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Long-term treatment with aldosterone slows the progression of age-related hearing loss

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ABSTRACT

Age-related hearing loss (ARHL), clinically referred to as presbycusis, is one of the three most prevalent chronic medical conditions of our elderly, with the majority of persons over the age of 60 suffering from some degree of ARHL. The progressive loss of auditory sensitivity and perceptual capability results in significant declines in workplace productivity, quality of life, cognition and abilities to communicate effectively. Aldosterone is a mineralocorticoid hormone produced in the adrenal glands and plays a role in the maintenance of key ion pumps, including the Na-K^+-Cl co-transporter 1 or NKCC1, which is involved in homeostatic maintenance of the endocochlear potential. Previously we reported that aldosterone (1 μM) increases NKCC1 protein expression *in vitro* and that this up-regulation of NKCC1 was not dose-dependent (dosing range from 1 nM to 100 μM). In the current study we measured behavioral and electrophysiological hearing function in middle-aged mice following long-term systemic treatment with aldosterone. We also confirmed that blood pressure remained stable during treatment and that NKCC1 protein expression was upregulated. Pre-pulse inhibition of the acoustic startle response was used as a functional measure of hearing, and the auditory brainstem response was used as an objective measure of peripheral sensitivity. Long-term treatment with aldosterone improved both behavioral and physiological measures of hearing (ABR thresholds). These results are the first to demonstrate a protective effect of aldosterone on age-related hearing loss and pave the way for translational drug development, using aldosterone as a key component to prevent or slow down the progression of ARHL.

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Age-related hearing loss (ARHL), or presbycusis, is one of the top three, major chronic medical conditions in elderly people, along with cardiovascular disease and arthritis. The ARHL loss of auditory sensitivity and speech perceptual capability has an extremely high prevalence, with the majority of persons over the age of 60 suffering from ARHL, so hundreds of millions of people worldwide. The psychological sequelae accompanying ARHL are associated with depression, anxiety, social isolation, loneliness and can even be life threatening (Dalton et al., 2003; Kramer et al., 2002; Strawbridge et al., 2000; Viljanen et al., 2009). Furthermore, presbycusis has been associated with more rapid cognitive decline in the elderly (Lin et al., 2011; Lindenberger and Ghisletta, 2009; Van et al., 2007). The perceptual difficulties in suprathreshold hearing faced by older listeners likely develop not only from impaired cochlear function, but also from age-related physiological changes in the parts of the brain used for hearing – central auditory system (Frisina and Frisina, 1997; Syka, 2002; Willott, 1991, 1996). Virtually all components of the nervous system suffer from numerous age-related declines such as a loss of neurons and atrophy of their processes (e.g., axons, dendrites, and synapses) that degrade auditory processing in neural circuits. Age-linked systemic changes in hormonal, cardiovascular, and metabolic functions provide additional challenges (Aspinall, 2003; Frisina et al., 2015; Guimaraes et al., 2006; Tadros et al., 2005; Willott and Turner, 1999). The auditory system is, of course, no exception in its susceptibility to these and other biological changes with age.

A key player in ARHL is the decline in function of cochlear stria vascularis (SV) cells located in the lateral wall of the inner ear.

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Within the SV there are specific ion channels and pumps, which control the concentrations of Na^+ and K^+ for the endolymph of scala media. Two of these important ion channels are Na^+-K^+-$2Cl^-$ co-transporter (NKCC1) and Na^+/K^+-ATPase, which are found in many physiological systems (Anderson and Cala, 2006; Ding et al., 2014; Garg et al., 2007; Dowd and Forbush, 2003; Wall et al., 2006). NKCC1 is a co-transporter protein that moves Na^+, K^+, and Cl^- into and out of cells (Pedersen et al., 2006). NKCC1 levels and the flow of the ions regulated by it functionally decline with age. In the auditory system, the cochlea depends heavily on the presence of NKCC1 transporters, specifically in the basolateral plasma membrane of marginal cells of the SV where endolymph is produced (Weaver et al., 2004). So, NKCC1 is critical for maintaining the endocochlear potential (EP), which powers auditory sensory transduction. ARHL, which can be caused by age-related degeneration of the SV, is linked to age-related reduction in the EP or "cochlear transduction battery" (Schmiedt et al., 2002; Lang et al., 2010).

The mineralocorticoid steroid hormone aldosterone is released from the adrenal cortex and can control NKCC1 and Na^+/K^+-ATPase via changes in mRNA/protein synthesis in the inner ear (Pitovski et al., 1993a, 1993b) and brain (Grillo et al., 1997). Further evidence for aldosterone as being beneficial for auditory processing comes from the pioneering studies of Trune and colleagues. They demonstrated that oral administration of aldosterone can reverse hearing loss in autoimmune mice, while administration of spironolactone (an aldosterone antagonist) blocked this effect (Trune and Kempton, 2001; Trune et al. 2000, 2006).

