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Sex Hormones and Hearing: A Pioneering Area of Enquiry

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Sensory neuroscience and biomedical research in general, have become extremely specialized. Most fields and subfields, for one attempting to enter them as a cutting-edge researcher, or as an investigator in a related field who wants to gain mastery of another area; it can take much time and effort to attain a useful, comfortable level of knowledge. Sometimes, this learning task is so daunting, few venture to undertake it, particularly as we advance professionally. The influence of sex hormones on the auditory system is one of those rare areas of investigation, where mastering what has been discovered to date, is actually feasible. This special issue of *Hearing Research* is a very effective introduction and summary of what is currently known about how sex hormones can effect hearing, and how in some cases, alterations in natural levels of sex hormones can lead to hearing impairment or deafness. Not surprisingly, the neonatal nature of this developing area of enquiry can be both satisfying and unsettling. Being able to master most of what is known about this sub-field of hearing research and auditory neuroscience, in real-time, is quite rewarding. However, from a mechanistic and clinical interventional point of view, it can be very frustrating. Delineation of mechanisms below the systems level, including working out of cellular and molecular pathways and biomarkers, a requirement of clinical translational innovations and drug discovery, is still a lengthy task. Some believe that one key mark of good science is that for every question that is answered, many more questions and hypotheses are generated from the experiments carried out. This is certainly the state-of-the-art stage we find ourselves in regarding what we know, and what further necessary experimentation is needed about how sex hormones can influence hearing and their involvement in hearing loss.

In terms of organization of this special issue, higher level studies, including those at behavioral and systems levels, the “phenotype” if you will, will be presented first, to give a flavor for how hormones and hormonal changes influence audition, be they triggered by stimuli intrinsic or extrinsic to the organism. Then, later articles will delve a little more deeply into the possible neural and cellular mechanisms of how sex hormones might carry out their actions, either beneficial, or detrimental, to hearing and the auditory system. Both ear and brain studies are presented, starting with the peripheral auditory system, and then moving more centrally.

The first article characterizes the effects of estrogen-deficiency on hearing in women who have a chronic lack of this hormone that provides important trophic support for many cell types, including neurons. Hederstierna et al. (2009) report some new aspects of the hearing impairment linked to Turner’s Syndrome, a congenital genetic condition where girls are born without some portions of the X chromosome. This is the most common sex-chromosome abnormality in human female conceptions. This research team characterizes in more detail peripheral aspects of the Turner’s hearing loss, such as reduced cochlear sensitivity as measured by otoacoustic emissions, auditory brainstem responses (ABRs) and speech recognition scores. They break new ground by including a test on sound localization, where critical processing

takes place in the brainstem of the central auditory system. They report a deficit here as well, implicating central auditory processing problems as part of the Turner's estrogen deficiency.

Keeping this clinical framework in mind, the next article is an enlightening example of how vertebrate model systems accelerate our understanding of how hormones interact with sensorimotor systems. In particular, utilizing the plainfin midshipman, a vocally active teleost fish, Sisneros (2009) charts us through a series of experiments where sexually-linked behaviors involving known hormonal changes influence auditory sensitivity and processing in neuroethologically important ways. Going further, associations between steroid-dependent auditory plasticity are tested for causality by inducing artificial hormonal levels and measuring changes in hearing behaviors. Insights into neural and molecular mechanisms are put forth.

Moving higher on the phylogenetic scale, Arch and Narins (2009) provide a discussion of the importance of sex hormones in frog and toad acoustic communication. Specifically, reproduction in these amphibians is critically dependent upon vocalization production and reception, both of which are modulated differentially by female and male sex hormones, including peptide neuromodulators and gonadal steroids. Actions of these hormones are carried out by altering spectral filtering and tonal sensitivities appropriate to the spectral properties of the species-specific calls. The authors point out the highly conserved nature of many hormonal influences on reproductive behaviors among vertebrate taxa, underscoring the importance and significance of studies involving sub-mammalian model systems.

Expanding on the theme of sex hormone-dependent auditory plasticity, in the next article we move from vertebrate animal models to a mammalian investigation of hormonal changes involved in mouse maternal behavior and hearing. Miranda and Liu (2009) draw upon a number of studies involving interactions of pups and pup calls with their mothers, including investigations where auditory behaviors in mothers are different from con-specific virgins, and relate these to hormonal influences. They glean additional information about sensory-dependent neural plasticity by examining other factors as well, such as whether a mother is nursing her pup or not. Changes in important brainstem and cortical neurotransmitter systems, including their receptor components, for transmitters such as dopamine, serotonin, acetylcholine and others, starts to get at the underlying mechanisms for the observed behavioral and sensory adaptive plasticity.

