Current Otorhinolaryngology Reports (2022) 10:322–328
https://doi.org/10.1007/s40136-022-00411-8

OTOLOGY: ADVANCES IN OTOLOGY (BD NICHOLAS, SECTION EDITOR)

Neuroinflammation in Tinnitus

Katherine Adcock[1,2] · **Sven Vanneste**[1,2]

Accepted: 21 June 2022 / Published online: 5 July 2022

Abstract

Purpose of Review The current review aims to explore recent studies that have illustrated a link between neuroinflammation and tinnitus and the consequential effect on neuronal functioning. We explore parallels amongst pain and tinnitus pathologies and a novel treatment option.

Recent Findings Genetic and pharmacological blockage of pro-inflammatory cytokines mitigates the physiological and behavioral tinnitus phenotype in acute rodent models. In addition, recent pain studies target a signaling pathway to prevent the transition from acute to chronic neuropathic pain, which could translate to tinnitus.

Summary Neuroinflammation likely mediates hyperexcitability of the auditory pathway, driving the development of acute tinnitus. In chronic tinnitus, we believe translational regulation plays a role in maintaining persistent tinnitus signaling. We therefore propose this pathway as a potential therapeutic strategy.

Keywords Neuroinflammation · Chronic tinnitus · Hearing loss · Pro-inflammatory cytokines

Introduction

Tinnitus, or "ringing in the ears," is an auditory percept that occurs in the absence of an external sound source and affects millions of individuals worldwide. Delineating the tinnitus mechanism would aid in the development of treatments to attenuate the tinnitus percept and improve quality of life. Many researchers posit an imbalance between excitatory and inhibitory input leads to maladaptive changes to the auditory system, which consequently leads to the chronic tinnitus percept [1–3]. However, what mechanism prompts and maintains the synaptic imbalance remains to be elucidated.

Emerging evidence suggests that neuroinflammation may play a large role in the development of tinnitus. Neuroinflammation is the central nervous system's response to potentially harmful stimuli such as injury, infection, disease, or abnormal neural activity [4, 5]. Studies demonstrate that hearing loss or noise exposure causes chronic neuroinflammation in the peripheral and central auditory pathway [6–9]. Furthermore, recent studies are exploring the implications of neuroinflammation in tinnitus. Researchers postulate that noise trauma or hearing loss-related disorders trigger a neuroinflammatory response in which pro-inflammatory cytokines influence synaptic transmission that results in an excitation–inhibition imbalance [4, 10••, 11•, 12]. It is this excitation–inhibition imbalance that is speculated to be the mechanism of tinnitus. However, the exact role of neuroinflammation on neuronal function and its impact on tinnitus remains to be elucidated. Below, we examine animal studies that have highlighted the potential role of inflammation in tinnitus, and its ramifications in neuronal function. We briefly explore the similarities of neuroinflammation's role in tinnitus and pain and possible treatment options.

The Neuroinflammatory Response

Recent studies have featured inflammatory processes as a major contributor in tinnitus [10••, 13–15]. Preclinical findings corroborate profound changes in neuroinflammation markers in animals with experimentally induced tinnitus, using methods such as noise exposure or administration of salicylate acid to induce tinnitus-like

This article is part of Topical Collection on *OTOLOGY: Advances in Otology*

✉ Sven Vanneste
sven.vanneste@tcd.ie

[1] Global Brain Health Institute & Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland

[2] Lab for Clinical & Integrative Neuroscience, School of Psychology, Trinity Institute for Neuroscience, Trinity College Dublin, Dublin, Ireland

behaviors. Gap detection impairment is a common phenotypic marker for tinnitus animal models, in which animals are unable to detect gaps embedded in a continuous stream of noise [16]. Impairments are attributed to the perception of the tinnitus sound, therefore unable to detect gaps, or the absence of sound.

