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Progress in Neuroinflammation Mechanisms and Targeted Therapy of Tinnitus

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Abstract

Tinnitus is a common auditory perception disorder, and its pathological mechanisms have not been fully elucidated. In recent years, neuroinflammation has garnered widespread attention as a new direction in the study of central mechanisms of tinnitus. This review systematically summarizes the roles of microglia and astrocytes, the TLR4/NF-κB/NLRP3 signaling axis, pro-inflammatory cytokines, and crosstalk between oxidative stress and inflammation in tinnitus. We highlight how neuroinflammation drives auditory central plasticity and remodeling, and discuss recent advances in anti-neuroinflammatory clinical interventions. Studies have shown that neuroinflammation plays a key role in the initiation and maintenance of tinnitus by affecting the neural plasticity of the auditory pathway and limbic system. Targeting neuroinflammation may provide new strategies for tinnitus treatment.

Keywords

Tinnitus, Neuroinflammation, Neural Remodeling, Signaling Pathway, Anti-Inflammatory Therapy

1. Introduction

Tinnitus refers to a clinical symptom of sound perception in the ear or brain of a patient without an external sound source [1] [2]. Epidemiological surveys show that the global prevalence of tinnitus is about 10% - 15%, of which about 1% - 2% of the population is plagued by severe tinnitus, which seriously affects the quality of life [3]. The causes of tinnitus are complex and diverse, including noise exposure, ototoxic drugs, head and neck trauma, infection, mental stress, and age-related hearing loss [4] [5]. Although the pathophysiological mechanism of tinnitus has not been fully elucidated, more and more evidence shows that the inflamma-

tory response of the central nervous system plays a key role in the development of tinnitus.

The traditional view is that tinnitus is mainly due to compensatory changes in the central nervous system after peripheral auditory injury. These changes include increased spontaneous discharge of neurons, enhanced synchronous discharge, and increased auditory central gain. Noise exposure or inner ear injury results in a decrease in peripheral auditory input, which triggers the neural plasticity response of the central auditory system, which is manifested as abnormal excitation and synchronous activity of neurons, and then produces auditory hallucination perception of tinnitus [6] [7]. These changes in neural activity are not limited to the auditory pathway, but also involve non-auditory brain regions, such as the limbic system, affecting mood and attention, thereby aggravating the perception and distress of tinnitus [8]. In addition, the occurrence of tinnitus is related to the interaction between auditory and somatosensory systems. Factors such as head and neck injury may also affect the intensity of tinnitus by changing somatosensory input. A variety of mechanisms work together to lead to complex manifestations of tinnitus, including excessive synchronization of neurons, increased spontaneous discharge rate, and imbalance of central gain regulation. These mechanisms provide a theoretical basis for the development of targeted therapies [7]. Peripheral auditory injury disrupts the blood–brain barrier, triggers central neuroinflammation, and further induces maladaptive neural plasticity and abnormal neural networks. Neuroinflammation acts as a critical bridge linking peripheral damage to central dysfunction and the chronicity of tinnitus.

Neuroinflammation refers to the inflammator response mediated by immune cells such as microglia and astrocytes in the central nervous system. Its core features include glial cell activation, pro-inflammatory factor release, and immune cell infiltration [9]. Moderate neuroinflammation helps to remove pathogens and repair tissue damage, but excessive or persistent neuroinflammation may lead to neuronal damage and dysfunction [10]. Tinnitus-inducing factors such as noise exposure and ototoxic drugs can cause neuroinflammatory reactions in the central nervous system, affecting neuronal excitability and synaptic plasticity in the auditory pathway and limbic system. Peripheral inner ear injury leads to the release of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6. These inflammatory mediators destroy the blood-brain barrier, allowing immune factors to enter the central auditory pathway, activating microglia and astrocytes, promoting neuronal overexcitation and synaptic remodeling, thereby consolidating tinnitus perception [11] [12]. The increase of TNF-α expression in the auditory cortex induced by noise is closely related to the activation of microglia. Blocking TNF-α signal can reduce tinnitus behavior and restore the balance of excitation and inhibition [13]. In addition, noise exposure activates neuroinflammation in the hippocampus through the TLR4/NF-κB/NLRP3 signaling pathway, affecting the function of the limbic system and exacerbating tinnitus symptoms [14]. Chronic neuroinflammation not only leads to abnormalities in the auditory pathway, but

also involves brain regions related to emotional regulation, such as the amygdala and hippocampus, promoting emotional comorbidity and cognitive impairment of tinnitus [15].

