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Sensory Transduction and Frequency Selectivity in the Basal Turn of the Guinea-Pig Cochlea

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Sensory transduction and frequency selectivity in the basal turn of the guinea-pig cochlea

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SUMMARY

Receptor potentials recorded from outer hair cells (OHC) and inner hair cells (IHC) in the basal high-frequency turn were compared. The DC component of the IHC receptor potential is maximized to ensure that IHCs can signal a voltage response to high-frequency tones. The OHC DC component is minimized so that OHCs transduce in the most sensitive region of their operating range. The phase and magnitude of OHC receptor potentials were recorded as an indicator of the magnitude and phase of the energy which is fed back to the basilar membrane to provide the basis for the sharp tuning and fine sensitivity of the cochlea to tones. IHC receptor potentials were recorded to assess the net effect of the feedback on the mechanics of the cochlea. It was concluded that OHCs generate feedback which enhances the IHC responses only at the best frequency. At frequencies below CF, IHC DC responses are elicited only when the OHC AC responses begin to saturate.

1. INTRODUCTION

The function of hearing in man is subserved in each cochlea by a single row of 3500 inner hair cells (IHCs) and 12 000 outer hair cells (OHCs) arranged in three rows. IHCs form synapses with the vast majority of afferent fibres in the auditory nerve whereas the OHCs have been described as the end organs of the efferent system (Davis 1983). The rows run parallel to the long axis of the spiral coil of the basilar membrane and the hair cells and their innervation are distributed tonotopically primarily as a consequence of the basilar membrane's mechanical tuning properties (see Evans, this symposium; Ruggero *et al.*, this symposium). Low-frequency hair cells are located at the apex of the cochlea and high-frequency hair cells are located in the basal turn. Hair cells are excited through displacements of the stereocilia bundle and the mechanosensitive channels are gated when the stereocilia are displaced towards the tallest row (Hudspeth & Corey 1977; Russell *et al.* 1986). The precise way in which the stereocilia of cochlear hair cells become displaced is not known but it is believed to occur as a consequence of shear displacements between the tectorial membrane and the basilar membrane which are the two principal structural components of the cochlear partition (Davis 1965). The rows of stereocilia of the OHCs in the mammalian cochlea are attached by their tips to the tectorial membrane and thus mechanically link the tectorial and basilar membranes. As a consequence of their strategic location in the cochlear partition. OHCs play an essential role in the frequency tuning and sensitivity of the cochlea. After selective damage to the OHCs, the electrophysiological and mechanical responses of the cochlea to acoustic stimulation become insensitive, linear and broadly tuned (Liberman & Dodds 1984; Brown *et al.* 1989). This finding, together with the measurement of acoustic emissions from the cochlea (Kemp 1978) and the discovery that isolated OHCs are capable of rapid voltage-dependent motility (Brownell *et al.* 1985; Ashmore 1987), has led to the proposal that OHCs have an interactive role in sensory transduction in the cochlea (see Dallos (1988) for a review). More specifically, it has been suggested that OHCs feedback energy which overcomes viscous damping of the cochlear partion and provides the sharp frequency tuning of the cochlear responses (see, for example, Weiss (1982); Davis (1983); Neely & Kim (1983)).

It might be expected that the effectiveness of the proposed feedback depends on the mechanical properties of the basilar and tectorial membranes and on the gain and phase of the feedback process which has been associated with the OHC transducer. If, at low and moderate sound levels, OHCs operate in a true electromotor feedback loop then they will contribute to their own voltage responses and hence to the mechanical responses of the cochlear partition. For high levels of the acoustic stimulus the OHC transducer is saturated and the mechanical responses of the basilar membrane and the voltage responses of the OHCs are governed by the passive mechanical properties of the basilar membrane (Patuzzi *et al.* 1989; Zwislocki 1986). Thus, differences in the magnitude and phase of OHC voltage responses to tones at low and high levels should

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provide an indication of the magnitude and phase of the OHC feedback relative to the passive mechanical properties of the basilar membrane. A comparison between OHC and IHC responses from the same region of the cochlea should provide information about the relationship between OHC feedback and the net mechanical response of the cochlear partition which is reflected in the IHC DC receptor potentials (Russell & Sellick 1978). To this end, measurements were made from hair cells in the basal, high-frequency turn of the guinea-pig cochlea to tones within an octave of the CF of the hair cells (15–19 kHz) in an attempt to understand how electromechanical feedback contributes to the tuning of the cochlea. Before dealing with the question of frequency tuning in the cochlea, attention is drawn to the functional significance of the differences in the tone-evoked voltage responses of basal turn IHCs and OHCs.

