs showed that flunarizine increased and accelerated vestibular compensation by inhibiting vestibular and nuclear activities of the intact labyrinth, and also exciting the cerebellar cortex [21,73,74]. At the vestibular receptor level, flunarizine prevented the influx of calcium ions into the cell, thus reducing the magnitude of mechano-electrical transduction, which is mainly dependent on the endolymphatic calcium concentration. At the vestibular nuclear level, it interfered with neurotransmitter release by regulating calcium entry into the presynaptic nerve terminations, facilitating the re-establishment of equilibrium between the two vestibular complexes. Equilibrium was achieved when the drug depressed the activity of the peripheral receptors and inhibited directly the vestibular nuclei of the intact side. The drug also excited the cerebellar cortex which modulated the activity of the vestibular nuclei of both sides, restoring the vestibular loss caused by labyrinthectomy.

Inhibition of CSD

CSD waves are associated with the dramatic failure of brain ion homeostasis, efflux of excitatory amino acids from nerve cells, increased energy metabolism and changes in cerebral blood flow (CBF) [75]. Recovery from CSD depends on activation of ion pump activity to increase metabolic activity and oxygen demand. In the brain, this is partially compensated by an increase in cerebral blood flow. Hypoxic conditions cause an increase in intracellular calcium, resulting in calcium overload and mitochondrial injury that trigger a series of downstream signalling events, ultimately resulting in cell death.

There have been suggestions that spreading depression could be the final pathophysiology target of migraine prophylactic drugs where flunarizine showed dose-dependent suppression of CSD [75]. A study on CSD using rats showed under normoxic and hypoxic conditions, flunarizine reduced the number of CSD through its inhibitory effects on L-, N-type voltage-gated



Flu : flunarizine; Flu*: Calcium Antagonist, inhibition of calcium overload; Flu** : Inhibition of CSD development and progression;
Flu#: Protecting cerebral cell/ endotheial cell /inner ear hair cells; Flu##: Improving central and cochlear ischemia and hypoxia;
Flu###: Facilitating vestibular compensation

Figure 1 Overview of the role of calcium in the pathophysiology of vertigo and its treatment with flunarizine.

calcium channels. Under the same conditions, the drug reduced the duration of CSD through its inhibitory effect on cortical hypoperfusion induced by CSD, where oxygen supply was an important factor for normalisation of extracellular potassium ions. Increasing the oxygen supply to the brain repolarised neurons and glial cells. The drug regulated and reduced the amplitude of CSD under normoxic condition, but it did not reduce the amplitude of CSD under hypoxic conditions. Under hypoxic conditions, CSD also decreased the maximal rate of coupled respiration, while it increased the rate of leakage of protons back across the inner mitochondrial membrane into the matrix, and further uncoupled the mitochondria. These results indicated that flunarizine can attenuate the changes caused by CSD in the brain by reducing the damage caused by oxidative stress and mitochondrial injury [75].

Other studies with CSD rats showed CSD inhibition is affected by different calcium ion channels that leads to the reduction of plasma CGRP and substance P levels, which are involved in activation of the trigeminovascular system and vasodilatory response that occur with a migraine attack [76,77].

The efficacy of flunarizine in the treatment of vertigo

Studies indicated that flunarizine was effective in patients with BPPV. A multi-centered double-blind study on 182 BPPV patients showed flunarizine was clearly more superior than betahistidine in treating vertigo and the associated symptoms, in particular, neurovegetative disorders and headaches [78]. Interestingly, one study showed combining Epley manoeuver with flunarizine treatment on 69 patients with posterior semicircular canal BPPV achieved a success rate of 93.75% in complete resolution or significant improvement in vertigo symptoms after four weeks compared to 79.16% if only the Epley manoeuver was used [79]. The recurrence after a 3-month follow-up in 8 patients was significantly lower with the combination therapy.

Similarly, flunarizine was proven to be effective in patients with VM. A 3-month randomized controlled trial on 23 VM patients showed the most commonly prescribed dosage of 10 mg flunarizine improved the frequency, duration and intensity of vertiginous episodes significantly ($p<0.05$) with no serious adverse effects [80]. In a retrospective study on 61 VM patients, 68% of flunarizine-treated patients (n=30) showed improvements in VM symptoms compared to 73% of propranolol-treated patients (n=31) ($p<0.001$) [81]. Another randomised controlled trial over 12 weeks on 48 VM patients compared those on 10 mg flunarizine daily with those on 16 mg betahistidine and vestibular exercises showed significant decreases in the frequency of vertiginous episodes ($p=0.010$) and severity of vertigo ($p=0.046$), though accompanied by weight gain and somnolence [82].

Flunarizine was also effective in patients with vascular vertigo in some studies [83]. In the study of mild to severe vertiginous patients due to VBI, 62 of 75 patients experienced complete remission with positive rates of blink reflex (BR), brain stem auditory evoked potential (BAEP) and transcranial doppler (TCD) after the treatment decreasing to 6%, 4% and 8%, respectively [84]. Using TCD in another study, flunarizine treatment of 22 patients with vertigo due to VBI showed improved cerebrovascular circulation [85].

Beyond that, a 2-month multicentred double-blind study on 117 patients with vestibular vertigo on either 10 mg flunarizine or 8 mg betahistidine (three times daily) showed flunarizine was

significantly more active against vertigo attacks and associated symptoms [86]. Thus, flunarizine is a useful and effective drug against vertiginous attacks [87] **(Figure 1)**.

Discussion and Conclusion

This article comprehensively reviewed calcium mechanisms in the pathophysiology of vertigo and its treatment with flunarizine. Vertigo is a common symptom, but is complicated because it can be caused by BPPV, VM or PCI, or other complex diseases, most often due to a dysfunctional central or peripheral vestibular system. Studies have indicated that calcium ion disorders played an important role in the pathogenesis of vertigo at the cellular level. As a calcium antagonist, pre-treatment of animals with flunarizine is able to protect brain, endothelial and hair cells of the inner ear. Treatment with the drug also alleviates angiospasm, normalizes blood viscosity, increases blood flow to the brain and inner ear, improves circulation in the brain and inner ear, and protects and/or restores them from hypoxic-ischemic damage, facilitates the acceleration of vestibular compensation and inhibits the propagation of CSD. In numerous studies, flunarizine was shown to be effective against vertiginous attacks and the associated symptoms caused by BPPV, VM and PCI with few serious adverse effects. It also appears to be more effective when used in combination therapy. Thus, flunarizine's effectiveness against both acute and chronic vertigo, be it of a peripheral vestibular or vascular origin, makes it a good choice for vertigo treatment. Moreover, further study of calcium ions in the pathogenesis of vertigo may provide a better solution for the treatment of this complicated symptom.

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