Introduction

Tinnitus refers to the sensation of sound without an external auditory stimulus. It is most common (10–15%) among elderly individuals aged 60 years or more [1]. Chronic tinnitus can occur at any age. Various theories explain the cause of tinnitus. The etiology of tinnitus involves aging, hearing loss, and environmental distress, such as loud noise, neck injury, trauma, and ototoxicity [2, 3]. The main cause of tinnitus is the damage to either the peripheral (cochlea and auditory nerve) or central auditory nervous system. People with tinnitus are often reported to have strong negative emotions, causing lifelong emotional distress [4]. Therefore, brain regions associated with emotional processing were also considered during tinnitus treatment. Tinnitus is categorized into two types, namely, central and peripheral tinnitus [5]. Central tinnitus refers to the auditory perception that is formed in auditory brain centers by anomalous neural activity [6]. Peripheral tinnitus refers to the auditory perception that results from abnormal neural activity at the cochlear level. This is then transmitted through the auditory pathways [7]. On assessing tinnitus pathophysiology, Martines et al. [8], demonstrated a significant association between tinnitus and age. The epidemiological data of their study and previous studies indicated that sensorineural hearing loss generally co-exists with tinnitus, which is known as presbytinnitus. The association is due to pathological changes of the auditory pathways, both peripheral and central, which are progressively more evident in elderly people [9, 10]. Of all the patients with tinnitus, 63.1% were diagnosed with hearing loss. Among these patients, 74.6% were reported to have sensorineural hearing loss. Most studies on sensorineural hearing loss suggest that the disruption of the mechano-electrical transduction at the tip of the outer hair cell is the main contribu-
tor to sensorineural hearing loss [11]. In this review, we compiled various causes of tinnitus, especially peripheral tinnitus. We have elucidated the role of excessive ROS production and glutamate secretion in the damage caused by hair cell loss and afferent nerve fibers. Statistical evidence indicates that the tinnitus that has affected the majority of population is associated with sensorineural hearing loss caused by hair cell damage; therefore, strategies that protect hair cells could be reliable for patients suffering from tinnitus for a prolonged period. We focused on the mechanism of autophagy activation as a viable way to tackle peripheral tinnitus, as autophagy functions as a cytoprotector during stress.

COMMON ETIOLOGY OF TINNITUS

Several theories have been proposed regarding the cause of tinnitus. One such theory involves damage to the peripheral nervous system and is called the discordant dysfunction theory [12]. According to this theory, degeneration of outer hair cells (OHCs), leading to functional loss, causes aberrant activity (typically hyperactivity) in the auditory nerve. Incidents such as noise trauma, ototoxic drug intake, and head and neck injuries cause challenges anywhere along the auditory pathway. As a variety of modes have been associated with tinnitus, numerous causes could be responsible for this condition.

In a study that investigated the relationship between auditory brainstem response and noise exposure in tinnitus, researchers found that the increase in the perception of tinnitus could be due to changes in the peripheral input at the inner hair cell (IHC) level [13]. The findings also suggested that the origin of tinnitus was not associated with OHC dysfunction. This could be because IHCs are responsible for synaptic and plastic changes in the auditory system. Increased glutamate exchange due to noise trauma causes cell excitation. Thus, tinnitus could have originated at the IHCs in most of the participants in this study.

Ma et al. [14] in their recent study observed the effects of acoustic trauma on the inferior colliculus of mice. When the experimental animals were subjected to acoustic trauma, the firing rate of glutamatergic neurons enhanced when compared with that of GA-Baergic neurons. Contradictory results were observed in control animals. These results suggest that plastic changes in the inferior colliculus caused by acoustic trauma deter the balancing activities of the inhibitory and excitatory neurons. This could be one of the important causes of tinnitus.

In contrast, another group identified different clusters located in the left higher auditory cortex (HAC) and right inferior colliculus (IC) from the smoothed mean amplitude of low-frequency fluctuation (smALFF) maps. These maps indicated increased HAC and decreased IC activity. The increased value of the smALFF cluster in the HAC was proportional to the tinnitus scores, but it did not show any correlation with decreased IC activity and tinnitus clinical characteristics [15]. The results revealed that the abnormal spontaneous activity in the HAC arising from the change in neural plasticity could cause tinnitus.