2. IHC DC RESPONSES ARE MAXIMIZED

The resting potentials of IHCs recorded *in situ* are about −45 mV (Russell & Sellick 1978; Dallos 1986) and the relationship between the peak IHC voltage response to low-frequency tones and peak sound pressure (figure 1*a*, the transducer function) is a typical asymmetrical S-shaped curve which can be fitted by pairs of hyperbolic tangent functions (Russell & Sellick 1983; Dallos 1986; Russell & Kössl 1991) (figure 1*b*). The resting potential and the shape of the transducer function largely define the important functional characteristics of IHCs and the afferent fibres

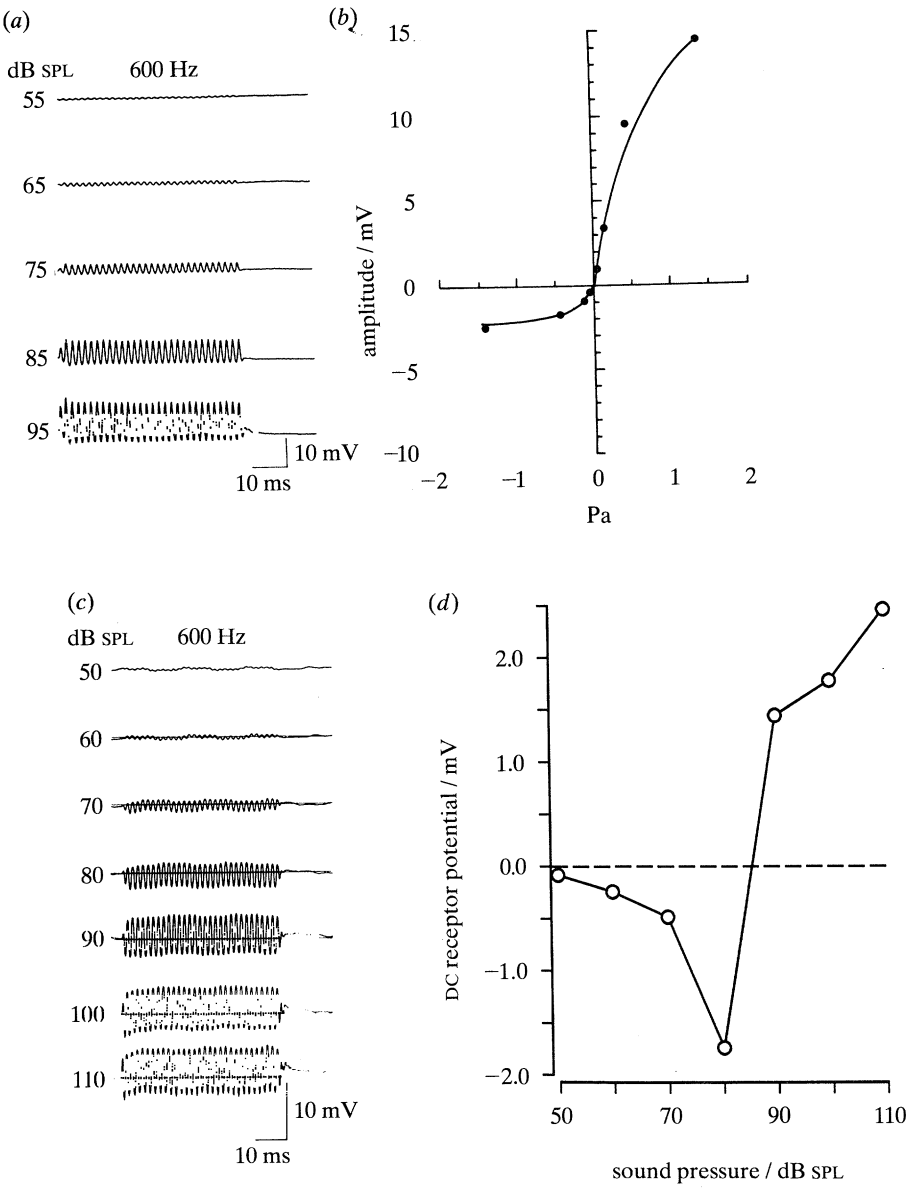

Figure 1. Intracellular receptor potentials recorded from (*a*) an IHC and (*c*) an OHC in the basal turn of the guinea-pig cochlea to 600 Hz tones at the sound pressures indicated by each trace. The peak positive and peak negative voltage responses of the IHC receptor potential as a function of the peak rarefaction and compression of the 600 Hz tone measured at the auditory meatus (transducer function) are shown in (*b*). The points are fitted by a pair of hyperbolic tangent functions. (*d*) The DC component of the OHC receptor potential as a function of the level of the 600 Hz tone. (*a*), (*b*) and (*c*) from Cody & Russell (1987).

with which they form synapses. At a resting potential of −45 mV, the voltage-dependent calcium conductance of the IHC basolateral membranes will be activated (Crawford & Kros 1990) and it is probable that calcium influx close to the presynaptic membrane of the IHC is instrumental in causing the spontaneous release of transmitter at the afferent synapses of the two spontaneously active classes of the three classes of afferent fibres which have so far been identified in the auditory nerve (Winter *et al.* 1990). The relatively depolarized IHC resting potential and spontaneous release of afferent transmitter ensure that the voltage responses of the IHCs are transmitted to the hind brain with maximum sensitivity through the modulation of a sustained level of transmitter and that a voltage threshold does not have to be exceeded before the afferent fibres are excited. The neural signalling