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Research Progress of Tinnitus and Neuroinflammation

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Abstract

Tinnitus is a subjective auditory perception produced in the absence of external sound source or electric stimulation. Its occurrence mechanism involves multiple factors, such as auditory pathway abnormalities, central nervous system remodeling and neuroinflammatory response. Recent studies have shown that neuroinflammation plays a key role in the development and chronicity of tinnitus. Factors such as noise exposure and ototoxic drugs can activate microglial cells in the central nervous system, and animal model studies have confirmed that targeting microglial cell polarization and anti-inflammatory drugs can effectively improve tinnitus symptoms. Nanodelivery system and combined target intervention strategy solve the challenges of poor BBB penetration and low drug delivery efficiency for precision treatment. This paper systematically reviews the association mechanism of neuroinflammation and tinnitus and the research progress of targeted therapy, which provides a theoretical basis for the clinical diagnosis and treatment of tinnitus.

Keywords

Tinnitus, Neuroinflammation, Microglia, Animal Models, Nanodelivery Systems

1. Introduction

Tinnitus is a kind of subjective auditory perception without external sound source, which is manifested as ringing in the ear or in the skull, electric current sound or other types of sounds [1]. As a common symptom of the auditory system, tinnitus is not an independent disease, but a manifestation of a variety of pathophysiological processes, abnormal auditory pathways, central nervous system remodeling and neuroinflammation are involved [2]-[5]. The incidence of tinnitus is high, and epidemiological data show that about 10% - 15% of the global population is affected by tinnitus, with 1% - 2% of patients suffering from symptoms that seriously affect the quality of life, even leading to anxiety, depression and other psychological problems [6]-[8]. The risk factors of tinnitus are various, including noise exposure, ear diseases, systemic diseases and drug use. Long-term exposure to high-intensity noise is one of the main causes of tinnitus. Occupational and recreational noise exposure may increase the risk of tinnitus.

As the innate immune cells of the central nervous system, microglia play a central role in the regulation of neuroinflammation. By sensing microenvironmental changes, releasing inflammatory mediators and reshaping the neural network, microglia participate in the initiation, amplification and regression of neuroinflammation, which directly affects the pathological process of tinnitus [9] [10]. Activation of classical inflammatory signaling pathways (TLR4/MyD88/NF-κB) can promote the release of proinflammatory factors such as TNF-α, IL-1β and other proinflammatory factors from microglia, and induce neuronal oxidative stress and synaptic plasticity changes. In addition, the blood-brain barrier (BBB) disruption leads to the infiltration of peripheral immune cells, which further amplifies the central inflammatory response [11] [12]. Animal model studies (e.g. noise exposure, salicylate induction) confirm that the dynamic balance of microglial polarization status (proinflammatory M1 versus anti-inflammatory M2) is critical for the development of tinnitus. M1 microglia release pro-inflammatory factors, increasing neuronal damage; M2 cells secrete anti-inflammatory factors to promote tissue repair [13]-[15]. At 24 hours after noise exposure, the microglial marker Iba-1 in the region of the cochlear nucleus increased significantly, accompanied by decreased neuronal dendritic spine branching, suggesting that neuroinflammation may influence auditory signal processing through synaptic remodeling [16]. In addition, the NLRP3 inflammasome activates caspase-1 through reactive oxygen species (ROS) or K^+ efflux, promoting IL-18 maturation, and exacerbating the excitability imbalance of neurons in the auditory cortex [17]. Clinical studies further support the association of neuroinflammation with tinnitus, with IL-1β levels in the CSF of chronic tinnitus patients being significantly increased compared with healthy controls [18].

Targeting neuroinflammation provides a new strategy for tinnitus treatment. Anti-inflammatory drugs (minocycline and N-acetylcysteine) inhibit microglial activation [19]-[22]; new technologies such as nanodelivery systems and optogenetics provide new ideas for precision intervention [23] [24]. However, neuroinflammatory regulation needs to weigh the intensity of intervention, and excessive inhibition may weaken the pathogen clearance capacity, while insufficient inhibition fails to block the inflammatory spread. Future studies should combine single-cell sequencing technology to resolve microglial subset heterogeneity, develop spatio-temporal specific intervention strategies, and explore new directions such as immunometabolic regulation.

