The Role of Prestin in the Generation of Electrically Evoked Otoacoustic Emissions in Mice

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INTRODUCTION

The enormous dynamic range of the auditory system of about six orders of magnitude is due largely to the capacity of the mammalian cochlea to amplify responses to low-level sounds and compress responses to high-level sounds. Amplification and compression are greatest at the characteristic frequency (CF) of each location along the length of the cochlea and have been attributed to an active process: the “cochlear amplifier” (Davis 1983). Cochlear amplification is attributed to electromechanical energy generated by the sensorimotor outer hair cells (OHCs) (Robles and Ruggero 2001) for which two mechanisms have been proposed: 1) somatic motility (Brownell et al. 1985), based on the cochlear motor protein prestin (Zheng et al. 2000), located in the OHC lateral membrane; and 2) the motility of the OHC stereocilia (Kennedy et al. 2006). Somatic motility is driven by receptor-current-induced voltage changes across the OHC membranes (Dullos et al. 2006). Stereocilia motility is driven by calcium ions in the receptor currents that flow through the mechanoelectrical transduction channels at their tips (e.g., Chan and Hudspeth 2005a). A by-product of cochlear amplification is the generation of otoacoustic emissions (OAEs), which are sounds measured at the tympanic membrane (TM) that originate in the inner ear (for review see Shera 2004).

OAEs can also be produced when the cochlea is electrically stimulated with AC. The current is injected either through an electrode placed on the round window membrane or via intra-cochlear electrodes in the fluid-filled spaces of the cochlea (Hubbard and Mountain 1983; Mountain and Hubbard 1989; Nuttall and Ren 1995). Electrical stimulation of the cochlea bypasses the normal mechatron-electrical transduction process and directly drives the electromechanical feedback mechanism of the OHCs (Nuttall and Ren 1995). Measurement and analysis of these electrically evoked otoacoustic emissions (EEOAEs) can thus reveal information about the nature of the active process in the cochlea.

An advanced multicomponent analysis (MCA) of EEOAEs (Ren et al. 2000) evoked with extracochlear stimulation (i.e., with an electrode touching the round window of the cochlea) revealed the EEOAEs to have a temporal structure consisting typically of a short-delay component (SDC) and a long-delay component (LDC). According to a model for the generation of EEOAEs (Ren and Nuttall 2000; Zou et al. 2003), the SDC is produced by OHCs only in close proximity to the stimulation electrode. These launch a mechanical traveling wave that moves toward the base of the cochlea, where it can be detected as an acoustic emission in the ear canal (Fig. 1). The LDC, however, was interpreted as being due to a traveling wave also launched at the site of electrical stimulation, which moves toward the apex of the cochlea (Fig. 1). On reaching its CF place, the wave is regenerated through the action of the cochlear amplifier before traveling back to the ear canal (Ren and Nuttall 2000). Ren and Nuttall (2000) and Halsey et al. (2005) showed the SDC of EEOAEs to be extremely robust, surviving almost complete elimination of the hair cells. The LDC, however, is more vulnerable and seems to better reflect the physiological state of the cochlea (Halsey et al. 2005).

Our aim was to discover the contributions of prestin and hair bundle motility to the generation of EEOAEs. To address these questions, we recorded EEOAEs from homozygous prestin+/− mice and Tecta+/-/ ENT mice, and corresponding wild-type (+/+) mice. Prestin knockout mice have OHCs without the

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cochlear motor protein prestin in the lateral membrane (Liberman et al. 2002) and thus lack somatic electromotility. *Tecta* mice lack the extracellular matrix molecule α-tectorin. Consequently, the tectorial membrane is vestigial and detached from the organ of Corti; thus the OHC stereocilia are freestanding and are displaced through interaction with the endolymph of the scala media only at high basilar membrane (BM) velocities (Legan et al. 2000). The corollary is that only when the basilar membrane is moving with high velocity can any forces generated by the stereocilia be exerted against the cochlear partition. On the basis of our measurements from wild-type mice and mice with detached tectorial membranes and absent or inactivated prestin, we conclude that near threshold, when cochlear amplification is greatest, EEOAEs are entirely generated by prestin-based OHC motility.