2. Core Cellular Components of Neuroinflammation

2.1. Bidirectional Regulation of Microglial Cells

Microglia exhibit a dual role in tinnitus via phenotypic polarization. M1-type microglia release TNF-α, IL-1β, and IL-6 to promote neuroinflammation, neuronal hyperactivity, and tinnitus. In contrast, M2-type microglia secrete anti-inflammatory and neurotrophic factors to suppress inflammation and facilitate neural repair. Shifting microglia from M1 to M2 represents a promising therapeutic approach.

Microglia are innate immune cells of the central nervous system with multifunctional roles, including maintaining tissue homeostasis, clearing pathogens and dead cells, and regulating neural networks. They are activated following neural injury and exhibit distinct phenotypes, primarily categorized into pro-inflammatory M1-type and anti-inflammatory reparative M2-type. M1-type microglia release pro-inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), exacerbating neural injury, whereas M2-type microglia secrete anti-inflammatory factors and neurotrophic factors to promote tissue repair and regeneration [16] [17]. Microglia clear damaged areas by phagocytosing dead cells and debris, thereby facilitating neural repair. However, their excessive activation may lead to chronic inflammation and further neurodegenerative damage [18]. In addition, microglia play a critical role in myelin maintenance and regeneration, which is essential for axonal health and function [19]. Studies have shown that regulating the activation state and phenotypic transition of microglia is a critical strategy for promoting repair and functional recovery after neural injury [20].

In animal models of acute tinnitus, microglia in the auditory cortex and medial geniculate body exhibited significant activation, characterized by increased numbers and morphological changes, suggesting their critical role in the central pathogenesis of tinnitus. Xia *et al*. [21] found that in sodium salicylate-induced tinnitus rats, microglia in the auditory cortex and medial geniculate body showed markedly upregulated expression of the marker Iba1, accompanied by a substantial increase in the pro-inflammatory factor IL-1β, indicating that microglial activation is closely associated with neuroinflammation related to tinnitus. Furthermore, Xia Qing's research demonstrated that ginkgolide B can inhibit the activation of microglia in the medial geniculate nucleus, thereby alleviating tinnitus symptoms induced by sodium salicylate in rats. This provides experimental evidence for treating tinnitus by modulating the activation state of microglia [22]. These findings support the critical role of microglia in the onset and progression of tinnitus, with regulation of their activation status potentially serving as a therapeutic target. In the central nervous system, microglia participate in neuropathological processes by releasing pro-inflammatory factors, and inhibiting their excessive activation may

help alleviate related symptoms. Microglia exhibit dual neuroinflammatory and neuroprotective effects during acute tinnitus development, which are closely associated with their M1/M2 phenotypes. Noise-induced hearing loss leads to activation of microglia in the primary auditory cortex (AI) and increased expression of pro-inflammatory cytokines (e.g., TNF-α), resulting in neuroinflammatory responses that are considered a key pathological mechanism of tinnitus. Gene knockout of TNF-α or pharmacological blockade of its expression can prevent neuroinflammation and improve tinnitus symptoms, whereas injection of TNF-α into the auditory cortex induces tinnitus in hearing-normal mice, demonstrating the central role of TNF-α in tinnitus pathogenesis [23]. Furthermore, pharmacological depletion of glial cells can also prevent tinnitus, further supporting that neuroinflammation and microglial activation serve as therapeutic targets. Nevertheless, the specific mechanisms by which microglia selectively transmit and regulate tinnitus signals in the central nervous system remain unclear, and the role of M2-type anti-inflammatory microglia in acute tinnitus requires further investigation [13]. Given that modulating microglial phenotypes and promoting M1-to-M2 transition have demonstrated therapeutic potential in neurodegenerative diseases such as Alzheimer's disease, similar strategies may be effective for acute tinnitus. Relevant drugs promote M2-type transformation by inhibiting signaling pathways such as NF-κB, thereby downregulating pro-inflammatory factor expression and alleviating tinnitus symptoms [24]. In summary, interventions targeting neuroinflammation and microglial activation, including anti-TNF-α therapy, inhibition of pro-inflammatory signaling pathways, and promotion of M2-type phenotypic transformation, represent current research priorities and potential therapeutic directions for tinnitus management.

