Radical scavengers for elderly patients with age-related hearing loss

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Abstract

Conclusion. The results of this study suggest that treatment with radical scavengers has the potential to become an effective new therapy for age-related hearing loss. Objective. To assess the efficacy of treatment with radical scavengers for age-related hearing loss. Subjects and methods. Rebamipide (300 mg/day), α-lipoic acid (60 mg/day), and vitamin C (600 mg/day) were given orally for at least 8 weeks to 46 elderly patients with age-related hearing loss. Results. Hearing levels after treatment were significantly improved at all frequencies.

Keywords: Presbyacusis, pilot study, radical scavengers, free radical

Introduction

Over the past century, research in the field of age-related hearing loss (presbyacusis) has made great progress in documenting anatomic, physiological, audiological, and other changes manifested by the aging auditory system. These changes include progressive degeneration of sensory, neural, strial, and supportive cells in the cochlea, as well as deterioration of the plasticity of central neural processing. The effects of age-related peripheral and central auditory changes interact with diminished cognitive support of auditory perception, thereby raising thresholds, reducing speech understanding in noisy and reverberant environments, interfering with the perception of rapidly modulated speech, and impairing sound source localization, all of which are characteristic of presbyacusis [1,2]. Our greatly improved knowledge regarding the causes, symptoms, and epidemiology of age-related hearing loss has not been matched by our ability to successfully alleviate its detrimental consequences.

In recent years, the effects of free radicals, i.e. reactive oxygen species (ROS), nitric oxide (NO), and their metabolites, on biological systems have attracted considerable attention. These agents are known to have serious pathological effects in many biological reactions that maintain normal cell functioning. Accumulating evidence shows that free radicals act as an important causative agent in several forms of tissue damage, such as that resulting from inflammatory responses, ischemic damage to organs, and damage caused by the intracellular metabolism of chemicals and drugs. Tissue damage during ischemia, and especially during the phase of reperfusion and prolonged hypoperfusion, is increasingly ascribed to free radicals [3].

It has also been claimed that, in the inner ear, free radicals may play a principal role in certain inner ear disorders, such as acoustic trauma, labyrinthitis, aminoglycoside ototoxicity, cisplatin ototoxicity, Ménière’s disease (MD), and age-related hearing loss (ARHL) [2,4]. In contrast, protection from inner ear damage caused by aminoglycosides, cisplatin, lipopolysaccharide-induced labyrinthitis, acoustic trauma, and ARHL is known to be provided by radical scavengers [4–7]. Furthermore, it has been claimed that treatment with antioxidants (such as vitamins E and C and α-lipoic acid), or with dietary restriction, attenuated ARHL in an animal model [8–11].

Based on these findings, we hypothesized that synthesis of free radicals in the inner ear may play an important part in the pathogenesis of ARHL and
that radical scavengers may therefore be an effective form of treatment. We have already examined the possibility that both prevention and treatment of sensorineural hearing loss can be effected by controlling free radicals, and that radical scavengers may be effective for the treatment of hearing loss caused by MD [12] and cisplatin [13]. The efficacy of radical scavengers was also noted in the treatment of idiopathic sudden hearing loss [14]. Encouraged by these results, we undertook a pilot study to establish whether radical scavengers can be used to treat ARHL. Our results were both successful and encouraging [15]. However, that study included cases with asymmetrical hearing loss, especially in the low frequencies. In order to avoid any cause of hearing loss other than ARHL, we selected patients even more carefully and increased their number, which gave us more precise findings about the treatment of sensorineural hearing loss in elderly patients [16].

**Subjects and methods**

**Subjects**

The study subjects were recruited from a group of patients who complained of age-accompanying hearing impairment but who had no other cause of hearing loss, such as otitis media, MD, acoustic trauma, or acoustic tumour, from June 2005 to July 2007. They were scheduled for treatment of their hearing impairment at the Department of Otalaryngology in Hiroshima University Hospital or at North Fuchu City Hospital, Hiroshima. All the patients received a detailed explanation of the study, including risks and possible benefits, and their informed consent was obtained. The average age of the 46 patients (10 males and 36 females) was 76.7 years (range 70–91 years). They were given rebamipide (300 mg/day), vitamin C (600 mg/day), and α-lipoic acid (60 mg/day) for at least 8 weeks. The treatment was tapered off if and when requested by a patient. The effects on hearing and general health as well as possible side effects were investigated.