Altogether, studies have reported abnormalities in TNF-α [10••, 17–20], IFNγ [17], Iba-1 [21, 22], GFAP [21, 22], IL-1β [10••, 19, 20, 22], and microglia [22] in animals with tinnitus. The observed inflammatory response has been linked to the tinnitus behavioral phenotype in rodents, in which impairments in gap detection performance are dependent on TNF-α levels. This was illustrated in a recent study, in which genetic knockout of TNF-α in mice prevented noise-induced impairments in gap detection performance compared to wild-type controls [10••]. In a separate experiment, TNF-α was infused to the primary auditory cortex of normal-hearing wild-type controls and TNF-α knockout mice resulting in impaired gap detection in both TNF-α knockout and wild-type control mice, thus confirming that the previous absence of noise-induced tinnitus behaviors in knockout mice was due to the lack of TNF-α [10••]. Additionally, the administration of TNF-α blockers alleviated tinnitus behaviors in mouse models [10••, 14, 15]. These studies provide initial evidence that TNF-α, amongst other pro-inflammatory cytokines, mediates the tinnitus phenotype.

Pro-inflammatory cytokines and microglial activation, two defining features of neuroinflammation, appear to depend on each other in noise-induced neuroinflammatory responses. Pharmacological depletion of microglia before noise exposure prevented noise-induced increases of TNF-α expression and noise-induced tinnitus behaviors [10••]. Conversely, both genetic knockout and pharmacological blockage of increased TNF-α after noise exposure prevented noise-induced tinnitus behaviors and microglial activation [10••]. These suggest that microglia activation requires an increase in TNF-α expression and that microglial activation contributes to noise-induced increased TNF-α expression. It is likely that noise-induced hearing loss or other hearing loss-related disorders creates a positive feedback loop of neuroinflammatory response, consistent with existing literature showing that activated microglia release pro-inflammatory cytokines and that pro-inflammatory cytokines increasingly activate microglia [23–25]. Additionally, other pro-inflammatory cytokines such as IL-1β are also increased in experimentally induced tinnitus [19] and known to stimulate microglia and the expression of inflammatory mediators, including triggering more release of its own expression [26]. This noise-induced neuroinflammatory response likely contributes to the excitatory–inhibitory synaptic imbalance associated with tinnitus.

Neuroinflammation	Neuroinflammation is an inflammatory response within the central or peripheral nervous system to potentially harmful stimuli such as toxins, injury, infection, disease, or abnormal neural activity
Microglia	Microglial cells function as immune cells responsible for maintaining central nervous system health through removing damaged neurons and infections. When activated, microglia release various neurotrophic factors and cytokines
Cytokines	Cytokines are small proteins released by cells that influence cell signaling. Cytokines can be pro-inflammatory cytokines or anti-inflammatory and include chemokines, interferons, interleukins (IL), lymphokines, and tumor necrosis factors (TNF)
Pro-inflammatory cytokines	Pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, and IL-12 are secreted when exposed to inflammatory stimuli. These pro-inflammatory mediators are involved in the recruitment of inflammatory cells and can produce systemic inflammatory effects. Pro-inflammatory cytokines are also involved in many cellular activities, including cell proliferation, signaling, differentiation, and apoptosis
Anti-inflammatory cytokines	Anti-inflammatory cytokines such as IL-4, IL-6, IL-10, and IL-11 act to limit the immune response and suppress macrophage activation and the production of TNF-α, IL-1β, IL-6, IL-8, and IL-12

Pathophysiology

Pro-inflammatory cytokines such as TNF-α reportedly affect excitatory and inhibitory synaptic function [27–29]. Studies have shown that the neuroinflammatory response to acoustic trauma drives a synaptic imbalance, demonstrated by increased excitatory and decreased inhibitory transmission in the auditory pathway [10••, 30]. The synaptic imbalance likely plays a factor in the physiological mechanism of the perceptual pathology of tinnitus.

Animal studies using genetic and pharmacological manipulation of TNF-α provide evidence that neuroinflammation affects neuronal functioning in hearing loss and tinnitus. A study blocking TNF-α expression prevented the synaptic abnormalities observed after

noise-induced hearing loss (NIHL), indicating that TNF-α expression is necessary for NIHL-induced synaptic imbalance [10••]. In addition to cortical aberrations, NIHL and salicylate administration elevates auditory brainstem response thresholds, a physiological signature of hearing loss [10••, 14]. While both control and TNF-α knockout mice develop hearing loss, accompanied by similar ABR thresholds, only controls develop tinnitus, indicating that TNF-α is required for tinnitus [10••]. Altogether, manipulation and blockage of neuroinflammatory markers provide support that pro-inflammatory cytokines are required for both behavioral and electrophysiological evidence of tinnitus.

