Research Article

Simultaneous Intracochlear Pressure Measurements from Two Cochlear Locations: Propagation of Distortion Products in Gerbil

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ABSTRACT

Sound energy propagates in the cochlea through a forward-traveling or slow wave supported by the cochlear partition and fluid inertia. Additionally, cochlear models support traveling wave propagation in the reverse direction as the expected mechanism for conveying otoacoustic emissions out of the cochlea. Recently, however, this hypothesis has been questioned, casting doubt on the process by which otoacoustic emissions travel back out through the cochlea. The proposed alternative reverse travel path for emissions is directly through the fluids of the cochlea as a compression pressure in the form of a fast wave. In the present study, a custom-made micro-pressure sensor was used *in vivo* in the gerbil cochlea to map two-tone-evoked pressure responses at distinct longitudinal and vertical locations in both the scala tympani and scala vestibuli. Analyses of the magnitude and phase of intracochlear pressure responses at the primary tone and distortion product frequencies were used to distinguish between fast and slow waves in both the forward- and reverse-propagation directions. Results demonstrated that distortion products may travel in both forward and reverse directions post-generation and the existence of both traveling and compression waves. The forward-traveling component appeared to duplicate the process of any external tone, tuned to the local characteristic-frequency place, as it increased compressively and nonlinearly

with primary-tone levels. A compression wave was evidenced at frequencies above the cutoff of the recording site. In the opposite direction, a reverse-traveling wave played the major role in driving the stapes reversely and contributed to the distortion product otoacoustic emission. The compression wave may also play a role in reverse propagation when distortion products are generated at a region close to the stapes.

Keywords: otoacoustic emissions, distortion products, cochlear mechanics, traveling wave, compression wave, cochlear fluids, hearing

INTRODUCTION

Since the discovery of otoacoustic emissions (OAEs) in 1978 (Kemp 1978), great attention has been given to the generation of various types of emissions, their properties, and their application in both the clinic and research laboratory as a monitor of cochlear function and condition (Lonsbury-Martin and Martin 1990). Nonetheless, some significant fundamental questions about OAEs remain, including how they are generated and how they propagate post-generation within the cochlea towards the outer ear canal (EC). Most cochlear models that include OAEs assume that they travel out of the cochlea via a reverse-traveling wave (TW) (Kemp 1986; Talmadge et al. 1998; Shera and Guinan 1999; Shera et al. 2007). Experimental support for the reverse-TW hypothesis

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comes from several studies, including the simultaneous measurement of OAEs from the EC and intracochlear pressure (Dong and Olson 2008), determinations of the cochlear microphonic potential in the gerbil (Meenderink and van der Heijden 2010a, b; Ren and Porsov 2010), and actual measurements of basilar membrane (BM) motion in the guinea pig (Cooper and Shera 2004; Shera and Cooper 2013). The different studies utilized novel approaches including unique stimulus strategies (Meenderink and van der Heijden 2010a), analyses based on cochlear modeling (Cooper and Shera 2004; Shera and Cooper 2013), or custom-built intracochlear pressure probes capable of parsing wave- and place-fixed OAE-generation types (Dong and Olson 2008, 2010). These investigations all arrived at the same conclusion that OAEs mainly propagate out of the cochlea via reverse cochlear TWs.

An alternative concept referred to as the fast compression wave (CW) hypothesis recently gained new attention based on the results of a series of studies by Ren and colleagues (Ren 2004; Ren et al. 2006; He et al. 2007; He et al. 2008; He et al. 2010; He and Ren 2013). According to their interpretation, two-tone evoked distortion products (DPs) appear to travel back to the stapes via cochlear fluids as a CW, where motion of the stapes then initiates a forward-TW along the cochlear partition. The hypothesis that the CW plays a key role in OAE propagation is also supported by interpretation of experiments comparing stimulus-frequency OAE (SFOAE) group delays, defined as the negative slope of the phase-versus-frequency function, with corresponding group delays of BM vibrations in chinchillas (Siegel et al. 2005). Other related evidence consists of observations of the presence of OAEs in animals such as frogs that lack a clear TW (Wilson 1980; van Dijk and Manley 2001).

The concept of reverse propagation is important, because it determines whether the total delay of the OAE signal can be decomposed into a forward and a reverse-wave delay. The question of how OAEs travel back to the stapes still remains unresolved for a number of reasons. To begin with, characterizing the reverse propagation of two-tone-evoked intracochlear DPs is more complicated than is often assumed (Dong and Olson 2008, 2010). Simultaneous measures of OAEs from the EC and intracochlear pressure indicate that the source of the reverse wave is not a single point, but rather a region related to the associated active processes of the cochlea [e.g., Kim (1980), Kemp (1986) Dong and Olson (2010), Dong (2015)], which may extend considerably basal to the characteristic or best frequency (BF) place, particularly at high primary-tone levels (Martin et al. 1999, 2010). Thus, the link between the intracochlear DP and distortion product otoacoustic emissions

(DPOAEs) measured from the EC is not as straightforward as a simple one-to-one relationship (Dong and Olson 2008). Moreover, the coupling of motion on the BM to cochlear fluids at DP frequencies has not yet been completely described.

In forward sound propagation, the TW and CW have been characterized both theoretically (Peterson and Bogert 1950) and experimentally by mapping intracochlear pressure responses to tonal stimuli using micro-pressure sensors (Olson 1998; Dong and Olson 2005a). Because the adjacent cochlear fluids move together with the BM, the pressure responses measured in scala tympani (ST), close to the BM, are tuned, nonlinear, and delayed several cycles relative to the stimulus inputs at the EC or stapes, and are consistent with the tuned and amplified TW propagating along the cochlear partition [e.g., Olson and Dong (2006), Dong and Olson (2013)]. Conversely, when measured at a location far away from the BM, or apical to the TW's BF, the ST pressure is dominated by the CW, moving in-phase with the motion of the stapes and longitudinally between the oval and round windows. The CW is considered as a background pressure in forward sound propagation, increasing linearly with the motion of the stapes (Dong and Olson 2006), and is relatively unimportant to cochlear mechanics, because it causes little vibration of the BM (Robles and Ruggero 2001) and neural excitation only at very high stimulus levels (Huang and Olson 2011).

In the current study, to explore the roles of the TW and CW in DP propagation through the cochlea, intracochlear pressure responses at two locations in the cochlea to single- and two-tone acoustic stimuli were measured simultaneously with EC pressure responses (note red stars in Fig. 1). Analyses of single- or two-tone responses at primary and DP frequencies were used to characterize sound transmission in both the forward and reverse directions, respectively. Understanding the characteristics of DPs measured at the BM level is important, because these DPs represent the intracochlear sources of the DPOAEs originating from the active processes of the outer hair cells (OHCs) [see review in (Dallos 1992)], even with high primary-tone intensities (Avan et al. 2003). In the present study, the characteristics of DPs were first demonstrated by DP pressure measured at a location close to the BM in ST of turn-one of the cochlea. Then the penetration of motion at the BM level to the cochlear fluids, i.e., within the ST, was addressed by mapping DP pressure at a series of distances from the BM. The pressure difference along this transverse direction is known as the pressure's spatial variation and should be proportional to fluid acceleration (Olson 1998). Additionally, the DP's longitudinal propagation was addressed using two

FIG. 1. Schematic of experimental set-up in uncoiled cochlea. P_{EC} , P_{T1} , and P_{RW} or P_{Stapes} were simultaneously measured using a microphone and micro-pressure sensors. P_{EC} : EC pressure measured by a Bruel and Kjaer or a Sokolich ultrasound probe-tube microphone at a location close to the TM; P_{T1} : ST pressure measured at turn-one, at ~ 2.5 mm from the stapes with a BF ~ 20 kHz at locations close to or far from the BM (P_{T1_close} and P_{T1_far} , respectively); P_{RW} : ST pressure measured at basal turn in the RW region, at ~ 1 – 1.2 mm

from the stapes with the BF between 35 and 40 kHz; P_{Stapes} : SV pressure measured next to the stapes; *BM*: basilar membrane; *BF*: best frequency; *DP*: distortion product; *DPOAEs*: distortion product otoacoustic emissions; *EC*: ear canal; *OHCs*: outer hair cells; *RW*: round window; *ST*: scala tympani; *SV*: scala vestibuli; *TM*: tympanic membrane.

distinct measurement sites either both in the ST, turn-one versus further basal at the round window (RW), or in turn-one in ST and in scala vestibuli (SV) next to the stapes. Finally, the relationship between intracochlear DPs and EC DPOAEs was explored. The combined results confirmed a reverse-TW as the main route for DPs to drive the stapes in reverse, while a CW pathway may also contribute, especially, to DPs generated at basal, high-frequency regions that are close to the stapes.