**Evaluation of hearing**

Determination of hearing change was based on pure-tone hearing levels at 125, 250, 500, 1000, 2000, 4000, and 8000 Hz and was accomplished by comparing the pretreatment hearing level with that after 8 weeks of treatment or with the final hearing level. An increase of ≥10 dB was deemed to denote a clinically significant improvement, a decrease or an increase <10 dB represented no change, and a decrease of ≥10 dB indicated deterioration.

**Results**

The average duration of treatment with radical scavengers during the study was 12.9 weeks (range 8–52 weeks). Two typical cases are illustrated in Figures 1 and 2.

The treatment outcome regarding hearing was evaluated in 92 ears. The average pure-tone hearing level threshold in patients during pretreatment was 48.7 ± 11.23 (mean ± SD) dB, which differed significantly from the average thresholds following radical scavengers therapy: 43.9 ± 10.63 dB after 8 weeks (p < 0.001) and 43.5 ± 10.67 dB at final observation (p < 0.001). Hearing levels after 8 weeks of treatment as well as the final hearing levels had improved significantly compared with pretreatment at 125 Hz (44.3 ± 13.63 → 6.9 ± 14.48 → 36.7 ± 14.09 dB; pretreatment → after 8 weeks → final) (p < 0.001), 250 Hz (42.8 ± 15.03 → 35.8 ± 13.79 → 35.4 ± 13.74 dB) (p < 0.001), 500 Hz (40.4 ± 13.56 → 34.3 ± 13.06 → 33.9 ± 12.69 dB) (p < 0.001), 1000 Hz (38.8 ± 12.78 → 35.6 ± 13.17 → 35.4 ± 13.06 dB) (p < 0.001), 2000 Hz (45.0 ± 12.73 → 43.4 ± 12.67 → 43.4 ± 12.56 dB) (p < 0.05), 4000 Hz (54.8 ± 14.74 → 51.9 ± 13.58 → 51.7 ± 14.21 dB) (p < 0.001), and 8000 Hz (74.9 ± 17.08 → 69.1 ± 15.89 → 68.3 ± 15.90 dB) (p < 0.001) (Figure 3).

At the final observation, 40 (43.5%) ears showed a clinically significant improvement of hearing (≥ 10 dB), 49 were unchanged, and 3 were worse at 125 Hz; 38 (41.3%) ears were improved, 50 unchanged, and 4 worse at 250 Hz; 34 (37.0%) ears were improved, 56 unchanged, and 2 worse at 500 Hz; 22 (23.9%) were improved, 64 unchanged, and 6 worse at 1000 Hz; 9 (9.8%) ears were improved, 78 unchanged, and 5 worse at 2000 Hz; 21 (22.8%) ears were improved, 68 unchanged, and

![Figure 1. Case 1](image-url)
3 worse at 4000 Hz; 34 (37.0%) ears were improved, 55 unchanged, and 3 worse at 8000 Hz (Figure 4).

The correlation between the pretreatment hearing level and the change in hearing level was calculated for each ear at different frequencies. The improvement in hearing was greater at low frequencies (125, 250, and 500 Hz) and at 8000 Hz. However, there was little change in hearing before and after the radical scavenger therapy at 1000, 2000, and 4000 Hz. Moreover, significant correlations between pretreatment hearing levels and changes in hearing were noticed at 125 Hz ($p < 0.001$), 250 Hz ($p < 0.01$), 500 Hz ($p < 0.001$), 1000 Hz ($p < 0.01$), 2000 Hz ($p < 0.05$), 4000 Hz ($p < 0.01$), 8000 Hz ($p < 0.001$), and average ($p < 0.001$) (Figure 5).

Steep audiogram vs flat audiogram
To evaluate the treatment results for ARHL more strictly, analysis was also made between the patients with a steep type audiogram (steep group without hearing loss at low frequencies; excluding patients with $\geq 50\,\text{dB}$ hearing level at 125, 250, or 500 Hz) and the patients with a flat type audiogram (flat group with hearing loss at low frequencies; patients with $\geq 50\,\text{dB}$ hearing level at 125, 250, or 500 Hz). The ‘steep’ group comprised 23 patients (6 males, 17 females) whose average age was 76 years (range 70–88 years). The average duration of treatment with radical scavengers during the study was 12.6 weeks (range 8–52 weeks). The treatment outcome regarding hearing was evaluated in 46 ears.