MECHANISM BEHIND SENSORY HAIR CELL DAMAGE AND TINNITUS

Mammalian sensory hair cells consist of one row of IHCs and three rows of OHCs localized in the organ of Corti above the basilar membrane in the inner ear (Fig. 1). Inner hair cells capture sound signals and transmit them to the brainstem along the auditory nerve, whereas OHCs amplify the received sound [16]. Unlike in lower organisms, the ability of the mammalian inner ear to replace lost hair cells is very limited. Upon maturation, the auditory sensory epithelium loses its ability to regenerate lost hair cells [17] and the vestibular sensory epithelium supports only a partial regenerative response to trauma [18, 19].

As mentioned above, during cochlear damage caused by external factors, loss of OHC motility occurs, which results in the loss of synapses between IHCs and spiral ganglion neurons. The death of OHCs or IHCs or the rupture of the basilar membrane leads to a decrease in the neuronal output from the cochlea to the brain (Fig. 1A). Another pathophysiological trigger for tinnitus is the change in the position of the tectorial membrane. Once the OHCs are damaged, the rootlets of the stereocilia are altered, leading to stiffness and an acute increase in the spontaneous activity of the cochlea. Therefore, the tectorial membrane touches the IHCs, resulting in depolarization [20]. Two fundamental processes can initiate the pathological process: intracellular calcium levels and biochemical changes in their structural proteins. Increased intracellular calcium, caused by the increase in neurotransmitter release and the subsequent activity of the auditory nerves, acts as a pathological substrate of peripheral tinnitus [21].

N-methyl-D-aspartate (NMDA) receptor plays an essential role in noise-induced tinnitus. Excessive accumulation of ionotropic glutamate and the resulting glutamate excitotoxicity are known to induce hair cell death [22]. The administration of ototoxic drugs or exposure to loud noise enhances glutamate secretion in the IHCs. Increased glutamate from IHCs activates NMDA receptors that promote the Ca\(^{2+}\) influx in spiral ganglion neurons (Fig. 1B) [23]. This process is hypothesized to be the cause of hearing loss and tinnitus through anomalous excitation of auditory nerves [24]. Consequently, over-excitation increases the demand for adenosine triphosphate (ATP) [25]. This demand elevates mitochondrial ox-
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Dative phosphorylation, leading to ROS overproduction [26]. This consequently increases ROS in synapses between IHCs and spiral ganglion neurons, resulting in the death of spiral ganglion neurons [27]. Eventually, the damaged auditory system results in synchronous excitation of the neurons in the inferior colliculus and causes this phantom sound.

**AUTOPHAGY AND STRESS RESPONSE**

Autophagy is a catabolic mechanism enabling scavenging activity inside the cells [28]. This is an evolutionarily conserved process [29]. Autophagy is categorized into three types: macroautophagy, microautophagy, and chaperone-mediated autophagy. All three types are morphologically distinct, but the end goal is to deliver cargo to the lysosome and degrade it. Of these, macroautophagy (from now referred as autophagy) is a cytoprotective mechanism [30]. It is a complex process involving the assembly of numerous autophagy-related (Atg) proteins to complete the entire process [31]. Autophagy is important for cells to maintain pristine protein functions. Usually, when a protein is used or misfolded owing to mutations, it aggregates in the cytoplasm of the cell [32]. Autophagy involves five stages: (i) initiation, that is, activation of upstream signaling pathways such as mammalian target of rapamycin (mTOR) and AMP-activated protein kinase; (ii) formation of the phagophore membrane; (iii) elongation of the membrane and the formation of an autophagosome, which recruits unwanted proteins and fuses with lysosomes to degrade and recycle them; (iv) autolysosome fusion; and finally, (v) the degradation of the cargo [33]. Autophagy is involved in recycling damaged proteins and damaged organelles [34]. Mitophagy is the autophagy mechanism that degrades damaged mitochondria. Eliminating damaged mitochondria is essential for cells in many ways because damaged mitochondria produce reactive oxygen species (ROS). These ROS oxidize essential proteins in the cell and block their activity. These inactive proteins begin to accumulate on the cytosolic surface of cells, resulting in the formation of toxic aggregates, eventually leading to cell death, and autophagy eventually eradicates these aggregates [35, 36]. This proves the importance of the autophagy

