Chapter 14

Sex Hormones and Inner Ear

Zi-Yu He and Dong-Dong Ren

Additional information is available at the end of the chapter

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Abstract

There are increasing evidence of interactions between sex hormones and the structure and function of inner ear, especially in hearing impairment and balance disorders. In this chapter, we will discuss the mechanism of sex hormones on the inner ear, describe both clinical and basic research that has led us to our current understanding, and conclude with future perspectives on avenues of investigation that may lead to innovative treatments on the hearing loss, tinnitus, and dizziness resulted from the changes in estrogen and progesterone levels. The presence of estrogen receptors α and β has earlier been shown in the inner ear of mice. Expression of estrogen receptors (ER) correlates with the protection of auditory function. Estrogen may have certain protective effects on the hearing. Evidence for the treatment of sex hormone-induced symptoms is principally restricted to case reports and retrospective studies. Recognition and understanding of sex hormone-related inner ear problems will allow otologists to notice and manage these patients. Also, basic studies on the mechanism of how sex hormones act on inner ear provide the way to further prevent and treat on hearing impairment and balance disorders. High-quality evidence for their management is limited, with further research required.

Keywords: sex hormones, inner ear, hearing, balancing functions, mechanism, treatment methods

1. Introduction

Hearing loss, vertigo, dizziness, and tinnitus are the common symptoms in otology clinics. The cochlea and vestibule in the inner ear are filled with endolymph and perilymph, and the homeostasis of the water and blood circulation in the inner ear is essential for maintaining its

hearing and equilibrium functions [1]. There are more evidence of interactions between sex hormones and the function of the inner ear, especially in the mechanism of hearing impairment and balance disorders in old women and pregnant women. Is the female sex steroid estrogen the key to preserved hearing in the aging human? Is the hearing loss more profound in elderly males than females? Is the hearing loss easier spontaneously recovered in pregnant women? All these questions remain unanswered. In this chapter, we will discuss the mechanism of sex hormones on the inner ear, describe both clinical and basic research that has led us to our current understanding, and conclude with future perspectives on avenues of investigation that will contribute to stratification strategies on the hearing loss, tinnitus, autophony, and dizziness resulted from the changes in sex hormone levels.

2. How the different sex hormones may influence the inner ear

The sex hormones, including estrogen, progesterone, and androgen, are known to be implicated in normal auditory function in different proportions [2]. It is the balance of all three hormones in the body that promotes human health and vitality, including inner ear functions. Estrogen is usually thought of a "female" hormone; it may act as an auditory protectant; it is made in the ovaries, adrenal glands, and fat cells; and its levels are higher in those of reproductive age, which is helpful to prevent bone loss and works toward maintaining good cholesterol levels. Estrogens are known to facilitate the loss of intravascular fluid into the extravascular space, producing edema; however, blood vessel permeability, blood circulation, or inflammation has been reported to be related to the inner ear diseases. Progesterone is the sex steroid frequently mentioned for sexual health. In women, it is produced in the ovaries and through ovulation, which performs different benefits in balancing the unwanted effects of estrogen, helping the body use fat for energy, maintaining healthy weight, promoting restful sleep, and protecting against breast and uterine cancer; however, it may have a negative effect on hearing [3]. Androgen is a "male" hormone, the primary and most well-known androgen is testosterone, produced in the testicles and to a lesser degree in the adrenal glands, which helps build muscle tome, increases energy, contributes to a healthy libido, and aids in sperm production [4]. Healthy levels are also important in women; testosterone is produced in the female ovaries and a small amount is made in the adrenal glands, which helps to increase libido, promote musculoskeletal tone and strength, and raise energy levels. When testosterone is too high, however, it can lead to acne, unwanted hair on the face and body, polycystic ovaries with resulting interference of ovulation, and aggression among other concerns. Getting all three sex hormones balanced can be helpful for both men and women, and the results often offer clues on how to prevent unwanted inner ear symptoms in the future.

2.1. Estrogen

Estrogens influence physiological functions of many organs and systems in both female and male, including the skeletal, cardiovascular, and nervous systems, as well as the male urogenital tracts, mammary glands, and female reproductive organs. Estrogen could lead to neural excitation and thus facilitate auditory transmission, but the possible increase in neurosteroids in the brainstem

may counteract this effect. Estrogen may act as an auditory protectant, which influences the inner ear at different levels, at the cochlea, vestibular organs, and more proximal levels.

