Hormones and Hearing: Too Much or Too Little of a Good Thing Can Be Ototoxic

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ABSTRACT

Hormones regulate and modulate many physiological processes of the body including the nervous, cardiac, respiratory, and gastrointestinal systems. So, it is not surprising that hormonal regulation can manifest itself at the sensory level as well. The present report reviews some recent studies on the relations between several key hormones—including aldosterone and sex hormones—and auditory processing in vertebrate animal models and in human clinical research investigations. Keeping with the theme of this issue of *Seminars in Hearing*, the present review is not meant to be exhaustively comprehensive but rather to provide synopses and key references of representative research reports that capture the flavor of what we know about important interactions between the auditory and hormonal systems, and how they relate to certain animal and human behaviors. Indeed, the old adage "too much or too little of a good thing is not good" applies here.

KEYWORDS: Hearing loss, hormone, aging auditory system, aldosterone, progesterone

Learning Outcomes: As a result of this activity, the participant will be able to (1) describe how hormones that are important for auditory function can change with age, (2) identify evidence suggesting that aldosterone application can serve as a treatment for certain types of hearing loss, and (3) name data indicating that progesterone (progestin), a key component of hormone therapy taken by menopausal women, can be detrimental to hearing.

Hormonal regulation of bodily systems has profound effects both in terms of physiology and human behavior. Not surprisingly, relatively recent research has made clear that hormones

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Proceedings of the 5th International NCRAR Conference–Expanding Our Horizons: Medical Conditions and Audiology; Guest Editors, Robert L. Folmer, Ph.D., and Gabrielle H. Saunders, Ph.D.

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DOI: http://dx.doi.org/10.1055/s-0032-1315722.
ISSN 0734-0451.

also can affect or modulate sensory processing. In particular, hormones involved in mating and reproduction can change auditory coding so as to improve a species' chances of producing and caring for the next generation.[1] In addition, aldosterone, the chief hormone involved in physiological regulation of sodium and potassium (key ions involved in processing of auditory and balance signals in the inner ear), has been shown to be linked to modulation of hearing in mammals. For example, as presented in more detail later, Trune and colleagues[2,3] discovered that aldosterone can reduce autoimmune hearing loss in a murine animal model. Human studies, as described in detail later, demonstrate that these alterations in hearing linked to aldosterone can occur in both the peripheral (cochlea) and central auditory systems (parts of the brain used for hearing). The present article's goal is to summarize some recent investigations of how processing of sound can be regulated or modified by changes in sex hormones or aldosterone.

ALDOSTERONE AND HEARING: ANIMAL MODEL DISCOVERIES

Sodium (Na^+) and potassium (K +) are very important ions for the proper functioning of the inner ear. Specifically, a K + -rich fluid bathes the tops of the hair cells, and this is required for proper transduction or conversion of auditory and vestibular signals into the code of the nervous system, which is then input to the brain. This K + -rich fluid, called *endolymph*, is produced in a specialized organ of the cochlea, the stria vascularis, which is located on the cochlear lateral wall. Unique marginal cells of the stria vascularis pump K+ into the endolymph against a steep K+ concentration gradient using membrane pumps such as Na^+/K + /ATPase and Na^+/K + /Cl^-/cotransporter (NKCC1). Because aldosterone is the main hormone in mammals for regulation of K+ and Na^+, Trune and colleagues[2,3] reasoned that alteration of aldosterone would have noteworthy effects on inner ear function, including auditory processing. They used a mouse model for autoimmune hearing loss and discovered that administration of aldosterone in the mouse's drinking water could slow down or reverse the progression of autoimmune hearing loss.[3] Specifically, 80% of the control group of autoimmune mice showed worse hearing thresholds over a 2-month period. In contrast, none of the autoimmune mice receiving aldosterone therapy over the same 2 months showed deterioration in hearing thresholds. Remarkably, 39% of the aldosterone-treated mice *showed improvement* in hearing thresholds, and 61% of these mice showed no change in their hearing. As a comparison, the researchers also treated mice with a common anti-inflammatory steroid, prednisolone, which is very similar to prednisone. The prevention of progression of autoimmune hearing loss was significant, but not as effective as the aldosterone treatments. Specifically, 14% of the prednisolone-treated mice showed worse hearing, 43% showed improved hearing thresholds, and 43% showed no change in hearing over the 2-month treatment time.

Wanting to gain insights into the biological mechanisms of action that produced these results, Trune and coworkers[3] examined structural/anatomic changes in the cochlea for the three groups of mice described above. As one might expect, given the importance of Na^+/K + /ATPase and NKCC1 in the cochlea and the fact that aldosterone can regulate these membrane ionic pumps, Trune and colleagues examined structural changes in the cochlear cells that have these pumps (i.e., the stria vascularis marginal cells). As presented in Fig. 1, these important cochlear lateral wall cells showed more degenerative changes over the 2-month treatment period in the control mice that had the more rapidly progressing autoimmune hearing loss. These pathological changes included dilation of strial microcapillaries, edema, and cell shrinkage. Similar to the results of Trune's hearing preservation findings, the aldosterone treatment was most effective at preventing these cochlear lateral wall structural declines, with the prednisolone treatments partially effective.