METHODS

Experimental Approach

Animal procedures were approved by the Institutional Animal Care and Use Committees (IACUCs) of Columbia University and the VA Loma Linda Healthcare System. Experiments were performed in deeply anesthetized young adult gerbils (pentobarbital 60 mg/kg for initial dose; 10 mg/kg for maintenance). The left pinna was surgically removed and the bulla was exposed and widely opened. The physiological condition of the cochlea was assessed by recording the thresholds for compound action potentials (CAPs) in response to tone pips measured with an electrode on the bony niche of the RW using a threshold criterion of ~ 5 μ V (p-p). Initial CAP thresholds were typical for the gerbil in that they were generally at low values, i.e., 20–30 dB SPL at frequencies < 20 kHz, and were often gradually increasing for frequencies > 20 kHz (Dong and Olson 2006, 2008). Such thresholds were consistent with the fragility of the base of the gerbil cochlea (Overstreet et al. 2002).

Experimental System

Single or two equilevel ($L_1 = L_2$) primary tones at f_1 (lower frequency) and f_2 (higher frequency) at a fixed f_2/f_1 ratio were generated by a commercial system with a sampling frequency of 200 kHz [System III,

Tucker-Davis Technologies (TDT)] driving one or two dynamic speakers (Radio Shack tweeters or Fostex). Stimulus and acquisition software was written in MATLAB, and the TDT visual design studio. Responses were analyzed by fast Fourier transforms (FFTs) using MATLAB offline. A T-tube sound system was coupled to the EC in a closed-sound field configuration with the microphone's probe tube (either Bruel and Kjaer, model 4290, or Sokolich ultrasound microphone) passing through the center of the sound tube, and the tip of the microphone positioned close to within ~ 3 mm of the tympanic membrane (TM) where the sound pressure levels (SPLs) of acoustic stimuli were calibrated in decibels (dBs) re 20 μ Pa p-p. The frequency-dependent transfer function of the probe-tube microphone was accounted for when setting the required SPLs for eliciting responses and analyzing the data. The two arms of the T-tube connected the two speakers. The microphone also served as the receiver of the acoustic pressure in the EC. With 1-s data acquisition times, the probe-tube microphone noise level was ~ 5 – 10 dB SPL, up to 30 kHz, and somewhat greater at the higher frequencies. The system distortion level was regularly checked in a cavity corresponding to the volume of the gerbil EC and was at least 60 dB below the level of the primary tones when their levels were 90 dB SPL (Dong and Olson 2008, 2010). System distortion was also checked by obtaining postmortem responses following each in vivo experiment.

Micro-Pressure Sensor and Experimental Design

Custom-made micro-pressure sensors have been used in the hearing-research field for over a decade to advance our understanding of middle ear sound transmission, cochlear mechanics, and the generation of DPOAEs (Olson 1998; Dong and Olson 2005a; Olson and Dong 2006; Dong and Olson 2013; Olson and Nakajima 2015). The construction and calibration

of micro-pressure sensors with inner and outer diameters of 75 and 125 μm , respectively, have been reported previously (Dong and Olson 2008). In the current study, the intracochlear pressure responses to tones were measured simultaneously at two sites within the cochlea. Specifically, as shown in the schematic of Figure 1, one sensor was introduced through a hand-drilled hole in the ST in turn-one of the cochlea, at ~ 2.5 mm from the stapes (Muller 1996), in a region with a BF of ~ 20 kHz (see red star at P_{TI} at #1 in Fig. 1). This sensor was held in a motorized micromanipulator capable of moving in 1- μm steps in three-dimensional (3D) space. Thus, the sensor was used to transversely map the intracochlear ST pressure responses to single- or two-tone stimuli at a series of locations resulting in, for example, $P_{\text{TI_close}}$ or $P_{\text{TI_far}}$, representing pressure responses measured at a location either close to or far from the BM, respectively (see #1. Transverse spatial variation in Fig. 1).

A second sensor was positioned at either a very basal site in the ST with a BF of $\sim 35\text{--}40$ kHz (i.e., $\sim 1\text{--}1.27$ mm from the stapes), through a tear in the RW membrane (P_{RW} in Fig. 1), or by the stapes via a hand-drilled hole in SV (P_{Stapes} in Fig. 1). Thus, comparisons between $P_{\text{TI_close}}$ and $P_{\text{RW}}/P_{\text{Stapes}}$ were used to address the longitudinal propagation of the DP in the cochlea and describe how the stapes was driven reversely (#2 and #3 in Fig. 1). Finally, the relationship between DPOAEs and DPs was explored via a comparison between pressures in the EC, i.e., P_{EC} and ST pressure at turn-one, i.e., P_{TI} (#4 in Fig. 1). It was recognized that placement of the ST and SV sensors could potentially cause a reduction in CAP thresholds (Olson 2001). However, variations in CAP thresholds were less problematic in the current study than in other previous studies, since comparisons were made between measurements taken simultaneously at the different locations. Although the introduction of the micro-pressure sensor close to the BM was expected to cause some mechanical perturbation, comparing measurements of the CAP thresholds and EC DPOAEs made both before and after introducing the sensor (Olson 2001; Dong and Olson 2008) confirmed that such perturbations were not significant.

Data Analysis

Both EC and intracochlear pressure responses were time averaged and analyzed via Fourier transform offline using MATLAB. Phase responses provide the crucial key to understanding the results in the current study and are for the most part presented relative to the propagation direction as “destination minus source,” i.e., in the forward sound propagation (single- and two-

tone responses at primary frequencies), apical intracochlear pressure phase was referenced to pressure measured at the basal location or in the EC: $\phi_{\text{forward}} = \phi_{P_{\text{TI}}}$ —either $\phi_{P_{\text{RW}}}$ or $\phi_{P_{\text{Stapes}}}$ or $\phi_{P_{\text{EC}}}$. In the reverse sound propagation at DP frequencies, the basal location or EC DPOAE phases were referenced to the phase measured at the apical turn-one location: $\phi_{\text{reverse}} = \text{either } \phi_{P_{\text{RW}}} \text{ or } \phi_{P_{\text{Stapes}}} \text{ or } \phi_{P_{\text{EC}}} - \phi_{P_{\text{TI}}}$. Therefore, if the intracochlear DP measured at apical turn-one propagated to the further basal location, or to the stapes or the EC via a reverse-TW, DP phase was expected to overlie the forward-TW phase representing wave propagation and taking the same amount of time traveling in the opposite direction. Otherwise, if the DP propagated back to the stapes via a CW, little phase difference between the two locations was expected, and an in-phase result should be observed, because the CW propagates rapidly at the speed of sound in water. The one exception to this referencing of the DP phase is in Figure 2, where the DP P_{TI} was referenced to P_{EC} for illustration of the characteristics of DPs measured at the level of the BM.

RESULTS

Findings from 18 gerbils studied in the above-described in vivo experiments are reported here. Nine animals were used to investigate the longitudinal transmission of the DP in the ST by recording simultaneously from two cochlear locations, i.e., one located in turn-one and the other at a more basal site approached through the RW (P_{TI} and P_{RW} , respectively), while the remaining nine gerbils were used to explore how the stapes was reversely driven via simultaneous measurements of ST pressures in turn-one and SV pressures next to the stapes (P_{TI} and P_{Stapes} , respectively). Pressure responses at locations close to and far from the BM at the turn-one location were measured routinely in each subject as $P_{\text{TI_close}}$ and $P_{\text{TI_far}}$. The outcomes described below were consistent across animals with the results shown here having been selected from a subset of these experiments. Since the general findings were similar for either the low- or high-frequency sideband DPs (e.g., the $2f_1 - f_2$ or the $2f_2 - f_1$), the $2f_1 - f_2$ in each individual experiment was chosen to illustrate the main findings. To address DP propagation within the cochlea, responses to single tones or to two tones at the primary-tone frequencies were used to show sound propagation in the forward direction for comparison and are presented as black or gray dotted lines in all the illustrations shown below.