The average pure-tone hearing level threshold in patients during pretreatment was $42.5 \pm 7.87\,\text{dB}$, i.e. differed significantly from the average thresholds following radical scavenger therapy: $38.2 \pm 8.06\,\text{dB}$ at final observation ($p < 0.001$). The final hearing levels had improved significantly compared with pretreatment at 125 Hz ($35.4 \pm 7.73 \rightarrow 29.3 \pm 10.41\,\text{dB}$; pretreatment $\rightarrow$ final) ($p < 0.001$), 250 Hz ($33.6 \pm 7.86 \rightarrow 27.1 \pm 8.34\,\text{dB}$) ($p < 0.01$), 500 Hz ($32.6 \pm 8.48 \rightarrow 27.1 \pm 8.60\,\text{dB}$) ($p < 0.001$), 1000 Hz ($33.4 \pm 10.90 \rightarrow 30.2 \pm 11.59\,\text{dB}$) ($p < 0.01$), 2000 Hz ($42.0 \pm 12.63 \rightarrow 40.2 \pm 13.25\,\text{dB}$) ($p < 0.05$), and 8000 Hz ($69.3 \pm 14.70 \rightarrow 63.8 \pm 14.57\,\text{dB}$) ($p < 0.001$), but were unchanged at 4000 Hz ($51.3 \pm 13.88 \rightarrow 49.2 \pm 13.94\,\text{dB}$) (Figure 6).

At the final observation, 17 (37.0%) ears showed a clinically significant hearing improvement ($\geq 10\,\text{dB}$), 27 were unchanged, and 2 were worse at 125 Hz; 22 (47.8%) ears were improved, 23 unchanged, and 1 worse at 250 Hz; 18 (39.1%) ears were improved, 27 unchanged, and 1 worse at 500 Hz; 10 (21.7%) were improved, 33 unchanged, and 3 worse at 1000 Hz; 5 (10.9%) ears were improved, 39 unchanged, and 2 worse at 2000 Hz; 5 (10.9%) ears were improved, 40 unchanged, and 1 worse at 4000 Hz; 17 (37.0%) ears were improved, 27 unchanged, and 2 worse at 8000 Hz (Figure 7a).

The ‘flat’ group comprised 23 patients (4 males, 19 females) whose average age was 77.4 years (range 70–91 years). The average duration of treatment with radical scavengers during the study was 13.3 weeks (range 8–36 weeks). The treatment outcome regarding hearing was evaluated in 46 ears. The average pure-tone hearing level threshold in patients during pretreatment was $54.8 \pm 10.77\,\text{dB}$, i.e. differed significantly from the average thresholds after radical scavenger therapy: $48.9 \pm 10.29\,\text{dB}$ at final observation ($p < 0.001$). The final hearing levels had improved significantly compared with pretreatment at 125 Hz ($53.2 \pm 12.49 \rightarrow 44.0 \pm 13.52\,\text{dB}$;
pretreatment → final) \( (p < 0.001) \), 250 Hz \( (52.0 \pm 14.92 \rightarrow 43.7 \pm 13.14 \text{ dB}) \) \( (p < 0.001) \), 500 Hz \( (48.3 \pm 13.22 \rightarrow 40.7 \pm 12.54 \text{ dB}) \) \( (p < 0.001) \), 1000 Hz \( (44.3 \pm 12.33 \rightarrow 40.7 \pm 12.45 \text{ dB}) \) \( (p < 0.01) \), 4000 Hz \( (58.2 \pm 14.92 \rightarrow 54.2 \pm 14.18 \text{ dB}) \) \( (p < 0.01) \), and 8000 Hz \( (79.8 \pm 17.82 \rightarrow 72.8 \pm 16.04 \text{ dB}) \) \( (p < 0.001) \), but were unchanged at 2000 Hz \( (48.0 \pm 12.22 \rightarrow 46.5 \pm 11.10 \text{ dB}) \) (Figure 6). There were no significant differences in hearing improvement between the ‘steep’ group and the ‘flat’ group at any frequency.

At the final follow-up, 23 (50.0%) ears showed a clinically significant hearing improvement (≥ 10 dB), 22 were unchanged, and 1 was worse at 125 Hz; 16 (34.8%) ears were improved, 27 unchanged, and 3 worse at 250 Hz; 16 (34.8%) ears were improved, 29 unchanged, and 1 worse at 500 Hz; 12 (26.1%) were improved, 31 unchanged, and 3 worse at 1000 Hz; 4 (8.7%) ears were improved, 39 unchanged, and 3 worse at 2000 Hz; 16 (34.8%) ears were improved, 28 unchanged, and 2 worse at 4000 Hz; 17 (37.0%) ears were improved, 28 unchanged, and 1 worse at 8000 Hz (Figure 7b).

