Table 1. Summary of structural changes in the cochlea at several time points after 3-NP administration

	3 h	1 day	7 days	14 days
Spiral ligament				
Type 2, type 4 fibrocytes	++	++	+++	+++
Type 1, type 3 fibrocytes	+	+	+	+
Spiral prominence				
Type 2 fibrocytes	++	++	+++	+++
Stria vascularis				
Marginal cell	++	++	++	+++
Intermediate cell	++	++	++	+++
Basal cell	N	N	N	N
Organ of Corti				
Outer hair cell	N	N	+	+
Inner hair cell	N	N	N	N
Deiters cell	N	N	N	+
Spiral ganglion				
Spiral ganglion cell	++	+	N	N

For the cells of the spiral ligament, spiral prominence and stria vascularis, the degree of cell degeneration is indicated. For the outer and inner hair cells, the occurrence of mitochondrial translocation is indicated. For the Deiters cell, the degree of shrinkage is indicated. For the spiral ganglion cell, the degree of mitochondrial swelling is indicated. None of these changes were observed in corresponding control rats. N = Normal morphology or absence of mitochondrial translocation; + = mild degeneration or mild mitochondrial swelling or presence of mitochondrial translocation; ++ = moderate degeneration or marked mitochondrial swelling; +++ = severe degeneration.

endocochlear potential [Salt, 2001; Wangemann, 1995; Wangemann and Schacht, 1996]. It has been postulated that the potassium recycling pathway toward the stria vascularis is critical for these functions although the exact mechanisms and pathway have not been definitely proved [Santos-Sacchi, 2000]. One candidate of such a ion transport system consists of extracellular flow through scala tympani and scala vestibuli, and transcellular flow through the organ of Corti, supporting cells, and cells of the lateral wall [Kikuchi et al., 1995; Spicer and Schulte, 1996]. According to this theory, type 2 and type 4 fibrocytes resorb potassium ions from the surrounding perilymph and from outer sulcus cells via the Na,K-ATPase. The potassium ions are then transported to type 1 fibrocytes, strial basal cells and intermediate cells through gap junctions, and are secreted into intrastrial space through the potassium channel. The secreted potassium ions are incorporated into marginal cells by Na,K-ATPase and the Na-K-Cl cotransporter, and are finally secreted into the endolymph through the potassium channel. In addition, a direct measurement of standing currents in the cochlea demonstrated ongoing ion movement, which most likely represented potassium ion movement, from scala tympani and scala vestibuli, through extracellular spaces in the spiral ligament, to the lateral surface of the stria vascularis [Zidanic and Brownell, 1990]. These potassium ion transport systems generate endocochlear potential and high potassium concentration in the endolymph, both of which are essential for the transduction of sound by hair cells [Santos-Sacchi, 2001].

Impairment of such a ion transport system has been assumed to result in hearing loss. For example, inhibition of the Na-K-Cl cotransporter with loop diuretics or mutations in the gene encoding the Na-K-Cl cotransporter reduces endocochlear potential, results in hearing loss and in an enlarged intrastrial space much like we found in the present study [Flagella et al., 1999; Quick and Duvall, 1970]. Another example that parallels our results is the Brn-4 gene-deficient mouse, which exhibits reduced endocochlear potential and hearing loss and shows severe ultrastructural alterations in spiral ligament fibrocytes, including cellular atrophy and a reduction in the number of mitochondria in these cells [Minowa et al., 1999].

In the present study, type 2 fibrocytes in the spiral prominence, type 4 fibrocytes in the spiral ligament, marginal cells and intermediate cells in the stria vascularis were all primarily affected. All these cell types are known to express Na,K-ATPase, and presumably constitute the potassium recycling pathway. Because of the alterations in the spiral ligament fibrocytes, we assume that intercellular communication through gap junctions was damaged, which may lead to the impairment of passive potassium transport through these cells. Marked atrophy or loss of type 2 and type 4 fibrocytes and less conspicuous alteration of type 1 and type 3 fibrocytes suggest impairment of active resorption of potassium ion and following diffusion through gap junctions. Marked atrophy of marginal and intermediate cells associated with loss of mitochondria in the marginal cells strongly indicates impaired potassium transport into the endolymph. The enlarged intrastrial space may be the result of impaired uptake of potassium ions by marginal cells, as was the case for inhibition of the Na-K-Cl cotransporter. Considering these morphological and functional correlations, elevated ABR thresholds observed in the present study may be the result of an impaired ion transport system in the lateral wall due to acute cochlear mitochondrial dysfunction.