FIG. 2. Level-dependency of $2f_1 - f_2$ DP. **a** Predicted $2f_1 - f_2$ velocity and phase from a 3D stylized classical nonlinear model of the cochlea constructed on the basis of data from an experimental animal (guinea pig) selected to yield a smooth BM impedance function [(adapted from Fig. 6 in de Boer et al. (2007))]. The effective DP pressure, P_{act} (thin black line), resulting from the overlapping region of the primary-tones f_1 and f_2 ($f_2/f_1 = 1.2$), generated the $2f_1 - f_2$ DP (thick black line), which propagates to the left and right intracochlearly post-generation and corresponds to the reverse- and forward-TWs. The DP phase (dotted black line) accumulates slowly as it propagates through the TW long-wave region towards the stapes in the reverse direction and more rapidly as it propagates through the short-wave region towards the apex in the forward direction. **b-d** Magnitude and phase of the $2f_1 - f_2$ evoked by two equal-level

primaries increasing in level from 50 to 80 dB SPL, in steps of 10 dB (color key above panel C) with $f_2/f_1 = 1.25$. Responses were measured in the turn-one ST close to the BM ($\sim 10 \mu\text{m}$). Red and black bars at the bottom of each graph indicate low- and high-frequency regions associated with the different DP characteristics (see text for details). **b** Phases of the $2f_1 - f_2$ referenced to EC primary-tone f_1 and f_2 phases. Red dotted line shows the phase-versus-frequency tendency in low-frequency red bar region. **c** Magnitude of the $2f_1 - f_2$. **d** Magnitude of the $2f_1 - f_2$ from **c** normalized to primary f_2 intensity. For comparison, phase and magnitude of f_2 were plotted as black dotted lines representing features in the forward-propagation direction in **b** and **d** (from Gerbil #wg176).

Characteristics of DPs and Their Physiological Vulnerability

To characterize intracochlear DPs measured at the BM level, we begin with predictions from a 3D stylized classical nonlinear cochlear model [Fig. 2a adapted from Fig. 6 in de Boer et al. (2007)]. This particular model used a smooth BM impedance function constructed from BM velocity measurements at 17 kHz in a guinea pig cochlea. With equal-intensity two-tone stimuli of 70 dB SPL and an f_2/f_1 ratio of 1.2, the $2f_1 - f_2$ DP was generated by the effective pressure, P_{act} (the thin line in Fig. 2a), which has a peak in the overlapping region between the two primary tones, close to the f_2 peak. The magnitude and phase of the simulated DP wave are plotted as thick

black solid and dotted lines, respectively, in Figure 2a. Post-generation, two DP waves were predicted along the cochlear partition, with one left-going in the reverse direction to the stapes (red arrow) and the other one right-going thus representing propagation in the forward direction towards the DP place (black arrow). The key to recognizing the direction of the DP propagation is in the phase, which accumulates and is delayed relative to the generation site [also see de Boer (2007), Shera et al. (2007), He et al. (2008)]. It is worth noting that the model envisions the complete BM in a spatial sense (i.e., distance from the stapes) in the presence of a single pair of primary tones generating, for the purpose of simplicity, a single emission at $2f_1 - f_2$. Because of local cochlear

scaling symmetry, the spatial pattern of the responses should have correspondence with responses measured from a singular location and presented in the frequency domain (de Boer et al. 2008).

The remainder of Figure 2b–d presents actual intracochlear pressure responses of the $2f_1 - f_2$, evoked by two equal-intensity primary tones ($L_1 = L_2 = 50\text{--}80$ dB SPL, in increasing 10-dB steps) at an f_2/f_1 ratio of 1.25 swept from 2 to 40 kHz measured at a location with BF = ~ 21 kHz. The micro-pressure sensor was positioned in the ST close to the BM at a distance of ~ 10 μm . Similar to BM measurements [i.e., Rhode (2007)], the amplitude of the $2f_1 - f_2$ increased with increasing primary-tone levels and showed two distinct peaks, one at frequencies below 22 kHz and one above when plotted versus f_2 (red and black bar regions in Fig. 2c). The low-frequency DP peak with f_2 below 22 kHz (corresponds to $2f_1 - f_2$ below 13.2 kHz), appeared to increase almost linearly with the primary f_2 SPL (red bar region in Fig. 2d) and its phase, when referenced to EC f_1 and f_2 phases, departed from the forward-TW at primary SPL levels of 60 to 80 dB (red bar region solid curves compared to black dotted line f_2 phase in Fig. 2b). Focusing on the phase responses and using the model predicting DP phase (Fig. 2a) as a guide, the tendency of the $2f_1 - f_2$ DP phase-versus-frequency (red dotted line in Fig. 2b) seemed to be consistent with the prediction for a reverse-propagating wave. In addition, the fine structure in the magnitude was similar to that simultaneously measured from the DPOAE in the EC [shown in Fig. 7a and also see Dong and Olson (2008)]. Thus the $2f_1 - f_2$ DP at f_2 frequencies below 22 kHz appeared to be dominated by non-local, reverse-propagating components, which were being detected on their way out of the cochlea. This conclusion is confirmed by the detailed comparison of these DPs to the DPOAEs measured simultaneously in the EC, which is presented and further explained in Figure 7.

For the high-frequency peak (black bar frequency region with f_2 above 22 kHz in Fig. 2c), the $2f_1 - f_2$ was tuned to the local BF when plotted versus its own frequency at primary levels of 50 dB SPL (dark blue in Fig. 2d) and then increased compressively and nonlinearly with primary level in a similar manner as the f_2 (Fig. 2d). The phase at all the primary levels presented overlay f_2 phase after normalization to EC f_1 and f_2 phases (Fig. 2b), consistent with the model prediction of forward-traveling DP waves. Thus, the amplitude and phase characteristics of the $2f_1 - f_2$ with f_2 above 22 kHz seemed to suggest that these DPs were dominated by forward-traveling components generated by f_2 above the local BF, at more basal locations. The prominent notch at $f_2 = 22$ kHz (Fig. 2c) can be explained by cancellation among different components, i.e., local and non-local or forward- and reverse-propagating components. The correlation between these DPs and DPOAEs are discussed in Figure 7.

To address the question of how the DP propagates post-generation in the cochlea, understanding the characteristics of DPs is important. Especially in the current study, in order to demonstrate DP propagation post-generation using responses from two intracochlear sites, DPs need to be detectable over a relatively broader frequency region, which required higher primary-tone SPLs, such as those at 80 or 90 dB SPL. The interpretation of these high-level primary-tone evoked DPOAEs may be difficult as the generation mechanisms are still not well understood, despite experiments suggesting that high-level DPOAEs are produced by the same mechanism as low-level primary-tone elicited DPOAEs [e.g., Lukashkin et al. (2002), Dong and Olson (2010), Avan et al. (2013)]. However, regarding DP propagation post-generation, Figure 2 illustrates that DPs evoked by primary levels of 50 to 80 dB SPL share common features.

Figure 3 shows the physiological vulnerability of DPs and DPOAEs measured simultaneously in the ST

FIG. 3. Physiological vulnerability of $2f_1 - f_2$ DP and DPOAE. **a** Magnitude of the $2f_1 - f_2$ DP for P_{T1} measured at turn-one, from a location close to the BM, ~ 10 μm . **b** Magnitude of the $2f_1 - f_2$ DPOAE measured simultaneously in the EC, P_{EC} . Two-tone stimuli were $L_1 = L_2 = 90$ dB SPL, $f_2/f_1 = 1.05$. Black and gray lines represent

in vivo and ~ 10 min postmortem measurements, respectively. The dramatic decrease of the DP and DPOAE confirmed their cochlear origin (from Gerbil #wg121).

close to the BM and in the EC under in vivo (black lines) and postmortem ~ 10 min (gray lines) conditions in the same animal shown in Figure 5. The $2f_1 - f_2$ was evoked by two equilevel primary tones of 90 dB SPL, with $f_2/f_1 = 1.05$. The dramatic reduction of more than 20 dB in DPs postmortem within 10 min confirmed that they were of cochlear origin (Fig. 3a). In addition, this reduction in DP levels appeared to be the direct cause of the observed reduction in the DPOAE measured from the EC (Fig. 3b). The reductions in magnitude of DPs and DPOAEs postmortem confirmed that neither DPs nor DPOAEs generated by 90 dB SPL primary tones were from system distortions.