METHODS

Electrically evoked emissions

Experiments were performed on 4- to 6-wk-old male and female *Tecta* (Legan et al. 2000) and 3- to 4-wk-old *prestin* (Liberman et al. 2002) mice according to a protocol approved by the UK Home Office. *Tecta* mice were on a C57Bl6/J or CBA/J background and *prestin* mice were the F4–F6 generations of a mixed 129/SvEv and C57B6/J background. Animals were overdosed at the end of the experiment by intraperitoneal (ip) injection of pentobarbital sodium (150 mg/kg bodyweight). The animals were anesthetized with an injected mixture of sodium pentobarbitone (Sigma–Aldrich, Gillingham, UK) and medetomidine hydrochloride (0.5 mg/kg bodyweight; Pfizer, Sandwich, UK). Carbogen (95% O2-5% CO2, BOC Gases, Guildford, UK), and medetomidine hydrochloride (0.5 mg/kg bodyweight; Pfizer, Sandwich, UK), and a heated head holder. Anesthesia booster injections (intramuscular) were given via a catheter every 45 min (one half of the initial dose). The animal's head was placed in a metal head holder and, in addition, glued to a stabilizing metal bar attached to the head holder to prevent any changes in head position during experiments. The right auditory bulla was exposed using a ventrolateral approach and a large opening was made to gain access to the round window. To facilitate the insertion of the sound system, the pinna was removed and about two thirds of the meatus left intact.

Following the extracochlear approach (Ren and Nuttall 1995), a Teflon-coated silver or tungsten electrode was placed on the round window membrane and another Ag/AgCl ground electrode was positioned in the soft tissue of the neck. To evoke EEOAEs, a sinusoidal command voltage with a duration of 20 ms and a 1-ms rise/fall time at different frequencies was generated by a Data Translation DT3010 board (Marlboro, MA) and applied to a custom-built current pump with a sensitivity of 100 μA/V (J Hartley, University of Sussex, Brighton, UK). The D/A output of the Data Translation DT3010 board was low-pass filtered (eight-pole Bessel filter; cutoff frequency 100 kHz). The typical range of electrical frequencies used was from 20 to 80 kHz. A sinusoidal current corresponding to the applied command voltage was then produced by the current pump and delivered to the round window. The operation of the current pump is similar to that of a current clamp. The current at the electrode was monitored by measuring the voltage across a 1-kΩ resistor in series with the electrode. The resulting voltage served as the actual value for a comparison with the desired value set by the command voltage. A feedback mechanism ensured that the commanded current was forced through the electrode, irrespective of what potential was present. The level of command voltage was adjusted by a general-purpose interface bus-controlled attenuator (Hartley, University of Sussex). A sound system, consisting of a custom-built condenser loudspeaker (Schuller 1997) and a type 4133 1/4-in. measuring microphone (Brüel & Kjær, Nærum, Denmark) coupled into a small, two-channel plastic tip, was placed in the meatus. Optimal position of the sound system was checked by regular calibration routines as detailed in, e.g., Kössl et al. (1999), although it was difficult to avoid amplitude minima at 14, 35, and 62 kHz, which can be seen in measurements of EEOAEs in all preparations reported in this study.
filtered (cutoff frequency 900 Hz) by a custom-built amplifier (Hartley, University of Sussex) and then fed into the A/D input of the DT board. A fast Fourier transform (FFT) of the signals was performed on-line during experiments and the raw data were stored for later analysis. Signals were sampled at rates of 200 or 250 kHz and the FFT width was 4,096 or 2,048 points, respectively. Experimental control, data acquisition, and data analysis were performed using programs written in TestPoint (Measurement Computing, Norton, MA).

