Psychophysical Evaluation of Cochlear Hair Cell Damage Due to the A3243G Mitochondrial DNA Mutation

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ABSTRACT

Mitochondrial dysfunction is an important cause of human deafness, implicated in genetic deafness, toxin and noise damage. We assessed the mechanism of cochlear dysfunction in a population of 11 subjects with a specific mitochondrial disorder caused by the A3243G mitochondrial DNA mutation. Psychophysical tests were carried out to assess the inner and outer hair cell functions *in vivo*. Inner hair cell function was assessed using a measure of hearing threshold in the presence of “threshold-equalizing noise” which can indicate “dead regions” where the transduction mechanism fails. Outer hair cell function was assessed by using the notched-noise method to measure auditory filter width, dependent on active mechanisms in the outer hair cell. The results support the conclusion that this mitochondrial disorder causes both inner and outer hair cell dysfunctions. Evidence of inner hair cell dysfunction was found mainly in basal (high frequency) regions of the cochlea and occurred even in some subjects with only mild hearing loss. Evidence of outer hair cell dysfunction was found in some instances where pure tone threshold was at or close to normal. The common occurrence of dead regions in the basal cochlea has treatment implication for this form of deafness; such people may not be helped by amplification of high frequencies.

Keywords: deafness, mitochondria, cochlea, hair cell

INTRODUCTION

Mitochondrial dysfunction is an important cause of human deafness. Mitochondrial DNA (mtDNA) mutations are a well-recognized cause of syndromic deafness [accompanied by neurological features (DiMauro 1993)] and nonsyndromic deafness (Prezant et al. 1993; Reid et al. 1994; Oshima et al. 1999, 2000). Mitochondrial mechanisms have also been proposed in models of presbycusis and toxin and noise damage (Hyde and Rubel 1995; Seidman et al. 1997). This study addresses the mechanism of mitochondrial deafness in a population with a specific mitochondrial lesion. The study population has the A3243G mutation, one of the most common mtDNA mutations (Chinnery and Turnbull 1999; Chinnery et al. 2000b). The deafness resulting from this mutation has a cochlear basis (Sue et al. 1998; Chinnery et al. 2000a). The purpose of this study was to use psychophysical techniques to demonstrate the probable cochlear substrate for the deafness.

In the cochlea, sound transduction depends on the endolymphatic potential generated by the stria vascularis and the activity of the inner and outer hair cells [IHCs and OHCs (Dallos 1992; Nobili et al. 1998)]. The stria and hair cells all contain mitochondria and are highly metabolically active (Thalmann et al. 1979, 1982). *A priori*, then, deafness in mitochondrial disorders might be caused by dysfunction of the stria, dysfunction of the IHCs or OHCs, or some combination of these. Previous studies of mitochondrial deafness have emphasized the possible role of the stria vascularis (e.g., Sue et al. 1998). In this study we sought specific

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evidence for IHC and OHC dysfunctions. Failure of the transduction mechanism in the IHCs was examined using the psychophysical measurement of tone threshold in noise (Moore et al. 2000; see below for details). Unlike the pure tone audiogram, this technique is sensitive to the presence of “dead regions” where transduction cannot occur. OHC function was assessed by psychophysical measurement of frequency selectivity. This is associated with active mechanisms in the OHCs (Dallos 1992; Nobili et al. 1998), and psychophysical estimates of OHC function obtained using forward masking (Oxenham and Plack 1997) or loudness recruitment (Moore and Glasberg 1997) are more highly correlated with a measure of frequency selectivity than they are with the absolute threshold (Moore et al. 1999).

SUBJECTS AND METHODS

Subjects

Eleven subjects with the A3243G mutation were identified from the Newcastle mitochondrial database. Mitochondrial DNA analysis, including measurement of the percentage level of the A3243G mutation in blood and skeletal muscle, was carried out as previously described (Moraes et al. 1993; Chinnery et al. 2000a). The 11 subjects with mitochondrial disorder and 10 control subjects with normal hearing underwent detailed psychophysical assessment to assess IHC and OHC functions. Patients with the A3243G mutation had mean hearing levels ranging from 1 to 85 dB (Table 1). Subjects were classified as normal or as having mild, moderate, or severe hearing loss, according to the mean loss measured at octave intervals from 250 Hz to 8 kHz (Table 1).

Evaluation of IHC and OHC functions

IHC dysfunction was assessed using a procedure designed to detect regions of the cochlea where transduction does not occur (Moore et al. 2000); such regions are referred to as dead regions. If IHCs do not function in a certain region of the cochlea, defined in terms of the characteristic frequencies of the surviving IHCs or neurons adjacent to that region, sound with frequencies usually detected by that region may still be detected due to “off-frequency listening” (the spread of excitation to neighboring regions of the cochlea). The standard pure-tone audiogram, therefore, lacks sensitivity and specificity in demonstrating dead regions; without masking, pure-tone thresholds can be near normal in regions where there is damage to IHCs, and markedly abnormal thresholds can occur in regions where there is no damage to IHCs.