To summarize, the micro-pressure sensor measures the summed intracochlear pressures at one location. The DPs in intracochlear pressure responses to two-tone stimuli are of cochlear origin and are a combination of different components, which can be differentiated by the characteristics of their magnitudes and phases, and with relative contributions that relate to the f_2 primary, i.e., a non-local/reverse-traveling component seems dominant when f_2 is below the local BF, and a forward-traveling component dominates when f_2 is above the local BF. There was evidence of interference between different components [note notches in Fig. 2 and Dong and Olson (2005b), Rhode (2007), Dong and Olson (2008, 2010)]. Thus, recognizing these different components is important when addressing DP propagation in the cochlea for determining a source-and-effect relationship.

DP Penetration from the Cochlear Partition to Cochlear Fluids

In forward sound propagation in the cochlea, the spatial variation of pressure in cochlear fluids at frequencies around the BF, in the short-wave regime, is well understood both experimentally and theoretically (Peterson and Bogert 1950; Olson 1998). Moreover, such spatial variation of pressure is one of the fundamental features used to distinguish TW pressure from CW pressure, which is evenly distributed in the cochlea. During forward-propagation, adjacent fluid moves together with the BM; thus, pressure responses measured at ~ 15 μm from the BM (P_{TI}) to single-tone 60 dB SPL stimuli were dominated by TW pressure that was tuned to the local BF of ~ 23 kHz (black dotted curve in Fig. 4a), with phase accumulating about 3 cycles when referenced to P_{EC} (black dotted curve in Fig. 4d). At frequencies around the BF between 15 and 26 kHz, the $P_{\text{TI_far}}$ measures decreased about 10 dB when the sensor was moved further away to 115 μm from the BM (gray dotted curve in Fig. 4a) and showed less phase accumulation

at higher frequencies (gray dotted curve in Fig. 4d). The P_{TI} at the BF, 23 kHz decayed steadily with distance away from the BM up to 115 μm , then seemed to level off, which was likely due to the CW being dominant [dotted line in Fig. 4b and also in Olson (1998), Dong and Olson (2005a)].

At lower (<15 kHz) and higher frequencies (>26 kHz, the cutoff frequency in this case), the pressure's spatial variation was very small. At higher frequencies, pressure responses were dominated by the CW, which moved in-phase with the stapes [see phase plateau region of dotted lines indicated by arrows in Fig. 4d and see example in, e.g., (Olson 1998)]. The interference between the TW and CW was evidenced by the deep notch at ~ 24 kHz in pressure measured further away from the BM when the two waves were similar in amplitude but in an anti-phase relationship (arrowhead to dotted line in Fig. 4a and phase transition in gray dotted line of Fig. 4d). At lower frequencies, the unvarying spatial pressure can be explained by the very flexible RW membrane, which is expected to impose a boundary condition at which fluid pressure must be equal to atmospheric pressure, i.e., at "zero." Even though pressure measurements were made some distance from the RW, i.e., at ~ 2 mm away, they were still close enough to be influenced by this boundary condition (Peterson and Bogert 1950; Yoon et al. 2007; Kale and Olson 2015).

DP pressure, e.g., the $2f_1 - f_2$ evoked by two-tone stimuli with $L_1 = L_2 = 70$ dB SPL ($f_2/f_1 = 1.05$), tuned to the local BF when the sensor was close to the BM, 15 μm away (solid black line in Fig. 4a). This DP showed similar spatial variation at frequencies around the BF as the single-tone responses and was reduced by about 10 dB when measured at a location 115 μm from the BM (i.e., compare the levels of the two solid line curves of Fig. 4a). This pressure spatial variation at the DP frequency confirmed that the ST pressure was dominated by local transverse motion along the cochlear partition, i.e., the DP originated from the cochlear partition and penetrated into the cochlear fluids in a similar manner to that of the forward-TW (Dong and Olson 2005a, 2008). The DP pressure further decreased more than 10 dB when measured at a location that was 375 μm from the BM, a location very close to the cochlear wall (the last triangle point in Fig. 4b). This was consistent with a previous detailed analysis of the DP decay-with-depth (Dong and Olson 2005a) where the DP appeared to steadily decrease ~ 20 dB over a distance of ~ 375 μm , while being measured.

In contrast to the tuned DP responses above, simultaneously measured $2f_1 - f_2$ DPOAE pressure in the EC was relatively flat with frequency and was between 20 and 50 dB SPL (Fig. 4c). When comparing

FIG. 4. Spatial variations of $2f_1 - f_2$ DPs. **a** Magnitude of the $2f_1 - f_2$ measured at turn-one from locations close to ($\sim 15 \mu\text{m}$) and far from ($\sim 115 \mu\text{m}$) the BM. *Solid lines* indicate responses of the $2f_1 - f_2$ evoked by equilevel primary tones of 70 dB SPL, with $f_2/f_1 = 1.05$. For comparison, responses to single-tone 60 dB SPL stimuli measured at the same locations are plotted with *dotted lines*. **b** Decay-with-depth measured at several distances from the BM for both a 60 dB SPL tone and a $2f_1 - f_2$ DP at a BF of 23 kHz. **c** $2f_1 - f_2$ DPOAE measured simultaneously in the EC. **d** Relative phase of the DPOAE and DP at $2f_1 - f_2$. For comparison, single-tone phases of P_{T1} measured at the same locations referenced to P_{EC} were plotted as *dashed lines*. Note that in this and all subsequent figures, the relative phase of the DP and the single-tone responses are referenced in a “destination minus source” manner, i.e., for a single-tone the relative phase is calculated as P_{T1} minus P_{EC} but for the DP, it is P_{EC} minus P_{T1} .

Therefore, if the DP propagated in the reverse direction as a TW, the phase versus frequency curve at DP frequency (*solid lines*) should overlie the single-tone phase showing the typical forward-TW phase accumulation with frequency (*dotted lines*). By contrast, when the DP propagates in the forward direction as a TW, the DP phase should be the mirror image of the forward single-tone TW phase. At low frequencies (red bar region), the DPOAE phase lagged DP phase in a similar manner as the single-tone propagated in the forward direction as a TW, suggesting that these DPs propagated to the EC through a reverse-TW. At higher frequencies (black bar region), the $P_{EC} - P_{T1}$ phase was a mirror image of the single-tone phase indicating that the DP was dominated by a forward-traveling component (from Gerbil #wg175).

the DP phase to the DPOAE phase, at frequencies below 18 kHz (red bar region in Fig. 4d), the DPOAE phase lagged DP phase and the DP P_{EC} minus P_{T1} phase showed a similar phase-versus-frequency slope to that of the forward-TW phase, i.e., P_{T1} minus P_{EC} of the single-tone responses (solid vs. dotted lines in Fig. 4d), no matter whether the DP was measured close to or far from the BM. These results again suggest that the DP was dominated by the reverse-TW component, consistent with the model prediction in Figure 2a and propagated to the EC via a reverse-TW rather than via a CW. If backward transmission was by a fast CW, then the phase accumulation would be small because the CW would fill up the cochlea instantaneously. At higher frequencies above 18 kHz (black bar region), the DP P_{EC} minus P_{T1} phase showed a mirror image to that of the single-tone forward-TW phase. This occurred because the DP was

dominated by the forward-traveling component, which cannot be considered as the direct intracochlear source of the DPOAE (Dong and Olson 2008).

Longitudinal Propagation of DPs in the ST

Longitudinal DP pressure propagation in the ST was demonstrated by comparing pressures recorded simultaneously at two distinct cochlear locations, e.g., with the turn-one sensor positioned close to the BM at a BF of ~ 20 kHz ~ 2.5 mm from the stapes (P_{T1}), and the RW sensor located at a more basal site with a BF of ~ 35 to 40 kHz at ~ 1 mm from the stapes (P_{RW}) (see Fig. 5 and path #2 in Fig. 1). In the present study, because of the curvature of the BM at the cochlear base, simultaneously positioning the P_{RW} sensor close to the BM was not possible. As shown above in

Figure 4 for the forward-sound propagation, pressure measurements far from the BM appeared to be a summation of both local and non-local components. Consequently, measuring at a position that was further from the BM may facilitate describing DP propagation by a CW in ST, because there is little spatial variation in the CW.

