



The antioxidant N-Acetyl-L-Cysteine (NAC) as a pharmacological candidate for age-related hearing loss.

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Age-related hearing loss is the most common sensory disorder in the elderly population. This disorder impacts the quality of life and the most severe forms affect communication leading to social isolation, depression, and reduced physical and psychological well-being.

The senescence-accelerated prone strain 8 (SAMP8) mouse model presents an accelerated senescence with a mean life span of 12 months and has been identified as suitable for use as a model in aging (Kawamata et al., 1997) which closely mimics human ARHL. Several studies demonstrated that the molecular mechanisms associated with premature SAMP8 senescence and hearing loss involved oxidative stress, altered levels of antioxidant enzymes and decreased activity of Complexes I, II, and IV which in turn lead to chronic inflammation and triggering of apoptotic cell death pathways (Menardo et al., 2012).

HYPOTHESIS

We hypothesized that reduction of the oxidative stress using N-acetyl-L-cysteine (NAC), a strong antioxidant compound, could be a pharmacological candidate for decreasing ARHL or slowing down the senescence process (Fig 1). Moreover, the reduction of ROS could also prevent the memory degeneration well described in this accelerated aging model.

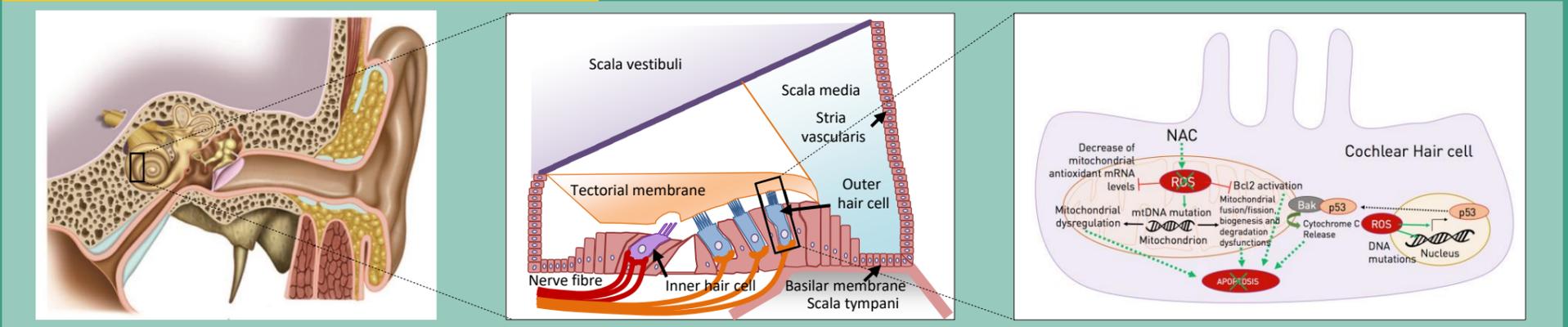
MATERIALS AND METHODS

To validate our hypothesis, 1-month old male SAMP8 mice received NAC in the drinking water at 61 mM and the auditory functions were assessed and compared to untreated SAMP8 mice. The two principal auditory parameters were measured every two weeks: the Auditory Brainstem Response (ABR) from 8 to 32 kHz from 90 to 10 dB SPL and the Distortion Product Otoacoustic Emissions (DPOAEs) from 32 kHz to 1 kHz at 63 dB SPL. ABRs are electric potentials recorded from scalp electrodes, and the first ABR wave represents the summed activity of the auditory nerve fibers contacting the cochlear inner hair cells. The DPOAEs are acoustic signals created and amplified by the cochlear epithelium offering an index of cochlear function and are linked to outer hair cell health which amplify sound-evoked cochlear vibrations.

In parallel, a behavioral test was performed. The first test day, anxiety was assessed placing the mouse in a squared open-field and measuring the time spent in the peripheric area. Then, memory performances of treated animals were determined using the novel object recognition test. A novel object differing in color shape and texture from the previous familiar object was placed in the open-field and the memory performance was determined by the preferential exploration index, calculated as the ratio of the number of contacts with the new object.

