

Mechanisms of neuroimmune crosstalk in vestibular disorders: Linking inflammation with neural circuit dysfunction (Review)

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Abstract. Vestibular disorders such as vestibular migraine (VM) and Menière's disease (MD) involve complex interactions between inflammation and neural circuit dysfunction. Emerging evidence highlights neuroimmune crosstalk as a unifying pathophysiological framework. The present review synthesized current knowledge on inflammatory cytokine networks; neuropeptide signaling including calcitonin gene-related peptide and histamine; glial responses; and systemic immune influences including the gut-vestibular axis. Emerging evidence suggests potentially distinct immunological

profiles may differentiate VM from MD. Illustrative examples include elevated IL-1 β and macrophage-derived C-X-C motif chemokine ligand (CXCL)8 in MD, whereas CXCL10 acting through the PI3K/AKT signaling pathway has been implicated in VM pathogenesis. However, direct comparative studies remain limited and findings across cytokine studies show some heterogeneity. These observations support the concept of mechanism-based subtyping as a promising framework requiring further validation. Neuroinflammation has dual effects on vestibular compensation, with appropriately calibrated responses promoting recovery and excessive or suppressed inflammation impairing plasticity. The present review integrates molecular, cellular and systemic neuroimmune mechanisms to provide a cohesive framework linking inflammation with vestibular neural circuit dysfunction. The purpose of the present study was to inform future biomarker development and precision therapeutic strategies for vestibular disorders.

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Abbreviations: AIED, autoimmune inner ear disease; BDNF, brain-derived neurotrophic factor; CGRP, calcitonin gene-related peptide; COVID-19, coronavirus disease 2019; CXCL8, C-X-C motif chemokine ligand 8; DFNA34, deafness, autosomal dominant 34; GABAA, gamma-aminobutyric acid type A; GFAP, glial fibrillary acidic protein; H1, H2, H3, H4, histamine receptors 1-4; ICI, immune checkpoint inhibitor; KCC2, potassium-chloride cotransporter 2; MD, Menière's disease; NLRP3, NOD-like receptor family pyrin domain containing 3; PACAP, pituitary adenylate cyclase-activating polypeptide; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th1, T helper type 1; TLR4, Toll-like receptor 4; TNF- α , tumor necrosis factor α ; TrkB, tropomyosin receptor kinase B; TRPV2, transient receptor potential vanilloid 2; TSPO, translocator protein; VM, vestibular migraine; VN, vestibular neuritis

Key words: neuroimmune crosstalk, vestibular disorders, Menière's disease, vestibular migraine, neuroinflammation, microglia, calcitonin gene-related peptide, vestibular compensation

Contents

1. Introduction
2. Neuroimmune architecture of the vestibular system
3. Inflammatory cytokines and immune signaling in vestibular disorders
4. Neuroglial mechanisms in vestibular pathophysiology
5. Neuropeptides and the vestibular neuroimmune network
6. Systemic immune influences and the gut-vestibular axis
7. Vestibular compensation and neuroimmune plasticity
8. Future perspectives
9. Conclusions

1. Introduction

Vestibular disorders represent a heterogeneous group of conditions characterized by dizziness, vertigo and postural instability, which collectively impose a substantial burden on healthcare systems and quality of life. Donovan *et al* (1) conducted a systematic review and meta-analysis demonstrating that vestibular dysfunction affects 30-50% of older

adults who experience falls, underscoring the high prevalence and clinical significance of these conditions. In addition to physical disability, Borsetto *et al* (2) reported that dizziness frequently coexists with psychological disorders and cognitive decline, suggesting that vestibular symptoms extend far beyond mere balance disturbances to encompass broader neuropsychological consequences. These observations point to a critical gap: Conventional models do not adequately explain the episodic nature, trigger sensitivity and inter-individual variability that characterize many vestibular disorders.

Traditional understanding of vestibular pathophysiology has focused primarily on peripheral structural abnormalities, endolymphatic hydrops and vascular mechanisms. Lopez-Escamez and Perez-Carpén (3) provided an updated overview of MD, emphasizing that while endolymphatic hydrops represents a histological hallmark, its correlation with clinical symptoms remains imperfect, indicating the involvement of additional pathogenic factors. Similarly, Villar-Martinez and Goadsby (4) reviewed VM and reported that although trigeminovascular activation and central sensitization contribute to symptomatology, the precise molecular links between migraine pathways and vestibular dysfunction are yet to be fully elucidated. These observations highlight a critical gap: Conventional models do not adequately explain the episodic nature, trigger sensitivity and interindividual variability that characterize many vestibular disorders.

Emerging evidence has positioned neuroimmune crosstalk as a unifying framework that may answer these unresolved questions. The vestibular system possesses a specialized neuroimmune architecture, including resident macrophages, mast cells and cytokine signaling networks that interface with neural circuits. Patel *et al* (5) reviewed the distribution of calcitonin gene-related peptide (CGRP) in the audiovestibular system; detailed mechanistic and therapeutic evidence is synthesized in the *CGRP in vestibular migraine* section. Parallel advances have been made in understanding histaminergic regulation: Tighilet *et al* (6) systematically characterized the histaminergic system's involvement in both normal and pathological vestibular function, demonstrating that histamine receptors 1-4 (H1, H2, H3 and H4) modulate not only neuronal excitability but also immune cell activity and vascular permeability. These findings collectively suggest that neuroimmune interactions are not epiphenomena but active drivers of vestibular pathophysiology.

The involvement of inflammatory and immune signaling in vestibular disorders has been supported by clinical and translational evidence. Patel *et al* (5) characterized the distribution of CGRP in the audiovestibular system, identifying this neuropeptide as a key mediator linking neural activity to neurogenic inflammation. Systemically, autoimmune mechanisms can directly target vestibular structures: Betancourt *et al* (7) reported two cases of anti-Kelchlike protein 11 antibody-associated encephalitis presenting with prominent vertigo, illustrating how autoantibodies may disrupt vestibular circuits. In the context of viral infection, Chen *et al* (8) systematically reviewed audiovestibular dysfunction related to long coronavirus disease 2019 (COVID-19) syndrome, concluding that persistent vertigo and imbalance in a subset of patients likely reflect immune-mediated injury rather than direct viral invasion.

Despite these advances, important knowledge gaps remain. The relative contributions of distinct neuroimmune pathways, namely CGRP-driven vs. histamine-driven vs. cytokine-mediated, across different vestibular disorders have not been directly compared, nor has it been established whether neuroinflammatory signatures can serve as reliable diagnostic biomarkers or predict treatment response. The optimal therapeutic strategies targeting neuroimmune crosstalk, including anti-CGRP monoclonal antibodies, histaminergic agents and immunomodulators, require systematic evaluation in vestibular-specific populations rather than extrapolation from other neurological conditions. The present review synthesized current evidence on neuroimmune mechanisms in vestibular disorders, focusing on inflammatory signaling, neuropeptide networks, glial involvement and systemic immune influences. By integrating findings from clinical, translational and epidemiological studies, the present review provided a cohesive framework linking inflammation with neural circuit dysfunction in vestibular disorders.

The present review was based on a comprehensive literature search of the PubMed database (<https://pubmed.ncbi.nlm.nih.gov/>) covering publications between January 2016 and December 2026. The search strategy employed combinations of the following keywords and MeSH terms: ('vestibular disorders' OR 'Meniere's disease' OR 'vestibular migraine' OR 'vestibular neuritis') AND ('neuroimmune' OR 'neuroinflammation' OR 'cytokine' OR 'microglia' OR 'astrocyte' OR 'CGRP' OR 'histamine' OR 'vestibular compensation' OR 'gut-brain axis'). Additional relevant studies were identified through manual screening of reference lists of retrieved articles and previous reviews. The following inclusion criteria were applied: English-language original research articles, systematic reviews, meta-analyses, clinical trials, guidelines and selected case reports/series with direct relevance to neuroimmune mechanisms in vestibular disorders or related models and with data from human tissues, clinical cohorts, or experimentally validated animal models. The exclusion criteria were as follows: Non-English publications; conference abstracts, editorials, commentaries, letters and non-peer-reviewed reports; studies lacking direct vestibular or neuroimmune relevance; and duplicate or insufficiently detailed reports. Narrative reviews were used only for background or reference screening, not as sole evidence for disease-specific mechanisms. Priority was given to original research articles, systematic reviews, meta-analyses and clinical trials that directly addressed neuroimmune mechanisms in vestibular disorders or related models. Studies were selected based on relevance to the thematic sections of the present review, with particular attention to evidence from human tissues, clinical cohorts and experimentally validated animal models. The reference lists of included articles were further screened to identify additional pertinent publications. This search strategy was designed to ensure comprehensive coverage of the major topics addressed in the present review, including inflammatory cytokine networks, neuropeptide signaling, glial responses, systemic immune influences and vestibular compensation.

2. Neuroimmune architecture of the vestibular system

The vestibular system possesses a specialized neuroimmune architecture that integrates peripheral sensory epithelia,

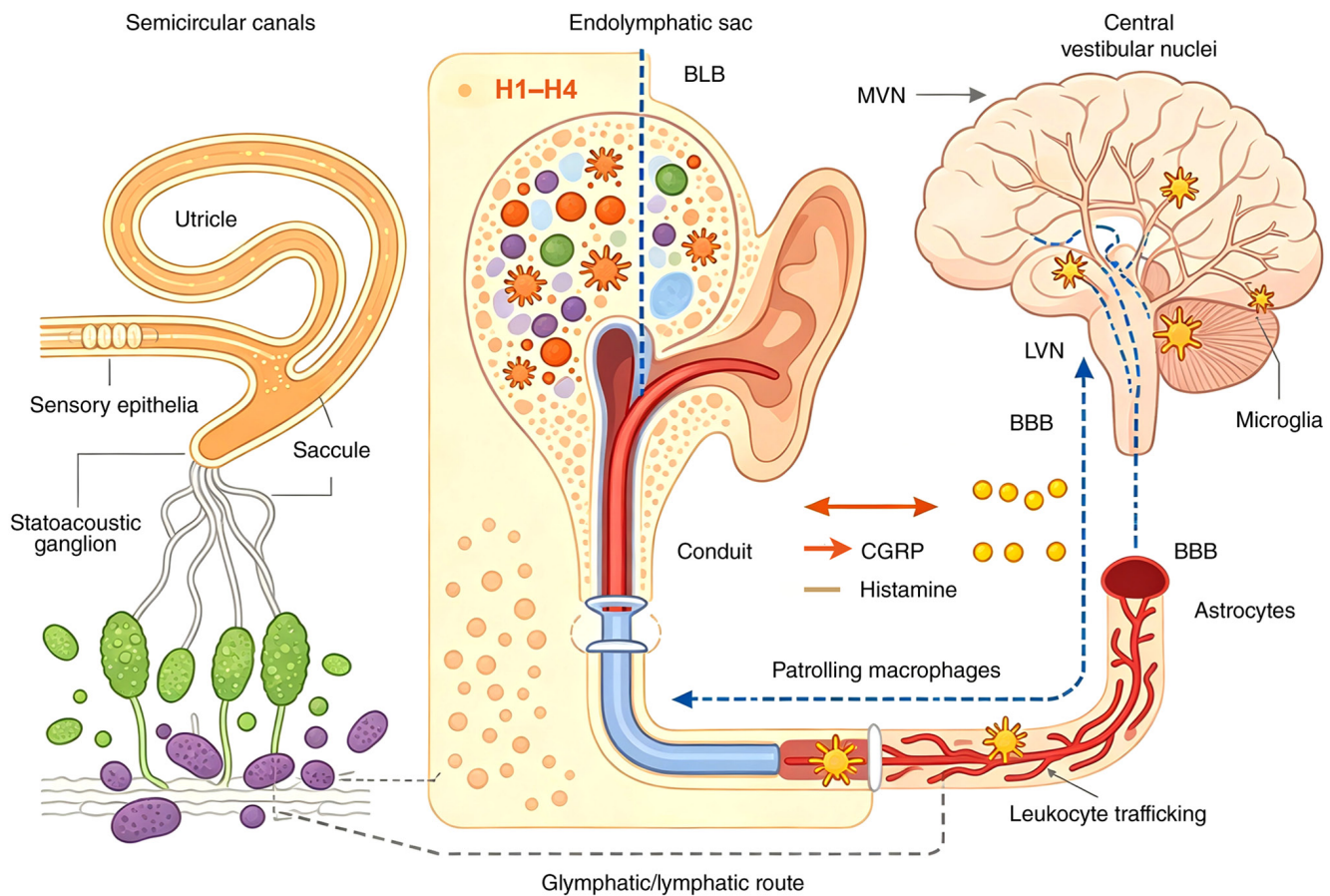


Figure 1. Neuroimmune architecture of the vestibular system. Peripheral vestibular organs (semicircular canals, utricle, saccule) are innervated by the SAG and contain resident macrophages and mast cells. The ES and RD express histamine receptors (H1-H4). The BLB and BBB regulate immune trafficking. TBM connects to the inner ear. Central vestibular nuclei (MVN, LVN) harbor microglia and astrocytes. Neuroimmune crosstalk involves CGRP, HA and the glymphatic system. Notably, the glymphatic/meningeal lymphatic routes within the vestibular periphery remain largely hypothetical and lack direct *in vivo* human validation, as indicated by the dashed graphic representation. SAG, statoacoustic ganglion; ES, endolymphatic sac; RD, reuniting duct; H1-H4, histamine receptors 1-4; BLB, blood-labyrinth barrier; BBB, blood-brain barrier; TBM, temporal bone marrow; MVN, medial vestibular nucleus; LVN, lateral vestibular nucleus; CGRP, calcitonin gene-related peptide; HA, histamine.

afferent neurons and central nuclei with immune surveillance mechanisms. Anatomical and molecular substrates enabling neuroimmune crosstalk include innervation patterns, barrier interfaces, resident immune cells and signaling molecules. Fig. 1 summarized the key components of this vestibular neuroimmune architecture.

