Hearing Research 264 (2010) 70–78

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Research paper

The Fischer 344 rat as a model of presbycusis

Josef Syka *

Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, 142 20 Prague, Czech Republic

ARTICLE INFO

Article history:
Received 24 August 2009
Received in revised form 12 October 2009
Accepted 4 November 2009
Available online 10 November 2009

Keywords:
Rat
Fischer 344
Presbycusis
Aging
Model

ABSTRACT

Due to the rising number of the aged human population all over the world, presbycusis is a phenomenon that deserves the increasing attention of the medical community as regards to prevention and treatment. This requires finding appropriate animal models for human presbycusis that will be useful in future experiments. Among the available rat strains, the Fischer 344 (F344) strain promises to serve as a model producing prompt and profound presbycusis. Hearing thresholds begin to increase in this strain during the first year of life; toward the end of the second year, the thresholds are very high. The threshold shifts progress independently in both ears. The rapid deterioration of distortion product otoacoustic emissions, with the majority of outer hair cells (OHC) being present and morphologically intact, is apparently produced by the disruption of prestin. The age-related changes within inner ear function are accompanied by deterioration of acoustical signal processing within central auditory system, mainly due to impaired GABA inhibition. The loss of GABA inhibition in old animals is expressed primarily in the inferior colliculus but is also present in the cochlear nuclei and the auditory cortex. Sound-evoked behavioral reactions are also impaired in old F344 rats. Taken together, the described characteristics of the aging F344 rat auditory system supports the idea that this strain may serve as a suitable model for studying the mechanisms of presbycusis, its prevention and treatment.

1. Introduction

The Fischer 344 (F344) is an inbred albino rat strain that has been widely used since its introduction in 1920 in cancer research and toxicology. The spontaneous age-related incidence of neoplasms and degenerative diseases is very high in this strain. For example, Sass et al. (1975) reported a high incidence of leukemias, mammary tumors, pituitary adenomas and testicular interstitial cell tumors in Fischer 344 rats combined with the presence of degenerative diseases such as myocardial degeneration and nephrosis. Numerous reports have accumulated about the toxic influence of several substances on Fischer 344 rats. Therefore, it is not surprising that the first information about the auditory system in Fischer 344 rats originated from an investigation of the toxic influence of toluene on hearing function in this strain (Rebert et al., 1983). Toluene was found to increase auditory thresholds indicated by measurement of the evoked auditory brainstem responses (ABR).

The first serious attempts to investigate the characteristic features of the aging auditory system in Fischer 344 rats appeared around 1990. These pioneering papers were motivated by a recommendation from the National Institute of Aging to use the F344 strain of rats as a model for studying the effects of aging. Caspary et al. (1990) described a substantial and selective age-related loss of the neurotransmitter GABA within the central nucleus of the inferior colliculus (CIC) comparing the content of GABA in this structure between young adult (2–7-month-old) and aged (18–29-month-old) Fischer 344 rats. Keithley and Croskrey (1990) examined the morphological parameters of the surviving spiral ganglion cell (SGC) endings in the cochlear nucleus of aged Fischer 344 rats (25–26-month-old) and compared them with those of young animals (2–3-month-old). Their motivation came from another study in Sprague–Dawley rats that showed a pronounced degeneration of SGCs with aging (Keithley and Feldman, 1979). The endings in old Fischer 344 rats were more complex; their area was sometimes twice as large as in young animals. Later, Keithley et al. (1992) described the details of age-related cochlear degeneration in four strains of rats. The authors compared the morphological features of inner ear structures, particularly the stria vascularis, in two pigmented strains (Brown Norway and F1 Lewis–Brown Norway) and two albino strains (Fischer 344 and

Abbreviations: F344, Fischer 344; OHC, outer hair cell; IHC, inner hair cell; GABA, γ-amino butyric acid; ABR, auditory brainstem responses; SGC, spiral ganglion cell; F344/DuCrl, Fischer 344 rat substrain from Charles River; Fischer344/NHsd, Fischer 344 rats substrain from National Institute of Health; CAP, compound action potential of the auditory nerve; DPOAE, distorsion product otoacoustic emissions; EP, endocochlear potential; LSO, lateral superior olive; MSO, medial superior olive; MNTB, medial nucleus of the trapezoid body; CN, cochlear nucleus; IC, inferior colliculus; GAD, glutamic acid decarboxylase; FBN, Fischer 344/Brown-Norway F1 hybrid; PV-ir, parvalbumin-immunoreactive; PPI, prepulse inhibition

* Tel.: +420 241062700; fax: +420 241062787.
E-mail address: syka@biomed.cas.cz

0378-5955/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.heares.2009.11.003

Lewis). The study was motivated by the hypothesis that albino strains, lacking melanin, may develop more pronounced degeneration with aging than pigmented strains. However, Keithley et al. (1992) did not find any essential differences in the signs of degeneration in the cochlea with aging among these strains. Their conclusion was that the presence or absence of melanin does not have any effect on cochlear degeneration in the rat with aging. In all of the strains of animals in their study, degeneration of spiral ganglion cells within the apical region was found, as well as the degeneration of the stria vascularis within this area.

Following the initial studies of hearing function in Fischer 344 rats, the strain was used as an animal model of presbycusis in several labs. These resulting studies were oriented either on the cochlea or on the central auditory system. The remainder of this review will describe the results of these studies independently, first concentrating on the typical changes in the cochlea, then on the central F344 auditory system.