In this study, dead regions were diagnosed using “threshold-equalizing noise” (TEN), designed to produce equal masked thresholds for normal subjects for all frequencies (Moore et al. 2000). The rationale behind the test is as follows: When the signal frequency falls in a dead region, the signal will be detected only when it produces sufficient basilar membrane vibration at a remote region in the cochlea where there are surviving IHCs and neurons. The amount of vibration at this remote region will be less than in the dead region, so the noise will be very effective in masking it. Thus, the signal threshold is expected to be markedly higher than normal.

The spectrum of the TEN was calculated in the following way: For normal-hearing subjects, the power of a sinusoidal signal, P_s , required to reach threshold in a broadband noise is given by

$$P_s = N_0 \cdot K \cdot \text{ERB} \quad (1)$$

where N_0 is noise power spectral density (intensity in a 1-Hz-wide band), K is the signal-to-noise ratio at the output of the auditory filter required for threshold, and ERB is the (normal value of the) equivalent rectangular bandwidth of the auditory filter in hertz (Patterson and Moore 1986). The value of N_0 as a function of frequency was chosen to render P_s a constant, taking into account the variation of K and the ERB with frequency (Moore et al. 1997). The noise level is specified as the level in a 1-ERB-wide band centered at 1 kHz. For normal-hearing listeners, the threshold of a sinusoidal signal in the TEN is approximately equal to the noise level/ERB, independent of overall noise level, provided that the noise is sufficiently intense to produce at least 10 dB of masking (Moore et al. 2000).

The TEN test has been validated by comparing results obtained using TEN with measures of psychophysical tuning curves (PTCs). When the signal frequency falls in a dead region, the tip of the PTC (the masker frequency at which the threshold is lowest) is shifted away from the signal frequency (Florentine and Houtsma 1983; Moore 1998; Thornton and Abbas 1980; Turner et al. 1983). Moore et al. (2000) found that, for signal frequencies where the PTC showed a shifted tip, the signal threshold in the TEN was usually 10 dB or more higher than the noise level/ERB (i.e., 10 dB or more higher than normal and outside the normal range). Therefore, this was taken as a criterion for defining a dead region.

To run the TEN test, the test signals and the noise were obtained from separate channels of a compact disc and fed to a GSI-16 audiometer fitted with TDH 50-P earphones. Absolute thresholds in dB SPL were determined between 250 Hz and 10 kHz (at 250 Hz, 500 Hz, 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz, 5 kHz, 6 kHz, 8 kHz, and 10 kHz). Masked thresholds were determined with noise at levels (in dB/ERB) that were

TABLE 1

Characterization of study population, dead region findings, and auditory filter width values^a

Subject	Age	Sex	Mean hearing loss (dB HL)	Duration deafness (years)	% A3243G (muscle)	Dead regions	ERB			
							500 Hz	1 kHz	2 kHz	4 kHz
Normal (<20 dB mean loss)										
I	34	M	1		4		0.18	0.16	0.13	0.14
B	40	F	7		32		0.19	0.22*	0.16	0.13
F	33	F	15		50		0.15	0.27*	0.30*	0.40*
Mild hearing impairment (21–40 dB mean loss)										
K	26	F	26		86	5 kHz, 6 kHz	0.17	0.14	0.27*	0.24*
H	63	F	29			4 kHz, 5 kHz	0.21*	0.28*	0.20	0.71*
J	31	F	27		73	5 kHz–10 kHz	0.23*	0.14	0.17	0.27*
Moderate hearing impairment (41–70 dB mean loss)										
G	37	M	41	15	85	250 Hz–6 kHz	0.18	0.24*	0.43*	0.23*
A	51	F	68	15	53	1 kHz, 2 kHz, 6 kHz	0.82*	0.39*	0.69*	>1.0*
Severe hearing impairment (>70 dB mean loss)										
C	59	F	74	30	76	250 Hz, 1 kHz–8 kHz	0.73*	0.42*	>1.0*	>1.0*
E	47	M	>76	Birth	87	500 Hz, 1 kHz, 1.5 kHz	>1.0*	0.90*	>1.0*	
D	43	F	>85	13	80	2 kHz, 4 kHz	>1.0*	0.84*	>1.0*	>1.0*
Mean control data (<i>n</i> = 11)										
Mean	43		7				0.18 (0.16–0.20)	0.16 (0.14–0.17)	0.16 (0.13–0.20)	0.16 (0.10–0.22)

^aHearing loss is expressed as the mean hearing level measured at octave intervals from 250 Hz to 8 kHz. Duration of loss refers to the duration of symptomatic loss. Control data ERB values given as a proportion of center frequency with 95% confidence intervals.