Peripheral vestibular innervation and immune surveillance.

The peripheral vestibular apparatus receives dense innervation from the statoacoustic ganglion, whose neurons project to sensory epithelia of the utricle, saccule and semicircular canals. Eberhard *et al* (9) characterized neurotransmitter and receptor expression in the human saccule, revealing a complex molecular landscape that supports bidirectional neuroimmune signaling. Immune surveillance of these peripheral structures involves resident macrophages that respond rapidly to hair cell injury. Kaur *et al* (10) demonstrated that macrophage recruitment to the mouse utricle following hair cell damage occurs within hours and precedes epithelial repair, suggesting an early immune component in vestibular tissue maintenance. Complementing these findings, Hirose *et al* (11) identified two distinct cell populations participating in damaged hair cell clearance from sensory epithelia, indicating redundant

immune mechanisms for maintaining epithelial integrity. A critical aspect requiring further investigation is whether human vestibular end organs exhibit similar or distinct immune cell dynamics compared to rodent models.

Vestibular nuclei and barrier interfaces as neuroimmune hubs.

The vestibular nuclei within the brainstem serve as central integration sites where peripheral afferent signals converge with descending modulatory inputs. These nuclei are positioned behind the blood-brain barrier, yet they remain accessible to circulating immune mediators under pathological conditions. Nordström *et al* (12) demonstrated that the human endolymphatic sac contains abundant macrophages and expresses multiple immune-related molecules, establishing this structure as a potential neuroimmune interface. Using super-resolution immunohistochemistry, Liu *et al* (13) further characterized immune activity within the human inner ear, identifying regional heterogeneity in immune cell distribution and activation states. The blood-labyrinth barrier, analogous to the blood-brain barrier, regulates exchange between the systemic circulation and inner ear fluids. Disruption of these barriers during inflammation may permit entry of immune cells and cytokines into vestibular compartments, although

the temporal dynamics and functional consequences of barrier breakdown remain incompletely understood.

Resident immune cells in the vestibular system. Resident immune cells populate both peripheral and central vestibular structures, providing first-line defense and tissue surveillance. Keithley (14) comprehensively reviewed inner ear immunity, emphasizing that macrophages represent the predominant resident immune population, with additional contributions from mast cells and perivascular macrophages. Histamine receptor subtypes H1-H4 are expressed in rodent and human vestibular tissues (15,16); their functional and therapeutic roles are detailed in the *Histaminergic regulation of neuroinflammation and vestibular compensation* section. Notably, the density and phenotype of resident microglia within vestibular nuclei differ from those in adjacent brainstem regions, as recently shown by Zhai *et al* (17), who identified transient receptor potential vanilloid 2 (TRPV2)-mediated inflammasome activation in deafferented vestibular nuclei. These regional specializations may underlie differential vulnerability of vestibular circuits to neuroinflammatory insults.

Conduits for neuroimmune communication. Several anatomical pathways facilitate communication between the vestibular system and peripheral immune organs. Perin *et al* (18) recently characterized temporal bone marrow in the rat and its connections to the inner ear, identifying a direct anatomical conduit for leukocyte trafficking. Using iDISCO+ tissue clearing and micro computed tomography, Cossellu *et al* (19) generated a volumetric atlas of the rat inner ear, revealing spatial relationships between vestibular structures and adjacent immune compartments. Additionally, Vivado *et al* (20) localized macrophages within the reuniting duct and endolymphatic duct, proposing that these cells patrol endolymphatic spaces and respond to local disturbances. The glymphatic pathway and meningeal lymphatics, although well-characterized in the brain, remain underexplored in the context of vestibular neuroimmune communication. Whether similar clearance systems operate in the vestibular periphery represents an important unanswered question.

Neuroimmune signaling molecules in vestibular tissues. A diverse array of signaling molecules mediates neuroimmune interactions within the vestibular system. In human vestibular tissues, Eberhard *et al* (9) documented expression of multiple neurotransmitters and their receptors, establishing molecular substrates for neuromodulation of immune responses. CGRP and histaminergic signaling are key neuroimmune molecules in vestibular tissues. CGRP facilitates sensitization of the vestibular nucleus in chronic migraine models (21) and anti-CGRP monoclonal antibodies have shown clinical benefit in VM (22). Histamine H1-H4 receptors modulate neuronal excitability and immune function (15,16). Disease-specific evidence and therapeutic implications are discussed in sections *CGRP in vestibular migraine* and *Histaminergic regulation of neuroinflammation and vestibular compensation*. A working hypothesis, derived from separate literatures rather than head-to-head studies, is that CGRP signaling may be more prominent in migraine-related vestibular dysfunction, whereas histamine pathways may be more central in MD; this remains testable (16,21,22).

3. Inflammatory cytokines and immune signaling in vestibular disorders

Dysregulated cytokine networks and inflammatory signaling pathways contribute to the pathogenesis of diverse vestibular disorders. Pro-inflammatory signatures, T helper type 1 (Th1)/Th2 imbalances, monocyte-related chemokines, emerging cytokine profiles and inflammasome activation each play distinct roles, revealing both shared and divergent immunological mechanisms across MD, VM and vestibular neuritis (Fig. 2). However, it should be noted that direct comparative studies between MD and VM remain limited and many of the observed differences are derived from independent cohort studies rather than head-to-head comparisons. To appropriately evaluate the strength of evidence supporting neuroimmune mechanisms in vestibular disorders, this section distinguishes between clinical association studies demonstrating correlations between inflammatory mediators and disease phenotypes, mechanistic evidence from experimental models elucidating biological pathways, causality-supporting evidence from genetic and Mendelian randomization studies and therapeutic evidence from clinical intervention studies. This hierarchical framework acknowledges that different study designs provide complementary but non-equivalent support for causal relationships.

Pro-inflammatory cytokine signatures in MD. Elevated levels of classical pro-inflammatory cytokines have been consistently documented in patients with MD. Frejo *et al* (23) demonstrated that peripheral blood mononuclear cells from MD patients produced markedly higher amounts of tumor necrosis factor- α (TNF- α), IL-1 β and IL-6 following mold antigen stimulation compared to controls. Huang *et al* (24) extended these findings by showing upregulated expression of interferon- γ (IFN- γ), IL-6 and TNF- α within the endolymphatic sac of MD patients, providing direct tissue-level evidence for local inflammation. A critical appraisal of the literature reveals some heterogeneity in cytokine profiles across studies. While Frejo *et al* (23) reported undetectable baseline IL-6 in unstimulated mononuclear cells, Huang *et al* (24) found elevated IL-6 in endolymphatic sac tissue, suggesting that cytokine expression may be compartment-specific and activation-dependent. Xie *et al* (25) employed Mendelian randomization to demonstrate causal relationships between genetically predicted IL-1 receptor antagonist, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 beta levels and MD risk, moving beyond association to suggest causality. Collectively, MD is associated with a multifaceted pro-inflammatory state involving TNF- α , IL-1 β , IL-6 and IFN- γ pathways (23,24), with Mendelian randomization supporting causal roles for IL-1 receptor antagonist and MCP-1 (25).

Th1/Th2 balance and cytokine disturbances in vestibular neuritis (VN). VN presents a distinct immunological profile characterized by alterations in T-helper cell polarity. Zhou *et al* (26) conducted a prospective study measuring peripheral cytokine levels in patients with acute VN, revealing significant elevations of IL-6 and IL-8 alongside reduced IFN- γ levels compared to healthy controls. This pattern

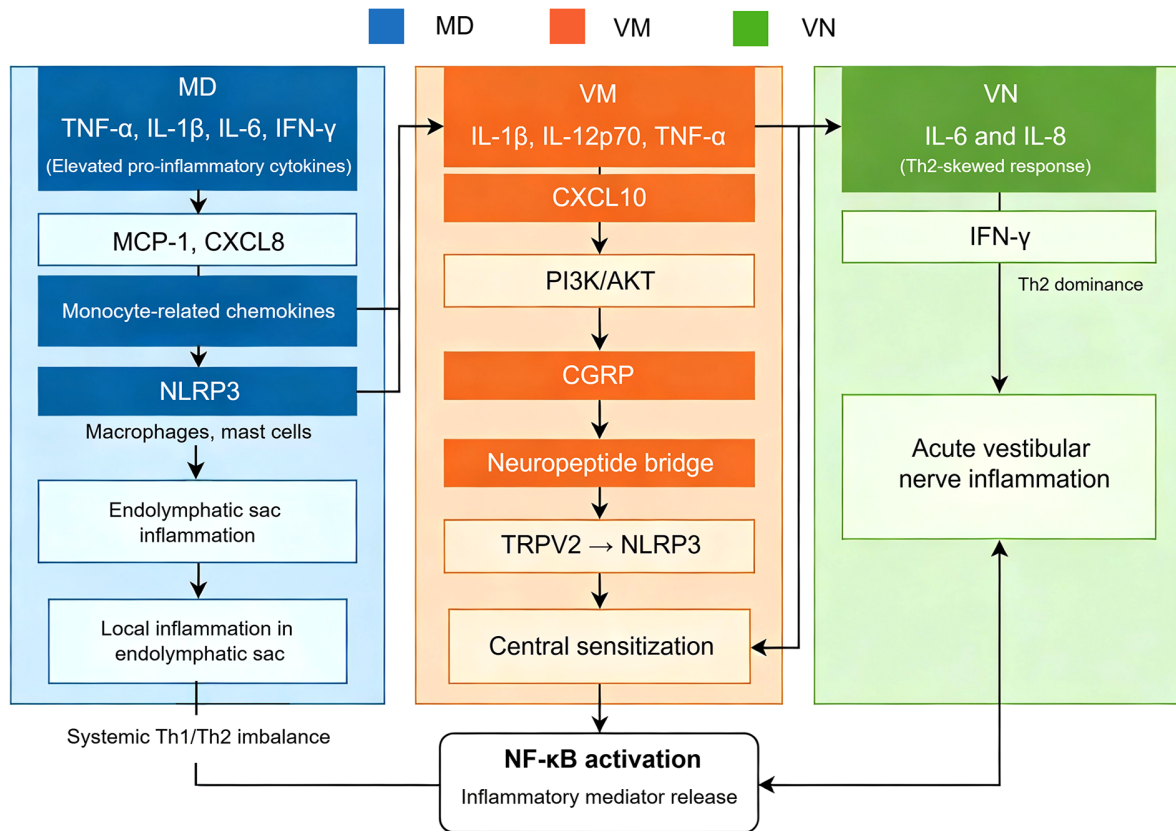


Figure 2. Overview of inflammatory and immune signaling mechanisms in MD, VM and VN. Disease-specific cascades illustrated here represent working mechanistic hypotheses; direct head-to-head comparative human studies across MD, VM and VN remain scarce and some cytokine findings show inter-study heterogeneity. MD, Menière's disease; VM, vestibular migraine; VN, vestibular neuritis; TNF- α , tumor necrosis factor α ; IL, interleukin; IFN- γ , interferon γ ; MCP-1, monocyte chemoattractant protein-1; CXCL8, C-X-C motif chemokine ligand 8; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; CGRP, calcitonin gene-related peptide; TRPV2, transient receptor potential vanilloid 2; NLRP3, NOD-like receptor family pyrin domain containing 3; NF- κ B, nuclear factor κ -light-chain-enhancer of activated B cells; Th1, T helper type 1.

suggests a predominant Th2-skewed response, though this interpretation derives from peripheral cytokine associations and awaits confirmation through tissue-level mechanistic studies. By contrast, a Th1-dominant profile has been described in experimental autoimmune inner ear disease (AIED) models, where the evidence derives from adoptive-transfer studies in mice rather than from human tissue analyses. Solares *et al* (27) demonstrated that inner ear peptide-specific CD4⁺ T cells with a Th1-like phenotype induce hearing loss upon transfer to naïve recipients. Zhou *et al* (28) further showed that β -tubulin-reactive, IFN- γ -producing CD4⁺ T cells are necessary and sufficient to transfer experimental autoimmune hearing loss. Thus, the Th1-dominant profile in autoimmune inner ear conditions is supported by preclinical mechanistic evidence, whereas direct human tissue-level evidence for this profile has not been described in the human studies cited in the present review. Notably, the investigators also documented negative correlations between IL-6 levels and canal paresis severity, raising the possibility that the inflammatory response may exert both deleterious and protective effects during acute vestibular nerve injury. When comparing VN with MD, a key distinction emerges: MD patients typically exhibit elevations in both Th1- and Th2-associated cytokines (29), whereas VN appears characterized by a more restricted Th2-favored signature. This dichotomy may reflect differences in the underlying triggers, specifically viral vs. autoimmune or idiopathic and

warrants further investigation through direct comparative cohort studies.