ALDOSTERONE AND HEARING: CLINICAL RESEARCH FINDINGS

Inspired by Trune et al's[2,3] breakthrough animal research on hormones and hearing, Tadros and colleagues performed an initial

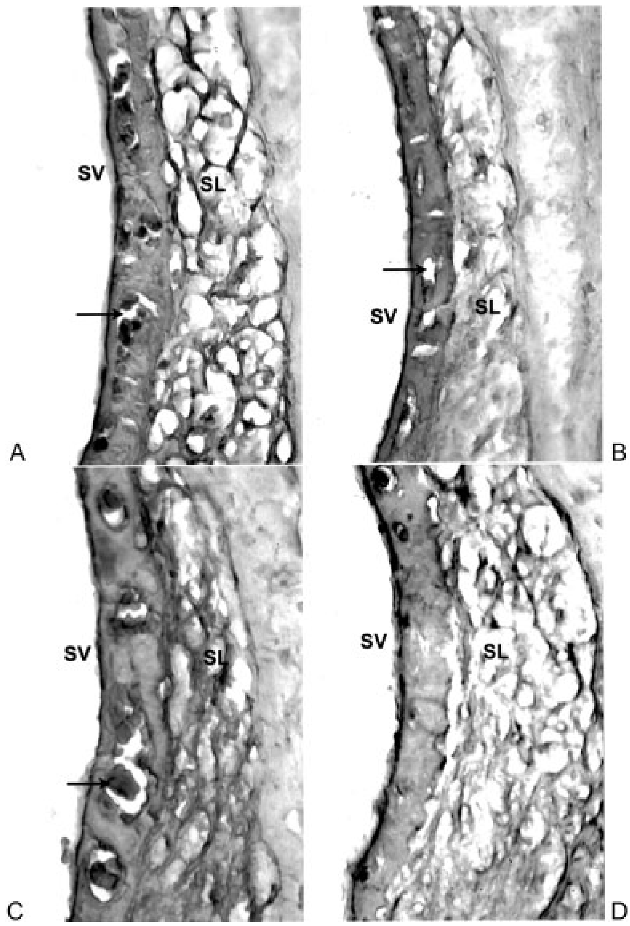

Figure 1 Basal-turn stria vascularis (SV) from young (A) and old (B) untreated MRL/MpJ-Faslpr autoimmune mice show the typical edema, dilated vessels (arrows), and stria thinning with disease progression. The prednisolone-treated stria (C) recovered some of its normal thickness and function, but still was edematous and had dilated vessels (arrow). Aldosterone treatment (D) restored the stria to a normal appearance. SL, spiral ligament. (A–D) Original magnification ×650. Figure and legend adapted with permission from Trune et al. Aldosterone (mineralocorticoid) equivalent to prednisolone (glucocorticoid) in reversing hearing loss in MRL/MpJ-Fas1pr autoimmune mice. Laryngoscope 2000;110: 1902–1906.[3] (Fig. 1).

investigation of aldosterone and hearing loss in older human listeners.[4] These investigators were aware that most hormones, including aldosterone, tend to decline with age in mammals, including humans. So, we looked for associations between hearing functions and serum (blood) aldosterone levels. Using a comprehensive battery of standard and experimental hearing and speech tests, Tadros et al[4] tested auditory capabilities and then obtained blood samples from otherwise healthy human subjects who were all over 58 years old. A significant difference in serum aldosterone levels for older subjects when comparing subjects with hearing thresholds in the normal range and subjects with age-related hearing loss was identified. Specifically, as displayed in Figs. 2 and 3, aldosterone levels were highly correlated with pure-tone thresholds (peripheral hearing): subjects with serum aldosterone levels at the top of the normal range had better hearing than subjects with lower levels of aldosterone. As presented in Fig. 4, Hearing in Noise Test (HINT) scores (indicative of both peripheral and central auditory brain stem speech processing in background noise) were most favorable for subjects with higher levels of aldosterone (i.e., these subjects' abilities to hear speech in the presence of background noise were superior to those subjects with lower aldosterone levels). Tadros