Estrogens are mediated through estrogen receptors (ERs). There are at least three and possibly four distinct estrogen receptors. The most common estrogen receptors are ERα, which is encoded by a gene on chromosome 6, and ERβ, encoded by a gene on chromosome 14. Other ERs include G protein-coupled receptor (GFER, GPR30, and a putative receptor (ER-X), which has been studied mostly in brain [5]. Estrogen receptors α and β containing cells were also found in the inner ear, with a specific distribution pattern, both in auditory pathways and in the water/ion regulating areas. The presence of ERs in the inner ear cell nuclei implies that estrogen may have an influence on the inner ear and auditory functions. Estrogen receptors have been found in the inner ear of rats and mice in different cell types, including inner and outer hair cells, stria vascularis, spiral ligament, Reissner's membrane, and spiral ganglion cells especially type I cells [5]. Moreover, estrogen receptors in the auditory epithelium of vertebrates also occur in fishes [6], cichlid [7], songbird [5], and rodents [8], which suggest a widespread occurrence of steroid-dependent auditory plasticity among the vertebrates.

But in adult human inner ear, ERα-containing cells were only found in the spiral ganglion, and ERβ-containing cells in the stria vascularis selectively, which are important for hearing transmission and inner ear homeostasis [8]. It has been shown that there is less expression of ERα in strial marginal cells, outer hair cells, and type II ganglion cells [9]. ERα and ERβ are regulated depending on the stage of maturation, development, and pregnancy, suggesting that estrogen may have an effect on the cochlea during different life time. ERs were not found in the cochlea of the growing fetus, which implied that estrogen does not have an influence on the cochlea during the period of gestation [10]. Estrogen receptor mRNA is expressed in supporting cells with similar functions within the saccular epithelium of midshipman fish [6].

The expression of ERα was found in forebrain nuclei, including anterior parvocellular (PPa) and anterior tuberal (AT), which are sites of the integration between auditory and vocal motor system [11], and anterior tuberal is densely innervated by the neuropeptides, arginine vasotocin and isotocin, which modulate vocal motor patterning in midshipman [12–14]. Also, in some gene knockout studies, estradiol plays an important role in the regulation of both vasopressin and oxytocin, especially by ERα in limbic regions [15, 16] and by ERβ in hypothalamic areas [17].

The expression of ERs in known target organs is influenced by the amount of estrogen in the serum. Lots of studies have shown a gender difference in hearing function. And some of them suggested that part of this variation was because of the difference in estrogen levels between the two genders. As for the expression pattern of ERs, there is no gender- or age-related difference to be found. However, the fluorescence intensity of ERα was stronger in female mice than in young male ones. To compare with, ERβ showed no significant difference. Also, the expression of ERs decreased with age. In the old mice, the fluorescence intensities of ERs were significantly decreased in both male and female [9].

Many clinical and basic studies have proved that estradiol plays an important role in auditory physiology, neuronal plasticity, and the metabolic levels of neurotransmitters [18, 19]. ERα might change cochlea and vestibular sensory transduction, and ERβ may have a neuroprotective effect

in the inner ear [9]. ERβ protects the auditory system from acoustic trauma in young male and female mice. ERβ in accordance with brain-derived neurotrophic factor (BDNF) promotes neuronal plasticity and protection against trauma in the auditory system [20]. But experimental estrogen-induced hyperprolactinemia leads to hearing loss in the guinea pig. It suggests that otic capsule and hair cell pathology related with estrogen-induced prolonged hyperprolactinemia and conditions such as pregnancy may lead to similar auditory pathology [21]. 17β-estradiol leads to adjustments in the molecular biology of the cochlea and the inferior colliculus of mouse accompanied with behavioral alternations [22]. Estrogen-related receptor gama (ESSR) plays a role in maintenance of hearing in both humans and mice [23].