2.2. Functional Integration Role of Astrocytes

Astrocytes are the most abundant glial cells in the central nervous system, and their roles in neuroinflammation and neural plasticity regulation have garnered significant attention in recent years. Perin and Pizzala (2024) conducted a systematic review of the potential functions of astrocytes in the neural mechanisms of tinnitus, highlighting that astrocytes not only participate in inflammatory responses but also rapidly modulate both local and global neuronal circuit functions [25].

Astrocytes integrate synaptic transmission regulation through a "triple synapse structure," sensing neurotransmitter release from neurons that triggers intracellular calcium level elevation, subsequently releasing glial neurotransmitters (e.g., ATP, glutamate, etc.) to counteract synaptic transmission and plasticity. This bidirectional signaling mechanism between glia and neurons positions astrocytes as critical regulators in neural networks, capable of both enhancing and inhibiting synaptic efficacy, thereby influencing the dynamic balance of neural circuits [26]-[28]. In the dorsal cochlear nucleus (DCN) associated with tinnitus, there exist specialized ependymoid-like astrocytes capable of sensing chemical signals in cer-

ebrospinal fluid. This may explain how systemic inflammation affects auditory pathway function and contributes to the initiation of tinnitus [25]. In addition, astrocytes influence the excitatory-inhibitory balance in the auditory system by regulating the clearance and release of neurotransmitters such as GABA and glutamate, which is of significant importance for the onset and maintenance of tinnitus [29]. Overall, astrocytes not only serve as "perceivers" of synaptic transmission but also participate in the regulation of tinnitus-related neural plasticity through complex signaling networks, making them a potential important therapeutic target [30]. Mutant mice with glial fibrillary acidic protein (GFAP) mutations exhibited more severe cochlear damage and elevated auditory brainstem response thresholds following noise exposure. Dysfunction of astrocytes in the putamen increases susceptibility of the auditory system to injury [31]. In the mouse model of Alexander's disease, mutant GFAP forms aggregates within GFAP-positive cells of the auditory nerve. Although this does not affect the basal hearing threshold, it exacerbates noise-induced outer hair cell damage, further supporting the association between astrocyte dysfunction and auditory impairment. Additionally, astrocytes are activated under oxidative stress and inflammatory conditions, releasing pro-inflammatory factors and regulating gap junction protein expression—changes that may worsen auditory system damage. In summary, abnormal astrocyte function not only impairs neuroprotection but may also increase auditory system sensitivity to harmful stimuli like noise by promoting inflammation and structural damage, making it a critical target for understanding and treating related hearing disorders [32].

2.3. Signaling Role of Oligodendrocytes

Oligodendrocytes are myelinating cells of the central nervous system that maintain myelin sheaths to ensure rapid and synchronous signal transmission in the auditory pathway.

Oligodendrocyte damage or dysfunction impairs myelin integrity, slows axonal conduction, and increases abnormal neural synchrony, thereby contributing to tinnitus. Although less studied in tinnitus, oligodendrocyte protection may help prevent or alleviate tinnitus by preserving auditory circuit function and stability. Pathological changes in oligodendrocytes or Schwann cells may accompany auditory nerve lesions, impairing signal input and inducing central compensatory changes. Therefore, oligodendrocytes represent a potential research direction for understanding tinnitus pathogenesis.

3. Molecular Signaling Pathways of Neuroinflammation

3.1. TLR4/NF-κB/NLRP3 Signal Axis

The TLR4/NF-κB/NLRP3 signaling axis plays a central role in tinnitus-related neuroinflammation. Noise or ototoxic insults activate TLR4, which promotes NF-κB nuclear translocation and upregulates NLRP3 inflammasome assembly. Activated NLRP3 cleaves caspase-1, which further matures and releases IL-1β, trigger-

ing robust neuroinflammation and tinnitus-related behaviors.

