3xTgAD/Polβ$^{+/-}$ Hearing Loss and Synaptopathy

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ABSTRACT

There is a high prevalence of hearing loss within the Alzheimer's Disease (AD) patient population, but a causal relationship has yet to be determined. Early onset hearing loss was found in two AD mouse models, 3xTgAD and 3xTgAD/Polβ$^{+/-}$. We investigated the hearing loss phenotype in the AD mouse model 3xTgAD, and the DNA repair deficient mouse 3xTgAD/Polβ$^{+/-}$. Hearing function for both AD models were determined using auditory brain responses (ABRs) and distortion product otoacoustic emissions (DPOAEs). Inner and outer hair cells were quantified using 20x images as the basal, middle, and apical regions of the cochlea. Regions of interest (ROI's) were defined around individual inner hair cells, and the pre and post synaptic puncta were imaged and quantified using high-resolution Airyscan confocal microscopy. In the present study, two AD mouse models 3xTgAD and 3xTgAD/Polβ$^{+/-}$ were found to have early onset hearing loss prior to the onset of cognitive and behavioral AD symptoms. At 4 weeks, both models exhibit increased ABR thresholds between 16 kHz and 32 kHz. The 3xTgAD/Polβ$^{+/-}$ mice ABR thresholds and DPOAEs were more perturbed than 3xTgAD mice. Both models also showed decreased wave 1 amplitudes, and increased latencies at 16kHz. Synaptic density is significantly reduced in basal turn (32kHz) of the cochlea in the 3xTgAD/Polβ$^{+/-}$ mice, while there is no significant difference in the apical (8kHz) and middle (16kHz) turns between the WT and DNA repair-deficient AD model. 3xTgAD/Polβ$^{+/-}$ male mice also exhibited significantly fewer IHCs in the basal region and a slight reduction in OHCs (p-value 0.0648), reflecting the loss of synaptic density. The apical and middle regions did not exhibit a decrease in IHCs. In conclusion, the 3xTgAD/Polβ$^{+/-}$ mouse has shown a significantly accelerated hearing loss phenotype that may serve as a useful model for progressive hearing loss.

REFERENCES

Park, Jae-Hyeon, Burcin Duan Sahbaz, Komal Pekhale, Xixia Chu, Mustafa N. Okur, Mhamed Grati, Kevin Isgrig, et al. "Early-Onset Hearing Loss in Mouse Models of Alzheimer's Disease and Increased DNA Damage in the Cochlea." *Aging Biology* 2 (2024). https://doi.org/10.59368/agingbio.20240025.

Okur, Mustafa N., Beatrice Mao, Risako Kimura, Scott Haraczy, Tracy Fitzgerald, Kamren Edwards-Hollingsworth, Jane Tian, et al. "Short-Term NAD+ Supplementation Prevents Hearing Loss in Mouse Models of Cockayne Syndrome." *Npj Aging and Mechanisms of Disease* 6, no. 1 (January 7, 2020): 1–10. https://doi.org/10.1038/s41514-019-0040-z.

Hou, Yujun, Xiuli Dan, Mansi Babbar, Yong Wei, Steen G. Hasselbalch, Deborah L. Croteau, and Vilhelm A. Bohr. "Ageing as a Risk Factor for Neurodegenerative Disease." *Nature Reviews Neurology* 15, no. 10 (October 2019): 565–81. https://doi.org/10.1038/s41582-019-0244-7.