2.2. Progesterone

Progesterone is secreted principally by the granulosa lutein cells of the corpus luteum, which are formed from granulosa cells after the luteinizing hormone surge. Progesterone is the main hormone of pregnancy, and in pregnancy, after week 8, the placenta replaces the corpus luteum as the main source of progesterone. Several steroids have similar properties and are together classified as the "progestogens." These include 17*α*-hydroxyprogesterone and pregnenolone as well as progesterone itself.

The two main progesterone receptors are progesterone receptor-A and progesterone receptor-B. And, there are two isoforms of the progesterone receptor encoded by the same gene, but with different start sites for transcription, hence the increased size of progesterone receptor-B compared with progesterone receptor-A. Expression of the progesterone receptor is regulated by estrogens, while progesterone receptors have an important effect, mediated by progesterone receptor-A, in inhibiting the proliferative actions of estrogen. For this reason, progesterone is nearly always given in addition to estrogen therapy, for example, in the oral contraceptive pill and in hormone replacement therapy. The presence of progesterone as a component in hormone replacement therapy leads to poorer hearing in aged women, affecting both the peripheral and central auditory system, and it interferes with the perception of speech in background noise [21].

Nevertheless, there is no direct nuclear effect of progesterone in the inner ear. There is no nuclear progesterone receptor being found in human or rat stria vascularis, organ of Corti or spiral ganglion with immunohistochemistry, or polymerase chain reaction (PCR). But, progesterone receptor-B is being found with Western blot in the cochlea. It probably indicates the staining in the cochlea bone. In this case, the effect of progesterone on hearing is probably not relevant to the action in the inner ear [25].

Progesterone receptors are important for integration of external signals and internal physiological cues in the brain to output an appropriate behavior. In a study using the frog, *Physalaemus pustulosus*, as a model system, progesterone receptor immunoreactivity was found in key brain regions known to modulate the processing of auditory clues [26].

2.3. Androgen

Androgens, which are produced by Leydig cells, like all steroid hormones, are made from cholesterol. A range of androgens is made in the body and, although most of these come from the testes, some are made in the adrenal cortex. The most potent and important of these

androgens is testosterone, and by far the highest production of testosterone is in the testes. Testosterone has two main actions: the initiation of spermatogenesis and the development and maintenance of secondary sexual characteristics. In order to achieve the second group of actions, testosterone must be converted to 5α-dihydrotestosterone (DHT). This conversion happens outside the testes, in peripheral tissues. Furthermore, both testosterone and DHT act on the same receptor, the androgen receptor (AR).

In contrast to these well-known effects of estradiol on hearing function, relatively little is known about how androgens might influence hearing or whether androgen receptors (AR) are also expressed in the inner ear of vertebrates. The lack of regenerative ability of adult mammalian cochlea and the irreversible degeneration of cochlear sensory hair cells leads to permanent hearing loss. Whether the androgen receptors (ARs) establish in the inner ear, there are many studies on it, in a transcriptomic analysis of the developing and adult mouse cochlear sensory epithelia, the adult cochlear sensory epithelium overexpressed 2542 transcripts including new transcripts, such as AR, which previously were not reported to be expressed in the adult cochlea [27].

In all major vertebrate animals, androgen receptors have been identified in neural circuits that shape vocalization. Many of those nuclei mentioned above are part of the known vocal and auditory circuit in midshipman. The distribution of androgen receptor mRNA supports that androgens modulate behaviorally defined vocal, auditory, and neuroendocrine circuits in teleost fish and vertebrates in general [28].

Additionally, testosterone in serum increased neural thresholds in females in a frequency-specific way [29]. And hyperandrogenism may be responsible for the elevation of hearing threshold, particularly in the high frequency, in patients with polycystic ovary syndrome [30–32]. On the contrary, hyperandrogenism did not seem to affect otoacoustic emission levels or the medial olivocochlear reflex response in adult female subjects [33].

In audiology, the usage of biomedical interventions and biotherapeutic methods could play an important role in modulating or preventing some kinds of hearing loss. Planar cell polarity is of high importance as it regulates cochlea extension and coordinates orientation of sensory hair cells in the inner ear. If we could use the effect of sex hormone in the inner ear, the establishment of ectopic hair cell-like cell polarity could be built. Testosterone is related to the neuroprotection and regeneration in central nervous system. We could promote an increase in hair cell-like cell polarity in the LER through proliferation and transdifferentiation by using testosterone-3-(O-carboxymethyl) oxime bovine serum albumin and Math1 treatment [34]. In the treatment of immune-mediated sensorineural hearing loss, it was confirmed that testosterone has the preventive and therapeutic effects induced by sensitization using bovine inner ear antigens [35].