Neuroinflammation drives the onset and chronicity of tinnitus through microglia activation, inflammatory cytokine release, and neural network remodeling. In-depth study of the molecular mechanism of neuroinflammation and its role in tinnitus will provide new ideas and targets for the diagnosis and treatment of tinnitus. Future research needs to focus on the time window and spatial specificity of precise regulation of specific inflammatory pathways, and develop hierarchical treatment strategies combined with multi-omics technologies to provide new directions for breaking through the bottleneck of tinnitus treatment.

2. Association of the Occurrence Mechanism of Tinnitus with Neuroinflammation

The pathophysiological mechanism of tinnitus is complex, involving multidimensional interactions such as peripheral auditory system injury, central nervous system remodeling and neuroinflammation [23].

2.1. Abnormalities of the Peripheral Auditory System

Cochlear injury is a common initiating factor in tinnitus. Hair cell damage caused by noise exposure, ototoxic drugs or aging, and disruption of stereocilia structure can lead to signal abnormalities in the afferent auditory nerve [24]. Internal potential in the cochlea and increased excitability of spiral ganglion cells trigger spontaneous electrical activity and up-regulation of central compensatory gain. Recent studies have found that cochlear synaptic lesions (ribbon synapse loss) may predate hair cell damage and are the core mechanism of occult hearing loss. With the continuous strengthening of noise intensity and the continuous extension of time, the number of zonal process damage is increasing. When the number of damage is greater than 50%, hearing appears irreversible damage [25]-[27]. Further reduced auditory afferents triggering central compensatory hyperactivity [28].

2.2. Central Nervous System Remodeling

Central nervous system remodeling refers to the adaptive structural, functional and molecular changes in the central auditory pathway and non-auditory brain regions in the case of injury or abnormal function of the peripheral auditory system. These changes drive the occurrence and chronicity of tinnitus by affecting neuronal excitability, synaptic plasticity, and neural network synchronization. After decreased peripheral afferents, such as the cochlear nucleus and the upper olive complex, the neuronal spontaneous activity increases and the frequency tuning range expands. Primary auditory cortex (A1) neurons showed excessive synchronous firing in tinnitus, showing enhanced blood oxygen level-dependent signal (BOLD), and functional MRI showed that the BOLD signal in area A1 of tinnitus patients was significantly increased compared with normal controls [29]. In the tinnitus state, overactivation of the glutamatergic system combined with reduced GABA inhibitory function leads to an imbalance of excitability of the central auditory system [30].