of IHC voltage responses through the modulation of a sustained release of afferent synaptic transmitter provides the opportunity to signal negative as well as positive changes in sound pressure at levels close to the threshold of hearing for frequencies below about 1 kHz. Hence, at these levels afferent fibres can signal both rarefaction and compression in sound pressure (Palmer & Russell 1986). The asymmetrical transfer function provides the basis of the IHC DC receptor potential and the means to signal responses to high-frequency tones (Russell & Sellick 1978). The transducer function is shaped by the gating characteristics of the transducer channel which, for cochlear hair cells, can be modelled as a three state process with one open and two closed states (Kros *et al.* 1991), and the voltage- and ion-dependent conductances of the basolateral channels (Kros & Crawford 1990; Dallos & Cheatham 1991). At rest, about 10% of the transducer conductance is open (Russell & Kössl 1991) and it is likely that the proportion of channels open at rest is governed by the concentration of intracellular free calcium (Crawford *et al.* 1991).

For frequencies above about 600 Hz, the AC receptor potential is attenuated by the low pass electrical characteristics of the hair cell so that the principal voltage responses of IHCs in the basal turn to tones at CF is the DC receptor potential (Russell & Sellick 1978; 1983). If the IHC afferent synapse is conventional, then transmitter release is primarily controlled by changes in presynaptic potential. This suggestion is supported by the close correspondence between phase-locking in the auditory nerve and the cut-off frequency of the IHC membrane time constant (Palmer & Russell 1986). For frequencies above the cut-off frequency, phase-locking declines according to the membrane time constant. However, for frequencies above about 3 kHz phase-locking is also limited by transmission at the afferent synapse (Weiss & Rose 1988), possibly due to limits which include those set by the speed of the calcium influx, transmitter mobilization and release, the kinetics of the post synaptic ligand gated channel and the spike generator.

