Review

An Overview of Electrically Evoked Otoacoustic Emissions in the Mammalian Cochlea

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Abstract Alternating currents injected into the cochlea are able to evoke outer hair cell-mediated basilar membrane motion, thus give rise to production of otoacoustic emissions. This electrically evoked otoacoustic emission(EEOAE) provides a useful tool for the research of out hair cell electromotility in vivo. This article reviews the research work on EEOAEs in mammals. Features of the EEOAEs and theories of their generation are introduced. Methods of EEOAE measurement are also described.

Key Words cochlea; out hair cell; electromotility; otoacoustic emissions; electrical stimulation

Introduction

Since the discovery of the click-evoked otoacoustic emissions(OAEs) (Kemp, 1978), various types of OAEs have been reported (Probst et al, 1991). The OAEs are divided into two categories, i.e., spontaneous and evoked OAEs. The spontaneous and acoustically evoked OAEs have been intensively investigated. However, less attention has been paid to another type of evoked OAEs, the electrically evoked otoacoustic emissions (EEOAEs). EEOAEs are acoustic signals generated in the cochlea and emitted to the external ear canal when alternating current(AC) is delivered into the cochlea (Hubbard and Mountain, 1983; Mountain and Hubbard, 1989; Murata et al, 1991; Ren and Nuttall, 1995). Unlike the acoustically-evoked OAEs, EEOAEs are not considered "natural" because electric current is not a normal stimulus to the cochlea. In addition, due to the need of opening the bulla for placing stimulating electrodes into/onto the cochlea, the procedures for EEOAE measurement are invasive. The sinusoidal electrical stimulation for the purpose of generating an EEOAE differs from the electrical stimulation for the purposes of evoking cochlear compound action potential, or eliciting brainstem responses, which are electrical pulses (Brown et al, 1990; Nikolopoulos et al, 2000). In general, there are two ways to inject current into the cochlea, i.e., intra-cochlear and extra-cochlear stimulation. To our knowledge, all published EEOAE measurements were conducted on animals. Animal species used for EEOAE research include gerbil, guinea pigs, chinchilla, lizards, and chicken (Hubbard and Mountain, 1983; Nuttall and Ren, 1995; Sun et al, 2000; Manley 2001; Chen et al, 2001). EEOAEs can always be observed in normal ears. This paper will outline the work on the mammalian cochlea.

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Generation of EEOAEs

In the mammalian cochlea, the capability of voltage-dependent somatic contraction and elongation of OHCs (termed "electromotility") is believed to be the basis of the active process in sensitive cochlea, which provides mechanical force for cochlear amplification and generation of OAEs(Brownell, 1985; Dallos,

1992). A motor protein, named "prestin", has been identified in the lateral wall of OHCs, and has been demonstrated to be required in OHC electromotility and cochlear amplification(Zheng et al, 2000; Liberman et al, 2002). Recently, stereocilia motility of mammalian OHCs has also been proposed to be an alternative source of mechanical force generation for cochlear amplification (Kennedy et al, 2005). Experimental data shows that OHC electromotile responses evoked by AC current is able to produce high-fidelity, high-frequency mechanical energy, which initiates conventional traveling waves along the basilar membrane (BM), and gives rise to emissions of sound from the cochlea(Kirk and Yates, 1994; Xue et al, 1995; Nuttall and Ren, 1995; Grosh et al, 2004). The OHC-origin of EEOAEs is supported by observations that EEOAEs were reduced in cochlea with OHCs damage by ototoxic drugs or by acoustic injury (Ren and Nuttall, 2000; Reyes et al, 2001; Zheng et al, 2001; Nakajima et al, 1996; Halsey et al, 2005).

EEOAEs are thought to be generated by OHCs at the location near the stimulating electrode. However, the mechanisms of EEOAE generation differ with methods for current delivery (Figure 1). In scala media (SM) stimulation(Figure 1A), electric currents may pass through the transduction channels of OHCs. Thus the EEOAEs are likely generated by mechanisms related to the forward transduction (Yates and Kirk, 1998). In contrast, current delivered into the scala tympani (ST), directly or through round window stimulation (Figure 1B), may stimulate OHCs by affecting their transmembrane voltage, thereby resulting in voltage-dependent OHC motion(Ren and Nuttall, 1995; Nuttall and Ren, 1995; Nuttall et al, 2001).