Monocyte-related cytokines and chemokines across vestibular disorders. Chemokines of the monocyte-related family have emerged as important mediators across multiple vestibular conditions. In MD patients, Iinuma *et al* (30) reported elevated serum MCP-1 levels that correlated with progressive hearing impairment and bilateral disease involvement, suggesting that MCP-1 may serve as a biomarker for disease severity. Expanding upon this, Zou *et al* (31) identified markedly increased granulocyte colony-stimulating factor, IL-8 and hepatocyte growth factor in definite MD patients, proposing that neutrophil extracellular trap formation may drive autoinflammatory cascades. A particularly noteworthy recent contribution comes from Peng *et al* (32), who demonstrated that macrophage-derived CXCL8 acts as a mediator of inflammatory attacks in MD, with elevated levels coinciding with acute vertiginous episodes. In the context of VM, Song *et al* (33) identified CXCL10 as a key player acting through the PI3K/AKT signaling pathway, providing mechanistic insight into how chemokine signaling may contribute to central vestibular hyperexcitability. The CXCL8-predominant profile in MD vs. CXCL10 involvement in VM suggests pathway-specific chemokine signatures that may aid differential diagnosis if validated prospectively.

Cytokine networks in VM: Overlapping yet distinct profiles. VM exhibits a cytokine profile that partially overlaps with MD while maintaining distinguishing features. Flook *et al* (34) performed a comprehensive comparison, revealing that VM patients display elevated IL-1 β , IL-12p70 and TNF- α but, unlike MD, do not show significant alterations in IL-2 or IL-6. Contrasting findings have emerged regarding C-reactive protein and other acute-phase mediators: Karaaslan *et al* (35) found no significant differences in plasma levels of IL-1 β , IL-6, TNF- α , or high-sensitivity C-reactive protein between VM patients and controls, although methodological differences in sampling timing (interictal vs. peri-ictal) may account for this discrepancy. More recent multiomic profiling by Cruz-Granados *et al* (36) demonstrated that VM shares some inflammatory features with migraine without aura but exhibits unique transcriptomic signatures in circulating immune cells. A critical unresolved question concerns whether the observed cytokine elevations in VM represent cause or consequence of trigeminovascular activation. Monaghan *et al* (37) directly compared pro-inflammatory profiles in MD and VM, finding that while both disorders display evidence of systemic inflammation, only MD showed significant elevations of IL-1 β and IL-12p70, suggesting potentially immunologically distinct profiles despite their overlapping clinical presentations. However, this pilot study had a limited sample size and replication in larger cohorts is required.

Inflammasome activation in vestibular pathology. The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation has been established as a molecular link between innate immune sensing and vestibular injury. NLRP3 mutations cause deafness, autosomal dominant 34 (DFNA34), an autosomal dominant hearing loss syndrome with vestibular symptoms that responds to anakinra therapy (38,39). Preclinically, anakinra protects against endolymphatic hydrops and preserves vestibular function in murine models (40). Gregory *et al* (41) comprehensively reviewed the rationale for NLRP3 inhibition in sensorineural hearing loss, emphasizing the therapeutic potential of small-molecule inflammasome inhibitors. Extending these concepts to VM, Zhai *et al* (17) identified TRPV2-mediated inflammasome activation in deafferented vestibular nuclei. Translational implications are promising: Anakinra shows efficacy in DFNA34 patients with NLRP3 mutations (42) and protects against endolymphatic hydrops in murine models (40), but randomized controlled trials in MD and VM are lacking and whether inflammasome activation is a primary driver or epiphenomenon remains unresolved. Future research must determine whether inflammasome activation represents a primary pathological driver or an epiphenomenon of other inflammatory processes and whether therapeutic benefits vary according to specific genetic backgrounds.

Methodological heterogeneity and implications for generalizability. Interpretation of cytokine and immune profiling studies in vestibular disorders is constrained by substantial methodological heterogeneity. First, sample sizes are often modest, with several cohort studies including fewer than 30 patients per group (35,37); such underpowered designs increase the risk of false-positive findings and limit the ability to detect modest

but biologically meaningful differences. Monaghan *et al* (37) explicitly acknowledged that their pilot study required replication in larger cohorts and Karaaslan *et al* (35) noted that their negative findings could not be considered definitive due to limited sample size. Second, sampling timing varies widely (interictal, peri-ictal, or unspecified), which may explain discrepant findings for IL-6 and other acute-phase mediators (23,24); the absence of standardized timing relative to vertigo attacks precludes reliable assessment of cytokine dynamics and hampers comparability across studies. Third, outcome measures for vertigo severity and disease burden are not harmonized, with diverse instruments such as the Dizziness Handicap Inventory, Vertigo Severity Score and visual analog scales used interchangeably (43–47); this variability complicates direct comparisons of treatment effects and limits the robustness of meta-analytic syntheses. Fourth, patient populations differ in disease duration, comorbidity profiles (e.g., concomitant migraine, anxiety, allergic conditions) and prior treatments, all of which may influence immune parameters. Detailed phenotyping distinguishing definite from probable MD or VM with vs. without concomitant migraine remains exceptional (36), further increasing heterogeneity.

These limitations collectively hinder cross-study comparisons, meta-analysis and clinical translation. Most findings remain correlational and cross-sectional, precluding distinction between trait and state biomarkers. The predominance of single-center studies with non-standardized protocols also raises concerns about external validity and replicability. Future research should prioritize large, well-phenotyped, multi-center cohorts with standardized sampling protocols and harmonized outcome measures to enable robust biomarker validation and facilitate the development of clinically actionable signatures.

4. Neuroglial mechanisms in vestibular pathophysiology

Glial cells, including microglia, astrocytes and oligodendrocytes, have emerged as key regulators of vestibular pathophysiology, orchestrating inflammatory responses, synaptic remodeling and tissue repair following peripheral or central vestibular injury. Emerging evidence indicates that glial dynamics are not merely reactive but actively shape the trajectory of vestibular compensation and maladaptive plasticity. It is essential to distinguish between two conceptually distinct contexts in which neuroglial mechanisms operate. The first involves central compensatory plasticity following acute peripheral vestibular injury, as modeled by unilateral vestibular neurectomy, labyrinthectomy, or vestibular deafferentation. These surgical lesion models provide crucial insights into how the central nervous system restores balance and gaze stability after sudden unilateral peripheral loss. The second involves neuroinflammatory processes that may contribute to the pathogenesis or maintenance of primary vestibular disorders such as MD and VM, where inflammation may be integral to disease initiation or chronification rather than merely a consequence of deafferentation. Findings derived from deafferentation models should not be directly generalized to MD or VM pathogenesis without explicit acknowledgment of this distinction, as these models simulate post-lesional plasticity rather than the etiological mechanisms of these disorders. Current knowledge on neuroglial mechanisms in vestibular

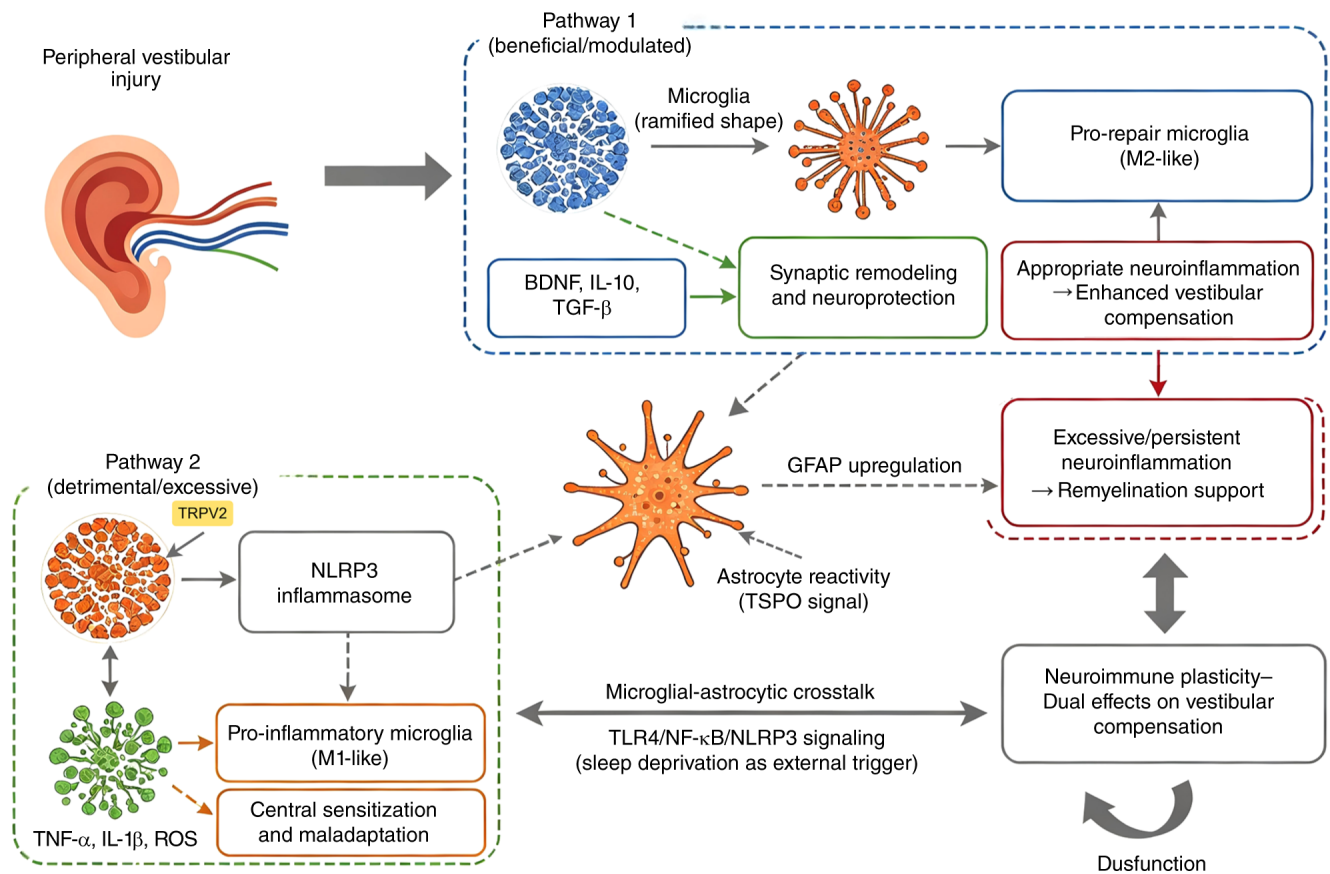


Figure 3. Neuroglial mechanisms in vestibular pathophysiology. Following peripheral vestibular injury, microglia and astrocytes respond in a biphasic manner. Appropriately calibrated neuroinflammation promotes repair via BDNF and anti-inflammatory signals, supporting vestibular compensation. Excessive or persistent neuroinflammation drives pro-inflammatory microglia, NLRP3 inflammasome activation and central sensitization, impairing compensation. Astrocyte reactivity (GFAP⁺, TSPO⁺) and OPCs also contribute. Bidirectional glial crosstalk involves TLR4/NF-κB/NLRP3 signaling. Most mechanistic evidence for neuroinflammatory regulation of vestibular compensation is derived from rodent experimental vestibular deafferentation (unilateral vestibular neurectomy/labyrinthectomy) models; these findings cannot be directly extrapolated to the primary pathogenesis of spontaneous clinical vestibular disorders such as Menière's disease or vestibular migraine without further validation. BDNF, brain-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; IL, interleukin; NLRP3, NOD-like receptor family pyrin domain containing 3; NF-κB, nuclear factor κB; OPCs, oligodendrocyte precursor cells; ROS, reactive oxygen species; TGF-β, transforming growth factor β; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor α; TRPV2, transient receptor potential vanilloid 2; TSPO, translocator protein.

disorders highlights regional heterogeneity, polarization states and the dual potential of neuroinflammation to either support recovery or drive chronic dysfunction (Fig. 3). The evidence reviewed in this section is graded by study type: most mechanistic findings derive from preclinical rodent deafferentation models, whereas human tissue and clinical data remain limited; disease-related neuroinflammatory findings are distinguished from post-lesional compensatory plasticity whenever possible (48-52).

Microglial dynamics and inflammasome activation. In post-lesional compensation models, unilateral vestibular neurectomy triggers a biphasic microglial response, characterized by early proliferation followed by sustained morphological activation and pharmacological modulation of microglial dynamics directly influences compensation outcomes (48). Microgliogenesis begins as early as 24 h post-lesion, preceding astrocytic responses (49). These findings in surgical deafferentation models provide direct evidence for microglial involvement in post-lesional vestibular compensation. Conversely, Mikheeva *et al* (50) reported that

vestibular stimulation alone, without surgical lesion, also induces microglial activation in the lateral vestibular nucleus, suggesting that even physiological challenges engage glial surveillance mechanisms.