The next contribution also utilizes mouse models to better understand hormonal influences on hearing. Price et al. (2009) took a group of middle age female mice and gave them either combination (estrogen + progestin) hormone replacement therapy (HRT), estrogen monotherapy, or placebo, using subcutaneous time-release pellets. They found that across the mouse range of hearing, peripheral measures of hearing declined for the combination HRT subject group relative to the control and estrogen groups, including measures of distortion-product otoacoustic emission levels, and ABR thresholds. In many regards, these findings are similar to results from human clinical studies of women taking HRT, underscoring the usefulness of mouse models to study the effects of sex hormones on the auditory portion of the cochlea.

The next contribution takes us from consideration of the female sex hormones' influences on hearing to effects that testosterone can have on the peripheral and brainstem auditory systems. McFadden (2009) summarizes an enlightening series of investigations that he and his colleagues have carried out demonstrating the negative consequences of testosterone on hair cells and hearing sensitivity, across a variety of mammals, including primates and humans. Intriguing interpretations of these data, including possible androgenizing influences of prenatal exposure of outer hair cells to testosterone, are put forth in a logical and provocative manner.

Next, Noirot et al. (2009) utilize an avian model system to map out the presence and distribution of important female hormones and receptors in the cochlea of the zebra finch. The presence of aromatase, the enzyme that naturally converts testosterone to estrogen, was assayed with immunocytochemistry, along with the immunoreactivity for the alpha subtype of the estrogen receptor (ER α). They found that for both females and males, ER α co-localized with aromatase in the vast majority of hair cells, with the former predominantly lying in the nuclei of hair cells and supporting cells, and the latter in the cytoplasm. The presence of ER α and aromatase in the cochlea is consistent with mammalian studies, but this is the first demonstration in any animal model of the nature of their co-localization in hair cells.

Sex hormones not only influence hearing via effects on sensory cells and neurons. Horner (2009) provides an interesting case of how the lack of estrogen, and other hormones such as prolactin and progesterone, known to induce or modulate bone reductions and osteoporosis in the skeletal system of peri- and post-menopausal women, can induce changes in the temporal bone relevant to audition. For example, analyses at the cellular level reveal that the decoy receptor osteoprotegerin (OPG), which is highly expressed in the mammalian cochlea and binds competitively to the receptor activator of nuclear factor- κ B, can disrupt inner ear calcium metabolism to the point of inducing hearing loss in experimental animals. Implications for contributing to combination HRT clinical hearing loss are explored.

McCullar and Oesterle (2009) approach the roles of how estrogen can influence cochlear regenerative capacities by interacting with other trophic agents. McCullar and Oesterle focus their presentation on how estrogen can potentiate the effects of the roles that endothelial growth factor and transforming growth factor- β have in proliferation capabilities of the inner ear sensory epithelia, particularly the vestibular epithelia. Both ligand-dependent and – independent cellular pathways, and genomic and non-genomic mechanisms are elucidated and discussed.

Continuing on the theme of the importance of sex hormone receptors, Charitidi et al. (2009) review the distribution and functionality of estrogen receptors in the ear and central auditory system in both female and male mice. Complex genomic and non-genomic mechanisms for the actions of estrogen, via both alpha and beta receptors are discussed. Differential distributions of these two receptor subtypes in the cochlea and central auditory system are described, along with possible interactive pathways with important auditory system neurotransmitters such as GABA, serotonin, dopamine and glutamate, and other sex hormones, including testosterone.

Continuing our journey into the central auditory system, Miranda and Wilczynski (2009) provide another example of how inventive utilization of sub-mammalian model systems, in this case the green treefrog, can reveal actions that sex hormones have on neural processing in the central auditory nervous system. By performing multi-neuron electrophysiology in the auditory midbrain (inferior colliculus) in female and male frogs, they discovered neural processing differences that are linked to male/female hormone differences, particularly testosterone. These sex-linked steroid hormone differences altered the filtering properties of the female and male auditory systems, including processing of tones and species-specific vocalizations.

Our last contribution comes from a researcher with a long history of investigating behavioral and neural aspects of age-related hearing loss in mouse models. In this special issue, Willott (2009) summarizes the interactions that aging, special acoustic environments and hormonal changes can have on hearing, with special emphasis on male/female differences and central auditory plasticity in the C57BL/6J mouse strain. In a series of coordinated experiments, Willott and colleagues have uncovered some sex differences in hearing sensitivities and

responses to augmented acoustic environments that generally delay the onset and progression of rapid, age-linked hearing loss in inbred mouse strains that have one or more copies of the *ahl* gene. For instance, changes in neuron numbers at the level of the cochlear nucleus were discovered.

In closing, this special edition of *Hearing Research* provides a unique exposition where the main findings in a youthful but burgeoning sub-field of hearing science and auditory neuroscience are put forth in one issue. Each contribution provides key references for the topic, rather than listing exhaustive bibliographies, giving the reader an opportunity to rapidly obtain most of the essence of what is known about how sex hormones can influence how and what we hear.