In the forward-propagation direction, the cochlea responds to sound in a tonotopic manner with low frequencies peaking at apical locations and high frequencies peaking at basal sites. This longitudinal-frequency pattern was observed for ST pressure responses to 60 dB SPL single-tone stimuli measured at two longitudinal locations demonstrated by the dashed curves in Figure 5, i.e., P_{T1} peaked at 20 kHz (Fig. 5b), and P_{RW} peaked between 30 and 40 kHz (Fig. 5a). The broader tuning apparent for the P_{RW} was due to the sensor not being close to the BM. Responses for 60 dB SPL stimulation were chosen, because their amplitude was comparable to that of the DP (solid curves in Fig. 5). The single-tone phase of P_{T1} minus P_{RW} showed the typical TW phase accumulation of 2 cycles up to 26 kHz as indicated by the dotted line in Figure 5c, which confirmed that the response propagated from the basal to turn-one location mainly as a TW. At higher frequencies, i.e., above 26 kHz, ST pressure should peak at locations basal to the turn-one sensor; thus, no TW should be detected at the turn-one site. The P_{T1} for these frequencies remained large, but was in-phase with the P_{RW} , which supported the notion that these pressures were dominated by the CW through the fluids of the cochlea (see arrow pointing to phase plateau region in dotted line above ~ 26 kHz in Fig. 5c). Again, the notch at 26 kHz in P_{T1} resulted from the cancellation of the TW and CW pressures (arrowhead in Fig. 5b).

Similar analyses were applied to DPs to better understand the mechanisms by which they are propagated along the cochlea. In these experiments, two-tone stimuli at equal intensities of 90 dB SPL ($f_2/f_1 = 1.05$) were used to permit the recording of DPs over a wide frequency range at both locations. The physiological vulnerability of these DPs was addressed in Figure 3, which compared in vivo to postmortem recordings. P_{RW} and P_{T1} responses for the $2f_1 - f_2$ DP are plotted as solid line functions (Fig. 5a, b). The phase of P_{RW} minus P_{T1} at the $2f_1 - f_2$ frequency is plotted as a solid line curve in Figure 5c. Based on the characteristics of the magnitudes and phases of the $2f_1 - f_2$, three frequency regions can be differentiated and are shown as red, black, and green bars in Figure 5a–c.

In region I, with f_2 frequencies well below the 20 kHz BF of the turn-one sensor (red bars, Fig. 5a–c), the $2f_1 - f_2$ response of P_{T1} was robust and increased in level as a function of increasing frequency similar to the pressure responses elicited by the single-tone stimuli (solid vs. dotted line in Fig. 5b). The level of the $2f_1 - f_2$ P_{RW} measured simultaneously at a more basal location was more than 10 dB less (solid line in Fig. 5a). The $2f_1 - f_2$ phase measured at P_{RW} lagged the P_{T1} phase in a manner similar to how the single tone's P_{RW} phase led P_{T1} phase in the forward direction (solid and dotted line in red square region in Fig. 5c). Since the single-tone propagated from the RW to turn-one as a TW, these results support the hypothesis that the $2f_1 - f_2$ DP propagated from an apical (turn-one location) to a basal location primarily as a reverse-TW. If the DP propagated as a CW, it would have been expected to exhibit in-phase behavior for the P_{RW} and P_{T1} responses (flat phase slope with frequency).

In region II, with f_2 frequencies close to the turn-one BF (black bars, Fig. 5a–c), the $2f_1 - f_2$ response of

FIG. 5. The $2f_1 - f_2$ DP longitudinal propagation in the ST. **a** Magnitude of $2f_1 - f_2$ DP, P_{RW} , measured at the basal turn close to the RW, and far from the BM, BF = 35–40 kHz. **b** Magnitude of $2f_1 - f_2$ DP, P_{T1} , simultaneously measured at turn-one, BF of ~ 22 kHz at a location close to the BM, $\sim 10 \mu\text{m}$. **c** Phase difference between basal turn and turn-one at $2f_1 - f_2$ frequencies. If a forward-propagating DP dominated the responses, the phase of P_{RW} minus

P_{T1} at DP frequency should be a mirror image of the forward-TW phase of the single-tone responses. This was not the case in the red bar region (red dashed square). Dotted lines indicate comparable single-tone 60 dB SPL responses measured at the same locations (from Gerbil #wg121, $L_1 = L_2 = 90$ dB SPL, $f_2/f_1 = 1.05$).

P_{T1} peaked at the local BF in a similar manner to what was observed with single-tone responses suggesting that the DP responses were dominated by a locally generated forward-traveling component and then processed through the local cochlear filter (Dong and Olson 2005b). At the same time, the $2f_1 - f_2$ at P_{RW} appeared to be a summation of different components, i.e., local and non-local, due to the presence of a deep notch around 25 kHz (arrowhead in Fig. 5a). Phase responses of P_{RW} minus P_{T1} at the $2f_1 - f_2$ frequency appeared to be the mirror image of the forward-TW phase, thus suggesting that the DP measured at basal site P_{RW} led that measured at the turn-one location, P_{T1} . This outcome was similar to observations on the BM published by the Ren and investigators [i.e., He et al. (2010)]. However, the apparent forward-propagation of the DP in this region can be easily explained by the idea that these DPs were generated mainly from a region between the two sensors, at f_2 frequencies between the BFs of turn-one and more basal sites. Therefore, P_{T1} was dominated by a forward-propagation component [see Fig. 2 above and de Boer et al. (2007), Dong and Olson (2008)], and P_{RW} was dominated by a local generation component. When these two measurements were compared, an apparent forward-propagation was seen.

In region III, with f_2 frequencies close to the basal-turn BF and above the cutoff frequency for the turn-one sensor (green bars, Fig. 5a–c), the DP of P_{RW} tuned to the basal-BF, as shown in Figure 5a, and exhibited greater amplitudes than when measured in turn-one P_{T1} as shown in Figure 5b. Thus, these observations indicate that region III DPs were generated at a location basal to the turn-one sensor, and close to the basal-turn sensor. Because the DP frequency was above the cutoff frequency of turn-one, it would be expected that there would be no forward-propagation via the TW. In this case, the DPs could only propagate to the turn-one sensor location via a CW. In the present study, consistent with these predictions, the DP pressure of P_{T1} was observed to be in-phase with the DP pressure of P_{RW} (see green-square region in Fig. 5c).

Reverse Propagation of DPs to Drive the Stapes

Figure 6 illustrates the stapes being driven in reverse at DP frequencies using simultaneous measured P_{T1} (Fig. 6a) in turn-one close to the BM and P_{Stapes} (Fig. 6b) in SV next to the stapes (labeled as #3 in Fig. 1). Single-tone (dashed curves representing 40 and 60 dB SPL stimuli) and two-tone responses at $2f_1 - f_2$ were plotted. The swept two-tone stimulation consisted of equal-intensity primaries at $L_1 = L_2 = 80$ dB

SPL with a fixed f_2/f_1 ratio of 1.05 (dark blue curves), 1.25 (green curves), and 1.35 (red curves).

The magnitude of the $2f_1 - f_2$ in P_{T1} was ratio dependent in that wider f_2/f_1 ratio resulted in smaller DP magnitudes (solid lines in Fig. 6a). The wiggles in pressure responses were likely due to interactions among different wavelets in the cochlea, i.e., forward- and reverse-traveling components or local and non-local components. On the other hand, P_{Stapes} was less sensitive to ratio and appeared “flat” with frequency, likely due to summation of reverse-traveling wavelets from different frequency regions with different magnitudes and phases (Fig. 6b). As previously mentioned, P_{Stapes} measures next to the stapes at DP frequencies represent the pressure driving the stapes in a reverse manner and, consequently, they can be considered as the intracochlear counterpart of DPOAEs in the P_{EC} [i.e., Magnan et al. (1997), Dong and Olson (2006)].