By contrast, in the context of disease-related neuroinflammation, a critical molecular pathway linking microglial activation to central sensitization involves TRPV2-mediated inflammasome signaling. As introduced in the *Inflammasome activation in vestibular pathology* section, NLRP3 inflammasome activation links innate immune sensing to vestibular injury. In disease-related neuroinflammation, microglial TRPV2 activation promotes NLRP3 assembly and pro-inflammatory polarization in a VM model (51), a mechanism distinct from neuroprotective microglial states during successful compensation (48). The functional divergence of microglial phenotypes, which ranges from neurosupportive to neurotoxic, likely depends on lesion chronicity, comorbid factors and genetic background. Importantly, Li *et al* (52) showed that sleep deprivation disrupts vestibular compensation in UVN models by activating Toll-like receptor 4 (TLR4)/NF-κB/NLRP3 signaling in deafferented vestibular nuclei, providing mechanistic insight into

how systemic disturbances adversely affect glial-mediated recovery. This finding pertains to modulation of post-lesional compensation rather than to primary MD or VM pathogenesis. Collectively, these findings establish that microglial dynamics are not uniformly beneficial or detrimental; rather, their temporal profile and polarization state critically determine vestibular outcomes.

Astrocyte reactivity in vestibular nuclei. In post-lesional compensation models, astrocytes undergo profound phenotypic and functional changes following vestibular injury, contributing to both structural remodeling and neuroinflammatory regulation. Unilateral labyrinthectomy induces redistribution of astrocyte phenotypes from quiescent to reactive states, with altered glial fibrillary acidic protein (GFAP) expression and regional heterogeneity across vestibular nuclei subregions (53). These reactive astrocytes exhibited regional heterogeneity, with subregions of the vestibular nuclei displaying differential susceptibility to activation (53). Using longitudinal [18F]GE180-positron emission tomography imaging, Zwergal *et al* (54) demonstrated that translocator protein (TSPO) signal, a marker of glial activation, increases progressively in the ipsilateral vestibular nuclei following unilateral labyrinthectomy, with activation persisting for weeks in addition to the acute injury phase. These findings describe glial dynamics during central compensation following acute peripheral vestibular loss and do not directly model the neuroinflammatory processes underlying MD or VM pathogenesis.

Contrasting findings have emerged regarding the relationship between astrocytic and microglial activation kinetics. While some studies suggest that microglial responses precede astrocytic activation (48,49), Wu *et al* (55) observed concurrent glial proliferation involving both cell types following early rehabilitation intervention, indicating that experience-dependent plasticity engages both glial populations synergistically. Mikheeva *et al* (50) further noted that vestibular stimulation alone induces astrocytic morphological changes without accompanying microglial proliferation, suggesting context-dependent activation thresholds. A notable unresolved question concerns whether astrocyte reactivity represents a primary driver of vestibular dysfunction or an epiphenomenon secondary to neuronal injury. The demonstration that astrocyte phenotype redistribution correlates with compensation outcomes (53) supports a functionally significant role, though causality remains to be established through selective astrocyte manipulation studies.

Glial support of vestibular nerve integrity. Oligodendrocytes and Schwann cells maintain axonal integrity and facilitate repair processes within the vestibular nerve and its central projections. Dutheil *et al* (56) demonstrated that brain-derived neurotrophic factor (BDNF) signaling promotes vestibular compensation not only through direct neuronal effects but also by remodeling the expression of potassium-chloride cotransporter potassium-chloride cotransporter 2 (KCC2) and gamma-aminobutyric acid type A (GABAA) receptors, processes that likely involve oligodendrocyte-mediated support of axonal conduction properties. Rastoldo *et al* (57) extended these observations by documenting adult neurogenesis within the vestibular nuclei after unilateral vestibular

neurectomy, with newly generated cells including oligodendrocyte precursors that may contribute to remyelination of deafferented pathways. The functional importance of glial support is further underscored by findings that L-thyroxine administration improves vestibular compensation while simultaneously enhancing glial proliferation and survival (58).

In contrast to the relatively robust literature on microglia and astrocytes, the specific contributions of Schwann cells to vestibular nerve pathology remain underexplored. Available evidence suggests that Schwann cell responses to vestibular nerve injury mirror those observed in other peripheral neuropathies, though systematic investigations in isolated vestibular disorders are lacking. A critical gap exists regarding whether primary demyelinating processes contribute to conditions such as vestibular paroxysmia or superior canal dehiscence syndrome, representing an important direction for future inquiry.

Dual roles of neuroinflammation in compensation. The dual effects of neuroinflammation are most clearly illustrated in the context of vestibular compensation following acute peripheral injury (UVN models). Neuroinflammatory signaling following vestibular injury exerts both protective and detrimental effects, depending on timing, intensity and molecular context. Dexamethasone administered immediately after unilateral vestibular neurectomy paradoxically impairs long-term compensation and suppresses endogenous plasticity, indicating that appropriately calibrated inflammation is necessary for optimal neuroplasticity (59). Supporting this interpretation, Mao *et al* (60) demonstrated that BDNF/tropomyosin receptor kinase B (TrkB) signaling, which can be modulated by inflammatory cytokines, promotes vestibular compensation in deafferentation models by enhancing synaptic plasticity and neuronal survival. These findings pertain exclusively to post-lesional adaptive plasticity and should not be generalized to primary disease pathogenesis.

The concept of neurohormesis, wherein moderate inflammatory challenge confers resilience, appears applicable to vestibular pathophysiology. Salinaro *et al* (61) proposed that low-grade neuroinflammation can precondition neural tissues against subsequent injury, though direct evidence in the vestibular system remains preliminary. It is important to emphasize that these protective effects pertain to post-lesional adaptive plasticity and should not be conflated with neuroinflammatory processes driving primary disease pathogenesis. In the context of primary vestibular disorders such as VM, persistent or excessive neuroinflammation drives maladaptive plasticity. Zhai *et al* (51) showed in a VM mouse model that sustained microglial TRPV2-mediated inflammasome activation promotes central sensitization in VM, transforming an acute protective mechanism into a chronic pain-like state. This finding describes a disease-specific neuroinflammatory mechanism in VM pathogenesis, distinct from the protective inflammation observed during post-lesional compensation in UVN models. Thus, the beneficial vs. detrimental dichotomy depends critically on whether the inflammatory response subserves adaptive post-lesional repair or disease-related central sensitization. The dual nature of neuroinflammation carries direct therapeutic implications: interventions that completely suppress glial activation may hinder compensation (59), while

those that modulate rather than eliminate inflammatory signaling, such as pro-histaminergic drugs (62) or early rehabilitation (55), may optimize outcomes. Future research must establish biomarkers to distinguish protective from pathologic neuroinflammation in individual patients, enabling precision targeting of neuroglial pathways.

5. Neuropeptides and the vestibular neuroimmune network

Neuropeptides serve as critical molecular bridges linking neuronal activity with immune cell function within the vestibular system. Current evidence indicates that CGRP, substance P, pituitary adenylate cyclase-activating polypeptide (PACAP) and histamine modulate neuroinflammatory cascades and contribute to vestibular disorder pathophysiology (Table I). The evidence base in this section is heterogeneous: CGRP and histamine findings include human tissue, clinical cohort, case report and preclinical model data, whereas PACAP and substance P evidence is derived mainly from human challenge studies and preclinical models; the relevant study type is specified in each subsection (5,16,22,62-66).

CGRP in VM. CGRP has emerged as a master regulator of neurogenic inflammation within the trigeminovascular system, with accumulating evidence implicating this pathway in VM pathogenesis. Iyengar *et al* (67) comprehensively reviewed CGRP's dual role in peripheral and central pain mechanisms, demonstrating that CGRP released from trigeminal afferents promotes vasodilation, mast cell degranulation and neuronal sensitization. Messlinger (68) further characterized the sources, sinks and signaling sites of CGRP within the trigeminovascular system, establishing that meningeal CGRP release represents a key event in migraine initiation. In the context of vestibular disorders, Russo *et al* (63) conducted a prospective observational cohort study demonstrating that anti-CGRP monoclonal antibodies markedly reduced vertigo attack frequency and severity in VM patients, providing clinical validation for CGRP pathway targeting. More recently, Inui *et al* (22) reported successful treatment of a VM case with erenumab, with documented improvements in both vertigo and headache outcomes. The mechanistic underpinnings of CGRP actions involve direct modulation of immune cells: Balczak and Russo (69) demonstrated that dural immune cells, particularly mast cells and macrophages, respond to CGRP stimulation by releasing pro-inflammatory mediators that sustain trigeminal sensitization. A critical distinction must be drawn between CGRP's acute protective roles and its chronic pathological effects. While physiological CGRP signaling supports vasoregulation and tissue repair, persistent CGRP elevation drives maladaptive neuroimmune plasticity. Nelson-Maney *et al* (70) recently established that meningeal lymphatic CGRP signaling governs pain behaviors through modulation of cerebrospinal fluid efflux and neuroinflammation, identifying a previously unrecognized clearance mechanism. Despite these advances, whether CGRP acts as a primary driver or an amplifying mediator in VM remains incompletely resolved and the relative contributions of peripheral vs. central CGRP sources require further delineation through compartment-specific intervention studies.

Substance P, PACAP and other immunomodulatory neuropeptides. In addition to CGRP, additional neuropeptides contribute to vestibular neuroimmune networks through distinct yet overlapping mechanisms. Substance P, a classic mediator of neurogenic inflammation, has been implicated in nociceptive transmission within vestibular pathways. Durham (71) reviewed the diverse physiological roles of CGRP in migraine pathology while acknowledging that substance P acts synergistically with CGRP to promote plasma extravasation and immune cell recruitment. However, Dux and Messlinger (72) recently reported an inverse correlation between substance P and CGRP release from rat dura mater following glyceryl trinitrate stimulation, suggesting that these two neuropeptides may be differentially regulated rather than co-released uniformly. This finding challenges the long-held assumption of coordinated neuropeptide release and implies pathway-specific regulatory mechanisms.

Pituitary adenylate cyclase-activating polypeptide has received increasing attention as a migraine mediator distinct from CGRP. Guo *et al* (64) demonstrated that PACAP-38 infusion in migraine patients induces prolonged headache and vasodilation through mechanisms partially independent of CGRP signaling. Kuburas and Russo (73) comprehensively compared shared and independent roles of CGRP and PACAP in migraine pathophysiology, noting that while both neuropeptides activate similar downstream effectors, their receptor distributions and temporal profiles differ substantially. In the vestibular context, Rahman *et al* (65) directly compared the effect of systemic PACAP vs. CGRP administration on motion-induced nausea and balance behaviors in mice, revealing that PACAP produces more pronounced vestibular disturbances, suggesting a potentially unique contribution of PACAP to vestibular-specific symptoms. Lund and Hannibal (66) localized PACAP, vasoactive intestinal peptide and their receptors in basal brain blood vessels and trigeminal ganglion, establishing the anatomical substrate for PACAP-mediated neuroimmune modulation. Collectively, these findings indicate that multiple neuropeptide systems operate in parallel and vestibular disorder phenotypes may reflect the integrated output of several peptidergic pathways rather than a single dominant mediator. The therapeutic implications are substantial: Targeting CGRP alone may prove insufficient for patients whose pathophysiology is driven predominantly by PACAP or substance P signaling.

Histaminergic regulation of neuroinflammation and vestibular compensation. The histaminergic system occupies a unique position within vestibular neuroimmune networks, simultaneously modulating neuronal excitability, immune cell function and glial responses. Møller *et al* (16) provided foundational evidence by demonstrating expression of histamine H1-H4 receptors in the human endolymphatic sac, establishing the molecular rationale for betahistidine use in MD. These findings have been substantially extended by Tighilet *et al* (6), who comprehensively reviewed histaminergic system involvement in both normal and pathological vestibular function.

H4 receptors are predominantly expressed on hematopoietic and immune cells, including microglia, mast cells, eosinophils, dendritic cells and T lymphocytes and are also present on rodent vestibular primary neurons and hair cells (5). Unlike

Table I. Original studies investigating neuropeptide-mediated neuroimmune mechanisms in vestibular disorders and related models.