**Multicomponent analysis**

We performed frequency runs, where the stimulation frequency was progressively increased in 0.1- or 1-kHz steps at a constant level of stimulation and level runs (not shown), where the level of stimulation was stepped in 2-dB increments. Phase \(\Phi(\omega)\) and amplitude \(A(\omega)\) of the EEOAE were derived from frequency runs at a constant level of stimulation. To estimate the delay components of the EEOAEs, we used a multicomponent analysis (MCA) as developed by Ren et al. (2000) and applied by Halsey et al. (2005). In Fig. 2, examples of several steps of the MCA are illustrated: the real part of the spectrum \([R(\omega)]\) can be calculated using the amplitude (Fig. 2A) and phase spectra (Fig. 2B) of EEOAEs evoked with frequency sweeps at a constant level of stimulation by applying

\[
R(\omega) = A(\omega) \times \cos[\Phi(\omega)]
\]

(1)

The amplitude and rate of the real part of the spectrum (Fig. 2C) are modulated by the delay characteristics of the EEOAEs and can consequently be detected by applying a discrete Fourier transform (DFT)

\[
\gamma(\tau_{\text{delay}}) = 2 \times |\text{DFT}[R(\omega)]| \]

(2)

This calculation transforms the spectrum from the frequency domain into the time domain. The result is a time-delay spectrum (Fig. 2D), denoted as \(\gamma(\tau_{\text{delay}})\). A time-delay spectrum has naturally no frequency information. Time-frequency analysis of the real part of the spectrum can provide additional information on the frequency dependence of delay components. For computing delay-frequency spectra, we applied a broad frequency domain window with a length of 30 kHz to sections of \(R(\omega)\). This broad frequency window ensured a suitable delay time resolution. The frequency window was moved along the frequency axis and the delay-frequency spectrum (Fig. 2E) was estimated by applying Eq. 2.

**Statistical methods**

Origin (OriginLab, Northampton, MA) and SPSS (SPSS, Chicago, IL) were used to perform one-sample Kolmogorov-Smirnov tests to confirm that data sets follow a normal distribution, followed by an independent sample t-test.

**Results**

**Amplitude spectra**

EEOAE amplitude spectra measured in Tecta\(^{\text{DENT} / \text{DENT}}\) and prestin\(^{-/-}\) mice, respectively) in response to electric stimulation with a fixed sinusoidal current of 22.4- \(\mu\)A root mean square (RMS) over a frequency range of 10 to 80 kHz. BM displacements elicited by electrical stimulation of the cochlea with the sinusoidal 22.4- \(\mu\)A RMS current are very similar in amplitude to BM displacements elicited by 30 dB SPL tones (Mellado Lagarde, unpublished BM displacement measurements). Such displacements are close to the detection threshold for both BM and neural responses in the basal turn of the mouse cochlea (Legan et al. 2000).

Prestin\(^{+/+}\), prestin\(^{-/-}\), Tecta\(^{+/+}\), and Tecta\(^{-/-}\) mice all show very broadly tuned frequency responses (Fig. 3, A and C), which are typical for round window extracochlear stimulation (Ren and Nuttall 1995). With the exception of the notch at 14 kHz, the responses of prestin\(^{+/+}\) mice exceed those of prestin\(^{-/-}\) mice by about 20 dB over the entire frequency range of the measurements (Fig. 3A). The responses of prestin\(^{-/-}\) mice usually exceed the noise floor by about 5 dB with the exception of the notches at 14, 35, and 62 kHz (Fig. 3B). Responses from Tecta\(^{+/+}\) and Tecta\(^{-/-}\) mice are very similar. For frequencies <45 kHz, however, responses from Tecta\(^{-/-}\) mice tend to exceed those from Tecta\(^{-/-}\) mice, whereas they tend to be smaller for frequencies >45 kHz (Fig. 3D). This trend is highlighted by the linear regression fitted to the difference data in Fig. 3D (dashed line).

**Multicomponent analysis**

The real parts of the spectra were derived from the amplitudes and phases of the frequency responses of EEOAEs recorded from the four different genotypes by applying Eq. 1. Multicomponent analysis was then performed using the real part of the spectra. Time-delay spectra, giving the relative amplitude of the EEOAE versus the delay, and delay-frequency spectra, which add the third dimension of frequency to the time-delay spectra, were computed. MCA of EEOAEs typically detects two components, a short-delay component (SDC, normally a sharp peak) and a long-delay component (LDC), which usually consists of a broad and variable range of peaks. In this study, we define the first sharp peak, found at 0.12 ms in all genotypes, as the SDC, and components with delays >0.25 ms as the LDC.