In the organ of Corti, translocation of mitochondria in the outer hair cells and slight shrinkage of the Deiters cells were detected after administration of 3-NP in contrast to the maintained normal structures in inner hair cells and

their nerve endings. The major function of outer hair cell is to enhance the sensitivity to specific sound frequencies through their fast motility, and the Deiters cells structurally support the outer hair cells on the basilar membrane. Although it has been reported that this active amplification of sound by the outer hair cell is independent of ATP [Ashmore, 1987; Santos-Sacchi, 1989], and rather is operated by its membrane potential [Ashmore, 1987; Santos-Sacchi and Dilger, 1988], any changes in the mitochondrial function in the outer hair cell are likely to affect mechanisms controlling its membrane potential, which may result in outer hair cell dysfunction.

The changes in outer hair cells and Deiters cells were first detected at 7 days and 14 days after 3-NP administration, respectively, in contrast to the structural changes in the cochlear lateral wall, which were detected as early as 3 h after 3-NP administration. This time difference suggests that mitochondrial translocation in the outer hair cells and shrinkage of the Deiters cells may be secondary to the changes in the cochlear lateral wall rather than a direct effect of 3-NP on the mitochondria of these cells.

Prominent mitochondrial swelling was transiently detected in the spiral ganglion cells after 3-NP treatment. In contrast, the mean area of spiral ganglion cells in rats treated with 3-NP was not significantly different from that in rats treated with control saline at most time points. The mean area in 3-NP-treated rats was smaller than that in control rats only at 3 h after administration, but was not significantly different from that in normal, untreated rats, suggesting that the difference is not likely to be of pathological significance.

Spiral ganglion cells are the primary afferent neurons that transmit signals from hair cells to the neurons in the brainstem, and dysfunction of the spiral ganglion cells causes hearing loss. For example, selective damage on the spiral ganglion neurons by application of ouabain in the gerbil cochlea resulted in profound hearing loss [Schmiedt et al., 2002]. Neural presbycusis is another example of such hearing loss, in which spiral ganglion neurons are predominantly affected in the aging cochlea [Schuknecht, 1964]. In the present study, dysfunction of cochlear ganglion cells is also likely to be involved in hearing impairment temporarily after 3-NP administration. However, it is unlikely that the dysfunction of these cells plays a role in persistent hearing loss because the mitochondria in these cells recovered their normal shape within 7 days following administration.

In contrast to the progressive degeneration observed in the lateral wall, mitochondrial swelling in these neurons was only temporary (at 3 h and at 1 day after 3-NP administration). At 7 days or 14 days after administration, the ultrastructural characteristics of the spiral ganglia were normal. The differences in the reaction to acute mitochondrial dysfunction may be explained by the distinct capacity to repair such damage in the spiral ganglion and the lateral wall. One of the candidate molecular mechanisms underlying such reparative capacity involves glial cell line-derived neurotrophic factor (GDNF) which has been reported to enhance survival of the spiral ganglion cells [Ylikoski et al., 1998]. GDNF family members and their receptors are expressed in the spiral ganglion cells of the mature rat cochlea [Stover et al., 2001] and GDNF is upregulated in the rat cochlea following exposure to noise [Nam et al., 2000]. It may be possible that GDNF was also upregulated following administration of 3-NP in the present study and played a role in repair of the damaged spiral ganglion cells. Further exploration of this hypothesis will be the subject of future studies.

To understand the basal-to-apical gradient in the cochlear damage observed in the present study, the pharmacokinetics of 3-NP applied to the round window membrane should be considered. Because of its relatively small size (molecular weight = 119), we assume that 3-NP applied to the round window membrane diffused in the perilymph within the scala tympani at the cochlear basal turn, and spread by local communication between two perilymphatic scalae, i.e. scala tympani and scala vestibuli, presumably across the extracellular spaces of the spiral ligament [Saijo and Kimura, 1984; Salt et al., 1991a, b]. Then, longitudinal gradients of 3-NP distribution along the cochlear scalae probably occurred, as is seen for ionic markers and gentamicin [Salt and Ma, 2001; Plontke et al., 2002]. Thus, exposure to 3-NP within the cochlea was expected to be higher at the basal region and lower at the apical region. This is in agreement with the basal-to-apical gradient of cochlear damage observed in this study.