While the exact mechanism is unknown, studies show that pro-inflammatory cytokines regulate receptor activity, thereby influencing excitatory and inhibitory neurotransmission [11•, 31–33]. For example, TNF-α can affect neuronal function by increasing NMDA receptor localization and decreasing GABA-A surface localization through endocytosis at postsynaptic densities [11•, 27, 28]. Moreover, increased NMDA receptor activity and decreased GABA-A receptor activity results in increased calcium influx and decreased chloride influx, respectively, influencing the excitatory–inhibitory balance [11•]. These changes in receptor expression and/or localization can lead to maladaptive changes, resulting in the amplification of afferent input to the central nervous system [11•, 31–33].

Consistent with cytokine-induced changes in excitatory and inhibitory neurotransmission, changes in cytokine expression and receptor activity are observed in animals with experimentally induced tinnitus [17, 18, 20, 30, 34–36]. Studies show an increase in NMDA receptor expression in animals with salicylate-induced tinnitus, concomitant with increases in TNF-α and IL-1B expression [17, 18, 20, 30]. Furthermore, administration of a non-competitive NMDA receptor antagonist decreases NMDA receptor expression, resulting in attenuated tinnitus behaviors in mice and decreased expression of TNF-α [30]. Additionally, experimentally induced tinnitus suppresses GABA-A-induced currents, which may contribute to increased excitability within the auditory pathway [34, 35]. Elevation of central GABA levels, through administration of a GABA agonist, attenuates tinnitus behaviors after noise exposure in rats [36]. Therefore, it's possible the pro-inflammatory cytokine-induced neuroinflammatory response mediates the excitatory–inhibitory imbalance in tinnitus through changes in receptor expression.

Altogether, the highlighted research provides the initial groundwork to support a new outlook in which neuroinflammation drives the development of tinnitus. In this scope, experimentally induced tinnitus via NIHL or salicylate produces inflammation in the auditory pathway. Microglia are then activated and release pro-inflammatory cytokines. These cytokines further activate microglia, creating a positive feedback loop. Enhanced levels of pro-inflammatory cytokines regulate receptor surface localization in which increased NMDA surface localization leads to increased calcium influx, and GABA-A endocytosis leads to decreased chloride influx and reduces inhibitory efficacy. These changes in NMDA and GABA-A activity lead to increased excitatory and decreased inhibitory synaptic activity in the auditory pathway, leading to neural plastic changes causing the tinnitus percept.

Translatability to Humans

Treatments targeting inflammation such as corticosteroids have become the standard treatment for forms of hearing loss and inner ear disorders [37]. However, the chance of recovery from hearing loss can be dependent on a number of factors including the severity of hearing loss, the presence of additional symptoms (such as tinnitus or dizziness), and the time of treatment [38]. Anti-inflammation interventions may also provide relief in individuals with tinnitus; however, this is inconclusive [39–41]. Shim et al. reported the onset time of treatment as the most important and sole factor correlating with the cure rate for acute subjective idiopathic tinnitus, as observed by a reduction in tinnitus awareness score to 0% [42].

Several conditions that are known to be associated with neuroinflammation can increase the risk of tinnitus, further supporting a potential role of neuroinflammation in the development of tinnitus [4]. However, despite robust evidence of a neuroinflammatory response in tinnitus animal models as previously described, human studies show conflicting results. Studies show inconsistencies in IL-6 and IL-10 expression in tinnitus participants. Additionally, both studies observe no differences in TNF-α expression, which is a persistent finding in several animal studies [43, 44].

Discrepancies between pro-inflammatory cytokine expression in animal and human studies could be due a number of variables. One critical variable is the tissue type that the inflammatory markers were measured in. In tinnitus rodent models, changes in inflammatory markers were observed in regions along the auditory pathway, such as the cochlea, cochlear nucleus, inferior colliculus, medial geniculate body, and auditory cortex [10••, 17–22]. In human studies, inflammatory markers were measured in blood samples [43, 44]. It is possible the inflammatory effect may only manifest along the auditory pathway and is not reflected in blood.