In prestin\(^{-/-}\) mice the time-delay spectra clearly show the two components, SDC and LDC (see Figs. 4A and 5). The delay-frequency spectrum reveals that the energy of the SDC is generated by the full range of frequencies from 20 to 80 kHz (see Fig. 4C for a typical example). The LDC is typically generated by frequencies from 40 to 80 kHz, whereas the frequency of maximum energy is usually identical to that of the SDC. The picture is very different in prestin\(^{-/-}\) mice. The reduced overall EEOAE amplitude (Fig. 3A) is reflected in the amplitude of the SDC, whereas the LDC is virtually missing (Fig. 4C). Consequently, the delay-frequency spectrum reveals energy only at the SDC generated over the whole frequency range (20 to 80 kHz, Fig. 4D). A comparison of the mean time delay spectra of prestin\(^{+/+}\) and prestin\(^{-/-}\) mice confirms that delay spectra of prestin\(^{-/-}\) mice are significantly lower in amplitude than delay spectra from prestin\(^{+/+}\) mice (\(P \leq 0.05\)) (Fig. 5). The SDC is greatly reduced and the LDC is hardly detectable, indicating that the EEOAEs recorded in the ears of prestin\(^{-/-}\) mice consist only of a SDC.

The time-delay spectra of Tecta\(^{+/+}\) are similar to the time-delay spectra of prestin\(^{+/+}\) mice and reveal both SDC and LDC (Figs. 6A and 7). The SDC generation, as apparent from the delay-frequency spectra, is again similar to that in prestin\(^{+/+}\) mice: the SDC is generated over the whole frequency range (20 to 80 kHz), whereas the LDC is generated over a narrower frequency range from about 40 to 80 kHz (Fig. 6C).
In contrast to the *prestin* mice, the time-delay spectra of *Tecta*<sup>+/+</sup> and *Tecta*<sup>ΔENT/ΔENT</sup> mice are very similar (Figs. 6B and 7). The time distribution, SDC/LDC ratio, and SDC and LDC frequency distributions are all similar to those of *prestin*<sup>+/+</sup> mice (Fig. 6D). A comparison of the mean time-delay spectra of *Tecta*<sup>+/+</sup> and *Tecta*<sup>ΔENT/ΔENT</sup> mice shows that the delay spectra of *Tecta*<sup>ΔENT/ΔENT</sup> mice are not significantly different in amplitude from delay spectra of *Tecta*<sup>+/+</sup> mice (Fig. 7), although there is a clear trend toward slightly reduced amplitudes of the SDC.

The mean delay of the SDC in our experiments, of about 0.12 ms, is shorter than that reported for the guinea pig (Halsey et al. 2005; Zheng et al. 2001) and the gerbil (Ren and Nuttall 2000), where the SDC is usually at about 0.2 ms. The range of LDC delays is usually broader and longer in gerbils (Ren and Nuttall 2000) and guinea pigs (Halsey et al. 2005; Zheng et al. 2001).
than that found in the mouse during this study. The calculated delays include middle ear delays and acoustic travel delays from the tympanum to the diaphragm of the microphone. The acoustic pathway in our system is only about 1.5 cm, corresponding to a travel delay of about 45 μs, which is much shorter than that in the sound systems used in guinea pig and gerbil measurements. The larger dimensions of the inner ear and outer ear in those species may also play a role. Taken together, the smaller acoustic pathways in our experiments can explain the shifts of LDC and SDC to shorter delays in our measurements.