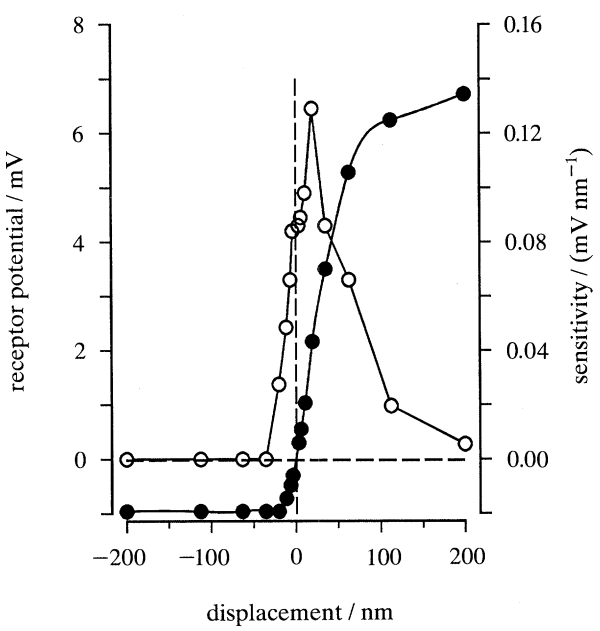

Figure 2. OHC receptor potential as a function of the displacement of the stereocilia bundle (solid circles). Sensitivity of OHC (open circles) based on the slope of the transducer function. Each point is the mean of measurements made from the receptor potentials recorded from five OHCs in an organ culture of a one-day post-natal mouse cochlea (the standard deviations do not exceed 12% of the mean). The dotted line represents the OHC resting membrane potential.

3. OHC DC VOLTAGE RESPONSES ARE MINIMIZED

The voltage responses of OHCs in the basal turn of the guinea pig cochlea to tones close to their CF are remarkable for their small size (Russell *et al.* 1986; Cody & Russell 1987). At the threshold for neural excitation the magnitude of OHC voltage responses at CF are about 30 μV compared with 800 μV for IHCs (Russell & Sellick 1983; Sellick *et al.* 1983; Cody & Russell 1987; Russell & Kössl 1992*a*, *b*). The small size of the OHC voltage responses may be attributed to the almost symmetrical transducer function and the membrane time constant which attenuates voltage signals at frequencies above about 1 kHz (Dallos 1984; Cody & Russell 1987). The symmetry of the OHC transducer function at the CF can only by presumed from the absence of a DC voltage response to tones. At frequencies well below the cut-off of the membrane time constant, the OHC transducer function is much more symmetrical than the IHC transducer function but level dependent (figure 1*c*, *d*; Russell *et al.* 1986; Cody & Russell 1987). For low-level stimuli, OHCs generate predominantly hyperpolarizing responses, almost symmetrical responses to tones around 85 dB SPL and depolarizing responses at levels above this (figure 1*c*, *d*). OHCs in the apical turn of the guinea-pig cochlea exhibit similar level-dependent voltage responses to tones (Dallos *et al.* 1982) and very recently these level-dependent tone-evoked voltage responses have been compared with level-dependent length changes in isolated OHCs caused by transcellular current stimulation (Evans *et al.* 1988). The amplitude and polarity of the length change varies as

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a function of current strength in a way analogous to the level dependency of tone-evoked voltage responses.

In neonatal mouse OHCs the steepest and hence most sensitive region of the transducer function is reached at about 20 nm displacement of the stereocilia in the excitatory direction (figure 2). This position corresponds to the operating point *in vivo* where the DC component of the receptor potential is at a minimum and the response is symmetrical. This feature of OHC transduction and the relatively hyperpolarized OHC resting membrane potential ensures maximum current flow through the transducer channels for a given displacement. Thus in contrast to the response characteristics of IHCs which are set to maximize the DC receptor potential and hence ensure a voltage response to a high-frequency tone, operating characteristics of OHCs ensure that OHCs operate in a most sensitive region of their operating range at the expense of not generating substantial voltage responses to tones at the CF and perhaps the opportunity to communicate these responses to the central nervous system.

The mechanism responsible for controlling the operating point of OHCs in the basal region of the cochlea is not known. OHC receptor potentials (Russell *et al.* 1986) and receptor currents (Kros *et al.* 1991) in the organ culture of the mouse cochlea and in the apical turns of the guinea-pig cochlea (Dallos *et al.* 1982) are asymmetrical with a substantial DC component. It is possible that the hair bundle is biassed through interaction with the tectorial membrane so that at rest about 50% of the transducer conductance is open (Russell *et al.* 1986; Russell & Kössl 1991).