There is evidence implying that EEOAEs recorded in the ear canal have more than one origin on the BM. A long delay component (LDC) and a short delay component (SDC) of EEOAEs have been identified using a multiple component analysis method (Ren and Nuttall, 2000; Zou et al, 2003). The LDC is closely related to the cochlear sensitivity and is vulnerable to cochlear damage such as from furosemide, quinine, and other pathophysiological cochlear conditions (Ren and Nuttall, 1998, 2000; Zheng et al, 2001). It is hypothesized that electric currents delivered into the cochlea result in OHC motion and hence BM vibration at the site near the stimulating electrode, which then give rise to energy propagation in both forward(to apical) and backward(to basal) directions. The backward energy gives rise to SDC; whereas, the forward energy propagates to the location corresponding to its characteristic frequency (CF), then propagate back, giving rise to LDC (Ren and Nuttall, 2000; Zou et al, 2003; Figure 1B).

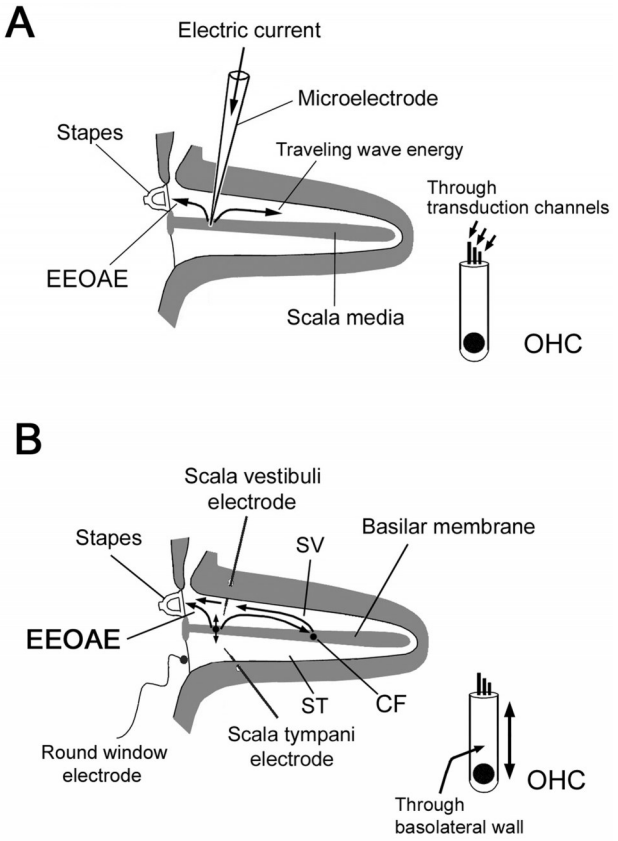

Figure 1. Electrical stimulation of the cochlea and EEOAE generation. The cochlea is uncoiled and straitened in the scheme. Arrows in the cochlea indicate directions of energy propagation.(A) Scala media-current injection and EEOAE generation. (B) Scale tympani-current injection and EEOAE generation. Electrode configurations shown here are scala tympani-scala vestibuli and round window electrodes. SV: scala vestibuli; ST: scala tympani; CF: characteristic trequency

It is important to point out that OHC may not be the only origin of EEOAE generation. Residual EEOAEs have been observed in cochleae with ototoxic drug-induced OHC loss and mechanical damage to the cochlea (Zheng et al, 1999; Halsey et al, 2005), indicating another source of EEOAE generation that is not related to OHC motility and is less physiologically vulnerable.

Basic features of EEOAEs

EEOAEs occur at the same frequency as the electric stimulus, resulting from fast electromotile responses of OHCs (Mountain and Hubbard, 1989; Nuttall and Ren, 1995). SM-current-evoked EEOAEs exhibit tonotopical and band-pass features, which are related to the tonotopic location of the SM electrode(Murata et al,

1991; Nakajima et al, 1994; Kirk and Yates, 1996) (Figure 2). Similar features can be observed in ST-current-evoked EEOAEs as well(Nuttall et al, 2001) (Figure 3). In contrast, passing current onto the round window(RW) gives rise to a broader EEOAE transfer function, i.e., the responses range from several hundred hertz to approximately 50 kHz in guinea pigs as shown in Figure 3 (Ren and Nuttall, 1995; Nuttall et al, 2001).