Because there was a basal-to-apical gradient in the extent of cochlear damage and we mainly examined the apical side of the middle turn in the present study, we searched the literature for the effect of damage in the lateral wall of the cochlear basal turn on the middle turn. Previously, it has been proposed that damage in the lower cochlear turn has a depressant effect on the sound perception mechanism lying apical to this [Mattox and Simmons, 1977]. In an animal model of localized lesion in the cochlear lateral wall, it was also reported that endocochlear potential values were significantly depressed at all sites apical to the localized lesions in the cochlear lateral wall [Gao et al., 1998; Wu and Hoshino, 1999, 2001]. These results suggest that cochlear lateral wall damage in

the basal turn may affect endocochlear potential and ion composition in the apical turns when the damage is severe and their effect on the apical turns beyond the capacity of local maintenance of the endolymph ion composition [Salt, 2001]. In contrast, morphological changes were restricted to the region where the local lesion was produced in this animal model and normal structures were maintained in the apical sites [Gao et al., 1998; Miyashita et al., 1998; Wu and Hoshino, 1999, 2001]. This result indicates that, to a certain degree, damage in the lateral wall in the basal turn and associated changes in the endolymph ion composition do not affect the structure in the higher turns. Because the degree of lateral wall damage appeared structurally milder in the present study than in these reported studies, structural changes in the middle turn reported in the present study are likely to be the result of the direct and local effect of 3-NP rather than the effect of lateral wall damage in the basal turn.

In interpreting the apparent distinct susceptibilities to 3-NP of the lateral wall, organ of Corti, and spiral ganglion, the difference in exposure to 3-NP among these compartments should be considered. Basolateral membranes of the sensory and supporting cells in the organ of Corti and afferent nerve fibers of spiral ganglion cells are surrounded by cortilymph, which is continuous with perilymph. Fibrocytes in the spiral ligament are also surrounded by perilymph. Thus, the degree of 3-NP exposure in these structures at the same region of the cochlear turn was likely to be the same. In contrast, 3-NP exposure was likely to be low for the stria vascularis, where solute movement from the adjacent tissues or fluids is limited because of tight junctions between adjacent marginal cells and basal cells [Salt, 2001]. Furthermore, 3-NP exposure to the spiral ganglion cell bodies was also likely to be low because these cells are located in Rosenthal's canal, which has only limited interaction with the perilymph by way of the endoneurium of nerve fibers, habenula perforata and osseous spiral lamina. Taken together, these differences in the exposure to 3-NP did not coincide with faster and more severe morphological changes in the spiral ligament, stria vascularis, and spiral ganglion cell bodies than in the organ of Corti, and suggest that the susceptibility to 3-NP is higher in the lateral wall and spiral ganglion than in the organ of Corti.

Previously, the effects of acute energy failure on the cochlea have been studied using anoxia or chemical asphyxiants such as carbon monoxide, cyanide and nitric oxide [Brown et al., 1983; Kong et al., 1996; Nuttall and Lawrence, 1979; Pai et al., 1998; Rao and Fechter, 2000; Ruan et al., 1997; Tawackoli et al., 2001; Thalmann et al., 1977]. In these studies, electrophysiological methods were primarily used to investigate the pathophysiology of cochlear dysfunction, and only a small number of morphological studies limited to the organ of Corti and spiral ganglion cells have been conducted [Kong et al., 1996; Pai et al., 1998; Ruan et al., 1997]. No study demonstrated morphological changes in the cochlear spiral ligament.

In contrast to the models using anoxia or chemical asphyxiants, there have been a number of studies examining morphological changes of the cochlea exposed to ischemia-reperfusion which is likely to cause acute cochlear energy failure similar to that seen in the present model [Billett et al., 1989; Hakuba et al., 2003; Kimura and Perlman, 1958; Koga et al., 2003; Ohlemiller and Dugan, 1999; Perlman et al., 1959; Pujol et al., 1992; Puel et al., 1994; Tabuchi et al., 2002; Tsuji et al., 2002]. In most of these studies, however, the observation periods between the exposure and the morphological analysis were relatively short (usually several hours), and the cochlear structures most readily affected included afferent dendrites, hair cells, stria vascularis, pillar cells, Deiters and Hensen cells. In two animal models of the cochlear ischemia-reperfusion, cochlear morphology was examined after relatively long observation periods, 5 days and 7 days after exposure [Tsuji et al., 2002; Koga et al., 2003; Hakuba et al., 2003]. However, only the organ of Corti and spiral ganglion cells were examined in these studies.