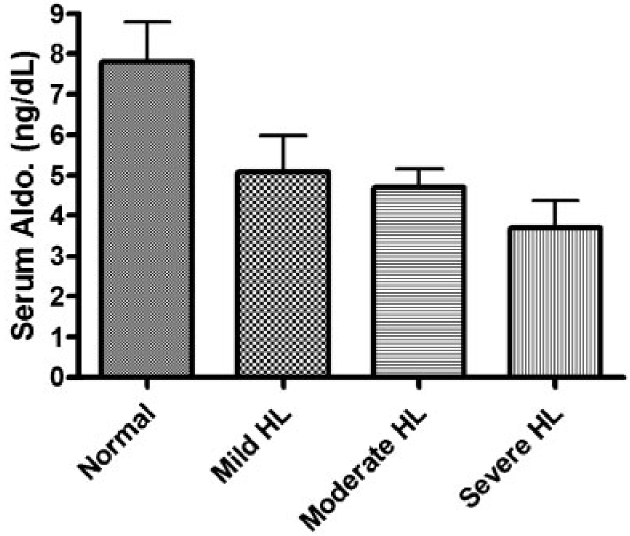

Figure 2 A significant difference in serum aldosterone concentrations was found between normal hearing subjects and aged subjects with presbycusis and mild, moderate, and severe hearing loss (HL). The lower the serum aldosterone levels within the normal clinical range, the worse the hearing. Error bars represent standard errors of the mean. Figure and legend adapted with permission from Tadros et al. High serum aldosterone levels correlate with lower hearing thresholds in aged humans: a possible protective hormone against presbycusis. Hear Res 2005;209:10–18[4] (Fig. 1).

et al[4] concluded that serum aldosterone levels at the top of the normal range may have a protective effect on hearing in old age, both peripherally and centrally.

SEX HORMONES AND HEARING: SOME LESSONS LEARNED FROM ANIMAL MODELS

Perhaps one of the most fascinating and provocative areas of inquiry for neurobiologists, biomedical researchers, and experimental psychologists is investigating differences between the two sexes. In that spirit, hearing scientists have investigated differences and changes in auditory processing in women and men and also have used animal models to study sex differences in hearing.

Fish Can Modulate Their Auditory Processing During Mating Season

Sisneros and Bass pioneered neurobiology studies of how fish can alter the processing capabilities of their auditory system to enhance mating and reproduction success.[5,6] For instance, they captured female plainfin midshipman fish, brought them to their auditory testing laboratory, controlled for body temperature, and tested these animals' hearing during mating season (summer) and during the nonproductive winter season. As presented in Figs. 5A and 5B, the temporal responses (vector strength) of the female fish's auditory system were amplified (greater vector strength) in the summer mating season, especially in the middle frequencies (150 to 350 Hz) of this fish's hearing range. Consistent with this finding, the proportion of auditory nerve cells tuned to the middle frequencies was greater for the mating season fish versus the winter season fish, as shown in Figs. 5C and 5D. The operative difference in the physiology of these female fish is that there is an alteration of the sex hormones during this fish's mating season. For example, there are major increases in estrogen levels related to this portion of the behavioral mating cycle.[7]

Testosterone Affects Central Auditory Signal Processing in Anurans

Miranda and Wilczynski[8] conducted an interesting series of experiments in frogs, which uncovered new knowledge about how sex

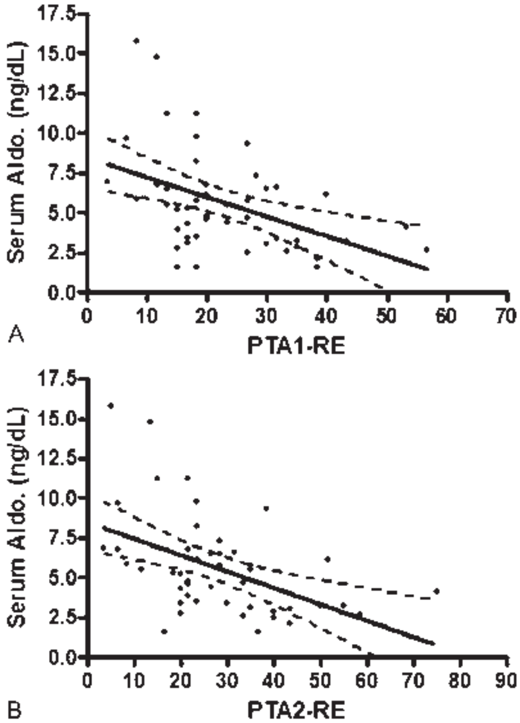

Figure 3 (A) Significant correlation between serum aldosterone concentration and pure tone average (PTA1) was found for both ears, right ear data shown. (B) Same for PTA2. PTA1 represents the average of thresholds for frequencies 0.5, 1, and 2 kHz; PTA2 for 1, 2, and 4 kHz. Pure tone average right ear (PTA1-RE), (PTA2-RE). Figure and legend adapted with permission from Tadros et al. High serum aldosterone levels correlate with lower hearing thresholds in aged humans: a possible protective hormone against presbycusis. Hear Res 2005;209:10–18[4] (Fig. 2).