When sweeping electric current by small frequency steps, the magnitude transfer function of EEOAE (i. e., the magnitude as a function of frequency at a given current level) exhibits peaks and notches. This appearance is termed as "fine structure" (Figure 3), which is similar to what has been observed in DPOAE-gram (He and Schmiedt, 1993). The fine structure is postulated to result from the cancellation/enhancement effects

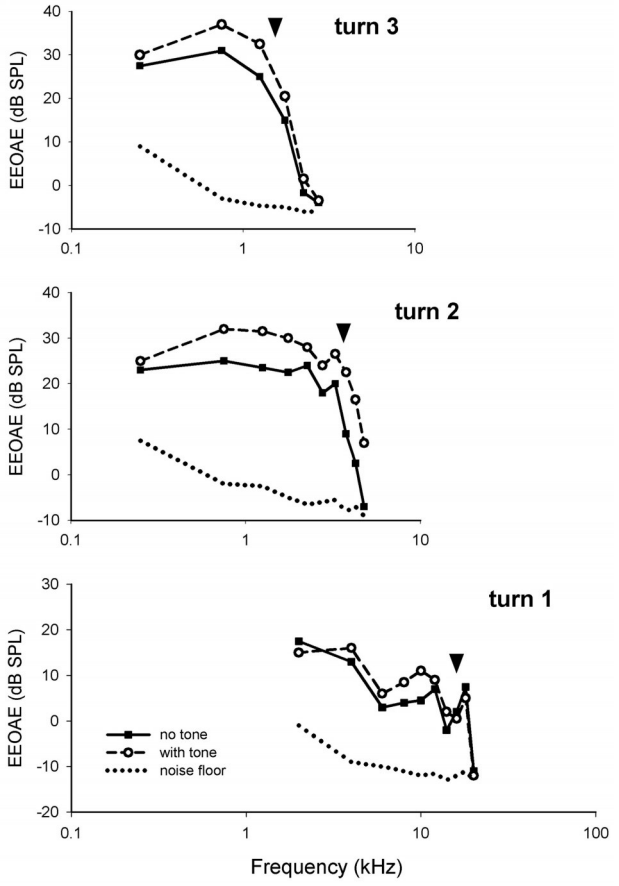

Figure2. Scala media electrode-evoked EEOAEs. (A) Magnitude transfer functions of different turns obtained from the guinea pig. The arrow heads indicate the characteristic frequency (CF) of the stimulation sites. (B) Phase transfer functions of different turns. (Reprinted from Kirk and Yates (1996), Frequency tuning and acoustic enhancement of electrically evoked otoacoustic emissions in the guinea pig cochlea, J. Acoust. Soc. Am. 100, 3714-3725, Copyright 1996, with permission from Acoustical Society of America)

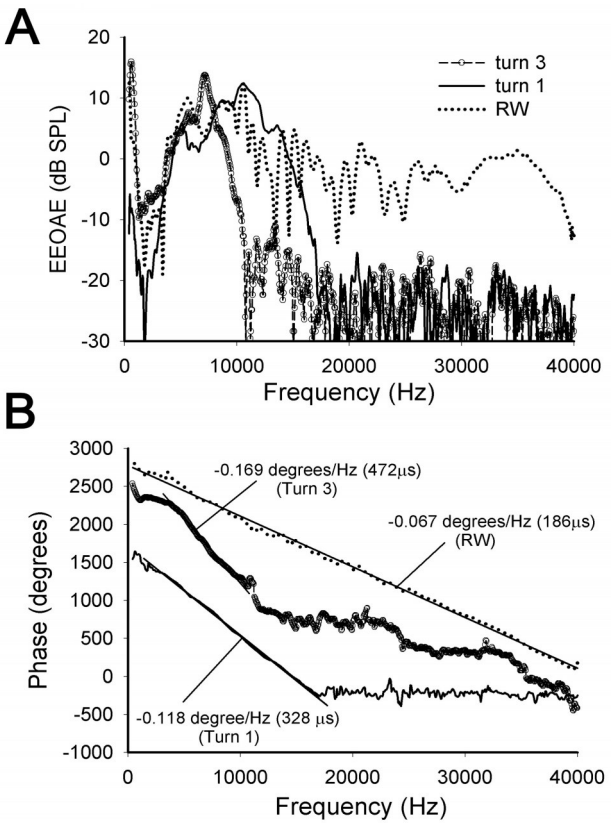

Figure 3. Scala tympani and round window electrode-evoked EEOAEs. The magnitude (A) and phase (B) transfer functions with scala tympani (turns 1 and 3) and round window (RW) current stimulation in the guinea pig are shown. Slopes of the phase transfer functions (in degrees/Hz) are measured as shown by straight lines superimposed on the transfer functions. Group delays (μs) are also calculated. (Reprinted from Nuttall, Zheng, Ren, de Bore (2001), Electrically evoked otoacoustic emissions from apical and basal perilymphatic electrode positions in the guinea pig cochlea, Hear Res., 152, 77-89, Copyright 2001, with permission from Elsevier)