2.3. Central Role of Neuroinflammation

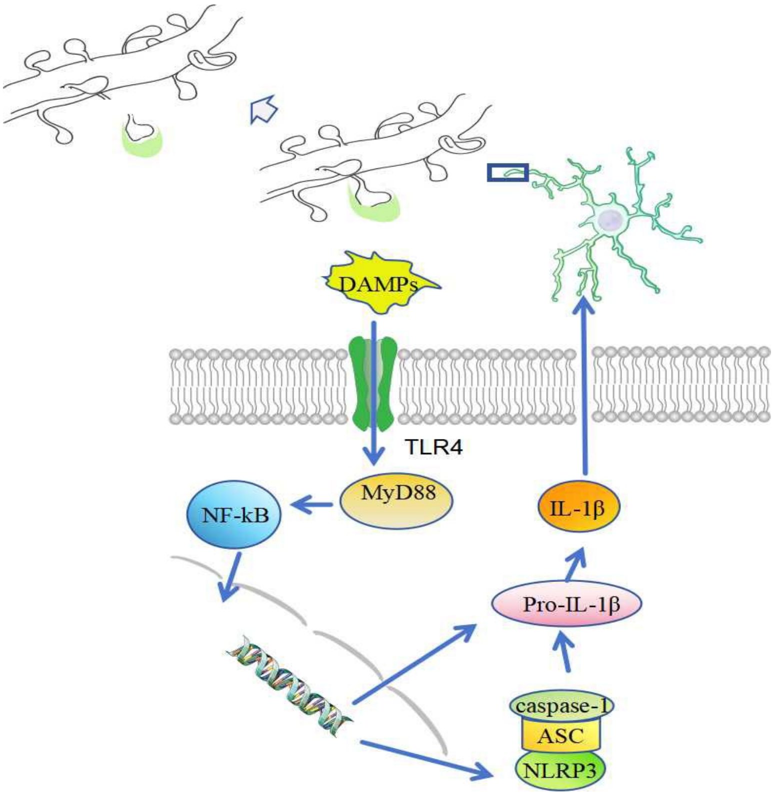
Microglia are the innate immune cells of the central nervous system and play a core regulatory role in neuroinflammation. By sensing microenvironment changes, releasing inflammatory mediators and reshaping the neural network, microglia participate in the initiation, amplification and resolution of neuroinflammation, affecting the occurrence and development of neurological diseases. Under physiological conditions, microglia appear in a resting state and play the role of "immune surveillance". In the pathological state, the microglia show an activated state, and the classical activated type (M1 polarized) microglia release pro-inflammatory factors and toxic substances to kill the pathogens. However, non-classical activated (M2 polarized) microglia can achieve neuroprotective effects by promoting tissue repair and regeneration [31] [32]. On the surface, hyperactivated M1 microglia causes neuronal disability, injury and degeneration, and plays an important role in cerebrovascular diseases, neurodegenerative diseases, neurodevelopmental disorders and neurological diseases [33]-[35].

Microglia trigger an inflammatory response by sensing pathogen-associated molecular patterns (PAMPs) or damage-related molecular patterns (DAMPs) through pattern recognition receptors (TLR4, NLRP3). TLR4 recognizes endogenous danger signals (HMGB1), activates the MyD88-dependent NF-κB pathway, and induces release of proinflammatory factors such as TNF-α and IL-1β *[36]*, as shown in **Figure 1**. NLRP3 inflammasome accumulates through ROS or calcium ions, activates caspase-1 and promotes IL-1β, IL-18 mature [37]. The microglial cell polarization changes dynamically: the M1 phenotype releases pro-inflammatory factors and exacerbates neuronal damage, and the M2 phenotype secretes anti-inflammatory factors to promote tissue repair. Noise exposure or ototoxic drugs by activating microglia, microglial activation, induction of TNF-α, IL-1β proinflammatory factors release, produce a series of cascade reactions, ROS increase, cause neuronal apoptosis, neurodegenerative changes, and excessive synaptic pruning can promote central gain increase, play a role in the development of tinnitus [38] [39].

3. Neuroinflammation in Different Animal Models of Tinnitus

3.1. Noise Tinnitus of the Animal Model and Neuroinflammation

With the increasing level of social industrialization and urbanization, automobile, entertainment and occupational noise can cause tinnitus. White noise is the closest to the above noise, so white noise exposure can be used to induce tinnitus in mice. Repeated exposure to 85 dB or above noise can cause permanent hearing loss [40], so the initial study of low or moderate intensity low dose noise exposure to cause high-frequency hearing loss in mice, in order to study the mechanism and treatment of patients with hearing loss with tinnitus. With the increasing attention to tinnitus, tinnitus without hearing loss is gradually pursued in animal model construction. Through continuous improvement of the model, it was found that after a short period of low and moderate-intensity noise exposure, mice only



Note: After TLR 4 recognizes the damage-associated molecular pattern DAMPs, after the recruitment of MyD 88, stimulation of NF-κB phosphorylation, phosphorylation of NF-κB into the nucleus, on the one hand, to promote IL-1β precursor cleavage, the IL-1β release; on the other hand, promoting NLRP 3 activation, NLRP 3 recruits both ASC and capsase-1, formation of the inflammasome, further promotion of IL-1β release; after the GSDMD was punched in the cell membrane, IL-1β can enter the cytoplasm, activation of the surrounding microglia, after microglial cell activation, can trim the synapses in the neurons, can also trim the synapses of the surrounding microglia, play a role of neural remodeling.