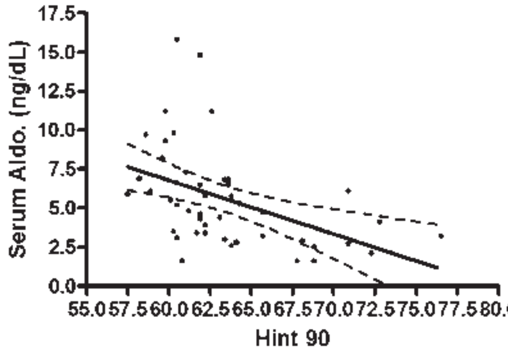

Figure 4 A significant correlation between serum aldosterone concentration and Hearing in Noise Test (Hint) Quiet and Hint Noise at 0 degrees (N0˚), Noise at 90 degrees (N90˚), and Noise at 270 degrees (N270˚) scores was found. Exemplary data for Hint 90˚ are shown here. Figure and legend adapted with permission from Tadros et al. High serum aldosterone levels correlate with lower hearing thresholds in aged humans: a possible protective hormone against presbycusis. Hear Res 2005;209:10–18[4] (Fig. 3).

hormones, including testosterone, can influence sound processing at the level of the central auditory system. In one of their experiments, Miranda and Wilczynski compared nerve cell thresholds in the frog auditory midbrain (comparable to the inferior colliculus in mammals) for normal male and female frogs and for frogs treated with elevated levels of testosterone (the primary male hormone in vertebrates, including amphibians and mammals).[9] An example of their findings is presented in Fig. 6, where normal thresholds are given on the left and the thresholds for the frogs receiving supplemental testosterone are plotted on the right. The main finding here is that the females, who normally have better thresholds than the males at the auditory midbrain level, have elevated thresholds and exhibit hearing sensitivity much more like the males after the females were treated with testosterone. This finding that testosterone can decrease hearing sensitivity is consistent with a series of human investigations conducted by McFadden[10] on men and women of different ages using otoacoustic emissions. He reported that boys and men tend to have lower otoacoustic emissions when compared to girls and women, with blood testosterone level differences being a primary contributing factor.[10]

Sex Hormones Change Auditory Perception in Mouse Mothers with New Pups

Interesting studies by Miranda and Liu[11] reveal associations among hormonal changes in postpartum mouse mothers, auditory processing, and newborn mouse pup vocalizations.[11] Specifically, these authors provide convincing evidence that fluctuations in female hormones (estrogen and progesterone), as diagrammed in Fig. 7, can drive auditory cortical sound processing via modulations of the dopaminergic and cholinergic neural circuitry in the cerebral cortex. These changes improve vocalization processing by the female mouse mothers so