The data illustrated in Figure 6 focus on comparing P_{Stapes} to P_{T1} in order to further explore whether the CW or the TW drove the stapes reversely. If the $2f_1 - f_2$ traveled back to the stapes through cochlear fluids instantaneously as a CW, thus causing a forward-TW as suggested by Ren and colleagues [e.g., He et al. (2010)], the comparison between the two pressures’ magnitudes, P_{T1} minus P_{Stapes} (Fig. 6c) should be similar to that of sounds propagating in the forward direction as a TW, i.e., single-tone responses measured at the same time and locations (dotted lines in Fig. 6). Thus, a smooth tuning curve similar to those that have been measured on the BM for many years should be observed [see review of Robles and Ruggero (2001)] and the phase of P_{Stapes} minus P_{T1} at the DP frequencies should be the mirror image of the forward-TW phases represented by the single-tone responses (comparing solid and dotted lines in Fig. 6d, e). However, that was not what the current results showed in the low-frequency region (i.e., at the red bar in Fig. 6).

Using the same analytical logic as above, we will describe how the relationship between P_{Stapes} and P_{T1} varies in three frequency regions indicating by the red, black, and green bars. At low frequencies (red bar region), the two pressures P_{Stapes} and P_{T1} tended to be identical (pressure difference close to zero, color lines in Fig. 6c), especially with wider f_2/f_1 ratios of 1.25 and 1.35 (f_2 below 7, 10, and 14 kHz at ratio of 1.05, 1.25, and 1.35, respectively). This is consistent with the DPs in this region being generated by f_2 frequencies well below the local BF of 20 kHz. The DP phase at P_{Stapes} lagged the P_{T1} phase in a manner similar to how the phases at P_{Stapes} led P_{T1} phases for the single tones propagating in the forward direction as a TW (solid lines vs. dotted lines in Fig. 6d, e) and thus were consistent with a reverse-TW. Taking these

FIG. 6. Comparisons between P_{Stapes} and P_{T1} for $2f_1 - f_2$ DP. **a** Magnitude of the $2f_1 - f_2$ DPs measured in turn-one ST with BF of ~ 20 kHz, P_{T1} , at a location close to the BM, ~ 10 μ m and about 2.5 mm away from the stapes. **b** Magnitude of the $2f_1 - f_2$ DPs simultaneously measured in the SV next to the stapes, P_{Stapes} . **c** Pressure difference between P_{T1} and P_{Stapes} . **d**, **e** Phase differences between P_{T1} and P_{Stapes} re f_2 and $2f_1 - f_2$ frequencies. Blue, green, and red represent responses to equal-intensity primary tones of 80 dB SPL with f_2/f_1 ratios of 1.05, 1.25, and 1.35, respectively. For comparison, single-tone 40 and 60 dB SPL responses measured at the same locations are plotted with gray dotted lines. **f** A cartoon to explain ratio-dependent phase behavior at an f_2 of 22 kHz (from Gerbil #wg191).

observations together, these DPs were generated in an apical region and were detected as a reverse-TW on the way back to the stapes at the turn-one sensor and appeared to become the major driving pressure to the stapes for DPs in this low-frequency red bar region.

At f_2 frequencies between 10 and 26 kHz, for $f_2/f_1 = 1.05$ and 1.25 (blue and green lines in roughly the black bar region), the DP measured at P_{T1} appeared to be dominated by a forward-traveling component whose corresponding phase lagged the phase measured at P_{Stapes} , likely because these DPs were generated from a region close to or slightly basal to the turn-one sensor. For $f_2/f_1 = 1.35$ in the black bar region, the phase seemed to change little (Fig. 6d, e). This ratio-dependent phase behavior is further explained in the panels of Figure 6f. When the cochlea was stimulated with two tones, for example, at

and red represent responses to equal-intensity primary tones of 80 dB SPL with f_2/f_1 ratios of 1.05, 1.25, and 1.35, respectively. For comparison, single-tone 40 and 60 dB SPL responses measured at the same locations are plotted with gray dotted lines. **f** A cartoon to explain ratio-dependent phase behavior at an f_2 of 22 kHz (from Gerbil #wg191).

$f_2 = 22$ kHz, with narrow f_2/f_1 ratio, the corresponding f_1 and $2f_1 - f_2$ are at 21 and 20 kHz, respectively (panel a in Fig. 6f). Under this scenario, the P_{T1} sensor with BF of 20 kHz would be in the short-wave region of the forward-traveling DP component, whose phase changed rapidly with frequency. Thus, the phase of P_{Stapes} minus P_{T1} at DP frequencies would be dominated by the forward-TW phase. With a wider ratio, i.e., $f_2/f_1 = 1.35$ (panel b in Fig. 6f), the corresponding f_1 and $2f_1 - f_2$ with f_2 at 22 kHz were 16.3 and 10.6 kHz, respectively. Therefore, P_{T1} measured the forward-propagating DP pressure in its long-wave region, with little phase accumulation and tended to be in-phase with the DP being measured at the stapes. Therefore, in this black bar frequency region, despite differing phase characteristics for the different f_2/f_1 ratios, the results are generally consistent with a DP

forward-TW which seemed not to be the main contributor for reversely driving the stapes. Reinforcing this conclusion, the magnitudes of P_{T1} minus P_{Stapes} in Figure 6c for this black bar region indicate that the DP magnitude at P_{T1} was much larger than at P_{Stapes} , thus indicating that in contrast to the DPs in the red bar region for which the P_{T1} and P_{Stapes} pressures were roughly equal the DPs detected in the this black bar frequency region are dominated by components not propagating reversely to drive the stapes.

At f_2 frequencies above 26 kHz for $f_2/f_1 = 1.05$, the DP of P_{T1} was in-phase with P_{Stapes} (blue curve in green bar region in Fig. 6d, e), again showing basally generated DPs with f_2 well above the local BF of turn-one, and was consistent with forward-propagation through the cochlear fluids to the turn-one sensor as a CW. The generation site of the DP with f_2 above 26 kHz was close to the stapes; thus, the DP distribution in cochlear fluid as a CW may play an important role in driving the stapes reversely for this condition.

Relationship Between DPs and DPOAEs

The ultimate goal of understanding the generation and propagation of DPOAEs is to establish the relationship between the DPOAE and its intracochlear source, the DP, so as to enhance the interpretations of EC-based DPOAE testing both in clinical and research settings. Simultaneously measured DPOAEs (P_{EC}) and DPs close to the BM at turn-one (P_{T1}) for the $2f_1 - f_2$ frequency are shown in

Figure 7a, b, respectively (Fig. 7b is a re-plot of Fig. 2a). The DPOAE minus DP phase was plotted in Figure 7c. Responses at f_2 were also included to represent features in the forward-propagation process (black dotted line in Fig. 7c). For comparison, results previously published by He et al. [Fig. 2g in He et al. (2010)] for $2f_1 - f_2$ BM DP phase relative to the DP at the stapes using the same stimuli ($L_1 = L_2 = 70$ dB SPL, $f_2/f_1 = 1.25$) are also included in Figure 7c (bold dashed gray curve).

As shown in Figure 7a, the EC $2f_1 - f_2$ DPOAEs were relatively “flat” as a function of the f_2 frequency. For the intracochlear $2f_1 - f_2$ DP in ST, measured at turn-one and close to the BM, as described in Figure 2, a notable notch was observed at an f_2 of ~ 22 kHz (Fig. 7b), along with the phase transition (Fig. 7c), which essentially separated the $2f_1 - f_2$ into two frequency regions, i.e., those below and above ~ 22 kHz.