Normal hearing ears vs impaired hearing ears

To evaluate the treatment outcome between the normal hearing group (better than mean age-corrected hearing level) and the impaired hearing group, treatment results in these two groups were compared. The two groups were divided according to the mean hearing level of the normal elderly population in Japan [17]. The average hearing level of those aged 70–74 years is 31.27 dB at 125 Hz, 31.91 dB at 250 Hz, 31.91 dB at 500 Hz, 34.79 dB at 1000 Hz, 42.41 dB at 2000 Hz, 55.01 dB at 4000 Hz and 67.60 dB at 8000 Hz; 35.11, 35.21, 35.55, 39.34, 46.84, 57.19, 71.55 dB, respectively, aged 75–79 years and 40.41, 41.01, 42.72, 45.20, 52.50, 64.88, 78.09 dB, respectively, aged over 80 years. The normal (appropriate to age) ears showed a significant improvement in hearing level at 125, 250, and 500 Hz after radical scavenger treatment, while impaired hearing ears showed a significant improvement at all frequencies. A significant difference in improved level was also noted at 125, 250, 500 1000, 4000, and 8000 Hz in the normal vs the impaired group (Table I, Figure 8).

Discussion

Age-related hearing loss is the primary cause of impaired hearing worldwide, implying a significant burden not only for sufferers, but also for those who communicate with them. The medical and socioeconomic costs are immense, and given the increase in the world’s population and the fact that the number of elderly individuals is expected to more than double by 2030, this problem is escalating [8].

In a number of studies, free radicals have been implicated in the damage associated with cochlear ischemia [18], noise trauma [5], aging, presbyacusis [8–11], and ototoxicity [6,7,20]. Biogerontologists have suggested possible ways to alleviate free radical-associated age-related changes (including presbyacusis). One way was to attempt to minimize the effects of mitochondrial damage, and to reduce free radical damage by dietary restriction and/or the use of dietary antioxidants [1]. Seideman and co-workers [8,9,18] also hypothesized that presbyacusis could be modulated by ingestion of dietary antioxidants (e.g. vitamins E and C, and antioxidant-rich...
Figure 5. The correlation between pretreatment hearing level and change in hearing level was calculated for each ear at different frequencies. Significant correlations between pretreatment hearing levels and changes in hearing were noted at all frequencies.
fruit and vegetables), as well as by dietary restriction. If dietary antioxidants or any other nutritional supplement have a beneficial effect on the efficiency of several human systems, it is conceivable that the functioning of the auditory system could also be improved, or at least maintained.

To apply radical scavengers for the treatment of age-related hearing loss, we selected rebamipide, α-lipoic acid, and vitamin C, as these drugs act as such and have already been widely used for other purposes, e.g. for the treatment of gastric ulcers and vitamin deficiency. These agents have also already been used clinically to treat cisplatin-induced hearing loss [13] and MD [12], and idiopathic sudden hearing loss [20], with satisfactory results [12].

The results of the present study demonstrated that some patients sustained a significant improvement in hearing, both subjectively and objectively, which would suggest the efficacy of this therapy. Radical
scavenger therapy produced significant hearing improvement at all frequencies.

Concerning the etiology of ARHL, various types of pathological changes, namely sensory, neural, strial, cochlear conductive, mixed, and intermediate, are known [2,21]. Changes in sensory functioning are generally associated with a steep high-frequency hearing loss but usually well preserved speech recognition ability. The main histopathological changes occur in the organ of Corti, with loss of sensory and supporting cells. Sensory cell degeneration occurs typically at the extreme basal end of the cochlea; the outer hair cells degenerate first, followed by inner hair cells. Improvement in hearing at high frequencies (especially at 8000 Hz) may be due to the improvement of sensory cell function, as it has been reported that the formation of free radicals in the sensory cells may be a crucial factor in such forms of hearing loss as acoustic trauma, labyrinthitis, aminoglycoside ototoxicity, cisplatin ototoxicity, MD, and presbyacusis [3–7]. It has also been demonstrated that radical scavengers provide protection from inner ear damage caused by aminoglycosides, cisplatin, lipopolysaccharide-induced labyrinthitis, acoustic trauma, and presbyacusis [3–7].

Improved hearing at low frequencies may result from improved functioning of the stria vascularis, in which free radical formation under pathological conditions has also been noted [4,7,19]. The stria vascularis appears to be an ion transport and control structure. It produces the necessary ion concentrations in the endolymph that enable generation of the endocochlear potential, an essential process for normal cochlear functioning. Atrophy of stria vascularis, including loss of both strial tissue and cells, chiefly in the apical and middle turns of the cochlea, is characteristic of age-related strial hearing loss. The loss of strial tissue in aging ears is believed to affect some endolymph characteristics, which in turn negatively affect the physical and chemical processes by which energy essential for cochlear functioning is provided. Although audiograms associated with age-related strial hearing loss are not uniform, findings typically include a slowly progressing, symmetrical,
Relatively flat, mild-to-moderate hearing loss, but good speech recognition [2,21].