Author/s, year	Neuropeptide/pathway	Level of evidence/study design	Key findings	Clinical/mechanistic significance	(Refs.)
Møller <i>et al.</i> , 2016	Histamine (H1-H4 receptors)	Clinical tissue expression study	All four histamine receptor subtypes are expressed in the human endolymphatic sac, providing a molecular rationale for betahistine use in Menière's disease.	Directly links histamine receptor expression in the human inner ear immune compartment to the pharmacology of betahistine.	(16)
Inui <i>et al.</i> , 2025	CGRP (erenumab)	Clinical case report	Erenumab treatment led to complete or near-complete resolution of vertiginous episodes with concurrent headache improvement.	Demonstrates durable vertigo control with anti-CGRP monotherapy in a VM patient, although controlled trials are lacking.	(22)
Trico <i>et al.</i> , 2025	Histamine (pro-histaminergic drug)	Preclinical animal model	Pro-histaminergic drug restores balance, promotes microgliogenesis and shifts microglial polarization toward a pro-repair phenotype, thereby facilitating vestibular compensation.	Demonstrates that histamine signaling actively shapes the neuroimmune environment and promotes functional recovery. In addition to neuronal modulation.	(62)
Russo <i>et al.</i> , 2023	CGRP (anti-CGRP mAbs)	Clinical cohort study	Anti-CGRP mAbs markedly reduced vertigo days (mean reduction 9.5 days/month), headache days (13.8) and MIDAS scores (36.1); 78% achieved ≥50% reduction in all three parameters at 12 months.	First real-world evidence that CGRP blockade specifically reduces vertigo burden in vestibular migraine, supporting a causative role for CGRP.	(63)
Nelson-Maney, 2024	CGRP (meningeal lymphatic)	Preclinical animal model	Meningeal lymphatic CGRP signaling governs cerebrospinal fluid efflux and neuroinflammation; pathway disruption drives migraine-like pain behaviors.	Identifies a novel clearance mechanism by which CGRP modulates pain via lymphatic function and neuroinflammation.	(70)
Dux <i>et al.</i> , 2025	Substance P vs. CGRP	Preclinical <i>ex vivo</i> model	Substance P release from cranial dura mater is inversely correlated with CGRP release; increased CGRP appears to inhibit SP-dependent plasma extravasation.	Challenges the assumption of coordinated SP/CGRP release in neurogenic inflammation, implying pathway-specific regulation.	(72)
Guo <i>et al.</i> , 2017	PACAP-38	Clinical human challenge study	PACAP-38 infusion induces prolonged headache and vasodilation through mechanisms partially independent of CGRP signaling.	Differentiates PACAP from CGRP in migraine pathogenesis, suggesting parallel peptidergic pathways may also contribute to vestibular symptoms.	(64)
Rahman, 2025	PACAP vs. CGRP	Preclinical animal model	Systemic PACAP produces more pronounced vestibular disturbances (nausea, imbalance) than equimolar CGRP, suggesting a unique contribution of PACAP to vestibular-specific symptoms.	First direct comparative evidence that PACAP may be a more potent mediator of vestibular dysfunction than CGRP, guiding future VM therapies.	(65)

Table I. Continued.

Author/s, year	Neuropeptide/pathway	Level of evidence/study design	Key findings	Clinical/mechanistic significance	(Refs.)
Lund <i>et al</i> , 2022	PACAP / VIP	Clinical tissue localization study	PACAP, VIP and their receptors are localized in basal brain blood vessels and trigeminal ganglion, providing anatomical substrate for PACAP-mediated neuroimmune modulation.	Establishes the structural framework for PACAP signaling in the trigeminovascular system, supporting its role as a candidate mediator in VM.	(66)
Göbel <i>et al</i> , 2022	CGRP (erenumab)	Clinical case report (safety)	First report of SDRIFE after erenumab application for migraine prevention.	Documents a novel cutaneous hypersensitivity reaction to anti-CGRP therapy, highlighting immunogenicity concerns.	(82)
Pico, 2024	CGRP (galcanezumab)	Clinical case report (safety)	Systemic allergic reaction (hypersensitivity) to galcanezumab in a migraine patient.	Further evidence of immunogenicity and allergic potential of CGRP-targeting mAbs, relevant for safety monitoring.	(83)
Chu <i>et al</i> , 2026	CGRP (rimegepant; gepant class)	Clinical study	Rimegepant demonstrated efficacy for acute treatment of VM, suggesting that small-molecule CGRP receptor antagonists may be suitable for on-demand therapy.	Supports the use of gepants as an alternative to monoclonal antibodies in VM patients requiring episodic rather than continuous prophylaxis.	(85)

CGRP, calcitonin gene-related peptide; CNS, central nervous system; GTN, glyceryl trinitrate; mAbs, monoclonal antibodies; MD, Menière's disease; MIDAS, Migraine Disability Assessment; PACAP, pituitary adenylate cyclase-activating polypeptide; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SP, substance P; VIP, vasoactive intestinal peptide; VM, vestibular migraine.

H1 receptors, which couple to Gαq, H4 receptors are coupled to pertussis toxin-sensitive Gαi/o proteins, leading to inhibition of adenylyl cyclase and reduced cAMP production (5). H4 receptor activation also mobilizes intracellular calcium via Gαi/o-dependent phospholipase C activation and promotes ERK1/2 and p38 MAPK phosphorylation, thereby linking H4 signaling to actin polymerization, cytoskeletal rearrangement and directed cell migration (74). This calcium-MAPK axis underlies the chemotactic response of mast cells, eosinophils and dendritic cells to histamine gradients, positioning H4 receptors as principal mediators of histamine-driven leukocyte recruitment to sites of inflammation.

In neuroinflammation, H4 receptor signaling exerts context-dependent effects on microglial function. Activation of microglial H4 receptors drives polarization toward a pro-inflammatory phenotype and stimulates release of TNF-α, IL-6 and IL-12 through NF-κB and MAPK signaling pathways (74). Conversely, H4R stimulation can induce persistent ERK1/2 phosphorylation that leads to pNF-κB downregulation and reduced NOX2 expression, dampening pro-inflammatory responses (75). H4 receptors also modulate adaptive immunity: H4R signaling regulates T regulatory cell frequency and chemotaxis within the central nervous system and H4R deficiency leads to impaired anti-inflammatory responses due to fewer T regulatory cells and an increased proportion of Th17 cells (76). These findings indicate that H4 receptors shape the balance between pro-inflammatory and regulatory immune responses through both innate and adaptive mechanisms.

The relevance of H4 receptors to vestibular pathophysiology is supported by pharmacological and genetic evidence. H4 receptor mRNA and protein are expressed in Scarpa's ganglion and rat vestibular primary neurons and selective H4R antagonists inhibit vestibular neuron excitability *in vitro* and reduce vestibular deficits in animal models (74). In a phase 1 randomized controlled trial involving 100 healthy subjects, the selective H4R antagonist SENS-111 markedly improved latency of vertigo appearance/disappearance, duration and European Evaluation of Vertigo questionnaire parameters vs. baseline, without markedly affecting nystagmus (75). Furthermore, the HRH4 rs77485247 polymorphism has been associated with increased risk of MD, with the A allele linked to vertigo attack frequency and basal IL-1β and TNF-α levels (76). Because microglia are the principal H4R-expressing cells in the central nervous system and undergo robust activation in vestibular nuclei following peripheral vestibular loss, H4R antagonism may represent a strategy to attenuate the neuroinflammatory component of vestibular pathology while preserving compensatory plasticity.

H3 receptors function mainly as presynaptic Gi/o-coupled autoreceptors that suppress histamine synthesis and release; H3 antagonism by betahistamine therefore enhances histamine release. In deafferented vestibular nuclei, pro-histaminergic treatment promotes microgliogenesis and shifts microglia toward a pro-repair phenotype while modulating neuroinflammation, thereby accelerating vestibular compensation (62). Functional specialization among histamine receptor subtypes further refines this mechanistic understanding: H4 receptors, as aforementioned, are predominantly expressed on immune cells and mediate chemotaxis, cytokine release and immunomodulation, whereas H3 receptors function primarily as

presynaptic autoreceptors that regulate histamine release and synthesis via negative feedback and also serve as heteroreceptors modulating the release of other neurotransmitters (5). Complementing these findings, Yuan and Silberstein (77) reviewed histamine's role in migraine, noting that histamine exerts complex, concentration-dependent effects on trigeminal nociception with low doses promoting sensitization and high doses inducing desensitization through H3 receptor-mediated feedback inhibition. A critical unresolved question concerns whether betahistamine's therapeutic effects in MD derive primarily from vascular, neuronal, or immunomodulatory actions and whether these mechanisms differ between acute vertigo attacks and interictal prophylaxis.

Therapeutic implications of targeting neuropeptide pathways.

The success of CGRP-targeting monoclonal antibodies in migraine has spurred investigation of these agents for VM and related disorders. Yuan *et al* (78) provided comprehensive rationales for CGRP monoclonal antibody development, establishing that ligand-neutralizing and receptor-blocking approaches yield comparable efficacy with favorable safety profiles. Cohen and Yuan *et al* (79) systematically reviewed current evidence for CGRP-targeted monoclonal antibodies and antagonists, noting that these agents represent the first pathophysiology-driven preventive therapies for migraine. In the vestibular domain, Russo *et al* (63) demonstrated that anti-CGRP monoclonal antibodies reduce vertigo burden and Frosolini and Lovato (80) conducted a rapid systematic review and meta-analysis confirming that CGRP monoclonal antibodies show promise for VM treatment, though randomized controlled trials remain lacking.

The clinical experience with anti-CGRP agents has also revealed important limitations. Several groups (81-83) have documented immunogenicity and hypersensitivity reactions, including a case of symmetrical drug-related intertriginous and flexural exanthema following erenumab administration reported by Göbel *et al* (82). More concerning, Straburzyński *et al* (84) performed a meta-analysis demonstrating increased infection risk in patients receiving preventive CGRP-targeting therapies, raising questions about the physiological role of CGRP in immune surveillance. Complementary to antibody-based approaches, the gepant class of small-molecule CGRP receptor antagonists offers oral administration and shorter half-lives. Cohen and Yuan (79) reviewed atogepant's role in episodic migraine treatment and Chu *et al* (85) recently reported rimegepant efficacy for acute treatment of VM, suggesting that this class may be suitable for VM patients requiring on-demand therapy rather than continuous prophylaxis.

For histaminergic pathways, betahistamine remains the primary therapeutic agent despite heterogeneous evidence. Møller *et al* (16) proposed that endolymphatic sac H2 receptor stimulation may modulate local immune activity, while Trico *et al* (62) provided preclinical proof-of-concept that pro-histaminergic drugs promote microgliogenesis and compensation, suggesting that optimization of histaminergic signaling, rather than simple receptor blockade, may represent a more effective therapeutic strategy. Comparison of CGRP and histamine targeting reveals a pattern that is consistent with the hypothesis that these pathways may differentially

contribute to VM and MD pathophysiology: anti-CGRP therapies have shown efficacy in VM (22,63), whereas histamine modulation has demonstrated greater utility in MD (16,62). However, this dichotomy should be interpreted with caution, as head-to-head comparative studies directly evaluating pathway-specific contributions across both conditions are lacking. If this hypothesis is validated by future comparative investigations, it would underscore the necessity for diagnostic biomarkers that can stratify patients according to dominant neuropeptide signatures, enabling precision targeting of vestibular neuroimmune networks rather than empirical trial-and-error prescribing.

6. Systemic immune influences and the gut-vestibular axis

The vestibular system integrates signals from systemic immune compartments, including circulating cytokines, autoantibodies and inflammatory mediators. A growing but still preliminary body of evidence suggests that gut-derived metabolites may also influence vestibular function, although this gut-vestibular interaction remains an emerging hypothesis requiring further validation. Systemic autoimmune conditions, immune checkpoint inhibitors, atopic tendencies, viral infections and gut dysbiosis can each modulate vestibular function through distinct but overlapping pathways (Table II).

Autoimmune-mediated vestibular dysfunction. Systemic autoimmune disorders frequently involve the vestibular apparatus, either as a primary manifestation or as part of a broader immune-mediated syndrome. Ralli *et al* (86) provided a comprehensive characterization of audiovestibular symptoms across systemic autoimmune diseases, documenting that vertigo and imbalance occur with notable frequency in conditions such as systemic lupus erythematosus, Sjögren's syndrome and antiphospholipid syndrome. Expanding these observations, Girasoli *et al* (87) systematically reviewed the diagnostic approach to autoimmune vertigo, emphasizing that vestibulopathy may precede the diagnosis of the underlying systemic disease in a substantial proportion of patients. AIED represents a distinct clinical entity where the inner ear is the primary or sole target of immune attack. Breslin *et al* (88) conducted a systematic review of AIED management, concluding that while corticosteroids remain first-line therapy, evidence for steroid-sparing agents and biologics remains limited. Balouch *et al* (89) evaluated biologic therapies for AIED, reporting that TNF- α inhibitors and anti-CD20 monoclonal antibodies may provide benefit in refractory cases, although randomized controlled trials are conspicuously absent.