In the low-frequency region, for f_2 frequencies < 22 kHz (red bar region), the DP exhibited a “fine” structure (Fig. 7b) that seemed to be mirrored in the EC DPOAE “fine” structure (Fig. 7a). When relating P_{EC} and P_{T1} at DP frequencies, the pressure difference of P_{T1} minus P_{EC} resulted in smoother curves similar to that of f_2 indicated by black dotted lines in Figure 2d (not shown, see vertical dotted lines indicating frequencies with similar “fine” structure). The DPOAE phase lagged the DP phase, indicating that the DP traveled back to the EC with a certain group delay. Similar results were also observed for measures of BM motion relative to the motion of stapes [bold dashed gray line in Fig. 7c and see

FIG. 7. Relationship between DPs and DPOAEs. **a** Magnitude of $2f_1 - f_2$ DPOAEs in P_{EC} . **b** Magnitude of the corresponding $2f_1 - f_2$ DPs in P_{T1} measured at turn-one close to the BM, $\sim 10 \mu\text{m}$ (re-plot of data in Fig. 2c). Different blue-shaded curves indicate equilevel primary tones of 50–80 dB SPL, in increasing 10 dB steps (color key above panel **b**), with $f_2/f_1 = 1.25$. Thin dotted vertical lines in **a** and **b** indicate fine structure alignments in the DPOAE and DP. **c** DPOAE minus DP phases. For comparison, responses of P_{T1} minus P_{EC} f_2 phase was plotted as a dotted line and represents the forward-TW phase accumulation. Gray bold dashed line represents published DP

phase measured at the stapes referenced to DP phase measured on the BM evoked by $L_1 = L_2 = 70$ dB SPL primaries with $f_2/f_1 = 1.25$ (He et al. 2010). DPOAE phase either lagged or led the DP phase at low- and high-frequency regions corresponding to the red and black bar frequency regions and confirms the conclusion that a CW was not the major path for DP propagation post-generation in the cochlea. Otherwise, less phase accumulation similar to that due to middle ear reverse transmission ($\sim 30 \mu\text{s}$, Dong and Olson 2006) should be present (from Gerbil #wg176).

also examples in Figs. 2g and 3g in He et al. (2010)].

By contrast, in the high-frequency region for f_2 frequencies > 22 kHz (black bar region), the DP was dominated by a forward-traveling component (Figs. 2 and 7b). When the DP phase was subtracted from the DPOAE phase, a paradoxical result was noted, i.e., DP phase led the DPOAE phase (Fig. 7c). The explanation for this observation is that these DPs were generated at a more basal location (f_2 above the turn-one local BF) and traveled to the sensor location in a forward direction [see analysis of black bar regions in Figs. 2, 4, 5, and 6]. This forward-TW component may contribute to the DPOAE as the reflection component in some species as proposed by Shera and Guinan (1999). However, the dominant component of the DPOAE is very stimulus-parameter dependent and the wider ratio of f_2/f_1 evoked DPOAE (current case, $f_2/f_1 = 1.25$) should be dominated by the generation component (Shera and Guinan 1999; Knight and Kemp 2000, 2001). Therefore, making the present one-to-one comparison seems to be too simple for addressing the reverse propagation of the DP in this frequency region (Dong and Olson 2008).

DISCUSSION

Efforts to find evidence of the reverse-TW have been ongoing for over a decade with little result. Published BM motion measurements rarely show the evidence of the reverse-TW. One reason is that most of the studies have focused on frequency regions around the BF, which seem to be dominated by the local/forward-traveling component, especially for the $2f_1 - f_2$ [see DP evoked by 50 dB SPL, blue lines in Fig. 2 and, i.e., Ren (2004) and de Boer et al. (2008)]. When an effort was made to make the comparison between the DPs measured at two longitudinal BM locations, the ~ 200 μm separation of two locations appeared to not be large enough to resolve the non-local reverse-traveling component when considering that the generation region broadens with increasing primary levels (He et al. 2007). An extensive exploration of the relationship between the DP measured on the BM and the DPOAE measured in the EC led to the suspicion that one single point BM measurement cannot be considered as the direct intracochlear source of the DPOAE, which apparently arises from the summed DP wavelets emanating from a broader region of the cochlea (Rhode 2007). In a recent paper published by Ren and colleagues (He et al. 2010), which compared the BM velocity to stapes velocity at the DP frequency, obvious group delay consistent with a reverse-TW was observed at low frequencies and was

similar to that seen in our pressure measurements [red bar region in Fig. 7c and Figs. 2, 3, and 4 in He et al. (2010)]. However, the authors concluded that the phase variation was due to the varying generation site of the DPs.

The roles of the TW and CW can be recognized by their distinct features. A main distinction being that they exhibit different propagation speeds. Because the TW progresses along the cochlear partition much more slowly in relative terms than the CW, which travels at the speed of sound in the cochlea's fluids (~ 1500 m/s), the TW normally presents a phase delay while the CW shows in-phase behavior. One reason this difference is not fully appreciated is that in the basal-to-BF, or long-wave region, the TW speed is much faster than it is in the near-BF, or short-wave region, although the TW speed is always much slower than that of the fast CW. Another difference is that they have different pressure distributions in the cochlear fluid. Since the wavelength of TW shortens and its amplitude increases as it approaches the BF, it is constrained by the height of the cochlear duct and travels through the cochlea in two different regions. The first is the long-wave region where the TW's wavelength is long with respect to the height of the cochlear duct. In this region, the motion of fluid particles can be considered as a plane wave, or like a wall of fluid moving back and forth within a tube. When the wavelength becomes short with respect to the height of the cochlear duct, the TW is in its short-wave region. In this region, wave propagation is similar to ripples on the surface of a deep pond, and fluid particles travel in elliptical traces with greater amplitudes near the BM. By contrast, the CW pressure fills up the cochlea evenly and is nearly unchanging in space (Peterson and Bogert 1950; Olson 1998).

In the current study, the two-tone-evoked intracochlear DPs and DPOAEs were simultaneously measured at two well-separated sites, turn-one in the ST (P_{TI}) and basal in ST (P_{RW}) or in SV close the stapes (P_{Stapes}), and in the EC. The micro-pressure sensors measured summed pressures in the fluid at these locations. By comparing intracochlear responses to single- or two-tone stimulation at primaries measured at the same time, in the same locations, the role of the TW and CW in DP propagation in the cochlear fluid was explored.

Propagation of DPs in the Cochlea

When a healthy cochlea is stimulated with two tones, DPs are generated within the cochlea. In such a scenario, a group of OHCs can be envisioned as dancing in rhythm with the DP frequency as well as with the primary-tone frequencies of f_1 and f_2 . Generation of DPs requires that both primary tones

are strong enough to interact in the OHC nonlinearity. Numerous studies support OHC electromechanics as the fundamental source of the emissions, because OAEs are reduced when OHCs are damaged or when the endocochlear potential, which is necessary for OHC electromotility is reduced (Henley et al. 1996; Avan et al. 2003; Mills 2003). For low primary level-evoked DPs, strong evidence has been shown that the generation of DPs can be summarized into a two-source model in which the generation sites are expected to be well localized to the f_2 and f_{dp} places (Mauermann et al. 1999a, b; Kalluri and Shera 2001). At moderate to high primary-tone levels, the cochlear excitation pattern broadens and regions responsible for the generation of OAEs appear to extend further basal (Martin et al. 1999; Knight and Kemp 2001; Martin et al. 2010). A recent study using a locally damaged gerbil model demonstrated that high-level DPOAEs were dominated by the generation component, which corresponded to a region at and basal to the f_2 frequency place (Dong and Olson 2010). As shown in Figure 2, the characteristics of DPs evoked by primary-tone levels from 50 to 80 dB SPL share common features and were consistent with the prediction of a classical 3D nonlinear cochlear model that DPs appear to originate from the primary overlap region close to the f_2 peak (de Boer et al. 2007). Furthermore, the dramatic and similar postmortem reduction in DPs and DPOAEs evoked by primaries of 90 dB SPL confirmed their cochlear origin (Fig. 3).

The characteristics of DPs are complex when measured at one location in the cochlea and appear to include both local and non-local or forward- and reverse-traveling components (de Boer 2007; de Boer et al. 2007; Rhode 2007; Shera et al. 2007; de Boer et al. 2008; Dong and Olson 2008, 2010). Therefore, recognizing different components of the measured intracochlear DP is an important starting point. Predictions from a 3D classical nonlinear model in which DPs originate from the f_1 and f_2 overlap region, close to f_2 peak, help us to distinguish between the different components of DPs [Figs. 2a and 6 in de Boer et al. (2007), also see de Boer (2007), Shera et al. (2007), de Boer et al. (2008), He et al. (2008)]. In the model prediction, two DP TWs exist post-generation, with the left-going wave traveling in the reverse direction and the right-going wave traveling in the forward direction. The key feature is in the phase, which accumulates as the wave propagates. DP pressure measured as P_{T1} at the turn-one location close to the BM showed similar characteristics to DPs measured on the BM [Fig. 2 and, i.e., in Rhode (2007), He et al. (2010)] and seemed to support the model predictions: at low frequencies with f_2 below the local BF, the DP seemed to be dominated by the reverse-propagation component, which showed simi-

lar fine structure to that of the DPOAE [vertical thin dotted lines in Fig. 7 and Dong and Olson (2008)], and was phase lagged to the DPs measured at more basal locations (red bar regions in Figs. 2, 4, 5, 6, and 7). Thus, they appeared to have a direct correspondence with the DPOAE measured for similar low frequencies (Dong and Olson 2008). At higher frequencies with f_2 above the local BF (black bar region in Figs. 2, 4, 5, 6, and 7), the DP showed tuning, nonlinear compressive growth with primary tone levels and phase accumulation similar to that of a forward-TW and thus seemed to be dominated by the forward-propagating component (black bar regions in Figs. 2, 4, 5, 6, and 7).