Comparing the morphological features in the previous studies with those observed in the present study, degeneration of the stria vascularis and the relatively well-preserved organ of Corti were common features. However, morphological changes in the afferent dendrites frequently reported after exposure to ischemia-reperfusion were not detected in the present model. Morphological changes in the spiral ligament fibrocytes detected in the present model have not been reported in the previous studies. These differences were most likely due to the differences in the onset, duration and degree of cochlear energy failure between the present animal model and the previous models. Because a long observation period is possible following exposure to 3-NP using the present model, further study of the molecular mechanism underlying the functional and morphological changes observed in this model may lead to the discovery of a novel therapeutic strategy.

Conclusion

The present study showed that the degeneration of the cochlear lateral wall was the primary pathological change in the permanent threshold shift model due to acute mito-

chondrial dysfunction, and suggests that cochlear ion transport may be impaired in this model. Therefore, protection, repair, or regeneration targeted to the lateral wall may constitute a key therapeutic strategy for hearing loss due to acute energy failure such as cochlear ischemia.

Acknowledgements

We thank Mr. S. Nakagawa for his excellent technical assistance in light and electron microscopy. We also thank Dr. Seiji Bito for his help with the statistical analysis. This work was funded by a Health Science Research Grant from the Ministry of Health, Labor and Welfare of Japan (to T.M.).

References

Alston TA, Mela I, Bright HJ: 3-Nitropropionate, the toxic substance of Indigofera, is a suicide inactivator of succinate dehydrogenase. Proc Natl Acad Sci USA 1977;74:3767–3771.

Ashmore JF: A fast motile response in guinea-pig outer hair cells: The cellular basis of the cochlear amplifier. J Physiol 1987;388:323–347.

Billett TE, Thorne PR, Gavin JB: The nature and progression of injury in the organ of Corti during ischemia. Hear Res 1989;41:189–198.

Braverman I, Jaber L, Levi H, Adelman C, Arons KS, Fischel-Ghodsian N, Shohat M, Elidan J: Audiovestibular findings in patients with deafness caused by a mitochondrial susceptibility mutation and precipitated by an inherited nuclear mutation or aminoglycosides. Arch Otolaryngol Head Neck Surg 1996;122:1001–1004.

Brouillet E, Hantraye P, Ferrante RJ, Dolan R, Leroy-Willig A, Kowall NW, Beal MF: Chronic mitochondrial energy impairment produces selective striatal degeneration and abnormal choreiform movements in primates. Proc Natl Acad Sci USA 1995;92:7105–7109.

Brown MC, Nuttall AL, Masta RI, Lawrence M: Cochlear inner hair cells: Effects of transient asphyxia on intracellular potentials. Hear Res 1983;9:131–144.

Coles CJ, Edmondson DE, Singer TP: Inactivation of succinate dehydrogenase by 3-nitropropionate. J Biol Chem 1979;254:5161–5167.

Flagella M, Clarke LL, Miller ML, Erway LC, Giannella RA, Andringa A, Gawenis LR, Kramer J, Duffy JJ, Doetschman T, Lorenz JN, Yamoah EN, Cardell EL, Shull GE: Mice lacking the basolateral Na-K-2Cl cotransporter have impaired epithelial chloride secretion and are profoundly deaf. J Biol Chem 1999;274:26946–26955.

Gao J, Hoshino T, Iwasaki S, Wu R: Photochemically induced focal cochlear lesions in the guinea pig. 1. DAB staining and SEM study. Microsc Res Tech 1998;41:323–333.

Green DR, Reed JC: Mitochondria and apoptosis. Science 1998;281:1309–1312.

Hakuba N, Matsubara A, Hyodo J, Taniguchi M, Maetani T, Shimizu Y, Tsujiuchi Y, Shudou M, Gyo K: AMPA/kainate-type glutamate receptor antagonist reduces progressive inner hair cell loss after transient cochlear ischemia. Brain Res 2003;979:194–202.

Hamilton BF, Gould DH: Nature and distribution of brain lesions in rats intoxicated with 3-nitropropionic acid: A type of hypoxic (energy deficient) brain damage. Acta Neuropathol (Berl) 1987;72:286–297.

Hoya N, Okamoto Y, Kamiya K, Fujii M, Matsunaga T: A novel animal model of acute cochlear mitochondrial dysfunction. Neuroreport 2004;15:1597–1600.