In our earlier, pilot study [15], we reported significant threshold improvements at 125, 250, 500, and 8000 Hz, but no significant improvement at 1000, 2000, or 4000 Hz. In the present investigation, the improvement of hearing was also lower at 1000, 2000, and 4000 Hz, but significant at all frequencies. Moreover, some patients did show marked improvements at 1000, 2000, and 4000 Hz as well. This was also the case in patients with MD [12] and cisplatin ototoxicity [13]. In animal experiments, it has been suggested that inner ear sensory cells are capable of sustaining sublethal damage, although it is virtually impossible to recover function after complete cell death [22]. This is also the case in human subjects.

In the present study, to avoid all causes of hearing loss other than presbyacusis, we selected the patients more strictly and increased their number. In addition, analysis was also made between the patients with a ‘steep’-type audiogram and the patients with a ‘flat’ audiogram. ‘Steep’ audiogram may represent sensory or neural presbyacusis and ‘flat’ audiogram may represent strial presbyacusis. The ‘steep’ group showed a significant improvement in hearing at all frequencies except 4000 Hz, while the ‘flat’ type showed a significant improvement at all frequencies except 2000 Hz. Moreover, there were no significant differences in the improvement of hearing at all frequencies between these two groups. These findings may corroborate the efficacy of radical scavengers for the treatment of any type of presbyacusis.

Concerning the limitation of this therapy, we studied the difference between normal hearing (appropriate to age) ears and impaired hearing ears. The former showed significant improvement only at low frequencies. Similar results were obtained in a double-blind, randomized, placebo-controlled trial of folic acid supplementation on hearing in older adults. After 3 years of folic acid supplementation, thresholds in the low frequencies rose by 1.0 dB and by 1.7 dB in the placebo groups ($p = 0.020$) [23]. Folic acid supplementation did not arrest the deterioration of hearing at high frequencies. This could be the limitation of this form of therapy. The present results also showed a positive correlation between pretreatment hearing levels and improvement in hearing at all frequencies, i.e. the ear with poorer hearing has a greater possibility to recover. Impaired hearing ears showed better treatment results than normal-hearing ears, but did not surpass normal-hearing levels. In other words, radical scavenger therapy can improve impaired hearing to the normal (mean) hearing level appropriate to age, but not to a better hearing level of younger age. This is the limitation of the treatment.

Regarding the application of radical scavengers to presbyacusis, there are two ways; one is for prevention, the other is for treatment. In animal studies, radical scavengers were used for both prevention and treatment. In a rat model, a 30 day treatment of 24-month-old rats with 50 mg/kg l-carnitine significantly ameliorated age-related deterioration of auditory pathways, thus demonstrating the efficacy of this therapy for treatment of presbyacusis [10]. In a dog model, an antioxidant diet ($\alpha$-tocopherol, l-carnitine, $\alpha$-lipoic acid, ascorbic acid) for 3 years showed reduced degeneration of spiral ganglion cells and stria vascularis vs the control diet group. Treatment with vitamins C, E, or melatonin gave protection from ARHL in rats [8,9]. These studies showed the efficacy of radical scavengers for prevention of presbyacusis [11]. The present study represents the treatment of presbyacusis. However, it does have one limitation: the treatment could not give any improvement beyond the normal hearing level appropriate to age. This may suggest that prevention of presbyacusis is more important, which is the next step. The antioxidant diet and/or supplementation with radical scavengers at a younger age might be a suitable way to prevent presbyacusis.

In this study, we chose rebamipide, vitamin C, and $\alpha$-lipoic acid as radical scavengers. Besides these drugs, there are several other candidates, i.e. vitamin E ($\alpha$-tocopherol) [8,14,20], l-carnitine [8], ebselen [24], edaravone [25], etc. All of these were confirmed as capable of reducing inner ear damage in an animal model. In addition, vitamin E [14] or a combination of vitamins B and E [20] has been used to treat idiopathic sudden hearing loss, with acceptable results. Further evaluation of this new drug combination may be useful for the treatment of presbyacusis.

In conclusion, the results of this study demonstrated that treatment with radical scavengers has the potential to become an effective new therapy for presbyacusis. However, this finding is only preliminary in view of the short follow-up period. Further evaluation of this treatment modality for recovery from or prevention of hearing loss is necessary. In addition, a closely controlled randomized study needs to be performed to confirm the efficacy of this treatment.

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References