4. PHASE AND MAGNITUDE OF IHC AND OHC RECEPTOR POTENTIALS

The magnitude–level and phase–level functions of the AC voltage responses of OHCs (CF, 16 kHz) measured intracellularly and just extracellularly (figure 3) are remarkably similar. For frequencies below about one half an octave below the CF of an OHC, the magnitude of the AC component of the receptor potential increases linearly with levels below about 70 dB SPL. Above this level the slope of the AC–level function decreases and the receptor potential contains a DC component. At these frequencies and for low levels,

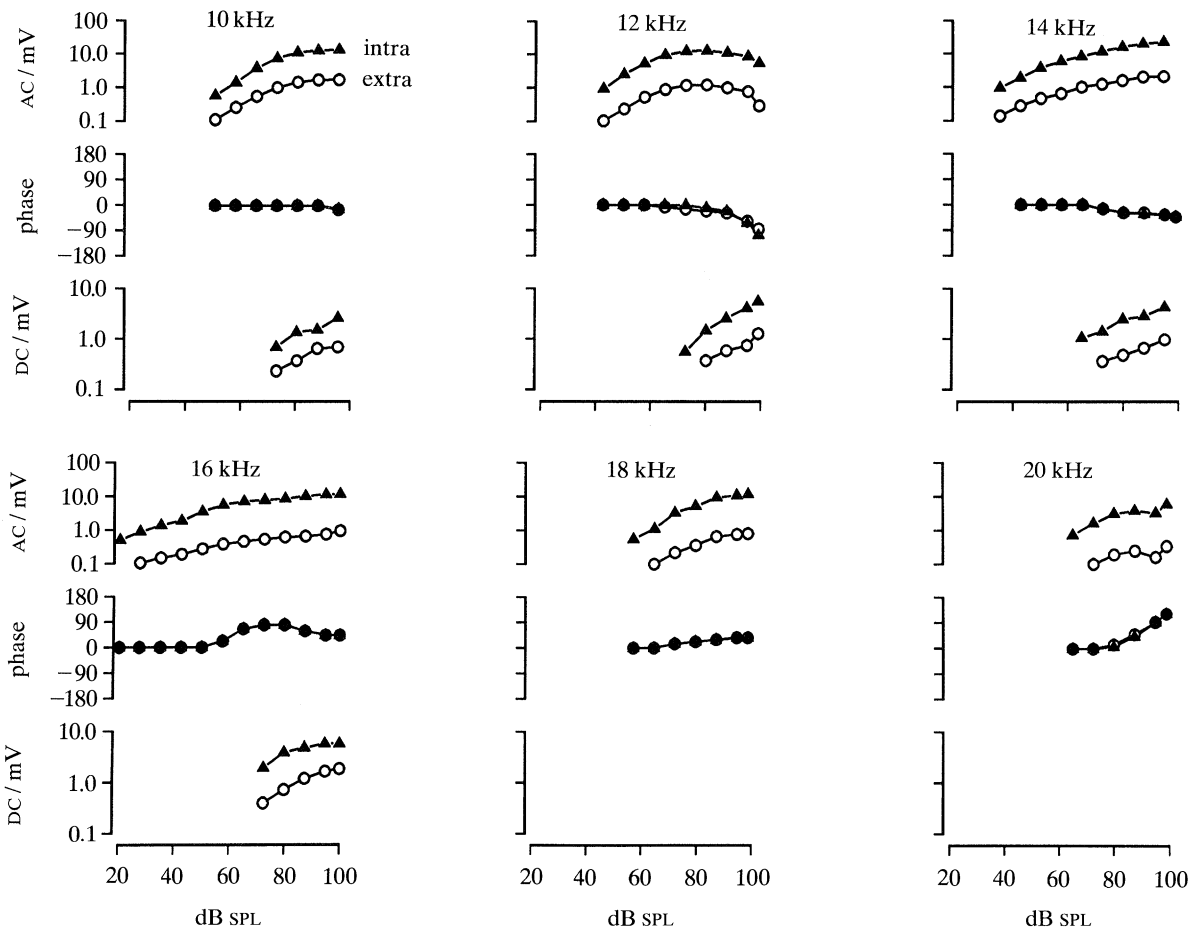

Figure 3. Tone-evoked voltage responses as functions of level (and at the frequencies shown) recorded intracellularly (solid triangle) and extracellularly (open circles) from an OHC. In each figure the magnitude of the AC response (upper), the phase of the AC response (middle) and the amplitude of the DC receptor potential (lower) is plotted as a function of tone level. Resting potential of OHC, −70 mV. Detection threshold at CF (16 kHz) was 20 dB SPL. The magnitudes of the responses are RMS values. Phase is measured with reference to the phase of the AC response at detection threshold (zero phase). Positive values of phase indicate leads and the data has been compensated for recording system and membrane time constants of 3.5 kHz and 1.1 kHz respectively. From Kössl & Russell (1992).