Therefore, post-generation intracochlear DPs may travel in a forward direction similar to an external tone traveling along the cochlear partition as a TW. The forward-traveling DP component has been observed on the BM and in intracochlear pressure responses [e.g., Robles et al. (1997), Dong and Olson (2005b), Rhode (2007), de Boer et al. (2008), Dong and Olson (2008), He et al. (2008)], in auditory nerve-fiber discharges (Siegel et al. 1982), acoustically by human listeners [Goldstein (1967), also see review of Avan et al. (2013)], and has recently been inferred from a noninvasive technique using secondary DPOAEs (Martin et al. 2016). The forward-propagating DP seems to go through similar cochlear signal processing as any external tone and thus tuned to the local BF, increased compressively and nonlinearly with the intensity of primary tones, and showed similar phase accumulation as the forward-TW [Fig. 2 and, e.g., Cooper and Rhode (1997), Dong and Olson (2005a, b), He et al. (2007), He et al. (2010)]. These forward-traveling DPs were confirmed in current study in intracochlear responses at frequencies between the local BF and cutoff of P_{T1} (the black bar regions), when comparing responses from different longitudinal locations within the cochlea, for example, between pressures measured at turn-one (P_{T1}) and further basal locations, in ST at the RW (black bar in Fig. 5c), in SV next to the stapes (black bar in Fig. 6d) or for DPOAEs measured in the EC (black bar in Fig. 7c).

Conversely, at frequencies below the local BF (red bar regions, Figs. 2, 4, 5, 6, and 7), the phase of turn-one P_{T1} DP, measured at an apical location, appeared to be consistent with the model predictions (Fig. 2) and was dominated by the reverse-propagation component. DP phases measured at more basal locations lagged the DP phases measured at the apical location in a manner similar to that of the forward-TW in the opposite direction (red bar regions, Figs. 4, 5, 6, and 7). In addition, similar “fine” structure of DPs appeared to be mirrored at the basal locations

(Figs. 5, 6, and 7). All of these observations supported the existence of a reverse-TW.

Furthermore, propagation of the DP through cochlear fluids was also observed in turn-one P_{TI} responses at frequencies above the cutoff frequency (green bars in Figs. 5c and 6d). When comparing pressure responses at simultaneously recorded basal points, these DPs seemed to be generated by an f_2 greater than the BF associated with turn-one. The only pathway for such DPs to be detected by the turn-one sensor, at a BF of ~ 20 kHz, was through cochlear fluids as a CW as verified by the in-phase behavior in these higher-frequency regions.

DP Penetration from the Cochlear Partition to Cochlear Fluids and Possible Contributions to the DPOAE through a CW Path

The penetration of DPs into cochlear fluids relates directly to the question of whether or not the fast CW wave could be the major route for DPs to reversely drive the stapes as suggested by Ren and colleagues [i.e., He et al. (2010)]. As demonstrated in Figure 4, the DP magnitude decreases with the distance away from the BM in a manner similar to that of the single-tone responses measured at the same locations. The decay-with-depth of intracochlear pressure, at both primary and DP frequencies, was analyzed in detail in Dong and Olson (2005a). Along the transverse direction, the pressure spatial variation is proportional to fluid acceleration. Fluid velocity can be calculated from pairs of pressure measurements at adjacent positions as $v \approx \left(\frac{i}{\omega \rho}\right) \nabla p$, where ω is the angular frequency and ρ is the fluid density (Olson 1998). As shown in Figure 4 and in our earlier studies (Dong and Olson 2005a, 2008), similar decay-with-depth at the primary and DP frequencies for frequencies around the local BF suggested motion on the cochlear partition penetrates the cochlear fluids in a similar manner and is governed by the anatomy of the cochlear partition, i.e., the width of the BM (Olson 1999). Based on these studies [e.g., Fig. 7 in Dong and Olson (2005a) and Fig. 4 of the present study], a simple calculation can be done to evaluate the DP contribution through the cochlear fluids, as a CW or evanescent wave to the DPOAE. In Figure 4 at the BF, the DP pressure magnitudes appeared to decrease steadily over a distance of 400 μm in depth to a pressure ~ 20 dB smaller than when they were measured close to the BM. The stapes is more than ~ 2 mm away from the recording place, thus extrapolating the data would result in at least another ~ 15 dB reduction. Considering that the middle ear pressure loss is ~ 40 dB SPL for reverse transmission in the gerbil (Dong and Olson 2006), a 90 dB SPL DP at the BM level's contribution to the DPOAE in the EC

through the fluids would be at a level of ~ 15 dB SPL. However, simultaneously measured $2f_1 - f_2$ DPOAE pressure in the EC was between 20 and 50 dB SPL (Fig. 4c). Therefore, from this perspective, the conclusion that DP reverse propagation is mainly through the cochlear fluids as a CW was not supported. In addition, the turn-one DP phases either lagged or led the DP phase measured at further basal locations or the DPOAE phase in the EC, thus arguing that there was not a dominant CW, which would have resulted in in-phase behavior. However, under certain circumstances, such as for high-frequency DPs generated at a basal location close to the stapes, the CW may play an important role in DP reverse propagation.

On the other hand, comparing the magnitude of EC and ST pressure, P_{TI} , responses in the same frequency region yielded results consistent with the notion that the DP was mainly traveling back through the cochlea as a reverse-TW: for example, in the forward sound transmission, a 60 dB SPL single-tone stimuli at the EC caused ~ 100 dB SPL pressure responses in ST close to the BM (black dotted line in Fig. 4a) or a gain of approximately ~ 40 dB at the BF. Thus, if the DP propagated to the EC via a reverse-TW, a 90 dB SPL DP would lose ~ 50 dB to result in a ~ 40 dB SPL DPOAE considering middle ear pressure loss in reverse is ~ 10 dB more than the pressure gain in the forward transmission (Dong and Olson 2006). And this is exactly what the results showed (black solid lines in Figs. 4a, c). In addition, the phase of the DPOAE or basal DP lagged the DP phase at low frequencies (red bar regions in Figs. 4, 5, 6, and 7) and showed similar phase accumulation as sound propagation in the forward direction, thus, confirming that the TW was the major pathway for reverse-DP propagation.

CONCLUSION

In summary, the present findings demonstrate the following: (1) Intracochlear DPs measured at a singular location are complex, and the characteristics of these DPs are consistent with outcomes from a 3D-classical cochlear model which predicts that their generation was from the primary overlap region close to the f_2 peak and includes both forward- and reverse-traveling components. (2) Penetration of the DP from the cochlear partition to the cochlear fluid was similar to that of a sound-evoked TW propagating in the forward direction, which appeared to be governed by the nature of the TW and anatomy of the cochlear partition, such as the width of the BM. (3) The hypothesis that the locally generated DP primarily

propagates through the cochlear fluids as a CW was not fully supported. If a CW-based propagation mechanism were correct, a purely forward-propagating DP would have been observed, which was not the case, especially in the comparison of apical to simultaneous basal recordings at low frequencies. In addition, the contribution through the CW path appeared not to account for the level of the DPOAE measured in the EC. However, under the circumstance when DPs were generated at basal locations close to the stapes, the CW may play an important role in driving the stapes reversely. (4) Our results emphasize the importance of establishing the correct source-and-effect relationship between the DP and DPOAE and largely support a mechanism favoring the existence of reverse-TWs by showing similar phase accumulation in reverse-DP propagation to that shown for tone-evoked TWs in the forward direction. In combination, these observations support the overall conclusion that OAE latency consists of a forward-wave delay plus a backward-wave delay (Goodman et al. 2003; Shera and Guinan 2003).

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