3. Physiological variation in sex hormones and effect on inner ear

The levels of sex hormones vary in response to endogenous and exogenous stimuli and many vary in a cyclic fashion. The endocrine changes related to reproductive function (ovarian cycle, pregnancy, and menopause) could in turn affect auditory and balance function. Additionally,

there are multiple interactions between the sex hormones involved in these physiological changes and this enhances the possible multidirectional effects on the inner ear.

3.1. Ovarian cycle

In the ovarian cycle, the levels of estrogen and progesterone in the body have a dynamic regulation. Both clinical and basic studies have proved that the changes of auditory and balance system are attributed to estradiol and progesterone. In other words, the fluctuating hearing levels are evident in females during the ovarian cycle. Across the life span, both women and men undergo transitions in reproductive status related in part to changes in sex hormone levels. There is controversy over how hormonal conditions influence cerebral physiology related to evoked potentials and perceptual speech processing in women during ovarian cycle. Hearing thresholds change upon different sex hormone levels during the menstrual cycle [36]. And hearing conduction, measured by auditory brainstem response, is better in postovulatory phase compared with preovulatory phase of menstrual/ovarian cycle [37]. Also, brainstem auditory evoked potentials change in the mid follicular and the mid luteal phases of the ovarian cycle [38]. Moreover, ovarian cycle effects on postural stability but not optokinetic function, and this needs to be considered when conducting studies of postural stability in women [39]. Studies of dichotic listening in women of the reproductive age also show that there is variation in laterality as a function of menstrual cycle phase. The perceptual speech processing of women is highly plastic and operates at varying states of functional asymmetry across days of the menstrual cycle, which are consistent with other works showing menstrual cycle-related changes in lateralized neurocognitive systems in the language domain [40–42].

3.2. Menopause

More organs are found to be influenced by the positive effects of estrogen, and estrogen has been expected to be benefit on auditory system by many investigators. As for the postmenopausal women, many studies suggested that the hearing and balancing problem appeared might be related to their sex hormone levels. Hearing loss in older people usually affects the highest frequencies early on and gradually affects the lower frequencies. Progesterone may have negative effects on the hearing of pre- and postmenopausal women and aging mice. On the contract, estrogen was found in some situation to have a positive influence [25]. The auditory brainstem response thresholds of postmenopausal female are higher than younger men or women [43, 44]. And the lower level of circulating serum estradiol possibly impedes hearing sensitivity in postmenopausal women, which has no relationship with bone mineral densities [45].

Intrinsic estrogen at physiological levels might slow down hearing loss in aging women [46]. At the same time, estrogen therapy may slow down the hearing loss in aging postmenopausal women [47]. Tibolone, a synthetic steroid drug with estrogenic, progestogenic, and weak androgenic actions, is often used in the hormone replacement therapy for menopausal or premenopausal women. And tibolone had no negative effect on hearing function and might decelerate hearing loss in aging postmenopausal women, intrinsic estrogen at physiological levels might slow down hearing loss in aging women [46]. After treatment of healthy

menopausal women with tibolone for 6 months, the improvement was more prominent on the right side in audiometry results at low frequency. It may be explained by differences in distribution of ER in the ear. ERs might be more dense in the right ear, so give better response to estrogen therapy [47]. Many studies have showed that estrogen affects hearing function, especially in the postmenopausal women; a recent study gets a result that there may be hearing lateralization in menopausal women, especially significant improvement on right ear can be explained by lower BMD on that side ear bones in turn better response to estrogen therapy due to this, which may be related to ER concentration and the more dense of type ERα and/or ERβ in the right ear [48].

According to the vestibular function, the level of estradiol and progesterone decreases obviously in postmenopausal women with benign paroxysmal positional vertigo, which can cause the inner ear microcirculation disorder, may be a risk factor of BPPV [49].