Another critical variable that could account for conflicting findings between human and animal studies is the time point in which cytokine expression is measured. Pro-inflammatory cytokine levels in animal studies were measured directly after induction of tinnitus (i.e., acutely), whereas cytokine expression in human studies were measured long after tinnitus started (i.e., chronically). This may suggest that neuroinflammation

only plays a partial role in the acute phase of tinnitus. Overall, further research is needed to delineate the mechanisms that transitions tinnitus from acute to chronic. Below, we will highlight parallels amongst pain and tinnitus pathologies, which could provide an infrastructure for future studies to build upon on the avenue to better treatments.

Pain and Tinnitus

Tinnitus and neuropathic pain share many similarities in pathophysiology, affected brain areas, and an existing perception of subjective sensations that may turn chronic [45]. Changes in nociception occurs following inflammation or injury in neuropathic pain, similar to how changes in the auditory system may occur after noise exposure or hearing loss-related neuroinflammation. Persistent inflammation leads to a synaptic imbalance, as demonstrated by an increase in excitatory transmission and decrease in inhibitory transmission, and the central nervous system becomes sensitized [12, 45, 46]. Evidence suggests that pro-inflammatory cytokines enhance excitability in both the sensory and auditory system, likely driving the development of neuropathic pain and the tinnitus percept, respectively [10••,11•, 12, 31, 46].

Changes in gene expression provide additional support in the development and maintenance of central sensitization. Translational regulation of particular mRNA subsets mediate changes in the immune and nervous system to maintain persistent signaling observed in sensitization [47, 48]. Consistent with this, recent studies have identified a protein involved in mRNA translation which likely mediates the chronification of neuropathic pain. Phosphorylation of eIF4E, forming the eIF4F complex, is associated with increased rates of translation initiation that impact a subset of mRNAs involved in neural plasticity [49]. Regulation of mRNA translation via inhibition of eIF4E phosphorylation reduces injury-induced neuronal hyperexcitability and

