

Inhibition of Estrogen Modulates Autophagic Processes and Auditory Function in Aging Female CBA/CaJ Mice

#XiaoXia Zhu^{1,3}, Bo Ding^{2,3}, McKenzie Watson³, Tanika T. Williamson^{1,3}, *Robert D. Frisina^{1,2,3}

1. Department of Medical Engineering, College of Engineering and Morsani College of Medicine, University of South Florida, Tampa, FL-33620
2. Department of Communication Sciences and Disorders, College of Behavioral & Community Sciences, University of South Florida, Tampa, FL-33620
3. Global Center of Hearing and Speech Research, University of South Florida, Tampa, FL-33612

Introduction: Female hormones play important roles in age-related hearing loss (ARHL- presbycusis) in both humans and mice. Autophagy is a highly conserved catabolic process essential for embryonic development and adult cellular homeostasis. Changes in autophagic processes are linked to age-related neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases. Here, we determine the roles of estrogen in cochlear autophagy, and possible involvement in ARHL mechanisms in female mice.

Methods: Two month (mon) old young adult CBA/CaJ mice (N= 18) were divided into three groups: females with ovariectomy (OVX) at 2 mon old, intact females, and male controls. These groups were treated with TAX (20mg/kg/day, intraperitoneal [IP] 2 weeks) at 12 mon old. The animals underwent measurement of auditory brainstem responses (ABRs) and distortion product otoacoustic emissions (DPOAEs). In addition, the cochlea cell line, SV-K1 was used as an *in vitro* model. Treatments, such as tamoxifen (TAX) and 17- β estradiol were administered to this cell line.

Results: ABRs thresholds were elevated at 12 mon old (post OVX 10 mon) in the OVX group compared to the same age intact females and male controls. In addition, for the mice treated with TAX at 12 month old, the ABRs thresholds in intact females were elevated relative to the OVX and male groups between 12 and 16 mon. DPOAE amplitudes were decreased in the OVX group at middle and high frequencies before and after TAX treatment compared to the 2 mon old baseline (per OVX), and there were significant shifts in the intact female and male groups after TAX treatment for high frequencies. The pattern of LC3II expression in the aged cochlea was different from the young adult expression, suggestive of autophagy inhibition with aging. In old-age females with or without OVX, the estradiol levels were the same as the males. 17 β -Estradiol treatment *in vitro* decreased expression levels of the autophagy markers LC3II and p62 compared to vehicle control treatment. However, TAX blocked these LC3II and p62 expression changes induced by 17 β -Estradiol. We also observed that TAX alone didn't change the LC3II and p62 expressive patterns compared with the vehicle control treatment.

Conclusion: Estrogen modulates auditory functional changes through age-related autophagic blocking.

Work Supported by NIH grant P01 AG009524 from the Nat. Inst. on Aging.

Poster only.