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Expression pattern of oxidative stress and antioxidant defense-related genes in the aging Fischer 344/NHsd rat cochlea

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Abstract

The biological mechanisms that give rise to age-related hearing loss (ARHL) are still poorly understood. However, there is growing recognition that oxidative stress may be an important factor. To address this issue, we measured the changes in the expression of cochlear oxidative stress and antioxidant defense-related genes in young (2 months old), middle-aged (12 months old), and old (21–25 months old) Fischer 344/NHsd (F344/NHsd) rats and compared gene expression changes with ARHL. A quantitative real-time reverse transcription polymerase chain reaction array revealed a significant age-related downregulation of only 1 gene, stearoyl-coenzyme A desaturase 1, and upregulation of 12 genes: 24-dehydrocholesterol reductase; aminoadipate-semialdehyde synthase; cytoglobin; dual oxidase 2; glutathione peroxidase 3; glutathione peroxidase 6; glutathione *S*-transferase, kappa 1; glutathione reductase; nicotinamide adenine dinucleotide phosphate (NAD(P)H) dehydrogenase, quinone 1; solute carrier Family 38, Member 5; thioredoxin interacting protein; and vimentin. Statistical analyses revealed significant correlations between gene expression and auditory function in 8 genes. Our results identified specific subsets of oxidative stress genes that appear to play an important role in ARHL in the Fischer 344/NHsd rat.
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Keywords: Age-related hearing loss; Presbycusis; Cochlea; Fischer 344; Antioxidant; Reactive oxygen species; Oxidative stress; Rat; Genes; Scd1; Dhcr24; Aass; Cygb; Duox2; Gpx3; Gpx6; Gstk1; Gsr; Nqo1; Slc38a5; Txnip; Vim

1. Introduction

Reactive oxygen species (ROS) that are generated during normal metabolism can be effectively eliminated by cellular antioxidant defense mechanisms. Excessive production of ROS, however, overwhelms the antioxidant defense system, leading to oxidative stress and tissue damage as seen in noise-induced hearing loss (Henderson et al., 2006). Increased free radical activity and oxidative stress have been proposed as key determinants of the aging process (Harman, 1956; Sohal and Weindruch, 1996) and tissue degeneration in aging mouse cochleae (Jiang et al., 2007; Staecker et al., 2001).

Mitochondria in particular are considered to be a major source of ROS overproduction in aging tissues (Harman, 1972), and excessive ROS could damage mitochondrial structures and molecules, leading to DNA mutations or deletions. Emerging evidence shows mitochondrial damage in age-related hearing loss (ARHL) in humans (Markaryan et al., 2008) and in various animal models, including DBA/2J and Polg(D257A) knockin mice (Someya et al., 2007; Yamasoba et al., 2007), and Fisher 344/NHsd (F344/NHsd) rats (Seidman et al., 2000; Yin et al., 2007).

The F344/NHsd rat exhibits increased mitochondrial DNA deletions in the cochlea at 6 and 9 months of age (Seidman et al., 2000; Yin et al., 2007). The accumulation of mitochondrial DNA deletions or mutations during aging is thought to impair mitochondrial function, resulting in the

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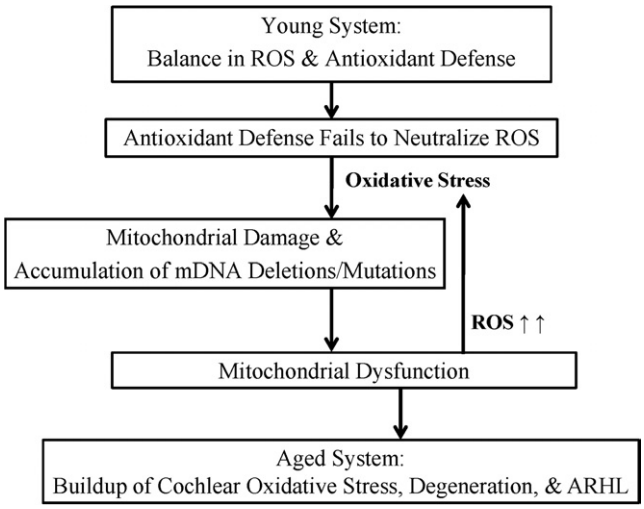

Fig. 1. Oxidative stress and age-related hearing loss (ARHL). Key: mDNA, mitochondrial DNA, ROS, reactive oxygen species.

buildup of cochlear oxidative stress and consequent cochlear degeneration and ARHL (Fig. 1).