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**Fig. 1.** Mechanism behind peripheral tinnitus: (A) Trauma such as loud noises, salicylate induction or other ototoxic conditions cause loss of either inner or outer hair cells, or damage to the auditory system. This results in tinnitus. (B) Once the hair cell is damaged by trauma, excessive glutamate is released, causing increase in the N-methyl-D-aspartate (NMDA) receptor activity. This enhances the influx of abundant Ca\(^{2+}\) ions into the auditory nerve that results in excitotoxicity.
Autophagy Activation to Treat Tinnitus

mechanism, especially the completion of the entire autophagic flux, in cell protection. Autophagic flux refers to the complete autophagy process over a given period, including target cargo selection (damaged proteins or organelles) and recruitment into the autophagosome. The cargo fuses with lysosomes and is subsequently degraded and released back into the cytosol [37]. Disturbance of the flux at any stage leads to the formation of damaged proteins and organelle aggregation.

Several signaling pathways modulate autophagy in mammalian cells [38]. The classical pathway involves serine/threonine kinases and the negative regulator of autophagy, mTOR [39]. Other signaling pathways that regulate autophagy include the phosphoinositide 3 kinase (PI3K)/Akt pathway, extracellular signal-regulated kinase (ERK) pathway, mitogen-activated protein kinase (MAPK), and Ras pathway [33, 40, 41]. The PI3K and MAPK pathways inhibit autophagy [42, 43], whereas ERK activation stimulates and inhibits autophagy, depending on the cell type [41, 44, 45]. Notably, cyclic AMP (cAMP) activation is known to either inhibit or activate ERK in a cell type-specific manner [46, 47]. Almost all of the above-mentioned pathways are oxidative, mitochondrial, or endoplasmic reticulum stress-responsive pathways. During stress, a cell needs to protect itself, and autophagy is one of the important mechanisms involved in stress response and helps in cell survival [48]. Utilizing the autophagy mechanism against the ROS generated as a result of ototoxicity clears the toxins and prevents further damage to the sensory hair cells.

SENSORY HAIR CELL PROTECTION BY AUTOPHAGY

Although tinnitus has various causes, one commonly observed criterion in patients with tinnitus is damage to the hair cells and degeneration of the auditory nerve of the spiral ganglion due to excitotoxicity. Excitotoxicity results from increased ROS production, which can lead to DNA damage, destabilization of proteostasis, and damage to organelles, ultimately leading to cell death. Activation of autophagy during these stages helps in the elimination of protein damage caused by ROS and defective mitochondria (Fig. 2). Therefore, inducing autophagy during ototoxic conditions could act as a preventive measure for cochlear hair cells and subsequently reduce tinnitus severity.

A study by He et al. [49] indicated that autophagy protects auditory hair cells against neomycin-induced damage. They demonstrated that, upon administration of the antibiotic neomycin (which causes ototoxicity), the cells produced autophagosomes as stress response elements to prevent hair cells from the ototoxic effect of neomycin. By knocking out the Atg5 gene, they also demonstrated that cells treated with neomycin expressed higher levels of apoptotic-related caspase3 protein when compared with that of cells treated with rapamycin (an activator of autophagy). This proves that autophagy activation was not due to neomycin treat-
ment but that autophagy activation protects hair cells from the apoptotic effect of neomycin. Autophagy activation also increased the survival of cochlear hair cells and HEI-OC1 cell line. Upon autophagy activation, the expression of antioxidant genes like Sod1, Gsr and Glrx were significantly upregulated. This indicates that autophagy is involved in the reduction of ROS by eliminating damaged mitochondria after neomycin treatment.

When cisplatin was used to induce hair cell death in the mouse cochlea and lateral line hair cells of zebrafish, the activation of autophagy and Sirtuin 1 attenuated hair cell death [50]. Previous studies have demonstrated that autophagy has protective functions, both in vitro and in vivo. Administration of rapamycin, a well-known autophagy activator, increased the survival of hair cells in cisplatin-induced cytotoxicity [51], indicating that autophagy protects hair cells against cisplatin.