Application of sodium salicylate

Earlier we revealed that the EEOAEs recorded from prestin−/− mice are greatly attenuated compared with those of their wild-type littermates. Here we used salicylate, a blocker of somatic motility, to test the contribution of prestin-based OHC motility to the generation of EEOAEs in Tecta+/+ and TectaΔENT/ΔENT mice. Salicylate, which impairs the function of the motor protein prestin (Oliver et al. 2001) and suppresses EEOAEs when administered by cochlear perfusion (Zheng et al. 2007), was applied to the round window and permitted to diffuse into the cochlea. Under the influence of salicylate, Tecta+/+ mice have an intact TM but no somatic electromotility, whereas TectaΔENT/ΔENT mice lack both somatic electromotility and a functional TM. Nonetheless, in both genotypes salicylate reduced the EEOAE amplitude to a similar extent over the tested frequency range. EEOAE amplitudes following salicylate were not significantly different (P < 0.001) from the mean noise floor for 22.4-μA RMS current level (Fig. 8, A and B). Increasing the current level (to 70.7-μA RMS, Fig. 8, D and E) revealed a residual EEOAE that was significantly different from the noise floor only for the TectaΔENT/ΔENT mouse (P < 0.1) (Fig. 8E). Salicylate treatment of prestin+/+ mice also resulted in the blockade of EEOAEs so that the residual did not differ significantly from the noise floor, even when currents of 70.7-μA RMS were used (Fig. 8, C and F).

Control recordings

Several controls were carried out to ensure that the recorded signals are not artifacts: disarticulation of the ossicular chain or blocking of the acoustic coupler resulted in a complete absence...
of EEOAEs with amplitudes larger than the mean noise floor. No sound emissions could be detected by repeating the experiment with the stimulating electrode placed into muscle tissue of the upper limbs.

DISCUSSION

Prestin as the basis for EEOAEs

To our knowledge, in this study EEOAEs were recorded for the first time from prestin\(^{+/+}\)/H11002/H11002 mice without the OHC motor protein prestin and from Tecta\(^{\Delta ENT/\Delta ENT}\) mice without a functional TM. For near-threshold electrical stimulation (22.4-\(\mu\)A RMS), EEOAEs recorded from prestin\(^{+/+}\) mice are greatly reduced compared with their wild-type littermates. EEOAEs recorded from Tecta\(^{\Delta ENT/\Delta ENT}\), Tecta\(^{+/+}\) and prestin\(^{+/+}\) mice are also greatly reduced following treatment with salicylate, which blocks the functioning of prestin (Kakehata and Santos-Sacchi 1996; Shehata et al. 1991). Similarly, distortion product otoacoustic emissions (DPOAEs) have been suppressed by round window application of sulfydryl compounds (Frolenkov et al. 1998) or cochlear perfusion of salicylate (Kujawa et al. 1992). Our observations reported here of salicylate-induced suppression of EEOAEs accord with previous reports of salicylate reducing BM motility to cochlear electrical stimulation (Grosh et al. 2004). On the basis of these data, we propose that the generation of EEOAEs at threshold excitation of the cochlea, when amplification is greatest (Robles and Ruggero 2001), is due to prestin-based OHC somatic motility.

The close similarity in the EEOAEs recorded from Tecta\(^{\Delta ENT/\Delta ENT}\) and Tecta\(^{+/+}\) mice excludes a contribution of hair bundle motility to the generation of EEOAEs at near-threshold level. In Tecta\(^{\Delta ENT/\Delta ENT}\) mice the hair bundles are not influenced by the TM, which is unattached to the organ of Corti, and are not effectively coupled to the endolymph at near-threshold levels. From cochlear microphonics and neural-threshold measurements in Tecta\(^{\Delta ENT/\Delta ENT}\) mice, it is only when the BM velocity exceeds a frequency-dependent critical value that the fluid boundary layer in contact with the reticular lamina becomes thin enough to permit the hair bundles to extend above it and to be effectively coupled to the endolymph (Legan et al. 2000). Below this frequency-dependent value any movement of the hair bundles will be restricted to within this
fluid boundary layer and will not be transmitted to the scala media. This critical value is >40 dB SPL and therefore above the level of electrical stimulation we have used in these experiments (22.4-μA RMS ↔ 30-dB SPL). Similar arguments have been presented to explain the characteristics of DPOAEs recorded from Tecta−/− mice (Lukashkin et al. 2004).