Toll-like receptor 4 (TLR4), as a key member of pattern recognition receptors, can recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), thereby initiating innate immune responses. Luo Lixia (2025) identified this through transcriptome sequencing analysis [16]. After noise exposure, 199 differentially expressed genes were identified in the hippocampal tissues of mice. Functional enrichment analysis revealed that these genes were primarily involved in responses to external stimuli and defensive reactions. Further mechanistic studies demonstrated significantly upregulated expression of TLR4, NF-κB, NLRP3, caspase-1, and IL-1β in the hippocampal tissues of noise-induced tinnitus mice, suggesting that the TLR4/NF-κB/NLRP3 signaling pathway participates in neuroinflammatory processes associated with tinnitus.

The NLRP3 inflammasome is a multiprotein complex whose activation can lead to caspase-1 activation and mature IL-1β release. Zhai Sijia (2020) [33] observed the activation of NLRP3-associated inflammasomes in rat cochlear spiral ganglion cells induced by sodium salicylate, further confirming the role of this signaling pathway in tinnitus-related structures. Schiel *et al*. (2024) [34] found in a study on hearing loss associated with chronic suppurative otitis media that the activation of NLRP3 inflammatory bodies in cochlear macrophages is a major driver of sensorineural hearing loss, and this mechanism may also apply to the pathological process of tinnitus.

3.2. Core Role of Pro-Inflammatory Cytokines

TNF-α is a key pro-inflammatory cytokine involved in neuroinflammation and plays a central role in the pathogenesis of tinnitus. Noise-induced hearing loss (NIHL) rapidly upregulates TNF-α expression in the auditory cortex, leading to microglial activation and elevated levels of pro-inflammatory cytokines such as IL-1β. These factors contribute to synaptic imbalance and tinnitus-related behaviors [11] [23]. Experimental injection of TNF-α combined with noise exposure resulted in microglial detachment, reduction of microalbumin-positive neurons, and impaired auditory processing tasks (such as gap detection and presynaptic inhibition), effects not observed with either TNF-α alone or noise alone. These findings indicate a synergistic interaction between neuroinflammation and peripheral auditory damage [35]. Genetic or pharmacological blockade of TNF-α can prevent neuroinflammation and alleviate tinnitus phenotypes in animal models, highlighting TNF-α as a promising therapeutic target [13]. Drugs that reduce TNF-α levels have been demonstrated in preclinical models to alleviate tinnitus symptoms and neural hyperactivity. However, clinical data indicate that systemic anti-TNF-α therapy has limited impact on tinnitus incidence in patients with autoimmune diseases, highlighting the complexity of translating these findings into human therapeutic applications.

TNF-α is a key mediator of neuroinflammation, which is associated with the pathogenesis of tinnitus. It has been demonstrated that blocking TNF-α can re-

duce salicylate-induced tinnitus-like behaviors in mice, supporting its role in modulating tinnitus symptoms [36]. Studies have shown that patients with tinnitus exhibit significantly lower levels of the anti-inflammatory cytokine IL-10 compared to those with only hearing loss, and genetic polymorphisms of TNF-α and other pro-inflammatory cytokines are associated with an increased risk of noise-induced tinnitus [11]. TNF-α-induced neuroinflammation promotes synaptic imbalance and microglial activation in the auditory cortex, which forms the basis for tinnitus development following noise exposure [23]. Although animal models have demonstrated that pharmacological or genetic inhibition of TNF-α can alleviate tinnitus phenotypes, clinical data indicate that systemic anti-TNF-α therapy does not significantly reduce the incidence of tinnitus in patients with autoimmune diseases, suggesting the complexity of translating these findings to human applications [37]. Overall, TNF-α represents a promising therapeutic target for tinnitus treatment by modulating neuroinflammatory pathways.

3.3. Interaction between Oxidative Stress and Inflammation

Oxidative stress and neuroinflammation form a positive feedback loop in tinnitus. Reactive oxygen species (ROS) promote glial activation and pro-inflammatory cytokine release, while inflammation further increases ROS production. This vicious cycle aggravates auditory pathway damage and sustains tinnitus.