Although estrogen has been expected to be benefits on auditory system, both clinician and patients need to take into concern that estrogen may have some unwanted side effects, such as increased risk of uterine cancer. Because in the central nervous system, ERβ is highly expressed in neurons and glial cells. And there is little ERβ in the mature uterus, selective ERβ agonists, then they become available [50, 51].

3.3. Pregnancy

Hearing loss appeared in pregnancy is not a commonly reported problem. Some investigators have noticed reversible and physiological sensorineural hearing loss at low frequencies during the period of pregnancy [52, 53]. In some case reports, sudden onset of sensorineural hearing loss during pregnancy has been described [54], and one report concerning a patient who had the hearing loss with each serial pregnancy [55]. But a nationwide population-based study suggested that sudden sensorineural hearing loss (SSNHL) in pregnancy is rare. SSNHL is defined as sudden, idiopathic, usually unilateral deafness developed at most in 72 hours in previously healthy people [56]. It often happens in the third trimester. And SSNHL in pregnancy does not increase the risks of delivery or subsequent stroke [57]. As for the mechanism, there is a hypothesis implied that SSNHL is connected with the changes in cardiovascular system, hematological system, and/or some other systems because of pregnancy. These changes in pregnancy may evoke disorders of cochlea circulation or cochlea fluid homeostasis resulting in SSNHL [57]. Otosclerosis is one of the most common causes of acquired hearing loss and is widely supposed as being related with pregnancy. Another study revealed that resonance frequency of middle ear was found to be low during the third trimester of the pregnancy. And low resonance frequency informs that the acoustic immittance of the middle ear changes during pregnancy [58].

Tinnitus is another auditory symptom in pregnant patients, with proposed theories of pathogenesis, including hyperdynamic circulation, increase in perilymphatic fluid pressure, and hormonal changes. Clinically, it appears that the hearing loss and tinnitus related to pregnancy can spontaneously recover. As for treatment, it depends on the otorhinolaryngologic doctors to decide whether they should administer steroid drugs for acute hearing loss, as it may recover after the delivery [54].

Autophony is a classic complaint of patients suffering from a patulous Eustachian tube (PET). The typical patients with PET have lost a drastic amount of weight, resulting in shrinkage of the peritubal mucous membranes. One third of the patients with PET are either pregnant or taking an estrogen replacement therapy [59]. In order to resolve the symptoms postpartum, management should consist of informative reassurance alone [60].

There is an increase in incidence of Bell's palsy (BP) during pregnancy [61]. One of the reasons could be a brain stem synaptic impairment caused by estrogen, presumably because of ischemic changes [62]. And most of them seem to be concentrated in the third trimester. The most likely explanation about the concentration in the third trimester may be the altered susceptibility to herpes simplex viral reactivation during pregnancy. And the prognosis of pregnant patients may be poorer [63].

3.4. Gender differences in auditory function

Many authors have shown that a gender differences in auditory function and some of them implied that part of this variation was due to the difference in estrogen levels between females and males. There are well-known sex differences in the auditory brainstem response, with women having shorter latencies than men [64]. Hearing loss is more profound in elderly males than females. Many early studies on otoacoustic emissions revealed the existence of sex and ear differences in human beings. Some also revealed that the sex and ear differences in adults are evident in newborns as well. These differences are in the direction of human females having stronger and more numerous spontaneous otoacoustic emissions and stronger click-evoked otoacoustic emissions than do males; also, human right ears have stronger and more numerous spontaneous otoacoustic emissions and stronger click-evoked otoacoustic emissions than do left ears. There is a so-called prenatal-androgen-exposure explanation. Prenatal androgen exposure apparently can alter auditory evoked potentials. The sex difference in otoacoustic emissions in newborns may be that the prenatal androgen exposure in some way weakens the cochlea amplifiers and thereby weakens spontaneous otoacoustic emissions and click-evoked otoacoustic emissions (and perhaps distortion product otoacoustic emissions less markedly) [65].

Sex differences are limited to frequency ranges, which are related to the processing of natural vocalizations and depend on the type of stimulus. In a research using green tree frog, *Hyla cinera*, sex did not change audiogram best frequencies, although sex did make a difference in the sensitivities at those frequencies with males more sensitive in the lower frequency range [29]. The auditory system exhibits differences by sex and by sexual orientation, and the implication is that relevant auditory structures are altered during prenatal development, possibly by exposure to androgens [66].