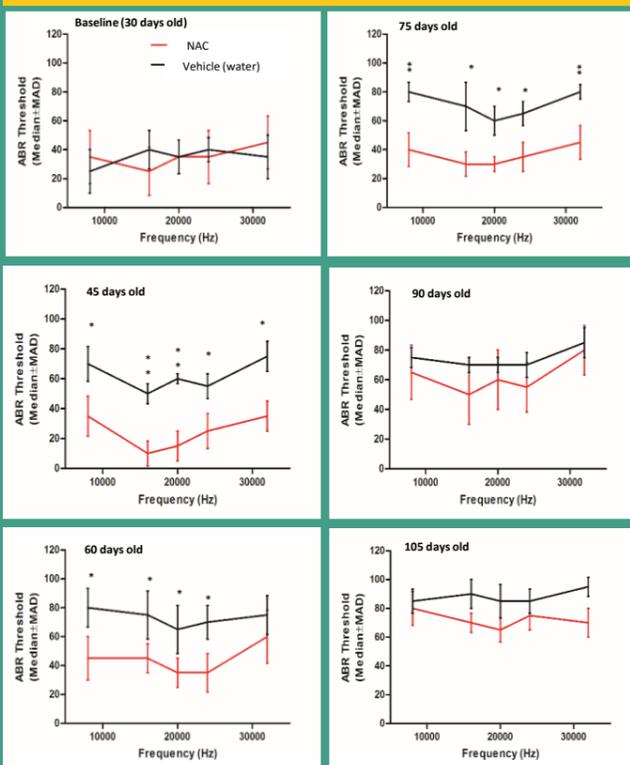
Marie et al., *Aging and disease*. 2017. Vol 9. Num 4

Fig. 1: Molecular mechanism of NAC in protecting hair cells



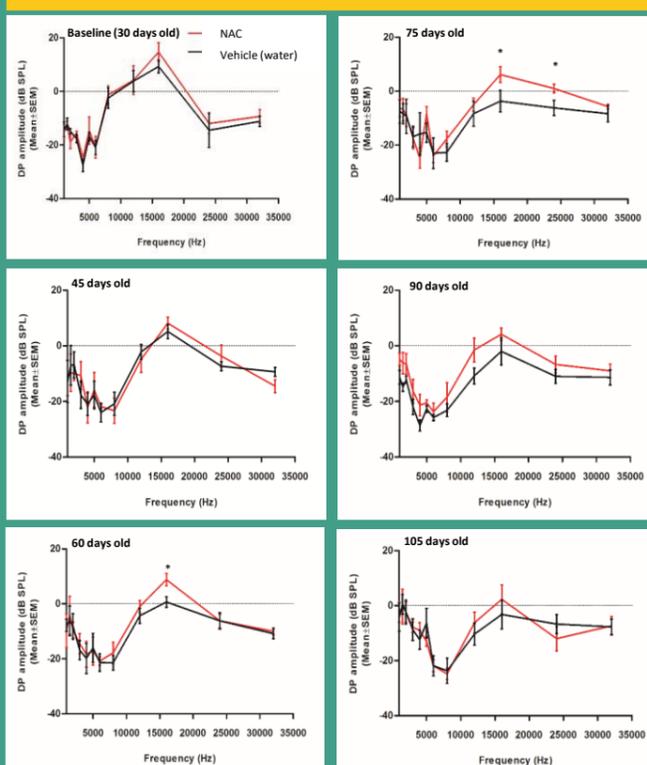
RESULTS

ABR thresholds



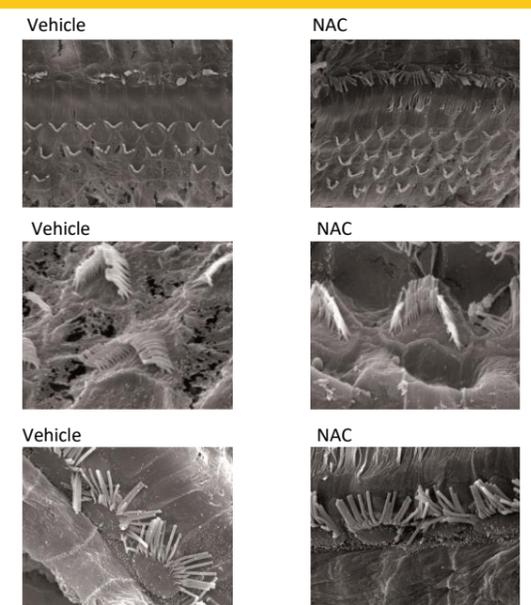
Daily NAC administration significantly reduced the increase of ABR thresholds due to the accelerated senescence process in SAMP8 mice from 45 days old to 75 days old. 1-way ANOVA * p<0.05; ** p<0.01; n = 6 mice/group

DPOAE amplitudes



A small but significant increase of DP amplitude was observed after NAC administration from 60 days old to 75 days old, suggesting that this antioxidant treatment protects outer hair cells from death. 1-way ANOVA * p<0.05; ** p<0.01; n = 6 mice/group

Scanning electron microscopy images



NAC treatment in SAMP8 mice protected cochlear outer and inner hair cells (top panels). However, no significant differences were observed in the morphology of outer hair cell (middle panels) and inner hair cell (bottom panels) stereocilia between vehicle and NAC treated groups. Arrows and asterisks mark the loss of outer and inner hair cells respectively.

NAC delays the senescence process by slowing age-related hearing loss and protecting cochlear hair cells. These results strongly suggest that antioxidants could be a pharmacological target for age-related hearing disorders.