A study by Yang *et al*. (2025) [38] found that Nrf2 (nuclear factor E2-related factor 2) deficiency enhances oxidative stress responses and increases susceptibility to tinnitus in mice. Nrf2 is a key transcription factor in the antioxidant response. Its functional deficiency leads to reduced antioxidant capacity, making the auditory system more susceptible to inflammatory damage.

Therapeutic strategies targeting neuroinflammation and oxidative stress have demonstrated potential in tinnitus management. Common triggers of tinnitus, such as noise exposure, lead to the generation of reactive oxygen species (ROS) within the cochlea, subsequently causing hair cell damage and death, and promoting neuroinflammatory responses [23] [38]. umPEALUT is a compound preparation combining palmitoyl ethanolamide (PEA) and luteolin. PEA exhibits neuroimmunomodulatory effects by regulating the activity of mast cells, macrophages, and microglia, while luteolin possesses antioxidant properties and improves microcirculation. The synergistic action of these two components can simultaneously intervene in inflammatory and oxidative stress pathways, thereby alleviating tinnitus. Additionally, clinical studies have demonstrated that medications containing anti-inflammatory and antioxidant components (e.g., oral melatonin combined with intracranial dexamethasone injection) show significant efficacy in reducing tinnitus severity [39]. Nrf2, as a key regulator of antioxidant responses, its deficiency exacerbates noise-induced tinnitus and associated neuroinflammation, suggesting that activation of the Nrf2 pathway may represent a novel strategy for tinnitus prevention and treatment. In summary, multi-target interventions targeting neuroinflammation and oxidative stress—including immunomodula-

tors, antioxidants, and neuromodulation techniques—offer promising therapeutic prospects for tinnitus patients.

4. Neuromediated Auditory Center Remodeling

4.1. Alteration of Synaptic Plasticity

Neuropathy can affect synaptic structure and function through multiple mechanisms. Wang *et al*. [23] demonstrated that noise-induced hearing loss leads to increased expression of pro-inflammatory cytokines and microglial activation in the primary auditory cortex. Gene knockout or pharmacological blockade of TNF-α can prevent neuroinflammation and improve tinnitus behavioral manifestations. At the synaptic level, micro-excitatory postsynaptic currents (mEPSCs) frequency increased while micro-inhibitory postsynaptic currents (mIPSCs) frequency decreased in auditory cortical pyramidal neurons following noise exposure. This excitatory-inhibitory imbalance was completely prevented by TNF-α blockade. The study provides direct evidence that neuroinflammation induces tinnitus through synaptic imbalance.

Astrocytes play a pivotal role in this process. They not only participate in the recycling of neurotransmitters such as glutamate and GABA but also directly modulate synaptic transmission efficiency by releasing glial neurotransmitters. Under pathological conditions, activated astrocytes may disrupt the excitatory-inhibitory balance, leading to abnormal gain in auditory centers [40].

4.2. Neural Network Reconstruction

Tinnitus involves not only alterations in auditory pathways but also functional remodeling of non-auditory brain regions such as the limbic system and default mode network. Chen Ganggang *et al*. [41] reviewed the mechanisms of auditory center remodeling in presbycusis, indicating that auditory deprivation can trigger neuroplasticity changes across brain regions. The hippocampus, as a key structure of the limbic system, plays a role in the persistence of tinnitus. Kraus *et al*. [42] demonstrated extensive neural connections and functional interactions between the auditory system and the limbic system, suggesting that neuroinflammation may participate in the emotional dimension and cognitive assessment of tinnitus by influencing these connections.

Zhang *et al*. [43] conducted an integrated analysis combining proteomics and phosphorylation proteomics, revealing that tinnitus models exhibited distinct characteristics compared to pure hearing loss models, including enhanced neuronal excitability, synaptic dysfunction, hyperactive energy metabolism, and diminished neuroprotective functions. Notably, multi-omics analysis demonstrated that tinnitus pathogenesis primarily relies on phosphorylation-mediated post-translational modifications to reshape cellular functions, rather than protein abundance alterations induced by gene transcriptional changes. This finding underscores the critical role of protein functional regulation in tinnitus mechanisms.