The origin and significance of LDCs

Our findings that the LDCs measured from Tecta−/− and Tecta+/+ mice are similar in magnitude, but the LDC is absent from EEOAEs measured from prestin−/− mice, accords with earlier findings that the LDC is an indicator of OHC viability (Ren and Nuttall 2000). In our experiments this depends on the presence of prestin in the OHCs.

A model for the origin of LDCs (Ren and Nuttall 2000; Zou et al. 2003) proposes that they are caused by waves that emanate from the stimulus location in the cochlea and travel to the CF location where they excite the OHCs to generate a second (backward) traveling wave. This wave carries the energy that will appear as an LDC at the TM. An expectation of this model is that if energy from the basal region of the cochlea arrives at frequency-specific sites via a traveling wave, then the LDC should show a frequency-dependent latency shift. This is apparently not the case from data presented here (Figs. 2E, 4C, and 6, C and D) or from other groups (Halsey et al. 2005; Ren and Nuttall 2000; Zou et al. 2003). Furthermore, excitation of OHCs by a traveling wave was not possible in our experiments with Tecta−/− mice because, as explained earlier, the stimulus amplitudes were too small to enable shearing forces on the OHC hair bundles at locations distal from the electrically stimulated place. Thus our data do not support the origin of the LDC from the distant CF place on the BM. We suggest that both components of the EEOAEs may be generated in regions of the cochlear partition directly influenced by the electrical stimulus.

Origin and significance of SDCs

We detected residual EEOAEs in Tecta−/− mice treated with salicylate in response to high-level current stimulation. Residual DPOAEs were also measured in response to high-level tones following salicylate treatment (Kujawa et al. 1992) but not with sulphydryl compounds (Frolenkov 1998). These findings seem to accord with in vitro measurements that show that salicylate causes an incomplete block of OHC motility (Kakehata and Santos-Sacchi 1996). However, we also detected a residual response in prestin−/− mice, even at near-
threshold level. In this case the MCA analysis showed that the residual is related only to the SDC component. Residual DPOAEs have also been recorded at high sound pressure levels from prestin \(^{-/-}\) mice by Liberman et al. (2004), although at these high levels system distortion could be a contributing factor to their measurements.

Our findings reported here are in agreement with previous results where residual EEOAEs (SDCs) were measured when the OHCs had been compromised or even eliminated (Halsey et al. 2005; Ren and Nuttall 2000). We suggest that the residual is greatest if cochlea structures are less stiff, or are poorly coupled, as may be the case when prestin is absent from the lateral membranes of the OHCs, as in prestin \(^{-/-}\) mice, than when prestin is present but blocked by salicylate. This later proposal may account for why residual EEOAEs are measured in prestin \(^{-/-}\) mice and not in salicylate-treated wild-type and Tecta\(^{\Delta ENT/\Delta ENT}\) mice at near-threshold electrical stimulation.

Differences in the impedance of the cochlear partition may also account for the small differences between EEOAEs generated by Tecta\(^{\Delta ENT/\Delta ENT}\) and Tecta\(^{+/+}\) mice (revealed by MCA to be due to differences in the SDCs rather than in LDCs). These differences could be explained if, as suggested by Freeman et al. (2003) and Chan and Hudspeth (2005b), the TM contributes to the impedance of the cochlear partition. If so, then different frequency dependencies of EEOAEs recorded in Tecta\(^{\Delta ENT/\Delta ENT}\) and Tecta\(^{+/+}\) mice might be expected. Such an explanation may account for our finding that for frequencies <45 kHz, the amplitudes of the EEOAEs measured from Tecta\(^{\Delta ENT/\Delta ENT}\) mice are larger than those of Tecta\(^{+/+}\) mice, whereas for frequencies >45 kHz they are smaller.

Prestin-mediated OHC electromotility appears to be the most important generator of EEOAEs and dominates at thresh-
old when cochlear amplification is greatest. Our results also lead us to suggest that only the LDC of EEOAEs is entirely dominated by prestin-mediated somatic motility. The measurement of a residual SDC with significant amplitude from mice without prestin is a clear indication that mechanisms other than prestin-mediated OHC electromotility contribute to the EEOAE generation.

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