the phase of the AC component is almost independent of level. When the level exceeds about 70 dB SPL, the phase slightly, but measurably, lags the low-level response by a few degrees (e.g. up to $-45°$, see figure 3, 12 kHz) when the level of the tone exceeds about 70 dB SPL and the OHC AC component (and hence feedback to the cochlear partition) begins to saturate. For frequencies below the CF, it is only when the OHC AC responses begin to saturate that the neighbouring IHCs generate DC responses to the high-frequency tones (compare figures 3 and 4). For frequencies between one half of an octave below CF and CF, the phase of the OHC AC response suddenly jumps 180° and the magnitude of the AC response increases steeply in amplitude with increasing level when the level of the tone exceeds about 90 dB SPL (figure 2, 12 kHz; figure 4, 13 kHz). The phase reversal of the OHC AC response at very high levels of stimulation may indicate that a mechanical change has taken place in the cochlear partition. With respect to this, it has been proposed that the phase of excitation of OHCs is determined by the relationship between the rotational stiffness of the OHC stereocilia and the transverse stiffness of the tectorial membrane (Zwislocki 1986; 1988). A change in the relative values of these stiffnesses during stimulation with high-intensity tones could switch the phase of excitatory displacement of the OHC stereocilia from basilar membrane displacements towards scala tympani to displacements towards scala media (Mountain & Cody 1988).

At the CF, the detection threshold of the OHC AC response and IHC DC response and the initial slopes of the response–level functions are similar (figures 3 and 4). At sound levels around 60 dB SPL the AC signal begins to phase lead, amounting to approximately 90° at 70 dB SPL. Within the same range of levels, the OHC DC potentials first appear and the slope of the IHC DC response–level function becomes more shallow. The interpretation that has been put on these findings is that for low-level CF tones, the vibration of the basilar membrane in a sensitive cochlea phase-lags by 90° passive basilar membrane vibration without feedback from the OHCs. Thus IHCs are excited when the phase of the OHC AC response corresponds to basilar membrane velocity. With increasing levels of the tone, the relative contribution of the feedback from the OHCs is reduced with a corresponding progressive decrease in the phase lag of the basilar membrane motion. When the phase of the OHC feedback and presumably the effectiveness of the feedback in driving the basilar membrane is reduced, the slopes of the IHC DC response–level functions are also reduced. For frequencies below CF (e.g. figure 2, 12 kHz and 14 kHz; figure 4, 13 kHz) the phase of the low level AC response leads the high-level response which is opposite to the situation at the CF. At frequencies below the CF and at levels where the relative contribution of the OHC responses to basilar membrane vibration should be at a maximum, OHC feedback to the cochlear partition is not effective in exciting the IHCs. In fact it may even prevent excitation because the IHC DC response appears only when the OHC AC response begins to saturate and the phase of OHC excitation approaches that of the passive basilar membrane. The observations presented above are in accordance with a model of frequency tuning in which OHCs contribute negative feedback to the cochlear partition which is reversed through a frequency-dependent phase delay (e.g. a low-pass filter) to become positive feedback at the CF (Mountain *et al.* 1983). That is electromotor feedback from the OHCs opposes basilar membrane displacement at frequencies away from the CF, but augments basilar membrane velocity at the CF.

5. THE EFFECT OF LOW-FREQUENCY TONES ON HAIR CELL HIGH-FREQUENCY RESPONSES

It has been proposed that by minimizing the DC component of the receptor potential, OHCs optimize electromechanical feedback by keeping the operating point in the steepest part of the transducer function (Russell *et al.* 1986; Russell & Kössl 1991). Any disturbance of the OHC transducer function away from this operating point should result in a decrease in sensitivity of cochlear responses, particularly at frequencies close to the CF. Decreases in frequency tuning, particularly at the CF have indeed been measured in the responses of hair cells, as a result of the modulation of the responses to high-frequency tones by low-frequency tones (Patuzzi & Sellick 1984).