Figure 1. Schematic of the classical inflammatory pathways of neuroinflammation.

showed temporary hearing threshold shift, and mice still had tinnitus [41]-[44] after hearing recovery. Mice temporary hearing threshold shift is called occult hearing loss, when the researchers through the basement membrane patch staining found no hair cells, and through research for the inner hair cells and spiral nerve fibers, with the noise intensity and increasing time, the number of zonal damage increasing, the last hearing appears irreversible damage [27].

Noise-induced tinnitus is an auditory system dysfunction caused by long-term exposure to a high-intensity noise environment, and neuroinflammation plays a central role in its occurrence and chronicity. Noise exposure, by activating microglia and releasing pro-inflammatory factors such as TNF-α and IL-1β, showed elevated microglia Iba-1 expression in the cochlear nucleus, accompanied by neuronal dendritic spine density decreased [45]. The NLRP3 inflammasome activates caspase-1 through ROS or K^+ efflux, promotes IL-18 maturation, and aggravates the neuronal excitability imbalance in the auditory cortex. Noise exposure induces oxidative stress (ROS) and the release of inflammatory factors, disrupting the blood-brain barrier (BBB) tight junctions. BBB permeability increases, and BBB destruction causes infiltration of peripheral immune cells and release of proinflammatory factors such as IL-1β and IL-18, which further activate microglia and aggravate neuronal damage [46]. After noise exposure, auditory pathway neurons enhanced synchronous firing and form central gain (central gain) upregulation. Functional MRI showed an increased blood oxygen level-dependent signal (BOLD) in the primary auditory cortex, accompanied by increased TNF-α and IL-1β levels in [47]. However, it is found that tinnitus caused by noise exposure has low film formation rate, and it is still questionable whether tinnitus can fill the gap in GPIAS inhibition rate detection.

3.2. Ototoxicity Induces Tinnitus in the Animal Model and Neuroinflammation

Aminoglycosides have ototoxicity. In some studies, after amikacin was used to induce tinnitus in mice, mice had tinnitus, but permanent hearing loss [48], which does not accord with the disease situation of most clinical patients. After switching to tobramycin-induced tinnitus in mice, mice only showed temporary hearing threshold shift, not permanent loss, but mice can develop auditory allergy [49]. Salicylic acid is the most common ototoxic drug, which has a quick onset time, simple operation, few side effects and is the first or only symptom of acute tinnitus. Salicylic acid-induced tinnitus mice can develop tinnitus, and clinically, fewer patients have tinnitus after the use of salicylic acid, which fails to reflect the occurrence of clinical tinnitus. Salicylic acid-induced tinnitus is consistent with high-frequency pure tone [50]. Large doses of salicylate caused permanent loss of spiral ganglion neurons and nerve fibers without damaging hair cells, while in a mouse model of small doses of salicylate, hair cells are not affected [51] [52]. In the study of Zuo *et al.*, we found that chronic injection increased GABARAP expression in the auditory cortex, which indirectly affected increased GABAA receptors on the cell membrane surface, thus controlling the efficacy of GABA-ergic synaptic transmission to increase [53].

Salicylic acid easily passes through the blood-brain barrier and acts on the central center, regulating serotonin and γ-amino-butyric acid (GABA) to induce tinnitus [54] [55]. Salicylic acid provides an important platform for mechanism research and therapeutic exploration by activating microglia, releasing inflammatory factors and reshaping the neural network. Salicylic acid affects nerve remodeling and growth by activating microglia, releasing pro-inflammatory factors such as TNF-α and IL-1β [56], increased central excitatory neurotransmitters, increased calcium ion channel permeability, and massive calcium ion influx. The NLRP3 inflammasome activates caspase-1 through ROS, promotes IL-18 maturation, and aggravates the imbalance of neuronal excitability in the auditory cortex. Salicylic acid induces oxidative stress and the release of inflammatory factors, disrupting the blood-brain barrier (BBB) tight junctions. Salicylate-induced spontaneous firing abnormalities in the tinnitus auditory cortex also further confirmed that the central spontaneous discharge abnormalities in tinnitus mice are involved in the tinnitus [57].