of multiple sound waves in healthy cochleae (Ren and Nuttall, 2000). When the cochlea becomes insensitive, the fine structure disappears, thus the magnitude transfer function is smoothened. In contrast, the overall magnitude of EEOAEs is relatively less sensitive to cochlear damage. When the current intensity rises, the overall level of EEOAEs increase, but the amplitude of fine structure tends to decrease. Furthermore, unlike the acoustically-evoked OAEs, the input-output function of EEOAE is generally linear even in sensitive cochlea, though nonlinearity could be observed in certain conditions (Ren and Nuttall, 1995; Nakajima et al, 1998). Nevertheless, simultaneously applied electric currents at two frequencies (f1 and f2) are able to evoke DPOAEs as are evoked by acoustic primaries (Ren et

al, 1996).

EEOAEs can be modulated by an acoustic stimulus. A simultaneously presented tone can enhance the SM-evoked EEOAEs(Mountain and Hubbard, 1989; Xue et al, 1993; Nakajima et al, 1994; Kirk and Yates, 1996)(Figure 2). The enhancement is largest when the acoustic frequencies are near the characteristic frequency (CF) of the location where electrical stimulation is applied(Xue et al, 1993). It is speculated that this enhancement is due to the opening of the negative feedback loop of cochlear amplification by acoustical stimulation, which removes the suppression of the mechanical responses and consequently results in an increase in amplitude of EEOAEs (Mountain and Hubbard, 1989). However, data inconsistent with this hypothesis have been reported by others(Kirk and Yates, 1996). In RW-evoked EEOAE, a high-sound-level tone enhances the fine structure at frequencies below the acoustical frequency, and suppresses the overall level of EEOAEs at frequencies above the acoustical frequency. The acoustic modulation on the EEOAEs is most efficient when the frequency of acoustic stimulus is a half octave lower than that of the electric stimulus (Ren and Nuttall, 1998). Interaction between the electrically- and acoustically-evoked BM motions and/or acoustic stimulus-induced BM impedance discontinuity at its CF location are assumed to be the mechanisms that lead to the above-mentioned modulation(Ren and Nuttall, 1998).

Methods of EEOAE measurement

Environment required for EEOAE measurement is similar to that for acoustically evoked OAE measurement. Experimental animals need to be anesthetized. A microphone is coupled to the ear canal to measure the acoustic signal. The bulla is opened to expose the cochlea for placement of the stimulation electrodes. The middle ear muscle tendons should be sectioned to avoid electrically evoked muscle contractions. The stimuli are usually sinusoidal constant currents delivered through an optically-isolated constant-current source. The acoustic signals in the ear canal are recorded in terms of magnitude and phase at the frequency of the electric current.

Two approaches for electrical current stimulation, namely the intra-cochlear and extra-cochlear stimulation, are used to evoke the OAEs.

1) Intra-cochlear stimulation. Holes are made in the cochlea and electrodes are placed into the cochlea to deliver AC currents. According to the location of electrode placement, there are two types of intra-cochlear stimulation, the scala media and scala tympani stimulation.

Scala media stimulation: A glass microelectrode is inserted into the scala media via the lateral wall or the basilar membrane (Figure 1A). Constant current is injected into the scala media through the microelectrode. The tip diameter of the microelectrode is approximately 5 μm, and the electrode is filled with 0.16 M, 1 M, or 3 M KCl. An Ag/AgCl wire is inserted into the neck muscles to serve as the return electrode. Intensity of the currents can range from 1 to 50 μA peak-to-peak, depending upon the tip size and impedance of the electrode.

Scala tympani stimulation: A platinum-iridium wire is usually used (50-75 μm in diameter) for electrical stimulation. The electrode is placed into the scala tympani. For monopolar electrode configuration, an Ag/AgCl wire (serving as the return electrode) is inserted into the neck muscles. For bipolar electrode configuration, a second platinum-iridium wire is placed into the scala tympani or scala vestibule, serving as the return electrode (Figure 1B). The intensity of currents can be 10-50 μA rms.

2) Extra-cochlear stimulation. A platinum-iridium electrode is placed in the round window niche so that the current is delivered through the round window membrane into the scala tympani (Figure 1B). An Ag/AgCl wire in the neck serves as the return electrode. The cochlea is kept intact in this situation. Electric current level can be 10-300 μA rms.