4.3. Relationship between Neuroinflammation and Chronicity of Tinnitus

Persistent neuroinflammation is a major driver of tinnitus chronicity. Acute inflammation resolves rapidly, but sustained glial activation leads to glial scar formation, aberrant synaptic pruning, and long-lasting neural network abnormalities. These changes convert temporary tinnitus into a chronic condition.

The transition from acute to chronic tinnitus represents a critical window for clinical treatment, yet its underlying mechanisms remain unclear. Preclinical studies suggest that persistent neuroinflammation may serve as a significant driving factor in the chronic progression of tinnitus. Shao *et al*. [44] observed time-dependent changes in functional and structural neuronal activity of the auditory system in an explosion-induced traumatic tinnitus model, which correlated with the dynamic progression of neuroinflammation.

The role of astrocytes in the chronic progression of tinnitus warrants particular attention. They are involved in glial scar formation, synaptic pruning, and neurovascular unit regulation, processes that may become aberrant under chronic neuroinflammatory conditions. Perin and Pizzala proposed [25], that astrocytes can encode "background information" for neuronal circuits, analogous to "expectations" in Bayesian brain models. Abnormality in this function may lead to the consolidation of erroneous auditory perception.

5. Clinical Intervention Strategies

5.1. Pharmacological Interventions Targeting Neuroinflammation

Based on the role of neuroinflammation in tinnitus, anti-inflammatory treatment strategies have garnered increasing attention. Roflumipram, as a novel phosphodiesterase 4 (PDE4) inhibitor, has demonstrated promising applications in neuroinflammation-related diseases. The study by Luo Lixia *et al*. confirmed that roflupram can alleviate neuroinflammation in the hippocampus of noise-induced tinnitus mice through the TLR4/NF-κB/NLRP3/caspase-1/IL-1β signaling pathway, thereby improving tinnitus behavioral manifestations.

Palmitoyl ethanolamide (PEA), as an endogenous lipid mediator, exerts anti-inflammatory effects by modulating the activity of mast cells, macrophages, and microglia. A registered clinical trial (NCT06718452) is evaluating the therapeutic efficacy of umPEALUT (ultramicro-pulverized PEA combined with luteolin) in treating tinnitus, hypothesizing that reduced neuroinflammation and oxidative stress may alleviate abnormal activity in peripheral and central auditory pathways.

Traditional Chinese Medicine (TCM) has also demonstrated potential in regulating neuroinflammation. A study by Jia Zhijiao *et al*. [45] demonstrated that Xiaoyao Cong'er Decoction could modulate inflammatory factors and neurotransmitter levels in rats with tinnitus of liver depression and spleen deficiency type, providing novel insights for integrated traditional Chinese and Western medicine treatment of tinnitus.

5.2. Non-Pharmacological Mechanisms of Inflammation Regulation

Acupuncture, as one of the alternative therapies for tinnitus, may exert its therapeutic effects through modulation of neuroinflammation. Hu *et al*. [46] reviewed the current status and prospects of acupuncture treatment for tinnitus-insomnia comorbidity, proposing that acupuncture may improve symptoms by bidirectionally modulating pathophysiological processes and integrating therapeutic effects. Animal studies suggest that acupuncture can inhibit microglial activation and reduce pro-inflammatory factor expression, which may be one of its mechanisms for treating tinnitus.

6. Summary

Neuroinflammation plays a central role in the onset, progression, and maintenance of tinnitus through the activation of microglia and astrocytes, release of pro-inflammatory factors, and cascading effects of multiple signaling pathways. Neuroinflammation not only directly impacts synaptic plasticity and neuronal excitability but also contributes to the chronic progression of tinnitus by remodeling neural networks in auditory pathways and non-auditory brain regions. Targeted pharmacological and non-pharmacological interventions for neuroinflammation demonstrate promising clinical applications, yet further high-quality preclinical and clinical studies are required to validate their efficacy and safety.

Projects

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Conflicts of Interest

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

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