4. Targeted Neuroinflammatory Therapy

4.1. PDE4 Inhibitors

PDE4 inhibitors, as microglial inhibitors, inhibit NF-*κ*B and MAPK signaling, and reduce pro-inflammatory factors (IL-1*β* and TNF-*α*) expression by increasing cAMP levels. Current PDE4 inhibitors include: Rolipram, Roflumilast, FCPR03, as shown in **Figure 2**. It is the first generation of PDE4 inhibitor, which cannot enter the clinic because of its gastrointestinal reactions such as nausea and vomiting, but can activate the neurons in the posterior area with cAMP to stimulate the vagus nerve, resulting in nausea and vomiting; the second-generation rofulast is improved, and its gastrointestinal response is significantly reduced. FCPR03, FCPR06 and others are further improvements to the second generation, and the study of contrast dogs found that the use of PDE4 inhibitors did not reduce the anesthesia time of methylazide/ketamine, and maintained the observation time for 3 h [58]. Inflammatory factor-specific inhibitors also play a role in the improvement of tinnitus, but together with PDE4 inhibitors, the disadvantage of drug concentration cannot be maintained after entering the BBB, and remarkable progress in the application of nanodelivery systems in inflammation-related diseases. Nanodelivery system is a nanotechnology-based drug delivery platform, that realizes targeted delivery, controlled release and efficiency enhancement by encapsulating drugs in nanocarriers (liposomes, polymer nanoparticles and exosomes). Nano delivery system has certain advantages. After use, it can accurately deliver to inflammatory sites through acid-base sensitivity or ROS sensitivity, improve the blood concentration of local drugs, increase the maintenance time, and reduce side reactions. In infectious diseases, nanodelivery systems increase the concentration of drugs at the infection site and enhance the antibacterial effect through targeted delivery of antibiotics. In neurodegenerative diseases, the nanodelivery system delivers anti-inflammatory drugs by crossing the blood-brain barrier (BBB) and delivering anti-inflammatory drugs to the central nervous system, inhibiting microglial activation and reducing neuroinflammation [59] [60]. Optogenetics also plays a role in the treatment of inflammation. Optogenetics is a technique that combines optics and genetics to genetically express light-sensitive proteins in specific cells, using light signals for precise regulation of cellular activities. With the spatial and temporal of non-invasive regulation

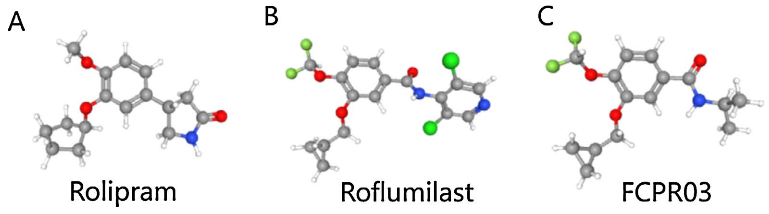


Figure 2. PDE4 inhibitors.

and targeting of precision cell types and cell activities [61].

4.2. Neuroinflammatory Factor Inhibitors

Recently, therapeutic strategies targeting the inhibition of inflammatory factors have made remarkable progress in the field of neurodegenerative diseases. TNF-α inhibitors (Adalimumab and Etanercept) are effective in reducing neuroinflammation by neutralizing TNF-α, and animal experiments have shown them to improve cognitive function in Alzheimer's disease (AD) mice [62]-[66]. IL-1β antagonists (anakinra) exert anti-inflammatory effects by blocking IL-1 signaling and are shown to delay progression in patients with mild cognitive impairment [67] [68]. Stuuximab targeting the IL-6 signaling pathway suppresses the neuroinflammatory response by targeting the IL-6 receptor. Compared with conventional anti-inflammatory drugs (Siltuximab), these targeted therapies have higher specificity and can significantly reduce systemic side effects [69] [70].

