"INFLAMMAGING" AND ITS MANAGEMENT IN PRESBYCUSIS

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Abstract

Background: From human studies there is little published evidence on the biological basis for presbycusis. We report a previously published study which tested the hypothesis that chronic inflammation in the elderly, known as "inflammaging" is a causal factor for presbycusis.

Method and Results: Analysis of biological and audiological data from a large population cohort showed an independent association between a range of inflammatory markers and mean hearing level.

Discussion: Our findings suggest that further investigation into the role of inflammation in causing presbycusis is warranted. We also discuss wider research plans, and argue for a greater understanding of the inter-relationship of systemic and cochlear inflammation and the role of inflammatory processes in causing a range of types of hearing loss.

Background

The aim of the paper is to report and discuss previously published results – which show a relationship between age-related hearing loss (ARHL, or presbycusis) and chronic inflammation in a cohort of older people – and to discuss the wider implications for future management and research in this area. ARHL is one of the most common and debilitating conditions associated with ageing and is thought, world-wide, to affect more than half of all adults over the age of 75 and over a third of those over 65. The condition has a range of effects in terms of increased social isolation and reduced economic and social activity. Despite this widespread impact, treatment of presbycusis is primarily limited to management through hearing aids, and there are no clearly identified methods to prevent the onset or progression of the condition.

Our understanding of the biological basis for ARHL is limited, and largely based on cadaver studies or animal models. There is potential to exploit recent advances in the understanding of the biological basis for ageing and seek to apply this to understanding ARHL more specifically. There are currently a number of proposed mechanisms and theories of ageing, which may provide both competing and complementary explanations for senescence. An important proposed mechanism is immunosenescence [1], according to which the ageing immune system becomes less adept at down-regulating on-going production of inflammatory proteins after acute inflammatory events, leading to a chronic state of low-level inflammation known as "inflammaging" [2].

There is growing evidence that inflammaging is a causal factor, or at least associated with, a range of age-related or age-accelerated diseases, including atherosclerosis, cardiovascular disease, peripheral arterial disease, type II diabetes, and Parkinson's disease. It seems plausible that chronic changes in inflammatory state play a role in causing or accelerating ARHL. The cochlea has its own immune response [3,4] and is not immune-privileged, with evidence of interaction between systemic and local inner ear inflammation. Interestingly, a number of age-related conditions with an inflammatory element, including cardiovascular disease [5], Alzheimer's disease [6], and diabetes [7] are associated with markedly increased severity and prevalence of ARHL. In a recently published study, we sought to investigate the hypothesis that inflammaging could cause, or accelerate, long-term damage to the hearing system with age [8]. The hypothesis was based on a model of the effect of peripheral inflammation on CNS function which shows that acute and chronic inflammation interact in causing disease [9].

Methods

We examined data from the Hertfordshire Ageing Study (HAS), a large birth cohort of individuals born in Hertfordshire, UK, between 1911 and 1948 [10,11]. Data from the HAS study were available on hearing level, inflammatory status, and a range of other physiological and medical variables that were measured during a cross-sectional data-sampling exercise undertaken in 1995. These data were analysed to determine the degree of independent association between inflammatory markers and hearing status, with additional lifestyle and demographic factors (e.g. gender, age, smoking, occupational and noise exposure history) taken into account. Data from blood samples taken during the data collection exercise included erythrocyte sedimentation rate (ESR) and white blood cell count, with differential numbers of neutrophils, lymphocytes, and monocytes. Stored serum was used subsequently to measure additional inflammatory markers using multiplex technology, including interleukins (IL-1, IL-6, and IL-10) and C-reactive protein (CRP). Audiometric thresholds measured by air conduction at four frequencies (500, 1000, 2000, and 4000 Hz) were also available.

Results

After excluding data from subjects with possible conductive hearing loss or significant audiometric asymmetry, data were analysed on a final cohort of 343 men and 268 women aged 63 to 74. Results showed that older age, smoking, history of noise exposure, and male gender were associated with higher mean hearing threshold in the worse ear. After adjustment for these factors in multiple regression models, four measures of immune or inflammatory status were significantly associated with hearing threshold, namely white blood cell count, neutrophil count, IL-6, and C-reactive protein, i.e. for these inflammatory measures, higher serum levels were associated with worse hearing among this group of older people.

Conclusions

Our findings are consistent with the hypothesis that inflammaging is a causative factor in ARHL. Findings also suggest, albeit indirectly, that there is a link between inflammatory markers measured via serum analysis and intra-cochlear inflammatory status. The latter issue is important, as direct measurement of cochlear inflammation via analysis of cochlear fluid is not practically possible. Interestingly, the association between hearing level and inflammatory markers was *continuous*, i.e. there was no threshold effect, exactly as predicted by the inflammaging hypothesis, which indicates a gradual variation in inflammatory status and co-existing morbidity, rather than a binary disease model of ageing.

It is worth noting that the identified association between inflammatory markers and hearing level was present despite a number of factors likely to dilute any such effect. Audiometric data were not available for frequencies above 4000 Hz and, although testing was undertaken by trained researchers using standardised audiometric methods, tests were undertaken in a community environment with the possibility of interference from background noise. Most crucially, the cohort were relatively young (mean age 67 years), thus at an early stage of presbycusis.

Finally, the data did not assess changes over time, which is crucial in determining a causal link between inflammaging and ARHL. The fact that, despite possible limitations in data collection methods, significant associations were identified between hearing loss and its known predictors (such as age and gender) and were also independently associated with levels of inflammatory markers, suggests that these associations are likely to be robust.

The findings raise a number of important questions requiring further investigation. One question is how systemic (particularly chronic) inflammation interacts with inflammation in the cochlea and related auditory structures, and what levels of inflammatory response are needed to produce either a gradual or sudden reduction in hearing threshold. Related to this is the question of what the mechanism might be, i.e. whether primary hair cell damage is implicated or whether other auditory structures, e.g. the stria vascularis [12], spiral ganglion cells, or auditory nerve [13] are affected. Addressing these questions, we are currently undertaking work to determine the causal relationship between systemic inflammation and damage to the auditory system in a mouse model of ARHL. We also plan to undertake a longitudinal study of inflammation *vs.* hearing in a cohort of older adults to optimise the sensitivity of both auditory measures and bio-markers of inflammation to better understand the relationship between inflammaging and ARHL.

The work has also been extended to hearing preservation in cochlear implant surgery, as inflammation is likely to be the key mediating factor in determining loss of residual hearing after surgery [14–16]. We suggest that a better understanding of the link between systemic and cochlear inflammation, and the role of different inflammatory processes as drivers of both acute and chronic cochlear (or auditory neural) damage, will be beneficial to understanding, preventing, and treating a range of different types of hearing loss, including ARHL.

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