OHC AC responses to tones at frequencies below CF are suppressed by simultaneously presented 80 dB SPL 100 Hz tones. Suppression is not associated with a phase change in the AC response and suppression of the high-frequency response disappears when the level of the high-frequency tone exceeds about 70 dB SPL and the AC response begins to saturate (figure 4). At these frequencies, IHC DC receptor potentials are not suppressed by the 100 Hz tone because they do not appear until the OHC AC response has begun to saturate and is no longer inhibited by the 100 Hz tone. At the CF, OHC responses are suppressed by the 100 Hz tone at levels below about 70 dB SPL. Suppression of the OHC AC response at the CF is associated with a phase lead of about 90° (figure 4) and by suppression of the DC response in neighbouring IHCs. It is suggested that these observations support the idea that OHCs feedback energy to the cochlea partition at the CF at a phase which would correspond to the velocity of the basilar membrane without feedback. Suppression of the OHC AC response at CF at levels below about 70 dB SPL causes a change in the phase of excitation of the OHC AC response so that it now corresponds to the displacement of the basilar membrane without feedback and is associated with suppression of the IHC DC response.

6. HAIR CELL ISORESPONSE TUNING CURVES

It was suggested above that, at low sound levels, the AC response of the OHC receptor potential provides a measure of the mechanical feedback to the cochlear partition and the DC response of the IHC receptor

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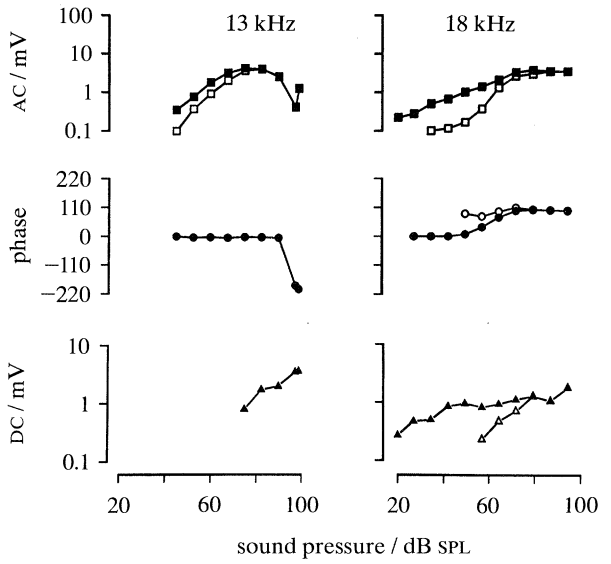

Figure 4. Magnitude, phase and DC response–level functions based on extracellular recordings close to an IHC at the frequencies indicated. In each figure the magnitude of the AC response (upper), the phase of the AC response (middle) and the DC receptor potential (lower) is plotted as a function of tone level. Solid symbols represent the response to the high frequency tone alone, open symbols represent the response to the combined 100 Hz, 80 dB SPL tone and high-frequency tone. The magnitude of the AC response is corrected by 6 dB per octave from 4 kHz to compensate for the low-pass filtering due to the recording system. From Russell & Kössl (1992*a*).

