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Higher serum aldosterone correlates with lower hearing thresholds: A possible protective hormone against presbycusis

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Abstract

Aldosterone hormone is a mineralocorticoid secreted by adrenal gland cortex and controls serum sodium (Na^+) and potassium (K^+) levels. Aldosterone has a stimulatory effect on expression of sodium–potassium ATPase (Na, K-ATPase) and sodium–potassium–chloride cotransporter (NKCC) in cell membranes. In the present investigation, the relation between serum aldosterone levels and age-related hearing loss (presbycusis) and the correlation between these levels versus the degree of presbycusis in humans were examined. Serum aldosterone concentrations were compared between normal hearing and presbycusic groups. Pure-tone audiometry, transient evoked otoacoustic emissions (TEOAE), hearing in noise test (HINT) and gap detection were tested for each subject and compared to the serum aldosterone levels. A highly significant difference between groups in serum aldosterone concentrations was found ($p = 0.0003$, $t = 3.95$, $df = 45$). Highly significant correlations between pure-tone thresholds in both right and left ears, and HINT scores versus serum aldosterone levels were also discovered. On the contrary, no significant correlations were seen in the case of TEOAEs and gap detection. We conclude that aldosterone hormone may have a protective effect on hearing in old age. This effect is more peripheral than central, appearing to affect inner hair cells more than outer hair cells.

Keywords: Aldosterone; Hormone; Mineralocorticoids; Adrenal; Age; Hearing loss; Presbycusis; HINT; Otoacoustic emissions; Stria vascularis

1. Introduction

Aldosterone is a mineralocorticoid secreted by the zona glomerulosa of the adrenal cortex. Aldosterone secretion is regulated by feedback loops in which renin and angiotensin play an important role. Several inhibitors and stimulants of aldosterone secretion are known, determining the multifactorial complexity of its regulation (Williams and Williams, 2003). Previous research reinforces the role of aldosterone as the primary hormone of Na^+ and K^+ homeostasis, extracellular fluid

Abbreviations: ANOVA, analysis of variance; HINT, hearing in noise test, speech perception in background noise; K^+ – potassium ion; MGT, minimum gap threshold; mRNA, messenger RNA; Na^+, sodium ion; Na, K-ATPase, sodium–potassium ATPase; NKCC, sodium–potassium–chloride cotransporter; PTA, pure tone threshold average from the audiogram; S/N, signal-to-noise ratio; TEOAE, transient evoked otoacoustic emission

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volume, and blood pressure (in association with angiotensin II, renin and Na^+ intake) (O'Neil, 1990; Bonvalet, 1998; Therien and Blostein, 2000).

Na, K-ATPase is a glycoprotein, consisting of one [α], one [β] and one [γ] subunit. The [α] subunit has three isoforms while the [β] subunit has at least two isoforms (Sweadner, 1989). The subunit combination has tissue and cell type-specific patterns (Ryan and Watts, 1991; Watts et al., 1991), but the subunit isoform distribution pattern in the inner ear appears to be similar among mammals (Weber et al., 2001).

Aldosterone is known to exert its effect through Na, K-ATPase that is subjected to both long- and short-term regulation. *The long-term regulatory effect* is the main effect of aldosterone on Na, K-ATPase to sustain the long-term increase in expression of Na^+ pumps and is generally mediated by changes in mRNA/protein synthesis induced by direct interactions of receptor/corticosteroid complexes with nuclear DNA.