Serum aldosterone levels decrease with age in humans (Kau et al., 1999; Hegstad et al., 1983; Bauer, 1993) and other mammals, including mice (Brudieux et al., 1995; Kau et al., 1999; Magdich, 1980; Wang et al., 2004). Although a direct clinical effect of aldosterone on age-related hearing loss has yet to be demonstrated in a prospective study, a correlation does exist between low serum aldosterone and severity of presbycusis in otherwise healthy elderly human subjects (Tadros et al., 2005). In addition, *in vitro* application of aldosterone to a human cell line (HT-29) revealed that aldosterone regulates NKCC1 activity and protein expression levels, quite sensitively and rapidly (Ding et al., 2014).

A biotherapeutic that can modulate NKCC1 protein expression opens the door for therapeutic interventions for diseases involving the dysregulation or depletion of NKCC1 or Na^+/K^+-ATPase. A prime example would be the age-related down-regulation of these ion channels observed in the cochlear lateral wall. Along with declines in serum levels of aldosterone in aging CBA mice (Zhu et al., 2011), we have discovered that NKCC1 and Na^+/K^+-ATPase expression levels decline with age in the CBA mouse cochlea, including the stria vascularis of the lateral wall (Zhu et al., 2012, 2013, 2014; Ding et al., 2012, 2013). These age changes suggest that aldosterone could be used as a therapeutic intervention for ARHL.

The acoustic startle reflex (ASR), a sensory-motor response that serves as a quantifiable measurement of arousal, was utilized in the present investigation to assess the effects of long-term aldosterone treatment on hearing function. In addition, we measured peripheral hearing sensitivity using auditory brainstem response audiometry. The ASR is an efficient behavioral measure to assess hearing in animal models and has been used extensively to examine the effects of various genetic mutations on hearing (e.g., Allen et al., 2008). The ASR manifests behaviorally as a rapid contraction of skeletal muscles in rodents (Hoffman and Ison, 1980). Rodents are typically placed on a platform where sensors transduce the motion generated by the reflex. Pre-pulse inhibition (PPI) is a reduction in the startle response observed when a stimulus placed prior to the startle elicitor is perceived by the animal, regardless of the sensory modality. The ASR can be inhibited by a pre-pulse stimulus presented before (~50–100 ms) the startle elicitor, for example a tone burst or silent gap in an ongoing noise can serve as a startle-eliciting stimulus (Ison and Hammond, 1971; Ison, 1982).

The goal of the present study was to determine if long-term, systemic, treatment with aldosterone can improve hearing function in a mouse model of ARHL. We hypothesized that chronic slow-release aldosterone treatment will improve hearing sensitivity thereby increasing the salience of pre-pulse stimuli without modifying the startle input-output function for the middle-aged CBA/CaJ mouse model of ARHL. ABR assessments were used to confirm the efficacy of the aldosterone treatment on peripheral auditory function.

1. Methods

1.1. Subjects

A total of 18 CBA/CaJ inbred mice were used, and were the same group utilized in our companion study (Frisina et al. Submitted). Animals were bred at the University of South Florida Vivarium with breeders obtained from Jackson Labs (Bar Harbor, ME). All mice were between 15 and 18 months of age at the time of baseline testing. Mice were randomly assigned to 2 groups, either control ($n = 10$) or treatment ($n = 8$). The treatment group was systemically administered 1.67 μg per day of D-aldosterone, via extended release pellets (Innovative Research of America, Sarasota, FL) implanted subcutaneously via syringe injection in a pocket of skin behind the shoulders while the mouse was under ketamine/xylazine (100/10 mg/kg) anesthesia. This dose and route of administration was chosen based on data showing that this dose reversed the reduction of serum aldosterone levels in older mice (Zhu et al., 2011). Control animals received a placebo pellet, inserted using the same technique as the treatment group. Baseline tests were followed by tests at 4 and 6 weeks. A second pellet was inserted at 8 weeks, and tests were done at 12 and 14 weeks post-hormone pellet treatment (Fig. 1).

1.2. Blood pressure measurements

In order to measure cardiovascular health mice were placed in a restraining tube for 15 min for 3 consecutive days to acclimate them to having their blood pressure (BP) measured using the Kent Scientific CODA™ tail-cuff blood pressure system. The animal was either placed in the holder by picking up the tail, or the animal entered freely. The rear hatch to the holder was carefully secured, and care taken to avoid pinching the tail or any other body parts while securing the rear hatch. The mouse was allowed to rest at least 5-min to acclimate to the holder. As shown in Fig. 2 there was no significant change in blood pressure over the course of the study when compared to the baseline (black bars) diastolic and systolic pressures.

1.3. Startle apparatus

Custom 3-D printed platforms housing piezoelectric transducers, located inside one of four identical sound attenuated chambers (40.6 × 40.6 × 40.6 cm), lined with sound dampening foam were used to collect startle reflex data. Each wire mesh cage (9.53 × 3.81 × 4.13 cm) was cleaned with Clidox (concentration ratio 1:18:1), rinsed with tap water, and dried after use, and fresh cages were used for each individual animal to avoid any odor contamination. Acoustic stimuli were generated by Tucker-Davis Technologies (Alachua, FL) System III RP2 processors and SA1 amplifiers. Tone and noise stimuli were presented through Fostex

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