The antioxidant defense system is our natural defense against oxidative stress. To understand the role of antioxidant enzymes in the aging degeneration, 2 studies have examined changes in the level of cochlear antioxidant enzyme activity in aging F344/NHsd cochlea (Coling et al., 2009; Lautermann et al., 1997). Compared with 3-month-old rats, 24-month-old F344/NHsd rats exhibit decreased glutathione levels in the auditory nerve. However, enzyme activities of glutathione reductase (Gsr) and glutathione S-transferase (Gst) remained unchanged in the cochlear sensory epithelium (CSE), the lateral wall (LW), auditory nerve, and the vestibular system (Lautermann et al., 1997). Mean glutathione peroxidase (Gpx) activity in the CSE, LW, and auditory nerve increased in the 24-month-old F344/NHsd rats, but the increase was not statistically significant. Another study (Coling et al., 2009) reported a statistically significant increase in Gpx in the LW, but not in the auditory nerve or CSE, suggesting that age-related changes in activities of these enzymes appear to be tissue-specific.

Changes in antioxidant capacity are likely to be caused by expression changes in antioxidant enzymes and molecules. So far, only 1 study has examined age-related changes in antioxidant enzyme gene expression in F344/NHsd rats (Chen and Ruan, 2009). However, this study revealed no significant changes in Cu/Zn-superoxide dismutase (Sod1), Mn-Sod (Sod2), catalase, or Gpx1 in either the auditory cortex or the cochleae. Therefore, a comprehensive analysis of expression patterns of the genes related to oxidative stress and antioxidant defense is necessary.

Human ARHL or presbycusis has been categorized into 6 types (Schuknecht and Gacek, 1993): (1) sensory presbycusis, caused primarily by loss of outer hair cells (OHCs) in the basal end of the cochlea; (2) neural presbycusis, characterized by degeneration of cochlear neurons; (3) strial or metabolic presbycusis, with degeneration in stria vascularis; (4) cochlear conductive presbycusis, hypothetically associated with changes in the stiffness properties of the basilar membrane; (5) mixed presbycusis, a combination of different pathologies; and (6) indeterminate presbycusis, with no obvious cellular pathology, indicating a possibility of impaired cellular function rather than cellular attrition.

To investigate these types of hearing loss, several animal species such as mice, rats, chinchillas, gerbils, and guinea pigs, have been used. Each animal model mimics distinct types of human presbycusis. For example, mice are reported to mimic all types of presbycusis, except for cochlear conductive and indeterminate presbycusis; and rats mimic all types, except for cochlear conductive presbycusis (see Ohlemiller, 2006, 2009 and Syka, 2010 for reviews).

The F344 inbred albino rat, with a median life span of 28–31 months (Chesky and Rockstein, 1976; Rao and Boorman, 1990), is widely used as an animal model of aging and ARHL. Despite the extensive use of the F344, genetic contributions to ARHL in the F344 are still not well understood and need to be investigated. The F344 was originally bred as a natural cancer model at Columbia University (Festing, 1979; Tanaka et al., 2000). Later, the F344 that was brought to the National Cancer Institute was denoted as F344/N and distributed in the USA. The substrain that went to the Charles River Laboratory was denoted as F344/Du and used in Europe for research.

Both the F344/NHsd and F344/DuCrl, which are used in ARHL research, initially develop high-frequency hearing loss that gradually progresses to the low-frequencies later in their lives (Bielefeld et al., 2008; Popelar et al., 2006). The deterioration of auditory function in F344/DuCrl rats is accompanied by pathological changes in the cochlea, including the loss of OHCs, decreased immunostaining of collagen, and fibrocytes in spiral ligament. Possible changes in the collagen of the tympanic membrane were also suggested (Buckiova et al., 2006, 2007; Popelar et al., 2006; Syka, 2010). These investigators also reported high numbers of apoptotic cells in the stria vascularis in 20- to 24-month-old F344/DuCrl rats, suggesting a possibility of abnormal endocochlear potentials (EPs). In contrast, F344/NHsd rats have normal endocochlear potentials at the same age. The differences in cochlear pathologies between the 2 substrains are difficult to assess because the 2 substrains have not been studied simultaneously in 1 laboratory.

The F344/NHsd substrain develops hearing loss starting in the 20–40 kHz range between 9 and 12 months of age, extending down to 5–10 kHz by 18 months of age (Bielefeld et al., 2008). Age-related decreases in distortion product otoacoustic emission (DPOAE) amplitudes were observed

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