The current study faces three key challenges: the blood-brain barrier (BBB) penetration limits the central delivery efficiency of antibody drugs; long-term immunosuppression may increase the risk of infection and tumor development; individual patients lead to variable treatment responses, and precise biomarkers are needed to guide clinical use. The latest study improves the brain distribution of drugs through nanocarrier delivery systems (such as liposomes and exosomes), and also adopts multi-target combination strategies to enhance the therapeutic effect. Future studies should focus on optimizing delivery techniques, improving safety assessment, and establishing individualized treatment options to drive the clinical translation of targeted therapy for neuroinflammation.

5. Summary and Outlook

Neuroinflammation plays a central role in the development and chronicity of tinnitus and involves multiple mechanisms such as microglial cell activation, inflammatory factor release, and neural network remodeling. Microglia release proinflammatory factors such as TNF-α and IL-1β through pathways such as TLR4/MyD88/NF-κB and NLRP3 inflammasome, and induce neuronal oxidative stress and synaptic plasticity changes. Disruption of the blood-brain barrier (BBB) leads to the infiltration of peripheral immune cells, which further amplifies the central inflammatory response. The role of neuroinflammation in tinnitus is gradually recognized, and more and more studies tend to use microglial inhibitors to reverse microglial M1 polarization or use anti-inflammatory and antioxidant drugs to treat tinnitus. After drug intervention, tinnitus has been improved to varying degrees.

The detection of neuroinflammation is difficult to some extent. IL-1β and TNF-α are secreted proteins that can be detected in cerebrospinal fluid or serum. In animal experiments, IL-1β and TNF-α are correlated with the severity of tinnitus, and clinically detectable serum concentrations of IL-1β and TNF-α in serum, but the degree of low specificity and measurement in CSF involves invasive operation and low coordination in patients. Testing the activation degree of microglia by neuroimaging can also reflect the activation of neuroinflammation to some extent, but it is impossible because it is expensive. In the future, more specific and sensitive peripheral inflammation markers can be found, or non-invasive detection techniques can be developed to improve the feasibility of clinical evaluation of neuroinflammation.

In the animal model of tinnitus, most male animals are used as the research object. In the clinical situation, the human body in tinnitus mechanism research is less, and the sample size and ethical review have certain requirements, unable to complete study the mechanism of tinnitus, in the future can complete full animal experiment verification, should actively carry out pre-clinical and clinical trials, evaluate the safety and effectiveness of anti-inflammatory treatment in tinnitus patients.

Nanocarriers (such as liposomes and polymer nanoparticles) and exosomes can penetrate the blood-brain barrier (BBB) to enhance the enrichment of drugs in tinnitus-related brain areas (auditory cortex, cochlear nucleus). Studies have found that intranasal administration or focused ultrasound-assisted delivery avoids systemic circulation and reduces the risk of immunosuppression of anti-inflammatory drugs (TNF-α inhibitors). The wrapping of drugs with degradable materials can achieve continuous release and prolong the therapeutic window. However, there are some defects in the stability and drug-loading efficiency of nanocarriers, and some combined materials can also cause the accumulation of immune organs. In the future, joint intervention of multiple targets can be used to block the cascade of microglial activation, inflammatory factors and oxidative stress, so as to avoid the phenomenon of single target escape.

The mechanism of tinnitus is complex, and neuroinflammation plays a role in the occurrence and development of tinnitus. Anti-inflammatory, antioxidant and other drugs were found to improve tinnitus in animal experiments. However, the intake and maintenance of drugs hinder the research to some extent. With the continuous development of pharmacology, new drug delivery methods are gradually developed. Multicombination, looking for peripheral specific markers, further validates the effects of different administration methods on neuroinflammation and tinnitus in animal experiments, contributes to the later clinical experiments, and provides the next treatment direction for the treatment of tinnitus.

Conflicts of Interest

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

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