Cogan's syndrome exemplifies a prototypic autoimmune disorder with prominent audiovestibular involvement. D'Aguanno *et al* (90) outlined optimal multidisciplinary management of Cogan's syndrome, noting that early immunosuppression is critical for preserving vestibular and auditory function. The 2025 French protocol by Arnaud *et al* (91) further refined diagnostic criteria and treatment algorithms, distinguishing typical from atypical presentations. A critical appraisal of the literature reveals substantial heterogeneity in outcome measures across studies, making cross-trial comparisons difficult. Moreover, whether vestibular dysfunction in

systemic autoimmunity arises from direct immune attack on inner ear antigens, immune-complex deposition, or secondary vascular compromise remains incompletely resolved. Amor-Dorado and González-Gay (92) recently performed a GRADE-based systematic review, concluding that while the association between systemic autoimmune diseases and vestibular impairment is well established, causality has been definitively proven only for a subset of conditions including Cogan's syndrome and Susac's syndrome. This causal evidence rests on direct immunopathological findings (cell-mediated inner ear antigen reactivity in Cogan's syndrome and anti-endothelial cell antibodies with CD8⁺ T-cell endothelial targeting in Susac syndrome), as detailed in the GRADE-based review by Amor-Dorado and González-Gay (92). These observations collectively indicate that systemic autoimmunity is associated with vestibular morbidity (86-88,90). However, evidence for causality is strongest for Cogan's syndrome and Susac's syndrome (92), whereas for conditions such as SLE and Sjögren's syndrome, vestibular involvement remains primarily documented through clinical association studies. The mechanistic pathways, whether direct immune attack, immune-complex deposition, or secondary vascular compromise, remain incompletely resolved.

Immune checkpoint inhibitors and iatrogenic vestibular syndromes. The expanding use of immune checkpoint inhibitors (ICIs) in oncology has unveiled novel iatrogenic vestibular syndromes mediated by unleashed immune responses. Tian *et al* (93) conducted a systematic review and meta-analysis of immune-related neurological toxicities of programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors, identifying vestibular symptoms as a rare but increasingly recognized adverse event. Complementing this, Guven *et al* (94) performed a systematic analysis of individual patient data on ICI-related hearing loss, documenting that concurrent vestibular involvement occurs in ~one-third of affected patients. The pathogenesis of ICI-induced vestibulopathy remains incompletely understood, but proposed mechanisms include T-cell and macrophage infiltration of the inner ear, autoantibody production against inner ear antigens and cytokine-mediated disruption of the blood-labyrinth barrier. Sunyur *et al* (95) reviewed ophthalmic and otologic events associated with ICIs, noting that vestibular symptoms often present as acute, bilateral and rapidly progressive, features that distinguish ICI-related vestibulopathy from most idiopathic peripheral vestibular disorders. Importantly, Boyer *et al* (96) recently reported a case of severe immuno-induced rhinosinusitis with deafness following ipilimumab and nivolumab combination therapy, underscoring that vestibular involvement may occur as part of a broader head and neck immune-related adverse event spectrum.

From a clinical management perspective, Wierzbicka *et al* (97) proposed that high-dose corticosteroids represent first-line treatment, although ICI discontinuation is often necessary for severe or refractory cases. A notable unresolved question concerns whether pre-existing subclinical autoimmune inner ear inflammation predisposes patients to ICI-induced vestibulopathy. Furthermore, the optimal monitoring strategy for early detection of vestibular toxicity in patients receiving ICIs has not been established. The

Table II. Summary of original studies investigating systemic immune influences on vestibular function.

Authors, year	Level of evidence/study design		Immune domain	Vestibular population	Key findings	Conclusion	(Refs.)
Ralli <i>et al.</i> , 2018	Systematic review		Autoimmunity	Patients with SLE, Sjögren's, APS, Cogan's, RP	Audiovestibular symptoms occur at notable frequency across systemic autoimmune diseases, with vertigo and imbalance commonly reported.	Systemic autoimmune disorders frequently involve the vestibular apparatus and warrant routine audiovestibular evaluation.	(86)
Girasoli <i>et al.</i> , 2018	Systematic review		Autoimmunity	Patients with autoimmune vertigo	Vestibulopathy may precede the diagnosis of underlying systemic autoimmune disease in a substantial proportion of patients.	Early recognition of autoimmune vertigo requires comprehensive diagnostic work-up including serologies and vestibular testing.	(87)
Breslin <i>et al.</i> , 2020	Systematic review		Autoimmunity	AIED patients	Corticosteroids remain first-line therapy for AIED; evidence for steroid-sparing agents and biologics remains limited.	Controlled trials are urgently needed to establish optimal management protocols for autoimmune inner ear disease.	(88)
Balouch <i>et al.</i> , 2022	Systematic review		Autoimmunity	Refractory AIED patients	TNF- α inhibitors and anti-CD20 monoclonal antibodies may provide benefit in refractory AIED cases.	Biologic therapies show promise but randomized controlled trials are conspicuously absent.	(89)
Arnaud <i>et al.</i> , 2025	Consensus guideline		Autoimmunity	Cogan's syndrome patients	Refined diagnostic criteria and treatment algorithms distinguish typical from atypical Cogan's syndrome presentations.	Standardized protocols enable earlier diagnosis and more consistent management of this prototypic autoimmune vestibulopathy.	(91)
Tian <i>et al.</i> , 2020	Systematic review		ICI-related	Cancer patients on PD-1/PD-L1 inhibitors	Vestibular symptoms identified as a rare but increasingly recognized immune-related adverse event of ICIs.	Clinicians should maintain awareness of vestibular toxicity in patients receiving checkpoint inhibitor therapy.	(93)
Guyen <i>et al.</i> , 2023	Systematic review		ICI-related	Cancer patients with ICI-related hearing loss	Concurrent vestibular involvement occurs in ~one-third of patients with ICI-related hearing loss.	Vestibular assessment should be included in the monitoring of patients receiving ICIs.	(94)
Boyer <i>et al.</i> , 2026	Clinical case report (safety)		ICI-related	Melanoma patient on ipilimumab + nivolumab	Severe immuno-induced rhinosinusitis with deafness occurred following combination ICI therapy, indicating vestibular involvement may be part of broader head and neck irAE spectrum.	Vestibular symptoms should prompt evaluation for other head and neck immune-related adverse events.	(96)
Qi <i>et al.</i> , 2020	Randomized controlled trial		Gut-vestibular axis	204 VM patients (aged 12-70)	Probiotic <i>Lactobacillus casei</i> Shirota markedly attenuated vertigo attack frequency, DHI and VSS scores and improved anxiety/depression scores at 4 months vs. placebo.	Gut microbiome-targeted therapy shows promise for vestibular migraine management and warrants larger confirmatory studies.	(43)

Table II. Continued.

Authors, year	Level of evidence/study design	Immune domain	Vestibular population	Key findings	Conclusion	(Refs.)
Ghavami <i>et al</i> , 2021	Randomized controlled trial	Gut-vestibular axis	Women with migraine	Synbiotic supplementation markedly reduced hs-CRP and TNF- α alongside improved clinical outcomes.	Anti-inflammatory effects of gut microbiome modulation extend to cranial and vestibular compartments.	(99)
Naghibi <i>et al</i> , 2019	Systematic review	Gut-vestibular axis	Migraine patients on probiotics	Meta-analysis shows modest benefit of probiotics for migraine prophylaxis; substantial heterogeneity in strains, doses and outcome measures precludes definitive recommendations.	Rigorous RCTs with vestibular-specific outcomes are needed before microbiome-based therapies can be recommended.	(101)
Xu <i>et al</i> , 2023	Systematic review	Allergy/atopy	MD patients with allergic sensitization	Prevalence of allergic sensitization in MD patients ranges 30-60% across studies, substantially higher than in the general population.	Allergy may contribute to MD pathogenesis in a subset of patients through immune-mediated mechanisms.	(103)
Zeng <i>et al</i> , 2024	Systematic review	Allergy/atopy	Patients with MD, ISSHL, ALHL	Cross-sectional studies consistently show positive associations between type I hypersensitivity and inner ear disorders; prospective studies with objective vestibular measures lacking.	Causal relationship between allergy and vertigo remains unproven despite strong epidemiologic associations.	(104)
Simard <i>et al</i> , 2024	Randomized pilot trial	Allergy/atopy	Patients undergoing allergy immunotherapy tablet administration	Local vestibular reactions to allergy immunotherapy tablets are rare and generally self-limited.	Vestibular allergy immunotherapy tablet administration is tolerable but further safety studies are needed.	(107)
Almufarrij <i>et al</i> , 2021	Systematic review	Post-viral (COVID-19)	SARS-CoV-2 infected individuals	Dizziness and vertigo occur in ~15-20% of infected individuals during acute phase; smaller subset develop persistent symptoms as part of long COVID.	Post-COVID vestibular symptoms represent an emerging clinical challenge requiring systematic characterization.	(109)
Korres <i>et al</i> , 2022	Systematic review	Post-viral (COVID-19)	COVID-19 patients with dizziness/vertigo	Vestibular symptoms often co-occur with other neurological manifestations including headache, anosmia and dysgeusia.	Dizziness and vertigo are common but under-recognized manifestations of COVID-19 requiring routine assessment.	(110)
Jafari <i>et al</i> , 2022	Meta-analysis	Post-viral (COVID-19)	COVID-19 patients with audiovestibular symptoms	Pooled prevalence of vertigo ~7%, with higher rates in hospitalized and severe COVID-19 cases.	Post-viral vestibular disorders following COVID-19 share clinical features with vestibular neuritis and vestibular migraine.	(111)

AD, atopic dermatitis; AIED, autoimmune inner ear disease; ALHL, acute low-tone hearing loss; APS, antiphospholipid syndrome; DHI, Dizziness Handicap Inventory; hs-CRP, high-sensitivity C-reactive protein; ICI, immune checkpoint inhibitor; ir-AE, immune-related adverse event; ISSHL, idiopathic sudden sensorineural hearing loss; MD, Menière's disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCT, randomized controlled trial; RP, relapsing polychondritis; SLE, systemic lupus erythematosus; TNF- α , tumor necrosis factor- α ; VM, vestibular migraine; VSS, Vertigo Severity Score.

emergence of ICI-related vestibular syndromes provides a human model of acute immune-mediated vestibular injury and suggests that therapeutic strategies aimed at re-establishing immune tolerance may have broader applicability to autoimmune vestibular disorders.

Gut-microbiota-immune-brain axis in VM. The concept of a gut-vestibular axis remains an emerging and hypothetical framework rather than an established biological pathway. The following discussion distinguishes between direct evidence obtained from vestibular disorder patients and evidence extrapolated from the broader migraine and gut-brain axis literature. Emerging evidence suggests that the gut-microbiota-immune-brain axis may modulate VM pathophysiology, although direct evidence in vestibular disorder populations remains limited (98). Evidence extrapolated from the broader migraine literature suggests that alterations in microbial composition, increased intestinal permeability and systemic low-grade inflammation collectively contribute to trigeminovascular sensitization (98). However, whether these mechanisms directly translate to VM pathophysiology remains to be established, as most studies have been conducted in migraine populations without vestibular phenotyping.

By contrast, direct evidence obtained specifically in vestibular disorder patients is limited but emerging. Qi *et al* (43) conducted a randomized placebo-controlled double-blind clinical trial demonstrating that the probiotic *Lactobacillus casei* Shirota attenuates vertigo attack frequency and severity in VM patients, providing the first direct clinical evidence for microbiome-targeted therapy in a vestibular disorder. This represents a notable exception in an otherwise predominantly extrapolated literature. The mechanistic underpinnings of this effect remain to be fully elucidated, but proposed pathways include modulation of systemic cytokine profiles, regulation of tryptophan metabolism and alteration of short-chain fatty acid production that influences blood-brain barrier integrity. Although conducted in migraine patients without vestibular phenotyping, Ghavami *et al* (99) reported that synbiotic supplementation reduced inflammatory biomarkers alongside improved clinical outcomes, suggesting potential anti-inflammatory effects that may be relevant to vestibular compartments. However, extrapolation of these findings to VM requires confirmation in vestibular-specific populations.

Zhou *et al* (100) delineated the cellular and molecular roles of immune cells in the gut-brain axis in migraine, demonstrating that gut-derived immune signals prime meningeal macrophages and promote dural mast cell degranulation. Whether this peripheral immune priming similarly lowers the threshold for vestibular nuclear sensitization remains hypothetical and awaits direct investigation in VM models. A systematic review of probiotics for migraine prophylaxis concluded that while meta-analysis shows modest benefit, substantial heterogeneity in strains, doses and outcome measures precludes definitive recommendations (101). Dietary interventions such as elimination diets, ketogenic diets and low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols diets may modulate VM through distinct mechanisms (102), although these observations derive primarily from migraine studies rather than vestibular-specific populations. Collectively, these findings suggest that the gut-vestibular axis represents a

promising but unproven therapeutic target. Rigorous randomized controlled trials with vestibular-specific outcomes are urgently needed before microbiome-based therapies can be recommended in clinical practice.

Allergy, atopy and vestibular dysfunction. Allergic and atopic conditions have long been suspected to influence vestibular function, yet the precise mechanisms linking type I hypersensitivity to vertigo remain incompletely defined. Xu *et al* (103) systematically reviewed the epidemiology, pathogenesis and therapy of MD in relation to allergy, documenting that the prevalence of allergic sensitization in MD patients ranges from 30-60% across studies, substantially higher than in the general population. Zeng *et al* (104) performed a systematic review of the clinical evidence for an association between type I hypersensitivity and inner ear disorders, concluding that while cross-sectional studies consistently show positive associations, prospective studies with objective vestibular outcome measures are lacking. The proposed mechanisms include immune-complex deposition in the endolymphatic sac, mast cell degranulation with release of histamine and leukotrienes that alter endolymph homeostasis and cytokine-mediated disruption of tight junctions in the stria vascularis. Derebery and Christopher (105) reviewed allergy, immunotherapy and alternative treatments for dizziness, noting that approximately one-third of patients with refractory MD experience symptom improvement following allergy management, although placebo effects cannot be excluded.