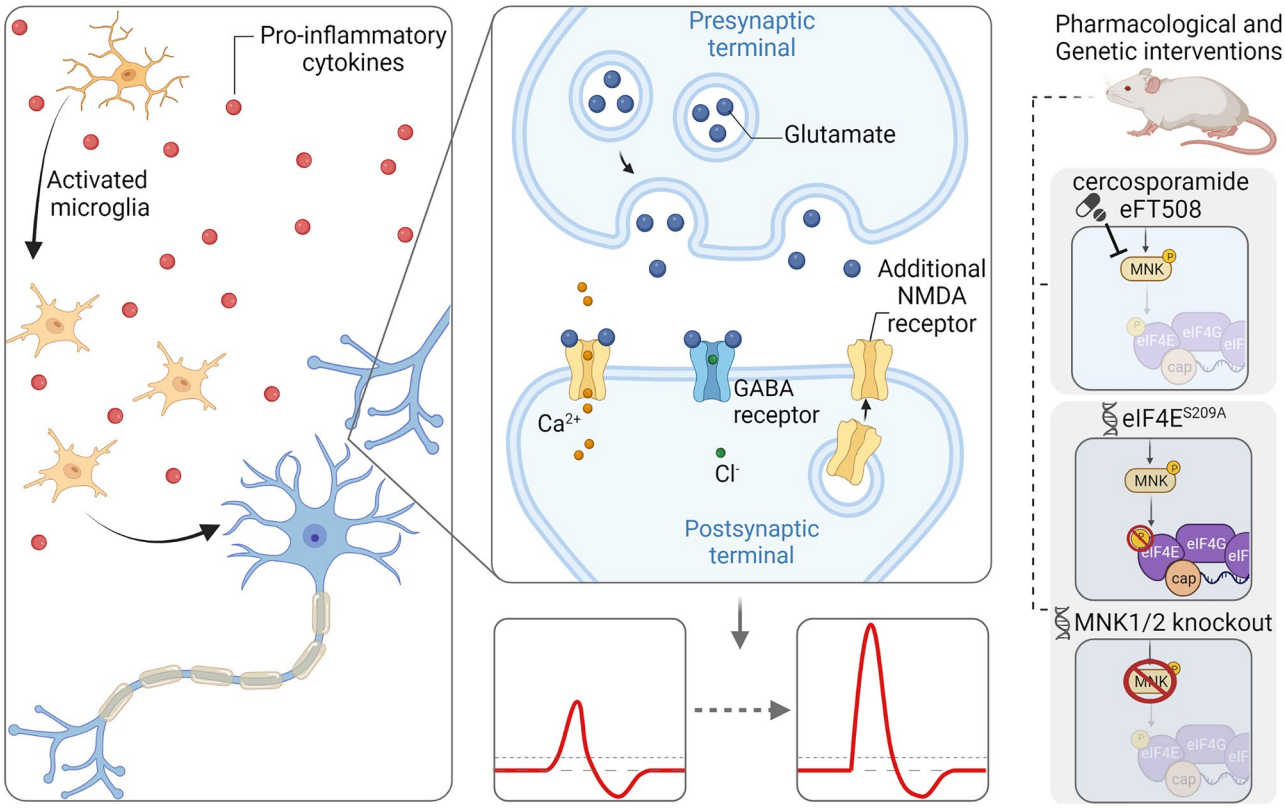

Fig. 1 Noise exposure or hearing loss-related disorders cause neuroinflammation in the auditory system, further increasing microglia activation and pro-inflammatory cytokine release. Enhanced levels of pro-inflammatory cytokines influence neurotransmission by driving changes in receptor activity (i.e., increased NMDA surface localization and GABA-A endocytosis resulting in increased calcium influx and decreased chloride influx, respectively). These changes in NMDA and GABA activity lead to increased excitatory and decreased inhibitory synaptic activity in the auditory pathway, leading to hyperexcitability. Changes in gene expression, via phosphorylation of eIF4E, may provide additional support in the maintenance of plasticity that generates chronic tinnitus, mediating persistent tinnitus signaling. Genetic or pharmacological interventions inhibiting eIF4E phosphorylation may prevent the development of chronic tinnitus. Current methods to test this in animal models include mutation of eIF4E serine 209 which lacks the phosphorylation site for MNK1/2 on eIF4E, as well as MNK1 inhibition using cercosporamide or genetic knockout of MNK 1/2

prevents the transition of acute to chronic pain in rodent models that generate both neuropathic and certain types of inflammatory pain [46, 50–52]. Furthermore, these studies provide compelling evidence that translation regulation (via preventing eIF4E phosphorylation) may be a successful therapeutic strategy for chronic neuropathic pain [53].

Translational Regulation May Provide Relief for Chronic Tinnitus

The current perspective proposes that while neuroinflammation may mediate acute tinnitus, changes in gene expression via phosphorylation of eIF4E may contribute to the maladaptive plasticity that drives the chronification of tinnitus (Fig. 1). Phosphorylation of eIF4E and subsequent local translation of specific mRNAs may mediate changes in neuroplasticity that maintains persistent afferent neuronal signaling in chronic tinnitus. We postulate that initial peripheral inflammation driven by a hearing loss-related disorder or acoustic trauma likely increases pro-inflammatory cytokines release that mediates changes in receptor excitability, causing a synaptic imbalance. Overtime, persistent inflammation may generate changes in local translation, leading to the expression of genes that alter the phenotype of the receptor long-term. Aberrant afferent input may then drive changes in central nervous system activity and connectivity, promoting the persistent tinnitus percept.

If true, potential anti-inflammatory treatments may fail to provide relief in individuals experiencing chronic tinnitus. Instead, treatments inhibiting eIF4E activation may yield greater relief, through the attenuation of the pathophysiology believed to drive persistent tinnitus signaling. Current animal models that genetically or pharmacologically inhibit eIF4E phosphorylation (i.e., MNK1/2 knockout mice, $eIF4E^{S209A}$ mice, or administration of cercosporamide) could provide a testbed of evaluation for future therapeutic developments [47, 50–52]. Targeting this signaling pathway as a therapeutic strategy may provide relief to individuals suffering from chronic tinnitus. However, future research is needed to delineate the role of eIF4E in chronic tinnitus.