Data analysis and presentation

Magnitude and phase transfer functions. Magnitude and phase are essential information in EEOAE research. The magnitude transfer function curve is obtained by plotting the magnitude as a function of the frequency at a given current level. It provides information on the frequency response or bandwidth features (Figure 2 and Figure 3A). As mentioned above, the EEOAE magnitude transfer function exhibits a feature of "fine structure" in sensitive cochlea. When the phase of EEOAE (in degrees or radians, relative to the current stimulus) is plotted against the frequency, the phase transfer function curve is obtained (Figure 3B). Group delay can be calculated from the slope of the phase transfer function (Figure 3B).

Input-output function. When the magnitude of EEOAEs is plotted as a function of the electric current intensity, the input-output function (I/O function) is obtained.

Multiple component analysis. Presence of fine structure suggests the existence of multiple sources of EEOAEs and consequently, multiple components of the recorded emissions. A method of multiple component analysis (MCA) has been developed (Ren and Nuttall, 2000), in that the real part of the emission is calculated from the magnitude and phase spectra, and then the multiple components are extracted. By using the MCA for EEOAE data analysis, long delay component (LDC) and short delay component (SDC) are observed.

Hearing sensitivity and EEOAEs

EEOAEs provide a tool for the study of in vivo OHC electromotility. The magnitude and fine structure of EEOAEs are associated with cochlear sensitivity (Ren and Nuttall, 1998, 2000; Zheng et al, 2001; Halsey et al, 2005). Insults to the cochlea that inhibit OHC function will result in EEOAEs fine structure diminution and/or magnitude reduction. The fine structure is a feature of the sensitive cochlea and is very vulnerable to any damages of the OHCs, whereas the overall magnitude of EEOAEs is relatively less sensitive to damages. In fact, reduction of EEOAE magnitude is not proportional to the loss in cochlear sensitivity. Even in the case of post-mortem, the overall magnitude of EEOAEs is reduced by only about 15-20 dB, and residual EEOAEs still can be observed (Nuttall et al, 2001). Moreover, total loss of hair cells significantly reduces EEOAE magnitude but generally residual emissions are still seen(Zheng et al, 1999; Halsey et al, 2005). In certain conditions (e.g., quinine administration or noise exposure), the magnitude of EEOAE could enhance despite of a loss in cochlear sensitivity (Zheng et al, 1999; Halsey et al, 2005).

Reference

1 Brownell WE, Bader CR, Bertrand D, de Ribaupierre Y. Evoked mechanical responses of isolated cochlear outer hair cells. Science, 1985, 227: 194-196.

2 Brown CJ, Abbas PJ, Gantz B. Electrically evoked whole-nerve potentials: data from human cochlear implant users. J Acoust Soc Am, 1990, 88：1385-1391.

3 Chen L, Sun W, Salvi RJ. Electrically evoked otoacoustic emissions from the chicken ear. Hear Res, 2001，161(1-2)：54-64.

4 Dallos P. The active cochlea. J Neurosci, 1992, 12(12): 4575-4585.

5 Grosh K, Zheng J, Zou Y, de Boer E, Nuttall AL. High-frequency electromotile responses in the cochlea. J Acoust Soc Am, 2004, 115 (5): 2178-2184.

6 Halsey K, Fegelman K, Raphael Y, Grosh K, and Dolan DF. Long-term effects of acoustic trauma on electrically evoked otoacoustic emission. J Assoc Res Otolaryngol, 2005, 6(4): 324-340.

7 He NJ, Schmiedt RA. Fine structure of the 2f1-f2 acoustic distortion product: changes with primary level. J. Acoust. Soc Am, 1993, 94: 2659-2669.

8 Hubbard AE, Mountain DC. Alternating current delivered into the scala media alters sound pressure at the eardrum. Science, 1983, 222: 510-512.

9 Kemp DT. Stimulated acoustic emissions from within the human auditory system. J Acoust Soc Am, 1978, 64: 1386-1391.

10 Kennedy HJ, Crawford AC, Fettiplace R. Force generation by mammalian hair bundles supports a role in cochlear amplification. Nature, 2005, 433(24): 880-883.

11 Kirk DL, Yates GK. Evidence for electrically evoked travelling waves in the guinea pig cochlea. Hear Res, 1994, 74(1-2)：38-50.