The histaminergic system represents a critical molecular bridge between allergic inflammation and vestibular dysfunction. Møller *et al* (16) demonstrated expression of histamine H1-H4 receptors in the human endolymphatic sac and Di Mauro *et al* (106) reviewed the roles of histamine and its receptors in central nervous system disorders associated with systemic mastocytosis, raising the possibility that mast cell activation syndromes may contribute to otherwise unexplained episodic vertigo. A critical appraisal of the literature reveals substantial confounding by comorbidity: patients with allergic rhinitis also have higher rates of migraine, anxiety and autonomic dysfunction, each of which can independently produce vestibular symptoms. Simard *et al* (107) recently conducted a randomized pilot study comparing sublingual vs. vestibular allergy immunotherapy tablet administration, reporting that local vestibular reactions are rare and generally self-limited. From a therapeutic perspective, Fein *et al* (108) emphasized that second-generation H1-antihistamines are safer and should be first-line for allergic rhinitis, but whether these agents confer benefit specifically for vestibular symptoms in atopic patients independent of their effect on nasal congestion remains unproven. Future research must employ rigorous vestibular phenotyping and control for migraine comorbidity to determine whether allergy-vestibular associations reflect causal pathways or shared epidemiological risk factors.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), neuroinflammation and post-viral vestibular disorders. The COVID-19 pandemic has provided an unprecedented opportunity to examine how systemic viral infection and its associated inflammatory response affect vestibular function. Systematic reviews and meta-analyses

consistently report that dizziness and vertigo occur in 15-20% of SARS-CoV-2-infected individuals during the acute phase, with a pooled vertigo prevalence of ~7% and higher rates in hospitalized or severe cases (109-111). These vestibular symptoms often co-occur with headache, anosmia and dysgeusia (110). Importantly, post-viral vestibular disorders following COVID-19 share clinical features with vestibular neuritis and VM, making differential diagnosis challenging in the absence of objective vestibular testing. Fancello *et al* (112) reviewed audio-vestibular disorders in SARS-CoV-2 infection, emphasizing that while most acute vestibular symptoms resolve spontaneously, a subset of patients develop persistent postural-perceptual dizziness or chronic subjective dizziness. The long-term trajectory of post-COVID vestibular symptoms was examined by Chen *et al* (8), who systematically characterized audiovestibular dysfunction related to long COVID-19 syndrome, identifying that vestibular symptoms persist in addition to six months in 5-10% of affected individuals. A critical unresolved question concerns whether SARS-CoV-2 infection triggers *de novo* AIED in susceptible individuals through molecular mimicry or epitope spreading. The observation that post-COVID vestibular symptoms occasionally respond to immunomodulatory therapy supports this hypothesis, although controlled trials have not been conducted. Collectively, the COVID-19 experience has reinvigorated interest in post-viral vestibular disorders and established that systemic viral infection, through both direct and immune-mediated pathways, represents a significant cause of acute and chronic vestibular morbidity.

7. Vestibular compensation and neuroimmune plasticity

Vestibular compensation represents a unique model of lesion-induced neuroplasticity, wherein the central nervous system partially restores balance and gaze stability following peripheral vestibular injury. This process involves coordinated cellular and molecular events, including synaptic remodeling, neurogenesis and glial activation. Emerging evidence indicates that neuroimmune signaling, ranging from microglial dynamics to cytokine networks and histaminergic modulation, critically shapes both the rate and quality of functional recovery (Table III). The neuroimmune mechanisms discussed in this section are specifically related to post-lesional central compensation following acute peripheral vestibular injury, as modeled by surgical deafferentation or labyrinthectomy. These findings should not be interpreted as directly modeling the primary pathogenesis of MD or VM, but rather as illustrating how neuroimmune signaling modulates adaptive plasticity after injury, a conceptually distinct process from the neuroinflammatory drivers of disease initiation or chronification. The evidence in this section is predominantly preclinical, derived from rodent unilateral vestibular neurectomy or labyrinthectomy models. Clinical data are mainly observational, diagnostic, or rehabilitation studies and are identified as such. These findings pertain to post-lesional compensation rather than primary MD or VM pathogenesis (44-47,55,56,59,60,113-123).

Cellular and molecular substrates of compensation. Vestibular compensation engages multiple cellular and molecular mechanisms that collectively restore symmetric resting

activity within the deafferented vestibular nuclei. BDNF signaling promotes vestibular compensation by increasing neurogenesis and remodeling KCC2 and GABAA receptor expression in vestibular nuclei (56). BDNF/TrkB signaling enhances synaptic plasticity and neuronal survival, with pharmacological modulation producing measurable effects on behavioral recovery (60).

In addition to neurotrophic mechanisms, histaminergic signaling has emerged as a key regulator of compensation. Chen *et al* (113) provided direct evidence that the histamine H1 receptor contributes to vestibular compensation, with H1 receptor knockout mice exhibiting delayed recovery of balance function after unilateral labyrinthectomy. This finding aligns with clinical observations that betahistidine, a histamine analogue, improves vertigo symptoms in patients with uncompensated vestibulopathy (124). Of note, while Parfenov *et al* (125) reported that high-dose betahistidine (48 mg/day) effectively reduces vertigo frequency in routine clinical practice, contrasting evidence from Fukuda *et al* (126) suggested that betahistidine effects on compensation in animal models may be more pronounced during early rather than late recovery phases. Collectively, these observations establish that both BDNF and histamine pathways operate in parallel to support compensation, though their relative contributions may vary according to lesion chronicity and etiology.

Neuroinflammatory modulation of vestibular recovery. As detailed in the *Microglial dynamics and inflammasome activation* section, the microglial response to deafferentation is biphasic (48,49); pharmacological modulation of this response alters compensation outcomes (48). The functional significance of this early response was further underscored by Marouane *et al* (114), who showed that sensorimotor rehabilitation promotes vestibular compensation by enhancing microgliogenesis in deafferented vestibular nuclei.

A critical insight emerged from a study challenging the conventional view that acute anti-inflammatory treatment uniformly benefits recovery. El Mahmoudi *et al* (59) reported that dexamethasone administration immediately after unilateral vestibular neurectomy paradoxically impaired long-term vestibular compensation and suppressed endogenous plasticity mechanisms. This finding specifically addresses the role of inflammation in post-lesional compensatory plasticity and does not imply that anti-inflammatory interventions are detrimental in MD or VM, where neuroinflammation may play a distinct pathogenic role. By contrast, excessive or persistent neuroinflammation exerts detrimental effects. Li *et al* (52) recently demonstrated that sleep deprivation disrupts vestibular compensation by activating TLR4/NF- κ B/NLRP3 signaling in the deafferented vestibular nuclei, providing mechanistic insight into how systemic disturbances adversely affect glial-mediated recovery in post-lesional models. Collectively, these findings indicate that the relationship between neuroinflammation and compensation follows an inverted U-shaped curve: Either insufficient or excessive inflammation impairs recovery, whereas appropriately regulated inflammation supports adaptive plasticity. This inverted U-shaped model applies specifically to post-lesional compensation and should not be extrapolated to the role of neuroinflammation in MD or VM, where the pathogenic context differs fundamentally.

Table III. Key experimental and clinical studies on vestibular compensation and neuroimmune plasticity.

Authors, year	Level of evidence/study design	Key focus area	Main findings	(Refs.)
El Mahmoudi <i>et al.</i> , 2022	Preclinical animal model	Microglial dynamics in compensation	UVN induced biphasic M1/M2 microglial phenotypes in deafferented VNs. LPS-induced M1 predominance impaired plasticity and delayed functional recovery.	(48)
Trico <i>et al.</i> , 2026	Preclinical animal model	Early microgliogenesis	Microgliogenesis began 24 h post-UVN, preceding astrocytic responses, establishing microglia as first responders to vestibular injury.	(49)
Li <i>et al.</i> , 2025	Preclinical animal model	Sleep deprivation and compensation	Sleep deprivation impaired compensation via TLR4/NF- κ B/NLRP3 activation in VNs, causing microglial overactivation. TLR4 inhibition or minocycline partially rescued the delay.	(52)
Wu <i>et al.</i> , 2025	Preclinical animal model	Early rehabilitation efficacy	Early rehabilitation enhanced compensation by promoting cellular proliferation and concurrent glial proliferation (microglia and astrocytes).	(55)
Dutheil <i>et al.</i> , 2016	Preclinical animal model	BDNF signaling in vestibular compensation	BDNF infusion accelerated vestibular recovery and neurogenesis; TrkB antagonist blocked this effect. BDNF remodeled KCC2 and GABAA receptor, making GABA transiently depolarizing during early compensation.	(56)
El Mahmoudi <i>et al.</i> , 2021	Preclinical animal model	Acute anti-inflammatory treatment	Acute methylprednisolone reduced glial reaction, cell proliferation and altered excitability, worsening vestibular syndrome and delaying compensation.	(59)
Mao <i>et al.</i> , 2021	Preclinical animal model	BDNF/TrkB signaling	BDNF/TrkB signaling promoted compensation by increasing new cells and astrocytes and rebalancing GABAergic neurons and GABAA receptor in bilateral medial vestibular nuclei.	(60)
Trico <i>et al.</i> , 2025	Preclinical animal model	Pro-histaminergic drug (betahistine)	Betahistine reduced astrocyte and microglial numbers after UVN, promoted microglial differentiation and accelerated compensation via H3 autoreceptor antagonism.	(62)
Chen <i>et al.</i> , 2019	Preclinical animal model	Histamine H1 receptor in compensation	H1 receptor expression increased in ipsilesional GABAergic neurons of MVN after labyrinthectomy; H1-mediated excitation rebalanced bilateral vestibular tone. H1 blockade or knockout delayed recovery and reduced betahistine effects.	(113)
Marouane <i>et al.</i> , 2021	Preclinical animal model	Sensorimotor rehabilitation	Rehabilitation accelerated posturo-locomotor recovery, decreased neurogenesis but increased microgliogenesis in deafferented medial vestibular nucleus.	(114)
Grosch <i>et al.</i> , 2021	Preclinical animal model	Whole-brain metabolic connectivity	Dynamic metabolic connectivity changes occurred after labyrinthectomy, peaking at day 3 and declining by day 15; brainstem-cerebellar and thalamocortical networks reorganized during compensation.	(115)

Table III. Continued.

Authors, year	Level of evidence/study design	Key focus area	Main findings	(Refs.)
Sjögren <i>et al</i> , 2018	Clinical diagnostic study	Functional head impulse testing	Active head-impulses toward the lesioned side gave improved visual acuity and shorter latencies than passive impulses; HITD-FT may assess compensation.	(44)
Trinidad-Ruiz <i>et al</i> , 2018	Clinical diagnostic study	Saccadic strategies in unilateral loss	Patients developed saccadic strategies reducing retinal smear; covert saccades increased and overt saccade latency decreased after vestibular rehabilitation.	(45)
Cerchiai <i>et al</i> , 2018	Clinical prognostic study	Prognostic value of VOR gain and saccades	Lower high-velocity VOR gain and high prevalence of overt saccades at 4-8 weeks predicted worse prognosis after acute unilateral vestibulopathy.	(46)
Casani <i>et al</i> , 2021	Clinical diagnostic study	SHIMP	SHIMP identified vestibular damage abler than HIMP and provided additional prognostic information after acute unilateral vestibulopathy.	(47)
Tighilet <i>et al</i> , 2019	Preclinical animal model	Apamin (SK channel blocker)	UVN up-regulated SK channels bilaterally; apamin given acutely reduced static and dynamic deficits (nystagmus, balance, gaze tabilization).	(121)
Shaabani <i>et al</i> , 2016	Preclinical animal model	GVS	Short-term GVS accelerated static and dynamic compensation, associated with cell proliferation in ipsilesional MVN.	(122)
Koganemaru <i>et al</i> , 2017	Exploratory clinical study	tcDCS plus vestibular rehabilitation	tcDCS combined with vestibular rehabilitation improved clinical outcomes in chronic dizziness, possibly by inducing cerebellar plasticity.	(123)

BDNF, brain-derived neurotrophic factor; GABAA, gamma-aminobutyric acid type A; GVS, galvanic vestibular stimulation; HIMP, head impulse paradigm; HITD-FT, functional head impulse test-dynamic visual acuity; LPS, lipopolysaccharide; MVN, medial vestibular nucleus; PET, positron emission tomography; SHIMP, suppression head impulse paradigm; SK, small conductance calcium-activated potassium; tcDCS, transcranial cerebellar direct current stimulation; TL4, Toll-like receptor 4; TrkB, tropomyosin receptor kinase B; UL, unilateral labyrinthectomy; UVN, unilateral vestibular neurectomy; VN, vestibular nuclei; VOR, vestibulo-ocular reflex.