2. Age-related changes in the structure and function of the cochlea in F344 rats

There are two substrains of F344 rats, both originating from the F344 colony developed in 1920 at Columbia University in New York (Bielefeld et al., 2008). The substrain denoted as F344/DuCrl stems from Charles River Laboratories, first produced in the USA, however, since 1987 in Germany. Another substrain is denoted as F344/NHsd and was derived from the original Columbia University population of F344 rats by breeding in the National Institute of Health in Bethesda. The possible differences between these two substrains in age-related hearing loss may result from the approximately sixty years genetic drift in their breeding. The results of the studies from our laboratory (Popelář et al., 2003, 2006; Buckiová et al., 2006, 2007) were obtained from the F344/DuCrl substrain obtained from Charles River Wiga, Sulzfeld, Germany, whereas those from the laboratory of D. Henderson (Bielefeld et al., 2008; Hu et al., 2008; Chen et al., 2009) were obtained from the F344/NHsd substrain obtained from Harlan Laboratories. Most of the data are identical or similar; if there are differences, they will be indicated.

2.1. Hearing thresholds, ABR audiograms and CAP

Hearing thresholds in young (1–3-month-old) Fischer 344 rats, as indicated by ABR audiograms, are similar to those observed in other strains of rats, for example in the pigmented strain Long Evans (Fig. 1), with a threshold increase seen as the frequency moves lower or higher from the best frequency of 10 kHz (Popelář et al., 2003, 2006). In the F344/DuCrl substrain the thresholds were found to be about 10 dB higher than in the control strain of pigmented Long Evans rats (Fig. 1). In contrast, the substrain F344/NHsd (Bielefeld et al., 2008) displays the same thresholds as the Long Evans strain. The reason for such differences is not known; speculation includes genetic differences as well as differences in the measurement methods (F344/DuCrl animals were anesthetized by ketamine/xylazine injection whereas the F344/NHsd rats by isoflurane). An essential feature of hearing function, present in both substrains of F344 rats, is the fast deterioration of the audiogram with aging, with threshold shifts reaching 20 dB at low frequencies and 40 dB at high frequencies in 18–20-month-old animals. Fig. 1 shows the contrast between the age-related threshold shifts in F344 rats and the threshold shifts in the Long Evans strain that even at 30 months of age increase by only 5–20 dB at different frequencies. Hearing function deteriorates in F344 rats relatively slowly during the first year of life, then at a faster pace in the second year of their life. Interestingly, in half of the F344 rats older than 12 months, large differences were present between the threshold shifts in the two ears, with one ear having a relatively low threshold shift and the other ear being almost deaf (Popelář et al., 2006). In addition, the large age-related threshold shifts were also combined with smaller amplitudes of ABR potentials in old F344/DuCrl rats in comparison with the control Long Evans rats (Popelář et al., 2006). This corresponds well with the decreased amplitudes of the compound action potential (CAP) of the auditory nerve found in 24-month-old F344/NHsd rats in comparison with 3-month-old animals (Bielefeld et al., 2008).

2.2. Distortion product otoacoustic emissions

Monitoring of distortion product otoacoustic emissions (DPOAEs) during the life span demonstrated that characteristic age-related changes occur in the inner ear of F344 rats (Fig. 2). At first, even in very young F344 rats, DPOAE amplitudes do not reach such values as in the control pigmented Long Evans rats (Popelář et al., 2003, 2006). The average values of DP-grams in 1-month-old F344 rats are approximately 10–15 dB lower than the average DP-grams of Long Evans rats of any age and correspondingly, they cross the level of background noise at higher frequencies than in the case of Long Evans rats. Most importantly, however, the amplitudes of DP-grams in F344 rats continuously decrease with aging until they completely disappear in the background noise in 18-month-old animals. In contrast, in the case of Long Evans rats, almost no differences in average DP-grams are evident when comparing very young and very old rats (Fig. 2). Similarly as in the case of ABR audiograms, the DPOAE amplitudes may decrease with age in F344 animals at different rates in the individual ears of the animals. For example, in the study by Popelář et al. (2006), in half of the 12-month-old rats the DPOAEs were recordable in only one ear, whereas in the opposite ear DPOAEs were totally absent. The deterioration of DPOAEs with age appears to be of the same magnitude and time course when the results obtained in F344/DuCrl rats are compared with the results obtained in F344/NHsd animals (Bielefeld et al., 2008). Taken together, these data demonstrate that: (i) the overall amplitudes of DPOAEs, produced by outer hair cells in F344 rats, are always lower than in control pigmented Long Evans rats; (ii) the DPOAE amplitudes significantly decline with aging in F344 rats, ultimately disappearing in the background noise. This implies that either the conditions for the normal activity of the outer hair cells in this species are pathological (for example, a low electrical gradient resulting from the insufficient activity of the stria vascularis) or intrinsic pathological conditions in the outer hair cells result in a deterioration of their function.

2.3. Hair cell loss

One of the reasons why DPOAE amplitudes decline with aging in F344 rats can be the gradual loss of their generators, i.e. a loss of outer hair cells (OHC) Evaluation of the number of outer hair cells present in old F344 rats (22-month- and 30-month-old, Popelář et al., 2006) resulted, however, in a surprise: a pronounced hair cell loss was observed only at the very apical and very basal parts of the cochlea (50–60% of cells missing) whereas only a few outer hair cells were missing from the middle part of the cochlea (less than 10%) (Fig. 3). The number of missing inner hair cells (IHC) was very low and did not exceed 10%. In 30-month-old Long Evans rats (with DPOAE amplitudes almost the same as those in young Long Evans rats) the pattern of OHC and IHC loss was similar as in the Fischer 344 rats, but the number of missing OHCs and IHCs at the basal end of the organ of Corti was even larger in Long Evans rats than in Fischer 344 rats. These findings are not compatible with the fact that in old Fischer 344 rats the DPOAEs are practically absent. A similar situation regarding OHC damage was