Conclusion

Here, we propose a novel perspective in the chronification of tinnitus. Emerging evidence from the tinnitus field reveals an undeniable involvement of neuroinflammation, though the exact mechanism remains to be elucidated. Recent results suggest neuroinflammation may play a role in the acute development of tinnitus.

Based on previous animal studies, findings suggest noise exposure or hearing loss-related disorders generate an initial neuroinflammatory response. This inflammatory response generates a positive feedback loop between cytokine expression and microglial activation, subsequently modifying neuronal functioning. Persistent inflammatory-induced changes in excitatory and inhibitory function thereby lead to hyperexcitability in the auditory system and therefore the development of tinnitus. In parallel to recent pain studies, we propose a specific signaling pathway important in regulating persistent, chronic tinnitus.

Limitations within this review merit consideration. Many animal studies found increased expression of multiple inflammatory markers (i.e., IFNγ, Iba-1, GFAP, IL-1β) after experimentally inducing tinnitus [10••, 17, 19–22]. However, few studies genetically or pharmacologically modified pro-inflammatory cytokine expression to investigate the direct effect of inflammation on behavior and physiology [10••, 14]. Because of this, this review primarily explores the function of TNF-α. In addition, few human studies investigated cytokine expression in individuals with tinnitus and healthy participants [43, 44]. Lastly, other mechanisms likely influence neuronal function in tinnitus. For example, parvalbumin neuron density was affected after noise-exposed mice; however, this effect was dependent on mouse strain and therefore not included in the review [54]. Further research is needed to delineate the neural correlates of tinnitus.

While this review highlights evidence that supports a proposed mechanism, the perspective itself is a simplified theory of an otherwise complex and heterogeneous pathology. Despite this, the current perspective can be used as an infrastructure for future studies to identify novel therapeutic targets. While efforts in controlling neuroinflammation may only heed benefits in acute tinnitus, further research in translational regulation may target the chronic tinnitus signaling pathway for relief.