Gender differences also occur in some pathological situations. In the presence of sex hormone receptors in human middle ear cholesteatoma, stronger expression of progesterone receptor was found in samples from male patients, while stronger expression of estrogen receptor was found in samples from female patients. It suggests that female sex hormones may stimulate proliferation of middle ear cholesteatoma keratinocytes [67]. Estrogen levels between females and males in different ages may influence the function of the auditory systems, and the details of the mechanism should be studied in the future.

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4. Sex hormones and auditory and vestibular pathology

Considerable anecdotal evidence and limited information from previous studies suggest that auditory and vestibular functions may be influenced by sex hormones resulting in pathological conditions such as hearing disorders in Turner syndrome, Presbyacusis, Otosclerosis, and Menière's disease.

4.1. Hearing disorders in Turner syndrome

Hearing disorders are obvious in mice and women with Turner syndrome (total or partial loss of one X chromosome) [68]. Approximately one-half of women with TS have a 45,X karyotype, about 20% have 45,X/46,XX mosaicism, and the remainder have structural abnormalities of the X chromosome such as X fragments, isochromosomes, or rings. TS is characterized by bilateral streak gonads, short stature, primary amenorrhea, streak ovaries, and no estrogen production, which often develop an early presbyacusis.

The hearing loss features in patients with Turner Syndrome should be taken into consideration. The common clinical complaints are recurrent otitis media, dysfunction of the Eustachian tube, conductive hearing loss during infancy, and sensorineural hearing loss in the adolescence. The karyotype appears to be important in the hearing loss, with studies demonstrating an increased prevalence in patients with monosomy 45,X or isochromosome 46,i (Xq). It is necessary of morphologic studies of the cochlea to help out in clarifying the etiology of the sensorineural hearing loss [69]. And sensorineural hearing loss is the most common type of hearing loss. It is mostly characterized by a high-frequency loss and/or a mid-frequent dip. It is uncommon for conductive hearing loss in young women with Turner Syndrome. But in a TS cohort, 91% of patients suffered middle ear disease, but the incidence of SNHL was 9%. It is suggested that TS patients should be screened for onset and progression of hearing loss [70]. Consequently, there is a need for hearing rehabilitation in these patients. Questions about hearing must be asked by physicians when treating women with Turner Syndrome to identify those who need hearing rehabilitation, even if they have an audiogram with a normal pure tone average [71].

Both the karyotype and sensorineural dip in hearing could be used to predict the future course of hearing levels for TS patients. And estrogen may have an influence on hearing loss in TS patients [72].

Progressive hearing loss is relatively common in human without a clear molecular basis and medical therapies. A new gene, WBP2, was defined to be involved in the molecular pathway linking hearing impairment to hormonal signaling and provides new therapeutic targets. WBP2 is required for normal glutamatergic synapses in the cochlea and is crucial for hearing [73].WBP2 encodes the protein that acts as a transcriptional coactivator for ERα (ESR1) and progesterone receptor. The loss of Wbp2 expression leads to progressive high-frequency hearing loss in mouse, as well as in two deaf children, each carrying two different variants in the WBP2 gene [73].

4.2. Presbyacusis

Presbyacusis or age-related hearing loss is a complex degenerative disease that affects many people worldwide. Gender does play a role in age-related hearing loss. Longitudinal studies of aging have

shown that hearing declines more rapidly in males than females. Elderly people with presbyacusis not only have a loss in sensitivity to sound but also have significant difficulties understanding speech in background noise at supra-threshold, conversational levels. Many researchers have identified sex-specific differences in presbyacusis in humans and animal models [74].

There is growing evidence that interactions between sex hormones and sensory systems are sometimes beneficial, but oftentimes detrimental, such as progesterone with negatively affect hearing in older women, whereas in some cases, estrogen may have positive effects [24]. Data from a large cohort of adults (48–92 years) in the Beaver Dam Epidemiology of Hearing Loss Study show significant age effects in word recognition scores in competing messages for both men and women, but performance is consistently poorer in men than in women at all age groups and hearing loss categories [75].