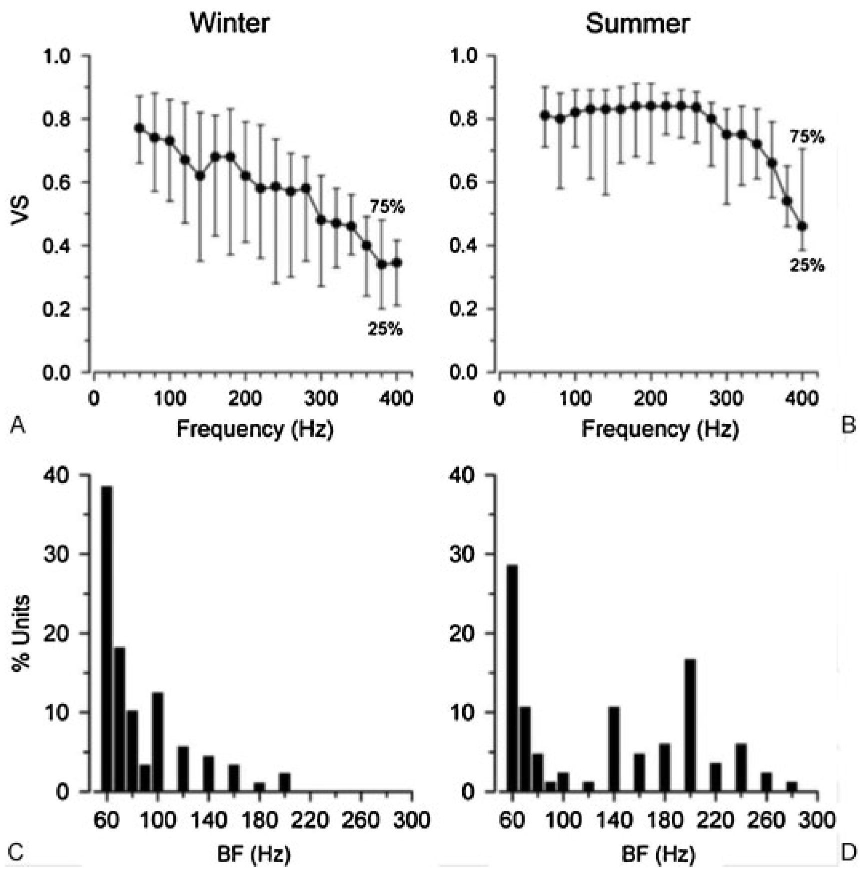

Figure 5 Isointensity response curves and best frequency histograms of auditory saccular afferent neurons recorded from a wild population of female midshipman fish. Adult females were collected during the nonreproductive winter (left column) and reproductive summer (right column) seasons. (A and B) Response curves of saccular afferents to 130 dB (reference 1 μPa) isointensity tones based on vector strength of synchronization (VS) that show the VS values for each frequency tested in terms of median (black circles), 25th percentile (bottom bar), and 75th percentile (top bar). (C and D) Distribution of best frequencies (BF) for saccular afferents of winter nonreproductive (C) and summer reproductive (D) females based on VS to isointensity tones of 130 dB (reference 1 μPa). Median BF was higher for summer females (95 Hz) than winter females (80 Hz). Figure and legend adapted with permission from Sisneros. Steroid-dependent auditory plasticity for the enhancement of acoustic communication: recent insights from a vocal teleost fish. Hear Res 2009;252:9–14[5] (Fig. 1).

they can better hear, feed, and care for their pups.

CLINICAL RESEARCH: PROGESTERONE AND ESTROGEN CAN AFFECT HEARING

The development of hormone replacement therapy (HRT) for menopausal women was noteworthy because it can help to reduce or eliminate physiological symptoms of menopause, such as difficulty sleeping, body temperature misregulation (hot flashes), irritability, mood swings, and so on. However, after years of study, it has been found that serious side effects of HRT can occur, some of which can be life-threatening, including ovarian cancer. Noting this, Guimaraes and colleagues[12] performed the largest clinical research study of its kind to date, examining hearing loss side effects for older women who had taken HRT for at least 5 years or more. Three subject groups were employed in the research design: (1) healthy women ($n = 32$), 60 years old and older, who had taken combination HRT (estrogen + progestin [E + P group]), which is the most

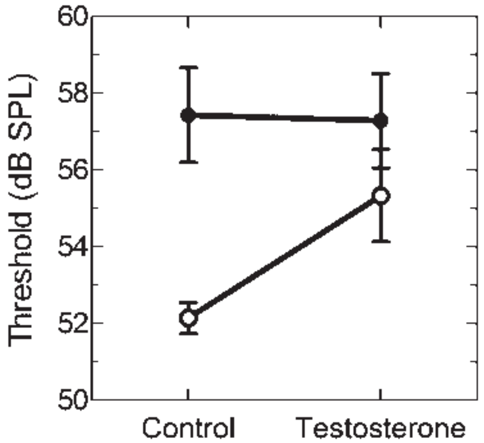

Figure 6 Thresholds in response to the male advertisement call for females (open circles) and males (filled circles). Refer to the results section for statistical comparisons of sex and testosterone effects. Figure and legend adapted with permission from Miranda and Wilczynski. Sex differences and androgen influences on midbrain auditory thresholds in the green tree frog, *Hyla cinerea*. Hear Res 2009;252:79–88[9] (Fig. 6). Sound pressure level (SPL).

common form of HRT taken by menopausal women; (2) controls ($n = 62$), who were matched for age, sex, and health history but had never taken HRT; (3) a comparison group of women ($n = 30$) of the same age and good health history, who had taken the estrogen-only form of HRT (E group). The research team performed audiometric and otoacoustic emissions tests of the peripheral auditory system and experimental hearing tests (HINT) that assess brain function and the abilities to perceive speech in background noise at suprathreshold, conversational levels. This investigative team found evidence for *accelerated* peripheral and central presbycusis in the E + P group, compared with the controls and E group. Specifically, pure-tone audiometry revealed that the E + P group had *higher thresholds* than the E group and control group for all frequencies tested (see Fig. 8). Otoacoustic emissions measure the physiological health and functionality of the cochlear outer hair cell system. In the present investigation, the E + P group exhibited *lower otoacoustic emissions amplitudes* than the E and control groups for both ears (see Fig. 9). The ability of the E + P group to process speech in background noise also was compromised. Specifically for the HINT, the E + P group showed *poorer performance* than the E and NHRT groups across all background noise speaker locations (see Fig. 10). These findings suggest that the presence of progestin as a component of HRT causes poorer hearing abilities in older women, at both peripheral (cochlear) and central levels of the auditory system. Put another way, sex hormone imbalances in middle and old age might accelerate age-related hearing loss (presbycusis).