Funding Open Access funding provided by the IReL Consortium.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Roberts LE. Neural plasticity and its initiating conditions in tinnitus. HNO. 2018;66:172–8.
2. Wu C, Stefanescu RA, Martel DT, Shore SE. Tinnitus: maladaptive auditory-somatosensory plasticity. Hear Res. 2016;334:20–9.
3. Eggermont JJ. Tinnitus: neurobiological substrates. Drug Discov Today. 2005;10:1283–90.
4. Shulman, A. et al. Neuroinflammation and tinnitus. in The Behavioral Neuroscience of Tinnitus 2021;161–174. https://doi.org/10.1007/7854_2021_238.
5. Shabab T, Khanabdali R, Moghadamtousi SZ, Kadir HA, Mohan G. Neuroinflammation pathways: a general review. Int J Neurosci. 2017;127:624–33.
6. Fuentes-Santamaría V, et al. Glia-related mechanisms in the anteroventral cochlear nucleus of the adult rat in response to unilateral conductive hearing loss. Front Neurosci. 2014;8:1–17.
7. Fuentes-Santamaría V, et al. The role of glia in the peripheral and central auditory system following noise overexposure: contribution of TNF-α and IL-1β to the pathogenesis of hearing loss. Front Neuroanat. 2017;11:1–26.
8. Baizer JS, et al. Effects of acoustic trauma on the auditory system of the rat: the role of microglia. Neuroscience. 2015;303:299–311.
9. Frye MD, Ryan AF, Kurabi A. Inflammation associated with noise-induced hearing loss. J Acoust Soc Am. 2019;146:4020–32.
10. •• Wang W, et al. Neuroinflammation mediates noise-induced synaptic imbalance and tinnitus in rodent models. PLoS Biol. 2019;17:1–25. **Findings from this study reveal that genetic and pharmacological blockage of TNF-α mitigates the behavioral and physiological tinnitus phenotype in rats.**
11. • Mennink LM, Aalbers MW, van Dijk P, van Dijk JMC The role of inflammation in tinnitus: a systematic review and meta-analysis. J Clin Med in press 2022. **This systematic review provided an extensive overview of the implications of neuroinflammtion in both humans with tinnitus and animal models of tinnitus.**
12. Wang, W, Bao, S. Neuroinflammation model of tinnitus. 2022.
13. Szczepek AJ, Haupt H, Klapp BF, Olze H, Mazurek B. Biological correlates of tinnitus-related distress: an exploratory study. Hear Res. 2014;318:23–30.
14. Gonzalez-Gonzalez S, Cazevieille C. 3,6'-Dithiothalidomide reduces tinnitus phenotype in two different mouse preclinical models of tinnitus. J Community Prev Med. 2020;3:1–8.
15. Hwang JH, Huang DCW, Lu YC, Yang WS, Liu TC. Effects of tumor necrosis factor blocker on salicylate-induced tinnitus in mice. Int Tinnitus J. 2017;21:24–9.
16. Turner JG, et al. Gap detection deficits in rats with tinnitus: a potential novel screening tool. Behav Neurosci. 2006;120:188–95.
17. Chen XH, Zheng LL. Expression of pro-inflammatory cytokines in the auditory cortex of rats with salicylate-induced tinnitus. Mol Med Rep. 2017;16:5643–8.
18. Hu S, Sen Mei L, Chen JY, Huang ZW, Wu H. Effects of salicylate on the inflammatory genes expression and synaptic ultrastructure in the cochlear nucleus of rats. Inflammation 2014;37:365–73.
19. Hwang JH, Chen JC, Yang SY, Wang MF, Chan YC. Expression of tumor necrosis factor-α and interleukin-1β genes in the cochlea and inferior colliculus in salicylate-induced tinnitus. J Neuroinflammation. 2011;8:2–7.
20. Hwang JH, Chen JC, Chan YC. Effects of C-phycocyanin and spirulina on salicylate-induced tinnitus, expression of NMDA receptor and inflammatory genes. Plos One. 2013;8:1–10.
21. Fang L, Fu YY Zhang, TY. Salicylate-induced hearing loss trigger structural synaptic modifications in the ventral cochlear nucleus of rats via medial olivocochlear (MOC) feedback circuit. Neurochem Res. 2016;41:1343–53.
22. Xia C, Yin M, Wu C, Ji Y, Zhou Y. Neuroglial activation in the auditory cortex and medial geniculate body of salicylate-induced tinnitus rats. Am J Transl Res. 2020;12:6043–59.
23. Graeber MB, Li W, Rodriguez ML. Role of microglia in CNS inflammation. FEBS Lett. 2011;585:3798–805.
24. Salter MW, Beggs S. Sublime microglia: expanding roles for the guardians of the CNS. Cell. 2014;158:15–24.
25. Donat CK, Scott G, Gentleman SM, Sastre M. Microglial activation in traumatic brain injury. Front Aging Neurosci. 2017;9:1–20.
26. Shaftel SS, Griffin WST, Kerry KM. The role of interleukin-1 in neuroinflammation and Alzheimer disease: an evolving perspective. J Neuroinflammation. 2008;5:1–12.
27. Stellwagen D, Beattie EC, Seo JY, Malenka RC. Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor-α. J Neurosci. 2005;25:3219–28.
28. Wheeler D, et al. Tumor necrosis factor-α-induced neutral sphingomyelinase-2 modulates synaptic plasticity by controlling the membrane insertion of NMDA receptors. J Neurochem. 2009;109:1237–49.
29. Pribiag H, Stellwagen D. Tnf-α downregulates inhibitory neurotransmission through protein phosphatase 1-dependent trafficking of GABAA receptors. J Neurosci. 2013;33:15879–93.
30. Jang CH, et al. Memantine attenuates salicylate-induced tinnitus possibly by reducing NR2B expression in auditory cortex of rat. Exp Neurobiol. 2019;28:495–503.
31. Kawasaki Y, Zhang L, Cheng JK, Ji RR. Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1β, interleukin-6, and tumor necrosis factor-α in regulating synaptic and neuronal activity in the superficial spinal cord. J Neurosci. 2008;28:5189–94.
32. Rizzo FR, et al. Tumor necrosis factor and interleukin-1 β modulate synaptic plasticity during neuroinflammation. Neural Plast. 2018.
33. Liu T, Jiang CY, Fujita T, Luo SW, Kumamoto E. Enhancement by interleukin-1β of AMPA and NMDA receptor-mediated currents in adult rat spinal superficial dorsal horn neurons. Mol Pain. 2013;9:1.
34. Wang HT, Luo B, Zhou KQ, Xu TL, Chen L. Sodium salicylate reduces inhibitory postsynaptic currents in neurons of rat auditory cortex. Hear Res. 2006;215:77–83.
35. Jin Y, et al. Sodium salicylate suppresses GABAergic inhibitory activity in neurons of rodent dorsal raphe nucleus. Plos One. 2015;10:1–21.
36. Brozoski TJ, Spires TJD, Bauer CA. Vigabatrin, a GABA transaminase inhibitor, reversibly eliminates tinnitus in an animal model. JARO - J Assoc Res Otolaryngol. 2007;8:105–18.
37. Trune DR, Canlon B. Corticosteroid therapy for hearing and balance disorders. Anat Rec. 2012;295:1928–43.
38. Slattery WH, Fisher LM, Iqbal Z, Liu N. Oral steroid regimens for idiopathic sudden sensorineural hearing loss. Otolaryngol - Head Neck Surg. 2005;132:5–10.
39. Chen JJ, et al. Efficacy of pharmacologic treatment in tinnitus patients without specific or treatable origin: a network meta-analysis of randomised controlled trials. eClinicalMedicine 2021;39:101080.