Aldosterone combines with mineralocorticoid receptors (type I) and glucocorticoid receptors (type II) in the cytoplasm to form aldosterone/receptor complex (40–100 kDa granules) that binds to nuclear pores and shift into the nucleoplasm. This process causes nuclear swelling that may be due to gene transcription. Then, macromolecules (800 kDa plugs) appear in the central channels of the nuclear pores. The plugs resemble ribonucleoproteins that carry aldosterone-induced mRNA to the ribosomes. Nuclear volume returns back to normal when mRNA export through the nuclear pores is finished (Oberleithner et al., 2000; Schafer et al., 2002). Aldosterone receptor complexes mediate mRNA synthesis by interacting with regulatory elements of both the α1 (Oguchi et al., 1993), α2 (Ramirez-Gil et al., 1998), α3 (Farman et al., 1994; Grillo et al., 1997) and β1 (Derfoul et al., 1998) subunit genes. Aldosterone-mediated increases in protein synthesis of Na^+ pumps may be dependent on changes in cytoplasmic Na^+ concentrations (Hayhurst and O'Neil, 1988) and thyroid hormone triiodothyronine (T3) (Wiener et al., 1993). This long-term effect is widespread and has been observed in different organs of the body (Verry et al., 1987; Fuller and Verity, 1990; Bhutada et al., 1991; Oguchi et al., 1993; Shahedi et al., 1993; Welling et al., 1993; Dorup and Clausen, 1997; Ramirez-Gil et al., 1998), including brain (Grillo et al., 1997)], and inner ear (Pitovski et al., 1993).

Whereas the classic effects of aldosterone on Na, K-ATPase are on long-term expression of the enzyme as described above, this mineralocorticoid has been shown to have specific *short-term effects* on epithelial Na^+ channels (Shigaev et al., 2000; Naray-Fejes-Toth and Fejes-Toth, 2000; Itani et al., 2002; Muller et al., 2003).

The Na–K–Cl cotransporter (NKCC) is responsible for the electroneutral transport of $1Na^+$: $1K^+$ and $2Cl^-$ across the plasma membrane of many cells (Hass, 1994). NKCC has two isoforms, NKCC1 (secretory) isoform which is abundant in the basolateral plasma membrane of strial marginal cells in human cochlea (Weber et al., 2001) and in dark cells of the gerbil's vestibular system (Marcus et al., 1987, 1994; Wangemann et al., 1995; Sakaguchi et al., 1998; Crouch et al., 1999) and NKCC2 (absorptive) isoform. NKCC1 provides a major pathway of Na^+ into marginal cells to drive their high Na, K-ATPase activity (Salt and Thalmann, 1988; Wangemann et al., 1995; Crouch et al., 1999) and also provides K^+ for diffusion into endolymph through apically located K^+ channels (Takeuchi et al., 1992; Wangemann et al., 1995). Aldosterone plays a role in regulation of NKCC. The mechanism by which aldosterone stimulates NKCC1 is unclear as there is no increase in NKCC1 mRNA (Jiang et al., 2003). Stimulation of NKCC1 activity could explain the increase in intracellular Na^+ noted in mineralocorticoid-treated vascular smooth cells (Jones and Hart, 1975; Kornel, 1981).

It is well established that the intracellular route of K^+ recycling in the human cochlea from the organ of Corti back to stria vascularis passing through fibroblasts is vital for hearing. Type II, IV and V fibroblasts play main roles in this recycling and are found in stria vascularis, outer sulcus cells and nerve endings of outer and inner hair cells. These cells are rich in Na, K-ATPase and NKCC1, both of which play a complimentary role in recycling of K^+ (Takeuchi et al., 1992; Marcus et al., 1993; Wangemann et al., 1995; Crouch et al., 1999; Marcus and Chiba, 1999; Weber et al., 2001).

The effect of aging on aldosterone secretion was examined in many studies, all of which showed that plasma aldosterone levels decrease with age (Weidmann et al., 1975; Crane and Harris, 1976; Zakharieva and Ankov, 1982; Hegstad et al., 1983; Tsunoda et al., 1986; Hallengren et al., 1992; Bauer, 1993; Belmin et al., 1994). The present study was conducted to gain some insights into the role of aldosterone deficiency in the pathogenesis of age-related hearing loss (presbycusis) and try to determine if a correlation exists between serum aldosterone levels and the degree of presbycusis.

2. Materials and methods

2.1. Subjects

This study was performed with 47 aged, volunteer subjects who were recruited to participate in a study of presbycusis, 30 females and 17 males. According to their pure tone thresholds at 1, 2, 4 and 8 kHz, the subjects were retrospectively divided into two main groups: Group A (average pure tone thresholds <23.0 dB HL) consisted of 16 subjects with normal audiometric thresholds (flat audiometry), 10 females and 6 males, 58–73 years (mean age = 64.6 years); Group B (average pure