4.3. Otosclerosis

Otosclerosis is a major cause of acquired hearing loss in adult life affecting exclusively the human temporal bone, which is reported to worsen during periods of intense hormonal activity. Many researchers show a possible link between aggravation of otosclerosis and pregnancy is still debated. Thus, sex hormones were believed to be involved in the progression of the disease. Estrogen deficiency is considered to be a cause of osteoporosis in menopause women, and estrogen substitute therapy has shown beneficial effect in those cases [76].

Otosclerosis becomes manifest between the ages of 20–50 years and is usually bilateral. It affects twice as many females as males [77]. A retrospective study on a sample of 479 women with otosclerosis showed that the risk of subjective hearing deterioration with bilateral otosclerosis increased from 33% after one pregnancy to 63% after six pregnancies [78]. Several reports have suggested that oral contraceptives may increase the risk of hearing loss and in particular otosclerosis, although no clear conclusion has been drawn [79].

Estrogen has an inhibitory effect on bone resorption by directly inhibiting osteoclast activity as well as decreasing auto and paracrine production of cytokines such as interleukin (IL) 1 and IL-6 and tumor necrosis factor, TNF [80]. Researchers investigated the effect of 17β-estradiol on bone remodeling via diastrophic dysplasia sulfate transporter (DTDST) in otosclerosis and in a human osteoblast-like cell line, and they have demonstrated that the response to estrogens in terms of DTDST activity might be related to the expressed receptor type. It is possible that exacerbating effects of estrogens in patients with otosclerosis may be mediated by peculiar profiles of estrogen receptor in otosclerotic cells [81]. However, the regulatory mechanisms of Otosclerosis related to the estrogen receptor profile in the otosclerotic cells need to be further analyzed.

4.4. Menière's disease

Menière's disease is characterized by hearing loss, tinnitus, and vestibular dysfunction. It is thought that endolymph malabsorption is the underlying cause of the swelling of the endolymphatic spaces. Estrogens are known to facilitate the loss of intravascular fluid into the extravascular space, producing edema. Endogenous alterations in concentrations of estrogen and progesterone in the premenstrual syndrome or with the use of exogenous hormones such as oral contraceptives may trigger vertigo in patients with Menière's disease. Many reports

show that women with Menière's disease were identified as having premenstrual phase of their monthly cycle or during pregnancy [82]. Genetic factors could contribute, at least partially to it. Many researchers have identified that in some women with Meniere's disease, attacks of vertigo, low frequency hearing loss, aural fullness and tinnitus are exacerbated in the premenstrual phase, when estrogen levels are low with edema in the endolymphatic spaces due to the loss of intravascular fluid into the extravascular space facilitated by estrogens [83–85]. One possible explanation may be estrogen-induced hyperprolactinemia, which was reported to provoke hearing loss and otic capsule dysmorphology in guinea pig [24].

Significant associations have been reported between Menière's disease and genetic polymorphisms. Polymorphisms associated with blood vessel permeability, blood circulation, or inflammation have been reported to be related to the inner ear pathology. AQP5 is known as an exocrine-type water channel with the roles in conveying a high degree of membrane water permeability [86]. Mice lacking AQP5 show lower frequency hearing impairment [87]. Some researchers demonstrated identified AQP5 as an ESα target gene in the mouse uterus using chromatin immunoprecipitation and DNA microarray analyses [88].

5. Summary

Sex hormone-related symptoms of auditory and vestibular systems are common in clinic. Here, we address by recognizing that interactions between sex hormones and sensory systems can be beneficial or detrimental to the peripheral and central auditory and vestibular systems. Knowing how sex steroids can alter hearing ability may give important clues as to how estrogen can preserve hearing in humans. The postmenopausal women have slightly better hearing if administered estrogen replacement therapy, physiological levels of estrogen would seem to have a possible protective effect on hearing function. The association described here shed light to the role of sex hormones and their receptors in the inner ear and behavior and underline the therapeutic potential of specific sex hormone agonists and antagonists.

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Author details

Zi-Yu He and Dong-Dong Ren*

*Address all correspondence to: dongdongren@fudan.edu.cn

Department of Otology and Skull Base Surgery, Eye, Ear, Nose and Throat Hospital (EENT Hospital), Fudan University, Shanghai, China

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