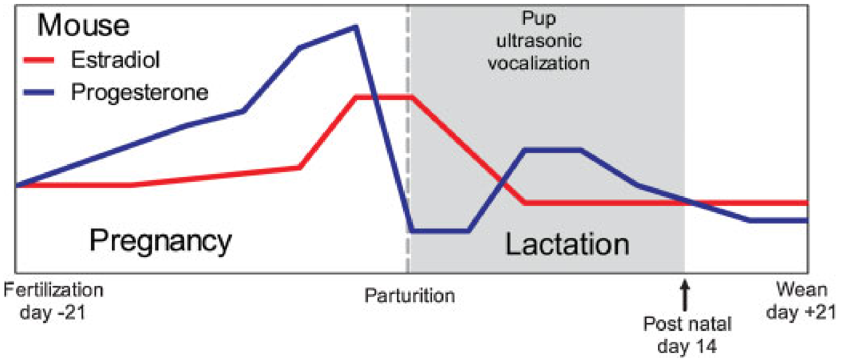

Figure 7 Schematic representation of estradiol and progesterone profiles during pregnancy and lactation in the mouse. The vertical dashed line denotes the time of parturition (birth). The gray shaded area encompasses the period in which pups produce ultrasonic vocalizations. Figure and legend adapted with permission from Miranda and Liu. Dissecting natural sensory plasticity: hormones and experience in a maternal context. Hear Res 2009;252, 21–28[11] (Fig. 2).

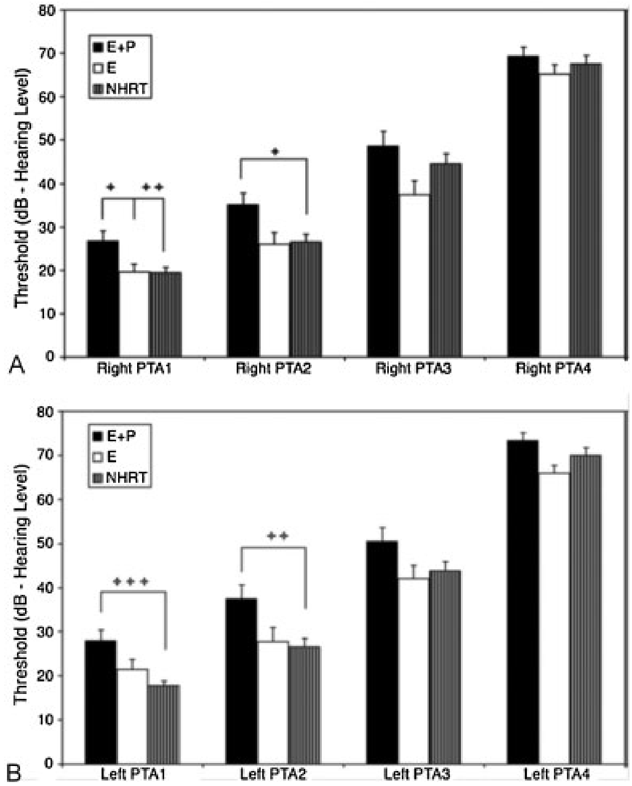

Figure 8 Comparisons between estrogen + progestin (E + P) group, estrogen alone (E) group, and controls (NHRT) for pure-tone thresholds in the right ear (A) and left ear (B). The E + P group presented with elevated thresholds relative to the E and the NHRT groups at all frequencies, with statistically significant differences for both ears for PTA1 and PTA2. PTA1 represents the average of thresholds for frequencies 0.5, 1, and 2 kHz; PTA2 for 1, 2, and 4 kHz; PTA3 for 4, 8, and 9 kHz; and PTA4 for 10, 11.2, 12.5, and 14 kHz. PTA, pure-tone average. $^{+}p < 0.05$; $^{++}p < 0.01$; $^{+++}p < 0.001$. Error bars represent standard error of the mean (SEM). Figure and Legend adapted with permission from Guimaraes et al. Progestin negatively affects hearing in aged women. Proc Nat Acad Sci USA 2006;103:14246–14249[12] (Fig. 1).