Autophagy activation attenuated hair cell death in gentamycin-treated rat auditory hair cells. Gentamycin (GM) is a well-known aminoglycoside antibiotic. Aminoglycosides are known to damage hair cells, and as a stress response, autophagosome accumulates upon gentamycin treatment. However, hair cell loss is not prevented due to the failure in lysosome formation; thereby it results in the failure of autophagic flux [52]. Apparently, the implementation of gentamycin suppressed the autophagic flux by decreasing the fusion of autophagosomes with lysosomes [52]. Autophagic flux is defined as the completion of the entire autophagy mechanism, starting from the formation of membrane-bound autophagosomes to the recruitment of LC3 II and degradation by lysosomes. The degradation process does not occur during aminoglycoside treatment because of the disruption of autophagic flux. When autophagic flux is inhibited by 3-methyladenine and chloroquine in HEI-OC1 cells, a significant increase in cell death is observed [49]. Late activation of autophagy may be responsible for the slower rate of hair cell loss in gentamycin-induced ototoxicity. When treated with aminoglycoside antibiotics, autophagosome formation and apoptotic features are observed [53]. This could be because apoptosis is a faster mechanism when compared with the speed of autophagy. Defects in both the early and late stages of autophagy result in dysfunction of the autophagy mechanism, subsequently resulting in cell death [54]. Transcription factor EB (TFEB) is a key transcription factor that controls lysosomal ability [55]. During the degeneration of sensory neural hair cells and spiral ganglion neurons, the translocation of TFEB into the nucleus increases autophagosome – lysosomal fusion, eventually decreasing oxidative stress and rectifying hair cell damage [56]. Observations from all of these studies form the basic framework of this article, that is, autophagy acts as a defensive mechanism and the enormous amount of ROS synthesized during excitotoxicity can be efficiently cleared through autophagy activation. The results of these studies indicate that it is not only important to activate autophagy, but the completion of the autophagic flux (the degradation process) must also occur for sensory hair cell survival.

**CURRENT PHARMACOLOGICAL STRATEGIES TO TREAT TINNITUS AND THEIR ROLE IN AUTOPHAGY**

As tinnitus involves psychological barriers, such as frustration, anxiety, and depression, one of the strategies of physicians is to recommend antidepressants to patients. In some cases, muscle relaxants were reported to reduce the adverse effects of tinnitus [57]. The administration of vitamin B12 is recommended by some physicians because vitamin B12 deficiency correlates with chronic tinnitus cases [58]. A list of the various pharmacological drugs used to treat tinnitus is provided in Table 1. All these drugs have different targets to reduce tinnitus severity, since the etiology for tinnitus cannot be fully established, and these drugs can only provide subjective relief from distress.

| Drugs         | Type of drug      | Results                                      | Role on autophagy                      | Authors                        |
|---------------|-------------------|----------------------------------------------|----------------------------------------|--------------------------------|
| Nortriptyline | Antidepressant    | Severity of tinnitus decreased               | Induction of autophagy                 | Sullivan et al. (1989) [86]    |
| Amitriptyline | Antidepressant    | Intensity of tinnitus reduced and subjective relief from distress was observed | Activation of ULK1, Beclin and LC3 | Bayar et al. (2001) [60]       |
| Imipramine    | Antidepressant    | Reduced the depression level                  | Increases the expression of LC3 II     | Tandon et al. (1987) [87]      |
| Naltrexone    | Anticonvulsant    | Reduced the distress and intensity            | Not known                              | Vanneste et al. (2013) [88]    |
| Cyclobenzaprine | Muscle relaxant | Intensity of tinnitus distress reduced       | Not known                              | Vanneste et al. (2012) [89]    |
| Memantine     | Glutamate antagonist | Partial recovery was observed                | Upregulate autophagic flux            | Figueiredo et al. (2008) [90]  |
| Flupirtine    | Glutamate antagonist | No significant difference was observed      | Not known                              | Salembier et al. (2006) [91]   |
| Neramexane    | Glutamate antagonist | At higher dosage, resulted in decrease in annoyance and psychological impact | Not known                              | Suckfüll et al. (2011) [70]    |
| Vitamin B12   |                   | No significant change                         | Restoration of autophagic flux         | Berkiten et al. (2013) [77]    |
Tinnitus is not established. From the studies on the role of autophagy in ototoxicity, autophagy is shown to be responsible for the delay in cell death or the failure of autophagy, leading to hair cell death. Therefore, the partial success of these drugs can be identified by examining the effects of these drugs on autophagy.