12 Kirk, Yates G. Frequency tuning and acoustic enhancement of electrically evoked otoacoustic emissions in the guinea pig cochlea. J Acoust Soc Am, 1996, 100: 3714-3725.

13 Liberman MC, Gao J, He DZ, Wu X, Jia S, Zuo J. Prestin is required for electromotility of the outer hair cell and for the cochlear amplifier. Nature, 2002, 419(6904): 300-304.

14 Mountain DC, Hubbard AE. Rapid force production in the cochlea. Hear Res, 1989, 42: 195-202.

15 Manley GA. Evidence for an active process and a cochlear amplifier in nonmammals. J. Neurophysiol, 2001, 86(2), 541-549. (Review)

16 Murata K, Moriyama T, Hosokawa Y, Minami S. Alternating current induced otoacoustic emissions in the guinea pig. Hear Res, 1991, 55: 201-214.

17 Nakajima HH and Olson ES. Electrically evked otoacoustic emissions from the apical turns of the gerbil cochlea. J Acoust Soc Am, 1994, 96 (2): 786-794.

18 Nakajima HH, Olson E., Mountain DC, and Bubbard AE. Acoustic overstimulation enhances low-frequency electrically-evoked otoacoustic emissions and reduces high-frequency emissions. Auditory Neuroscience, 1996, 3: 79-99.

19 Nikolopoulos TP, Mason SM, Gibbin KP, O'Donoghue GM. The prognostic value of promontory electric auditory brain stem response in pediatric cochlear implantation. Ear Hear, 2000, 21: 236-241.

20 Nuttall AL, Ren T. Electromotile hearing: evidence from basilar membrane motion and otoacoustic emissions. Hear Res, 1995, 92: 170-177.

21 Nuttall, AL, Zheng J, Ren T, de Bore E . Electrically evoked otoacoustic emissions from apical and basal perilymphatic electrode positions in the guinea pig cochlea. Hear Res, 2001, 152: 77-89.

22 Probst R. A review of otoacoustic emissions. J Acoust Soc Am, 1991, 89: 2027-2067.

23 Ren T, Nuttall AL. Extracochlear electrically evoked otoacoustic emissions: a model for in vivo assessment of outer hair cell electromotility. Hear Res, 1995, 92: 178-183.

24 Ren T, Nuttall AL, Miller JM. Electrically evoked cubic distortion product otoacoustic emissions from gerbil cochlea. Hear Res, 1996, 102 (1-2): 43-50.

25 Ren T, Nuttall AL. Acoustic modulation of electrically evoked otoacoustic emission in intact gerbil cochlea. Hear Res, 1998, 120: 7-16.

26 Ren T, Nuttall AL. Fine structure and multicomponents of the electrically evoked otoacoustic emission in gerbil. HearRes, 2000, 143: 58-68.
27 Reyes S, Ding D, Sun W, Salvi R. Effect of inner and outer hair cell lesions on electrically evoked otoacoustic emissions. Hear Res, 2001, 158: 139-150.
26 Sun W, Ding D, Reyes S, Salvi RJ. Effects of AC and DC stimulation on chinchilla SOAE amplitude and frequency. Hear Res, 2000, 150: 137-148.
27 Xue S, Mountain DC, Hubbard AE. Acoustic enhancement of electrically-evoked otoacoustic emeissions reflects basilar membrane tuning: Experiment results. Hear. Res, 1993, 70: 121-126.
28 Xue S, Mountain DC, Hubbard AE. Electrically evoked basilar membrane motion. J Acoust Soc Am, 1995, 97: 3030-3041.
29 Yates GK and Kirk DL. Cochlear electrically evoked emissions modulated by mechanical transduction channels. J Neurosci, 1998, 18 (6): 1996-2003.
30 Zheng J, Ren T and Nuttall AL. Electrically evoked otoacoustic emissions from the cochlea with outer hair cell damage. Abstr Assoc Res Otolaryngol, 1999, 22: 385.
31 Zheng J, Shen W, He DZ, Long KB, Madison LD, Dallos P. Prestin is the motor protein of cochlear outer hair cells. Nature, 2000, 405(6783): 149-155.
32 Zheng J, Ren T, Parthasarathi A, Nuttall AL. Quinine induced alterations of electrically evoked otoacoustic emissions and cochlear potentials in guinea pigs. Hear. Res, 2001, 154: 124-134.
33 Zou Y. Zheng J, Nuttall AL, Ren T. The sources of electrically evoked otoacoustic emissions. Hear Res, 2003, 180: 91-100.