ANIMAL MODEL FOLLOW-UP EXPERIMENTS: HRT IN AGING MICE

To understand some of the biological underpinnings and neural mechanisms of the HRT findings in older women, Price et al[13] conducted analogous experiments in aging mice to determine if similar disruptions of hearing occur in the animal model. Specifically, this investigative team administered HRT to middle-aged female CBA mice and measured their hearing abilities relative to female controls and male mice that were matched for age. Two × 60-day HRT pellets were implanted subcutaneously, with 12 mice in each group. Auditory brain stem response and otoacoustic emissions were measured longitudinally for the 4-month HRT treatment period. Evidence for accelerated peripheral auditory processing problems in the HRT groups was found. In particular, for the pure-tone auditory brain stem response thresholds, the E + P group had *greater threshold increases* than the E and NHRT groups, for middle and high frequencies, as shown in Fig. 11. In addition, the E + P group exhibited lower *otoacoustic emissions amplitudes* than the E and NHRT groups over the 4-month experiment, especially at middle and high frequencies (see Fig. 12). These findings

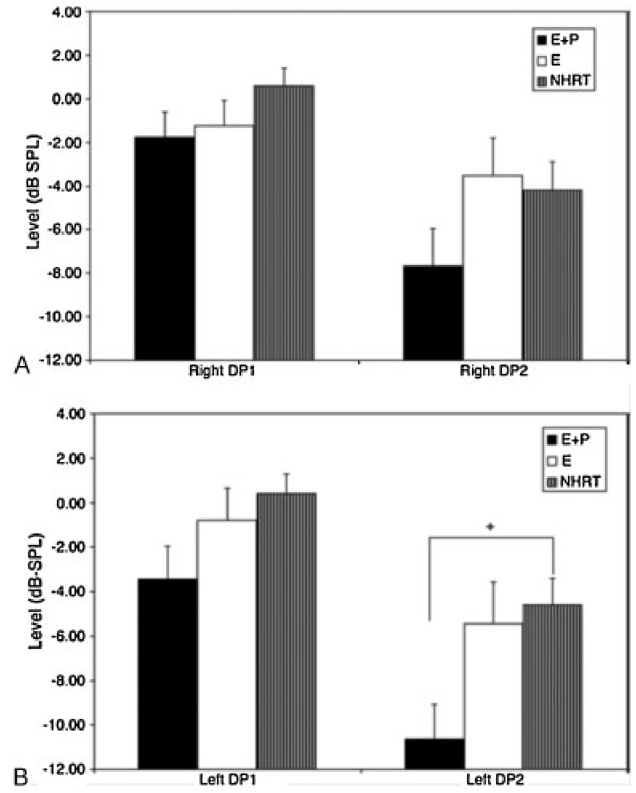

Figure 9 Histograms showing the comparison between results for estrogen + progestin (E + P) group, estrogen alone (E) group, and controls (NHRT) for distortion-product otoacoustic emission (DP) levels. Notice that for both sides [right ear (*A*) and left ear (*B*)], the E + P group presented with lower levels than the E and NHRT groups. Statistical significance was found for the left DP2 group main effect: *P*, 0.017; *F*, 4.24; *df*, 2, 121. Bonferroni posttests showed statistical significance for E + P versus NHRT for the left ear DP2 ($^{+}P < 0.05$; *t*, 2.89). DP1 represents the average for frequencies 1001, 1257, 1587, and 2002 Hz; and DP2 represents the average for frequencies 3174, 4004, 5042, and 6748 Hz. Error bars represent standard error of the mean. Figure and Legend adapted with permission from Guimaraes et al. Progestin negatively affects hearing in aged women. Proc Nat Acad Sci USA 2006;103:14246–14249[12] (Fig. 2). SPL, sound pressure level.

parallel the human clinical research findings of Guimaraes et al,[12] implicating the presence of progestin (a component of HRT) as a cause of poorer hearing abilities in aging CBA mice, specifically affecting the outer hair cells and peripheral auditory system.

SUMMARY AND CONCLUSIONS

Animal model studies, from fish to mammals, indicate that hormones can influence auditory processing at the levels of the inner ear and brain. These hormonal influences are linked to key behaviors that ensure survival of the individual and the species, such as mating and reproduction. Animal experiments and human clinical research studies suggest that aldosterone can have a positive effect on treating autoimmune hearing loss and slowing down the progression of age-related hearing loss (presbycusis). Similarly, findings from animal and human research suggest that unnatural levels of progesterone may be harmful to hearing in females as they progress from middle age to old age, whereas estrogen appears not to impose these negative effects.