40. Silverstein H, et al. Intratympanic steroid treatment of inner ear disease and tinnitus (preliminary report). Ear, Nose Throat J. 1996;75.
41. Topak M, et al. Intratympanic methylprednisolone injections for subjective tinnitus. J Laryngol Otol. 2009;123:1221–5.
42. Shim, HJ, Jun Song S, Choi AY, Hyung Lee R, Won Yoon S. Comparison of various treatment modalities for acute tinnitus. Laryngoscope 2011;121:2619–25.
43. Haider HF, et al. Tinnitus, hearing loss and inflammatory processes in an older Portuguese population. Int J Audiol. 2020;59:323–32.
44. Weber C, Arck P, Mazurek B, Klapp BF. Impact of a relaxation training on psychometric and immunologic parameters in tinnitus sufferers. J Psychosom Res. 2002;52:29–33.
45. Møller AR. Tinnitus and pain. Prog Brain Res. 2007;166:47–53.
46. Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. Trends Neurosci. 2009;32:611–8.
47. Mody PH, Dos Santos NL, Barron LR, Price TJ, Burton MD. eIF4E phosphorylation modulates pain and neuroinflammation in the aged. GeroScience. 2020;42:1663–74.
48. Khoutorsky A, Price TJ. Translational control mechanisms in persistent pain. Trends Neurosci. 2018;41:100–14.
49. Uttam S, Wong C, Price TJ, Khoutorsky A. eIF4E-dependent translational control: a central mechanism for regulation of pain plasticity. Front Genet. 2018;9:1–10.
50. Moy JK, et al. The MNK–eIF4E signaling axis contributes to injury-induced nociceptive plasticity and the development of chronic pain. J Neurosci. 2017;37:7481–99.
51. Moy JK, Kuhn JL, Szabo-Pardi TA, Pradhan G, Price TJ. eIF4E phosphorylation regulates ongoing pain, independently of inflammation, and hyperalgesic priming in the mouse CFA model. Neurobiol Pain. 2018;4:45–50.
52. Shiers S, et al. Reversal of peripheral nerve injury-induced neuropathic pain and cognitive dysfunction via genetic and tomivosertib targeting of MNK. Neuropsychopharmacology. 2020;45:524–33.
53. Yousuf MS, Shiers SI, Sahn JJ, Price TJ. Pharmacological manipulation of translation as a therapeutic target for chronic pain. Pharmacol Rev. 2021;73:59–88.
54. Zinsmaier AK, Wang W, Zhang L, Hossainy NN, Bao S. Resistance to noise-induced gap detection impairment in FVB mice is correlated with reduced neuroinflammatory response and parvalbumin-positive neuron loss. Sci Rep. 2020;10:1–9.