**Antidepressant**

A clinical trial report on the tricyclic antidepressant nortriptyline [59] indicated that administration of nortriptyline was useful in some patients with depression and insomnia. Another study that treated patients with amitriptyline [60] indicated a 95% success rate. A recent article [61] collated several publications that reported the involvement of autophagy in antidepressants. The studies included in this article reported an increased level of autophagy upon treatment with antidepressants [62-64]. One of the most recent studies indicated that tricyclic antidepressants target acid sphingomyelinase [64]. Upon treatment with amitriptyline and fluoxetine, researchers observed sphingomyelin accumulation in lysosomes. The endoplasmic reticulum also accumulated ceramide, which in turn stimulated autophagy through ULK1, Beclin, and LC3 II. These recent studies may be helpful in elucidating the role of autophagy in reducing the severity of tinnitus during treatment with antidepressants.

**Glutamate receptor antagonists**

Numerous studies have indicated that excess glutamate played a role as a primary trigger, which caused various other pathologies in the noise-exposed cochlea, especially the damage of the postsynaptic afferent nerves caused by AMPA receptor activity [65-68]. Excessive signaling via ionotrophic glutamate receptors has been observed to cause apoptotic hair cell death [22]. Therefore, one of the best strategies to tackle this condition is the use of glutamate receptor antagonists. Studies that included glutamate receptor antagonists such as memantine, flupirtine, and neramexane at a low dosage did not indicate significant results when compared with that of placebo groups, but neramexane at a tolerably high dose indicated a significant improvement over that of the placebo group for tinnitus treatment [69, 70]. In general moderate affinity NMDA receptor antagonists syndicate good efficacy and tolerability [71]. But NMDA antagonist memantine at lower doses does not show any significant effect as the authors who conducted the study conclude that the study methodology was not properly structured [72].

Excitotoxicity blocks autophagy at later stages [73], that is, autophagic flux is interrupted. Memantine activates autophagy independent of mTORC1 and enhances the degradation of damaged mitochondria [74]. Once damaged mitochondria are eliminated, ROS production can be reduced. Thus, the partial recovery from tinnitus is probably caused by autophagy activation. The derivative of flupirtine also seems to be highly involved in autophagy activation [75]. However, the mechanism is yet to be determined.

**Vitamin B12**

In addition to pharmacological interventions, few studies have focused on the use of vitamins to treat tinnitus. Vitamin B12 deficiency causes axonal degeneration, demyelination, and neuronal death [76]. Patients with vitamin B12 deficiency who also had hearing loss and tinnitus were chosen and administered vitamin B12 in a study. However, vitamin therapy was not effective as a complete cure for tinnitus in patients [77]. Another pilot study on tinnitus patients from north-Indian indicated a relationship between vitamin B12 deficiency and tinnitus [78].

A study conducted by Tripathi et al. [79] indicated that autophagic flux was restored upon vitamin B treatment, which also resulted in the alleviation of endoplasmic reticulum (ER) stress. As ER stress is also involved in excessive oxidative stress, autophagy activation reduces oxidative stress.

Almost all pharmacological interventions have major side effects, and the studies are not well structured to include various dimensions. Therefore, investigating multiple preventive facets to address tinnitus treatment is necessary. In the path to finding a treatment for a disease, finding a solution that can provide significant relief is essential. The basis of tinnitus is excitotoxicity in the hair cells, which leads to subsequent detrimental consequences in the central nervous system. Drugs that provide partial recovery to patients involve indirect autophagy activation. These drugs are selected for tinnitus treatment based on various aspects—tricyclic antidepressants are chosen based on psychotic depression, and NMDA receptor antagonists are selected to reduce excitotoxicity by alleviating NMDA receptor activity. Autophagy is not the main target in these cases. As the study by Ye et al. [56] clearly highlights, the completion of autophagic flux, which is indicated by the degradation of autolysosomes, results in the recovery of damaged hair cells and protects the degeneration of the spiral ganglion neurons. Additionally, autophagy activation during aminoglycoside treatment alleviates oxidative stress. This reduces excitotoxicity, and the rate of hair cell loss was also observed to be reduced. Therefore, choosing a drug that targets autophagy activation and promotes lysosomal degradation will enhance the success rate of therapeutic intervention in patients with tinnitus.