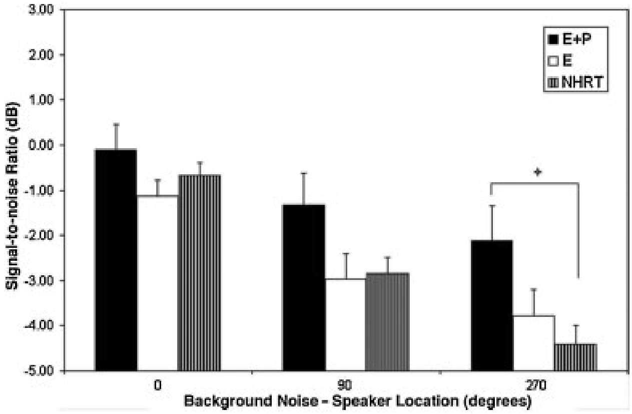

Figure 10 Comparisons for the Hearing in Noise Test (HINT) between estrogen + progestin (E + P) group, estrogen alone (E) group, and controls (NHRT). Notice that the E + P group presented with decreased recognition of speech in noise across all background-noise speaker locations. The group main effect was statistically significant for the 270-degree background-noise speaker position: $p = 0.016$; *F*, 4.27; *df*, 2, 121; Bonferroni posttests showed significant E + P versus NHRT for the background-noise speaker at 270° ($^{+}P < 0.05$; $t = 2.92$). The HINT quiet condition, although not depicted on the histogram, showed a statistically significant group main effect: $P < 0.025$; *F*, 3.83; *df*, 2, 121; the Bonferroni posttest for E + P versus NHRT was also statistically significant ($^{+}p < 0.05$; $t = 2.74$). Error bars represent standard error of the mean. Figure and legend adapted with permission from Guimaraes et al. Progestin negatively affects hearing in aged women. Proc Nat Acad Sci USA 2006;103:14246–14249[12] (Fig. 4).

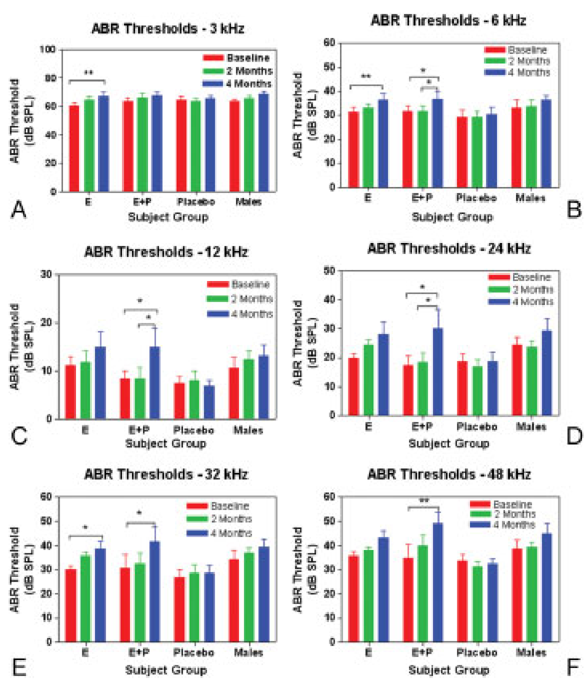

Figure 11 Longitudinal comparisons among aging mouse subject groups revealed statistically significant changes to auditory brain stem response (ABR) thresholds at 4 months of treatment when compared with baseline, across 6 to 48 kHz for the estrogen + progestin (E + P) group. The estrogen-only (E) treatment group revealed statistically significant changes at 3, 6, and 32 kHz only, with no corresponding changes in either the placebo or male groups. Error bars represent standard error of the mean (SEM). Sound pressure level (SPL). Figure and legend adapted with permission from Price et al. Hormone replacement therapy diminishes hearing in peri-menopausal mice. Hearing Res 2009;252:29–36[13] (Fig. 1).

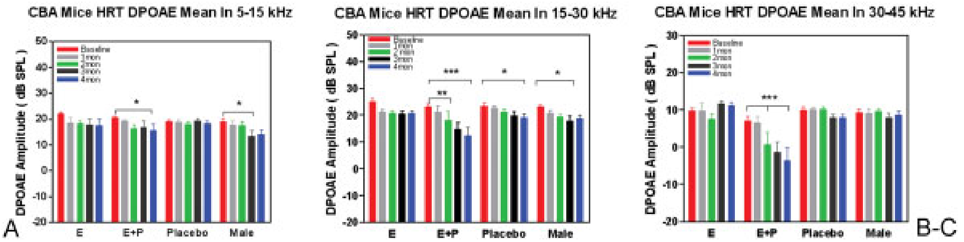

Figure 12 Longitudinal comparisons of otoacoustic emissions amplitudes among groups revealed statistically significant changes across: (A) low (5 to 15 kHz), (B) middle (15 to 30 kHz) and (C) high (30 to 45 kHz) frequency ranges for the estrogen + progestin (E + P) treatment group at 4 months of treatment, and as early as 2 months in the middle- and high-frequency ranges. Less significant changes were seen within the middle frequency range at 4 months for the placebo and male groups. Error bars represent standard error of the mean. HRT, hormone replacement therapy; DPOAE, otoacoustic emissions; SPL, sound pressure level. Figure and legend adapted with permission from Price et al. Hormone replacement therapy diminishes hearing in peri-menopausal mice. Hearing Res 2009;252:29–36[13] (Fig. 3).

ACKNOWLEDGMENTS

This work was supported by National Institute of Health Program Project Grant P01 AG009524, from the National Institute on Aging, USA.

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