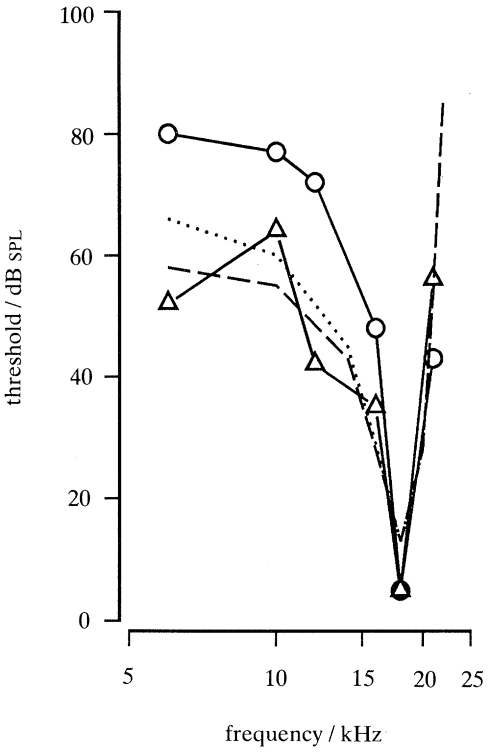

Figure 5. Isoresponse tuning curves measured intracellularly from an OHC and an IHC in the 18 kHz region of the same cochlea and isoresponse measurements of the displacement and velocity of the 18 kHz region of the guinea-pig basilar membrane taken from Sellick *et al.* (1982). The criteria for the isoresponse tuning curves were 0.5 mV (OHC AC, triangles), 0.8 mV (IHC DC, circles), 0.044 mm s^{-1} (basilar membrane velocity, dotted line), 3.5 Å (basilar membrane displacement, dashed line). The resting potentials of the IHC and OHC were −45 mV and −65 mV respectively. Threshold loss after exposure of the basilar membrane was less than 5 dB SPL. The AC responses were compensated for the recording system time constant (3 kHz). CF, 15 kHz; solid circles, IHC DC intracellularly; open triangles, OHC AC extracellularly.

potential is an indicator of the net effect of this feedback on the mechanics of the cochlear partition. Furthermore it has been proposed that OHC feedback reverses from negative feedback at frequencies below the CF to positive feedback at the CF (Mountain *et al.* 1983). Thus, it might be expected that the isoresponse frequency tuning curves of IHCs and OHC may differ from each other and from isoresponse tuning curves of the basilar membrane mechanics. On the basis of intracellular recordings from adjacent IHCs and OHCs without a measurable change in cochlear sensitivity between and following the recordings, the characteristics of IHC and OHC isoresponse tuning curves are very similar in the tip region (Russell *et al.* 1986; Cody & Russell 1987; Kössl & Russell 1992) (figure 5). The bandwidth of the tuning curve, measured 10 dB from the tip ($Q_{10\,dB}$) and high and low frequency slopes are similar to those which have been measured in primary afferent fibres and the basilar membrane in the basal turn of the guinea-pig cochlea (Sellick *et al.* 1982, 1983; Nuttall *et al.* 1991). In all respects, the tuning curves of IHCs and nerve fibres are almost identical which may indicate that synaptic transmission across the IHC afferent synapse is frequency independent, at least for frequencies above a few kHz. However, IHC and OHC tuning curves are dissimilar in that the difference between the tip and the low frequency 'tail' of OHC tuning curves is about 15 dB less than that of IHC and neural tuning curves. This property reflects the finding that, for frequencies on the low-frequency tail of the tuning curve, IHC DC receptor potentials are not generated until the OHC AC responses begin to saturate. In this respect OHC tuning curves resemble isodisplacement tuning curves of the basilar membrane (figure 5) where it has been observed that the sharp transition between the tip and the low frequency tail, which characterizes IHC and neural tuning curves, is absent (Sellick *et al.* 1983). It remains to be seen if the introduction of more sensitive laser Doppler velocimetry and optical techniques will result in basilar membrane isoamplitude tuning curves which more closely resemble neural tuning curves. The limited data which is currently available does not resolve this issue (Nuttall *et al.* 1991). It should be pointed out that differences exist between laboratories and species in the measurement of basilar membrane mechanics which have been discussed elsewhere (Robles *et al.* 1986; Ruggero *et al.* 1986; Ruggero & Rich 1991). For example, there is good agreement between isodisplacement basilar membrane tuning curves and neural tuning curves in the 7–10 kHz region of the chinchilla cochlea (Robles *et al.* 1986).

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On the basis of the available evidence to date it is suggested that in the guinea-pig cochlea the OHC tuning curves closely reflect iso-displacement tuning curves of the basilar membrane and that IHC and neural tuning curve reflect the net radial shear displacement between the basilar membrane and tectorial membrane.

7. CONCLUSION

There is increasing evidence from a wide variety of sources to show that cochlear sensitivity and tuning both depend on feedback from OHCs. It is clear that the phase of feedback relative to the passive motion of the basilar membrane is of crucial importance for the feedback to be effective. What is not clear is how the phase of the feedback is determined or indeed what is the source of the feedback. At present there are two candidates for the feedback process. One of these is the fast electromotile process which some argue may not be fast enough or large enough at high frequencies to provide the feedback (Santos-Sacchi 1989, 1990; Hudspeth 1990; Dallos 1991). The other is a proposed voltage or displacement dependent stiffness change in the hair bundle itself (see Dallos 1991). Time, as they say, will tell.

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