Huang T, Cheng AG, Stupak H, Liu W, Kim A, Staecker H, Lefebvre PP, Malgrange B, Kopke R, Moonen G, Van De Water TR: Oxidative stress-induced apoptosis of cochlear sensory cells: Otoprotective strategies. Int J Dev Neurosci 2000;18:259–270.

Hutchin TP, Cortopassi GA: Mitochondrial defects and hearing loss. Cell Mol Life Sci 2000;57:1927–1937.

Kikuchi T, Kimura RS, Paul DL, Adams JC : Gap junction in the rat cochlea: immunohistochemical and ultrastructural analysis. Anat Embryol 1995;191:101–118.

Kimura R, Perlman HB: Arterial obstruction of the labyrinth. 1. Cochlear changes. Ann Otol Rhinol Laryngol 1958;67:5–23.

Koga K, Hakuba N, Watanabe F, Shudou M, Nakagawa T, Gyo K: Transient Cochlear ischemia causes delayed cell death in the organ of Corti: An experimental study in gerbils. J Comp Neurol 2003;456:105–111.

Kong W, Ren T, Nuttall AL: Electrophysiological and morphological evaluation of the acute ototoxicity of sodium nitroprusside. Hear Res 1996;99:22–30.

Mattox DE, Simmons FB: Natural history of sudden sensorineural hearing loss. Ann Otol Rhinol Laryngol 1977;86:463–480.

Minowa O, Ikeda K, Sugitani Y, Oshima T, Nakai S, Katori Y, Suzuki M, Furukawa M, Kawase T, Zheng Y, Ogura M, Asada Y, Watanabe K, Yamanaka H, Gotoh S, Nishi-Takeshima M, Sugimoto T, Kikuchi T, Takasaka T, Noda T: Altered cochlear fibrocytes in a mouse. Science 1999;285:1408–1411.

Miyashita H, Iwasaki S, Hoshino T: Photochemically induced focal cochlear lesions in the guinea pig. 2. A transmission electron microscope study. Microsc Res Tech 1998;41:334–340.

Nam Y, Stover T, Hartman SS, Altschuler RA: Upregulation of glial cell line-derived neurotrophic factor (GDNF) in the rat cochlea following noise. Hear Res 2000;146:1–6.

Nicholls DG, Budd SL: Mitochondria and neuronal survival. Physiol Rev 2000;80:315–360.

Nuttall AL, Lawrence M: Intracellular potential changes of Corti's organ with anoxia. Arch Otolaryngol 1979;105:574–578.

Ohlemiller KK, Dugan LL: Elevation of reactive oxygen species following ischemia – Reperfusion in mouse cochlea observed in vivo. Audiol Neurootol 1999;4:219–228.

Pai N, Zdanski CJ, Gregory CW, Prazma J, Carrasco V: Sodium nitroprusside/nitric oxide causes apoptosis in spiral ganglion cells. Otolaryngol Head Neck Surg 1998;119:323–330.

Perlman HB, Kimura R, Fernandez C: Experiments on temporary obstruction of the internal auditory artery. Laryngoscope 1959;69:591–613.

Plontke SKR, Wood AW, Salt AN: Analysis of gentamicin kinetics in fluids of the inner ear with round window administration. Otol Neurotol 2002;23:967–974.

Puel JL, Pujol R, Tribillac F, Ladrech S, Eybalin M: Excitatory amino acid antagonists protect cochlear auditory neurons from excitotoxicity. J Comp Neurol 1994;341:241–256.

Pujol R, Puel JL, Eybalin M: Implication of non-NMDA and NMDA receptors in cochlear ischemia. Neuroreport 1992;3:299–302.

Quick CA, Duvall AJ: Early changes in the cochlea duct from ethacrynic acid: An electron microscopic evaluation. Laryngoscope 1970;80:954–965.

Rao DB, Fechter LD: Increased noise severity limits potentiation of noise induced hearing loss by carbon monoxide. Hear Res 2000;150:205–214.

Ruan RS, Leong SK, Yeoh KH: Ototoxicity of sodium nitroprusside. Hear Res 1997;114:169–178.

Saijo S, Kimura RS: Distribution of HRP in the inner ear after injection into the middle ear cavity. Acta Otolaryngol 1984;97:593–610.

Salt AN: Dynamics of the inner ear fluids; in Jahn AF, Santos-Sacchi J (eds): Physiology of the Ear, ed 2. San Diego, Singular, Thompson Learning, 2001, pp 333–355.

Salt AN, Ma Y: Quantification of solute entry into cochlear perilymph through the round window membrane. Hear Res 2001;154:88–97.