Synaptic and network plasticity in compensation. Compensation involves not only cellular changes but also large-scale reorganization of vestibular network connectivity. Using dynamic whole-brain metabolic connectivity mapping, Grosch *et al* (115) revealed that unilateral labyrinthectomy induces time-dependent reorganization of metabolic networks involving the vestibular nuclei, cerebellum and thalamus, with normalization of connectivity patterns correlating with behavioral recovery. This systems-level perspective complements molecular studies by demonstrating that compensation engages distributed circuits rather than isolated nuclei. At the synaptic level, Dutheil *et al* (56) demonstrated remodeling of KCC2 and GABAA receptors in the vestibular nuclei following vestibular injury. This finding was subsequently extended by Mao *et al* (60), who revealed that such plasticity-related changes exhibit regional heterogeneity, with differential profiles observed between the medial and lateral subregions of the vestibular nuclei.

From a functional perspective, compensatory strategies include adaptive changes in saccadic eye movements and vestibulo-ocular reflex gain. Sjögren *et al* (44) demonstrated that functional head impulse testing parameters correlate with compensation status, suggesting that objective oculomotor measures can serve as biomarkers of recovery. Expanding upon this, Trinidad-Ruiz *et al* (45) showed that patients with unilateral vestibular loss develop characteristic saccadic strategies that support visual performance during head movements, with the efficiency of these strategies improving progressively during compensation. Notably, the degree of saccadic compensation varies substantially across individuals. Cerchiai *et al* (46) identified that catch-up saccade characteristics predict recovery outcomes after acute unilateral vestibulopathy, whereas Casani *et al* (47) demonstrated that the suppression head impulse paradigm provides additional prognostic information. In addition to standard video head impulse testing. These observations collectively indicate that while synaptic and network plasticity mechanisms follow predictable temporal sequences, their expression exhibits inter-individual variability that may reflect differences in baseline neuroimmune status or genetic background.

Therapeutic strategies targeting neuroimmune pathways. The aforementioned mechanistic insights have inspired multiple therapeutic approaches aimed at enhancing vestibular compensation through neuroimmune modulation. Exercise-based vestibular rehabilitation remains the cornerstone of therapy, with Kundakci *et al* (116) conducting a systematic review confirming its effectiveness in chronic dizziness. More recent randomized controlled trials have refined this approach: Ding *et al* (117) demonstrated that short-term personalized home-based rehabilitation guided by professional therapists produces superior outcomes compared to generic exercise programs, whereas Wang *et al* (118) established specific clinical indicators for evaluating rehabilitation efficacy in patients with benign recurrent vestibular vertigo. Of note, Liu *et al* (119) used resting-state functional MRI to show that vestibular rehabilitation normalizes spontaneous brain activity in VM patients, providing neuroimaging evidence for therapy-induced plasticity.

Pharmacological augmentation of compensation has yielded mixed but promising results. Trico *et al* (62) recently demonstrated that a pro-histaminergic drug restores balance function, promotes microgliogenesis and modulates neuroinflammation after vestibular injury in a rodent deafferentation model. This preclinical finding pertains to enhancement of post-lesional vestibular compensation. This finding aligns with clinical evidence that betahistine, particularly at higher doses, benefits patients with uncompensated vestibulopathy (124). Van de Heyning *et al* (120) conducted a double-blind, randomized, placebo-controlled phase 2 study of intranasal betahistine for surgery-induced acute vestibular syndrome, reporting significant improvements in balance function with a favorable safety profile. These clinical findings also address vestibular compensation after acute peripheral injury rather than MD or VM pathogenesis. In addition to histaminergic agents, apamin (a small-conductance calcium-activated potassium channel blocker) has been shown to accelerate equilibrium recovery and gaze stabilization in vestibular neurectomized animals (121). Complementary approaches include galvanic vestibular stimulation: Shaabani *et al* (122) demonstrated that short-term galvanic stimulation promotes functional recovery and neurogenesis in labyrinthectomized rats, while Koganemaru *et al* (123) reported that transcranial cerebellar direct current stimulation combined with vestibular rehabilitation improves outcomes in chronic dizziness patients.

A critical appraisal of the literature reveals several unresolved questions. First, the optimal timing and duration of interventions remain poorly defined; early rehabilitation promotes glial proliferation and enhances compensation (55), but acute anti-inflammatory treatment impairs recovery (59), suggesting that interventions must be carefully timed relative to the injury phase. Second, whether pharmacological and rehabilitation approaches exert synergistic effects has not been rigorously tested. Third, most studies have employed short-term outcome measures, whereas compensation continues for months to years, raising questions about the durability of intervention effects. Future research should prioritize head-to-head comparisons of different therapeutic modalities and identify biomarkers that predict individual treatment responses, enabling precision targeting of neuroimmune pathways based on patient-specific inflammatory profiles.

8. Future perspectives

The mechanistic insights summarized in the present review carry several potential clinical implications, though most remain investigational. First, differential cytokine and chemokine signatures (elevated IL-1 β and CXCL8 in MD vs. CXCL10 in VM) raise the possibility of using peripheral blood immune profiling for challenging differential diagnoses, but the limited sample sizes and inter-study heterogeneity preclude current clinical application, requiring prospective validation (32-34). Second, anti-CGRP monoclonal antibodies have demonstrated efficacy in reducing vertigo burden in VM, suggesting consideration for refractory cases, although dedicated RCTs are lacking (22,63,80); gepants may offer on-demand flexibility for episodic prophylaxis (85). Third, preliminary evidence that probiotic supplementation attenuates vertigo attacks and that gut microbial composition correlates with severity suggests

that microbiota profiling and modulation could become adjunctive tools, but given the heterogeneity and extrapolated data, these approaches remain experimental (43,101). Fourth, the dual role of neuroinflammation in vestibular compensation, where complete suppression impairs recovery whereas excessive inflammation drives maladaptive plasticity, implies that immunomodulatory interventions should be carefully timed, with modulation rather than elimination appearing more beneficial (51,59,62). Overall, while these avenues are promising, most require prospective validation and current practice should continue to rely on established diagnostic criteria and guideline-based therapies.

A cohesive understanding of neuroimmune crosstalk in vestibular disorders now requires translation of mechanistic insights into diagnostic and therapeutic applications. A critical unresolved question requiring priority investigation is whether the apparent CGRP-VM and histamine-MD associations reflect true pathway-specific disease mechanisms or are merely epiphenomena of broader neuroimmune activation. Direct comparative studies examining CGRP and histamine pathway activity in well-phenotyped VM and MD cohorts are needed to validate or refute this working model. Notably, the strong female predominance observed in VM and MD raises the possibility of sex-dependent neuroimmune mechanisms. Lin *et al* (127) reported a female-to-male ratio of ~3.3:1 among VM patients in a tertiary referral center and Bruderer *et al* (128) conducted a population-based study in the United Kingdom on 5,508 patients with MD, finding that 65.4% of cases occurred in women. These epidemiological observations yet direct evidence on sex differences in microglial responses, CGRP signaling, or other neuroimmune pathways within the vestibular system remains scarce. Future investigations should incorporate sex as a biological variable to address this critical knowledge gap (127,129). The emerging picture is that VM and MD, despite overlapping clinical presentations, may possess distinct immunological profiles that could inform patient stratification pending further validation (130,131).

Diagnostic biomarker development has progressed substantially, yet several challenges remain. Klokman *et al* (132) systematically evaluated blood biomarkers for peripheral vestibular syndromes, concluding that while numerous candidates have been proposed, none have achieved clinical validation due to heterogeneous study designs and lack of replication cohorts. A particularly promising direction involves multiomic profiling at single cell resolution. Li *et al* (133) established a framework identifying immune cell drivers of migraine through integrated single cell multi omics, an approach that could be extended to vestibular disorders. Similarly, Pan *et al* (134) constructed a single cell atlas of peripheral immune and metabolic dysregulation across migraine, MD and VM, revealing cell type specific signatures that may enable precise disease subtyping. However, critical appraisal indicates that most biomarker studies remain cross sectional and whether identified signatures fluctuate with disease activity or represent stable traits has not been determined.

Therapeutic frontiers are expanding rapidly, particularly for CGRP targeting interventions. Romozzi *et al* (135) developed and validated a nomogram (the CGRP score) for predicting response to anti CGRP monoclonal antibodies in

migraine patients, an approach that could be adapted for VM. Vasireddy *et al* (136) performed a network meta-analysis of preventive treatments for VM, providing comparative effectiveness estimates that can guide clinical decision making, though they noted that most studies have short follow up durations. Nevertheless, Bai *et al* (137) reported that interictal plasma and salivary CGRP levels do not differ between VM patients and controls, raising questions about whether peripheral CGRP measurements can serve as reliable biomarkers or whether compartment specific sources predominate. In addition to CGRP targeting, histaminergic modulation remains relevant for MD. Yuan *et al* (138) comprehensively reviewed immunological mechanisms in MD, emphasizing that inflammasome activation and autoinflammatory pathways represent druggable targets. A critical unresolved issue concerns whether combination therapies targeting parallel neuroimmune pathways would produce synergistic benefits or increase adverse event risks.

Neuromodulation and rehabilitation approaches are gaining evidence but require optimization. El Ahdab *et al* (139) conducted a systematic review and meta-analysis demonstrating that vestibular rehabilitation effectively reduces vertigo frequency and improves balance in VM, though effect sizes vary substantially across studies. Sfakianaki *et al* (140) confirmed these findings, noting that rehabilitation outcomes correlate with baseline inflammatory profiles, suggesting that patients with predominant neuroinflammatory contributions may respond differently than those with primarily structural pathology. Non-invasive neuromodulation techniques, including transcranial magnetic stimulation and galvanic vestibular stimulation, have shown preliminary efficacy but remain limited by small sample sizes and inconsistent stimulation parameters.

Perhaps the most transformative future direction involves the gut vestibular axis. Hu *et al* (141) employed causal cross trait mapping at single cell resolution to identify shared immunogenetic drivers of migraine and MD, revealing T cell regulatory networks that link peripheral and central compartments. Yu *et al* (142) characterized gut microbiota alterations and metabolomic profiles in VM patients, demonstrating that microbial composition correlates with vertigo attack frequency. These findings raise the possibility that microbiome targeted interventions, including probiotics and dietary modifications, could modulate vestibular neuroimmune networks. However, as Cantillo-Martínez *et al* (143) noted, the heterogeneity of study designs and outcome measures currently precludes definitive clinical recommendations. A critical limitation of the current literature is the predominance of clinical association studies over mechanistic investigations. While these associations generate important hypotheses, establishing causality requires integration of experimental models, genetic evidence and therapeutic validation. Future research should prioritize prospective longitudinal studies with repeated inflammatory profiling to distinguish trait from state biomarkers and randomized controlled trials to validate therapeutic targets identified through mechanistic studies.

Several unanswered questions warrant priority in future research. First, whether neuroimmune signatures can predict treatment response to specific agents (anti CGRP antibodies, histaminergic drugs, or immunomodulators)

requires prospective validation. Second, the optimal timing and duration of interventions relative to disease phase (acute vertigo attacks vs. interictal prophylaxis) remain undefined. Third, most mechanistic studies have been conducted in animal models and whether human vestibular tissues exhibit similar immune dynamics needs confirmation through post mortem and surgical specimen analyses. Fourth, the role of the glymphatic system and meningeal lymphatics in vestibular neuroimmune communication remains almost entirely unexplored. Addressing these questions will require multi-disciplinary collaboration, standardized outcome measures and integration of advanced technologies including single cell genomics, spatial transcriptomics and explainable artificial intelligence models that can handle the complexity of neuroimmune interactions while remaining interpretable for clinicians.

9. Conclusions

Neuroimmune crosstalk fundamentally links inflammation with neural circuit dysfunction in vestibular disorders. Emerging evidence suggests potentially distinct immunological profiles differentiate MD from VM, although direct comparative studies are limited and findings require replication. This observation nonetheless supports the concept of mechanism-based subtyping as a promising direction for future research. Targeting neuropeptide pathways, inflammasomes and glial dynamics offers therapeutic promise. The gut-vestibular axis represents an emerging and hypothetical framework rather than an established pathway; direct evidence in vestibular disorder populations remains limited, with most supporting data extrapolated from the broader migraine and gut-brain axis literature. Future priorities include validating diagnostic biomarkers and translating neuroimmune insights into personalized treatments for vestibular patients.

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Authors' contributions

XP and JF conceptualized the review framework, conducted the literature search and data synthesis and drafted the initial manuscript. ZYa, ZYi and ZL performed critical analysis and interpretation of the cited literature, particularly regarding inflammatory cytokine networks, neuroglial mechanisms and systemic immune influences. ZR and HZ contributed to the design of figures and tables and revised sections on neuropeptide signaling and the gut-vestibular axis. YL and HZ supervised the overall project, provided senior intellectual input on the pathophysiological and therapeutic implications

and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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