**CONCLUDING REMARKS**

Tinnitus is a condition that severely damages the quality of life of
patients. Tinnitus is caused by aging, acoustic trauma, and ototoxic drugs. Although tinnitus is possibly the effect of physical damage to the auditory cortex and sensory hair cells, it creates major psychological distress in patients, leading to sleep deprivation, depression, and anxiety. Severe depression, in turn, aggravates tinnitus and has the worst outcome [80, 81]. Patients with tinnitus also experience distress and mood swings [82]. This could be an immense burden and impact the quality of life of patients. To address this issue, identifying an effective treatment for tinnitus is crucial.

This study aimed to provide a clear insight into tinnitus caused by the destruction of the peripheral auditory nervous system. Numerous statistical studies have indicated that most patients with tinnitus also experience sensorineural hearing loss. Glutamate-induced excitotoxicity is a major cause of damage to the peripheral auditory nervous system, as loud noise and ototoxic drugs, which are major sources of trauma, produce this excitotoxicity. Although various glutamate antagonists are used to reduce excitotoxicity, identifying a better strategy to treat tinnitus is crucial as the existing strategies have not been proven to provide long-term relief from tinnitus. One such strategy is to eliminate ROS, which are produced because of excitotoxicity, through autophagy activation. This will overcome the damage caused to mitochondria that is responsible for ROS synthesis and prevent the loss of hair cells. Thus, this strategy could be viable to reduce the effects of tinnitus.

Ye et al. [56] highlighted that the degeneration of hair cells and spiral ganglion neurons is the result of impaired autophagy degradation. Although many drugs activate various steps of autophagy, the whole autophagic flux must be completed to protect against excitotoxicity. Various recent studies suggested that the autophagy mechanism is implicated in the protection of the auditory pathway during several degenerative conditions. However, many glutamate antagonistic drugs, antidepressants, and muscle relaxants administered to treat tinnitus are ineffective. The above-mentioned studies on ototoxic drugs, such as cisplatin and gentamycin, clearly show that cell death is delayed owing to autophagy activation as a stress response. In addition, some of the current pharmacological interventions, such as memantine, amitriptyline, and fluoxetine, are known to be involved in autophagy. Therefore, in the future, researchers could conduct more studies on various autophagy-activating drugs as therapeutic agents for tinnitus. The family of drugs that inhibit mTOR, such as rapamycin, temsirolimus, metformin, everolimus, and deforolimus, are already known to activate autophagy and are efficient in the treatment of age-related neurodegenerative diseases, such as Alzheimer’s, Parkinson’s, and Huntington’s diseases [83]. Caloric or dietary restriction is one of the most widely discussed strategies to activate autophagy [84]. Neuroprotection by dietary restriction and dietary restriction mimetics has also been recently discussed [85]. Along with pharmacological interventions (especially drugs that both activate the autophagy mechanism and accompany the autophagosome and lysosomal fusion to complete autophagic flux), autophagy activation by unorthodox strategies such as dietary restrictions and mimetics could also be considered in the future as a strategy to alleviate tinnitus. This could preserve the pristine condition of the cell and result in better treatment for patients with tinnitus. In summary, this review attempts to provide evidence for the positive role of autophagy in tinnitus and provides an organized outline that unifies the known causes of tinnitus and paints a clearer picture of disease pathogenesis in association with ROS clearance and autophagy.

ACKNOWLEDGEMENTS

This study was supported by the National Research Foundation of Korea (NRF) grant from the Korean government (MSIT) (No. 2021R1A2C101417611), and was supported by research fund from Chosun University, 2022.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR’S CONTRIBUTION

All the authors contributed to the conception and design of the study. The literature review and the first draft of the manuscript were prepared by Karthikeyan A Vijayakumar and Gwang-Won Cho. Nagarajan Maharajan verified the content of the manuscript, and Chul Ho Jang and Gwang-Won Cho conceptualized and reviewed the manuscript and commented on its previous versions. All authors have read and approved the final manuscript.

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