METHODS

Full protocol can be found at : Park et. Al. 2024 *Aging Biology*

RESULTS

Hearing loss in 3xTgAD and 3xTgAD/Polβ$^{+/-}$ mice

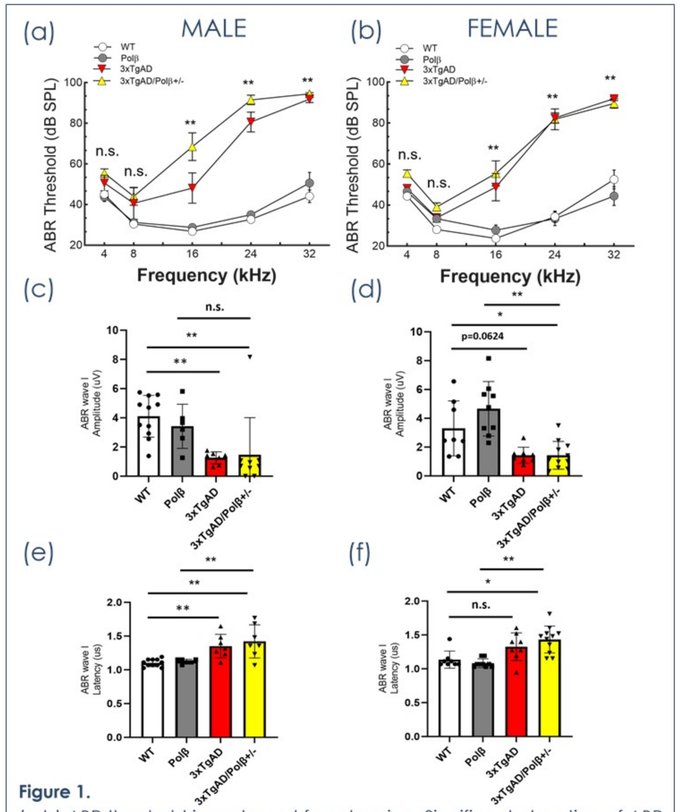

Figure 1.
(a-b) ABR threshold in male and female mice. Significant elevation of ABR thresholds at 4 weeks of age in 3xTgAD and 3xTgAD/Polβ+/− mice.
(c-b) Quantification of the amplitude of wave I in each group at 16 kHz and 90 dB. (e-f) Quantification of wave I latency at 16 kHz and 90 dB.

DNA damage in the cochlea induces defects in functional synapses in 3xTgAD/Polβ$^{+/-}$ mice

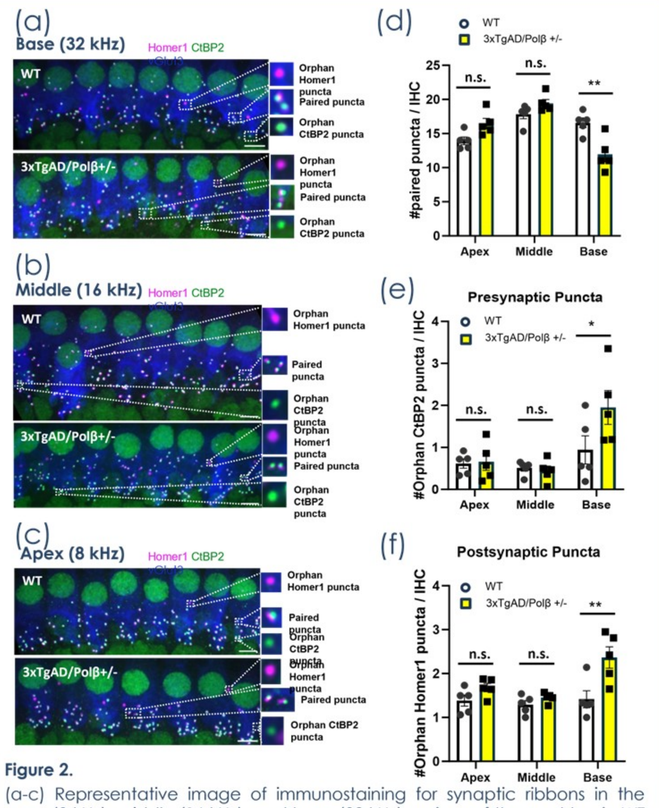

Figure 2.
(a-c) Representative image of immunostaining for synaptic ribbons in the apex (8 kHz), middle (16 kHz), and base (32 kHz) regions of the cochlea in WT and 3xTgAD/Polβ+/− mice at 4 weeks of age. (d) Quantitative analysis of paired puncta per inner hair cell (IHC) in the cochlea at 8, 16, and 32 kHz. (e,f) Average number of orphan ribbons per IHC at 8, 16, and 32 kHz.

3xTgAD/Polβ$^{+/-}$ mice have decreased IHC counts in the basal region of the cochlea

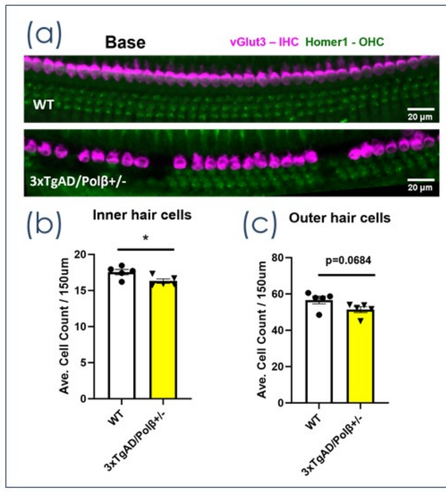

Figure 3.
(a)Representative images of base inner and outer hair cells of WT and 3xTgAD/Polβ+/− mice at 4 weeks of age.
(b,c) Average number of IHC and OHC / 150 µm in the basal region of the cochlea in WT or 3xTgAD/Polβ+/− mice.

CONCLUSION / FUTURE DIRECTIONS

- 3xTgAD and 3xTgAD/Polβ$^{+/-}$ exhibit significantly increased ABR thresholds at 16, 24, and 32kHz.
- The DNA repair deficit seen in the 3xTgAD/Polβ$^{+/-}$ mouse may cause the synaptopathy seen in the inner hair cells of the basal region of the cochlea.
- The severity of the synaptic and IHC loss does not appear to account for the severe hearing loss exhibited by the 3xTgAD/Polβ+/− mice.
- Measurement of the stria vascularis may provide more insight into the physiological cause oft the hearing loss phenotype.

ACKNOWLEDGMENTS