Salt AN, Ohyama K, Thalmann R: Radial communication between the perilymphatic scalae of the cochlea: Estimation by tracer perfusion. Hear Res 1991a;56:29–36.

Salt AN, Ohyama K, Thalmann R: Radial communication between the perilymphatic scalae of the cochlea: Estimation by bolus injection into the sealed cochlea. Hear Res 1991b;56:37–43.

Santos-Sacchi J: Asymmetry in voltage-dependent movements of isolated outer hair cells from the organ of Corti. J Neurosci 1989;9:2954–2962.

Santos-Sacchi J: Cell coupling in Corti's organ. Brain Res Brain Res Rev 2000;32:167–171.

Santos-Sacchi J: Cochlear physiology; in Jahn AF, Santos-Sacchi J (eds): Physiology of the Ear, ed 2. *San Diego, Singular*, Thompson Learning, 2001, pp 357–391.

Santos-Sacchi J, Dilger JP: Whole cell currents and mechanical responses of isolated outer hair cells. Hear Res 1988;35:143–150.

Schmiedt RA, Okamura H, Lang H, Schulte BA: Ouabain application to the round window of the gerbil cochlea: A model of auditory neuropathy and apoptosis. J Assoc Res Otolaryngol 2002;3:223–233.

Schuknecht HF: Further observations of presbycusis. Arch Otolaryngol 1964;80:369–382.

Spicer SS, Schulte BA: The fine structure of spiral ligament cells relates to ion return to the stria and varies with place-frequency. Hear Res 1996;100:80–100.

Stover T, Nam Y, Gong TL, Lomax MI, Altschuler RA: Glial cell line-derived neurotrophic factor (GDNF) and its receptor complex are expressed in the auditory nerve of the mature rat cochlea. Hear Res 2001;155:143–151.

Sue CM, Lipsett LJ, Crimmins DS, Tsang CS, Boyages SC, Presgrave CM, Gibson WPR, Byrne E, Morris JGL: Cochlear origin of hearing loss in MELAS syndrome. Ann Neurol 1998;43:350–359.

Tabuchi K, Tsuji S, Fujihira K, Oikawa K, Hara A, Kusakari J: Outer hair cells functionally and structurally deteriorate during reperfusion. Hear Res 2002;173:153–163.

Tawackoli W, Chen G, Fechter LD: Disruption of cochlear potentials by chemical asphyxiants cyanide and carbon monoxide. Neurotoxicol Teratol 2001;23:157–165.

Thalmann R, Thalmann I, Ise I, Paloheimo S: Noxious effects upon cochlear metabolism. Laryngoscope 1977;87:699–721.

Tsuji S, Tabuchi K, Hara A, Kusakari J: Long-term observations on the reversibility of cochlear dysfunction after transient ischemia. Hear Res 2002;166:72–81.

Wangemann P: Comparison of ion transport mechanisms between vestibular dark cells and strial marginal cell. Hear Res 1995;90:149–157.

Wangemann P, Schacht J: Homeostatic mechanisms in the cochlea; in Dallos P, Popper AN, Fay RR (eds): The Cochlea. New York, *Springer*, 1996, pp 130–185.

Wu R, Hoshino T: Changes in off-lesion endocochlear potential following localized lesion in the lateral wall. Acta Otolaryngol 1999;119: 550–554.

Wu R, Hoshino T: Long-term changes in off-lesion endocochlear potential after induction of localized lesions in the lateral wall. Ann Otol Rhinol Laryngol 2001;110:271–276.

Yamane H, Nakai Y, Takayama M, Iguchi H, Nakagawa T, Kojima A: Appearance of free radicals in the guinea pig inner ear after noise-induced acoustic trauma. Eur Arch Otorhinolaryngol 1995;252:504–508.

Yamasoba T, Oka Y, Tsukuda K, Nakamura M, Kaga K: Auditory findings in patients maternally inherited diabetes and deafness harboring a point mutation in the mitochondrial transfer RNA Leu (UUR) gene. Laryngoscope 1996; 106:49–53.

Ylikoski J, Pirvola U, Virkkala J, Suvanto P, Liang XQ, Magal E, Altschuler R, Miller JM, Saarma M: Guinea pig auditory neurons are protected by glial cell line-derived growth factor from degeneration after noise trauma. Hear Res 1998;124:17–26.

Zidanic M, Brownell WE: Fine structure of the intracochlear potential field. I. The silent current. Biophys J 1990;57:1253–1268.