*Significantly different from control data (*p* < 0.05)

higher than the lowest absolute threshold measured at any frequency. Dead regions were defined as regions where the masked threshold was at least 10 dB above absolute threshold (the lowest curves shown in Fig. 1) and 10 dB above the nominal noise level per ERB (shown as horizontal lines in Fig. 1).

OHC function was assessed by estimating frequency selectivity, which depends on OHC function. Motility in the OHCs is responsible for the cochlea acting as an *active* nonlinear filter (Dallos 1992; Nobili et al. 1998). This produces sharper frequency selectivity than can be explained by the passive mechanical properties of the cochlear partition. Frequency selectivity was assessed by psychophysical measurement of the auditory filter width using the notched-noise method (Patterson and Moore 1986; Hartmann 1997). Essentially, this technique uses bandstop noise as a masker to force the subject to use the auditory filter centered on the spectral notch for detection of a sinusoid at that frequency. Notched-noise stimuli with varying notch width and constant rms level were created digitally by summing sinusoids spaced at 0.1-Hz intervals; the amplitudes of the component sinusoids were selected randomly from a Rayleigh distribution, and the phases were selected randomly from the range 0°–360°. These stimuli and a continuous pulsed sinusoid were recorded onto separate channels of a compact disc.

The outputs from the two channels of the compact disc were fed to the audiometer. Notched noise was presented at 70 dB SPL for subjects with normal hearing levels, 80 dB SPL for mild to moderate hearing loss, and 90 dB SPL for severe hearing loss. Thresholds for detecting the sinusoid were determined for notch widths (expressed as a proportion of center frequency) of 0, 0.1, 0.2, and 0.3. This procedure was carried out for center frequencies of 500 Hz, 1 kHz, 2 kHz, and 4 kHz.

At each center frequency, threshold as a function of notch width was fitted with a symmetrical rounded-exponential (roex) function of the form

$$W(g) = (1 + pg) \exp(-pg) \quad (2)$$

where *p* is the constant determining the degree of selectivity and *g* is the deviation from the center frequency of the filter divided by center frequency. The value of *p* was determined by using a function of this form to predict the threshold data using an iterative least-squares algorithm. The ERB of the filter for a specific individual (specified henceforth as a proportion of center frequency) was derived from the value of *p* as $4/p$.

One problem in interpreting the ERB values is that, for normal-hearing listeners, the ERB increases with

FIG. 1. Threshold data for 11 subjects with the A3243G mutation and for 10 control subjects. Shown are unmasked thresholds and thresholds in the presence of threshold-equalizing noise at levels determined by unmasked threshold. For the control data, the mean and 95% confidence intervals are shown. *-regions that meet the criteria for dead regions, ↑-unresponsive regions.

increasing noise level. Thus, comparisons across subjects are partially confounded by differences in test level. However, we believe that this had only a small influence on our results for two reasons: First, the change in ERB with a 20-dB change in masker level is relatively small in normal-hearing subjects (typically a factor of 1.3–1.5; see Glasberg and Moore 1990, 2000). Second, changes in the ERB with noise level are smaller for hearing-impaired than for normal-hearing subjects (Moore and Glasberg 1997).

Correlation of mutation load with hearing loss and auditory filter width

We previously demonstrated correlation between the hearing loss in the subjects with the A3243G mutation and that of subjects with mutation load measured in muscle (Chinnery et al. 2000a). Mutation load is the percentage of mitochondrial genes in which the given mutation is present in a given tissue; the percentage and can be different in different tissue. A similar correlation was sought in the current data set. Additionally, we assessed correlation between the width of the auditory filter (at 500 Hz, 1 kHz, 2 kHz, and 4 kHz) and the mutation load.

RESULTS

Dead region evaluation

None of the control subjects showed any dead regions and all showed masked thresholds with 30 and 60 dB/ERB noise that were invariant with frequency below 8 kHz (Fig. 1). Dead regions were demonstrated in eight subjects with mitochondrial disorder: subjects A, C, D, E, G, H, J, and K (Table 1, Fig 1). These subjects fell into 3 groups with respect to the presence of dead regions: subjects with normal thresholds without dead regions, subjects with mild hearing loss with high-frequency dead regions, and subjects with moderate or severe hearing loss with extensive dead regions. Two subjects with severe deafness (D and E) demonstrated frequency regions of complete unresponsiveness. Although these regions do not fulfill the formal definition of a dead region given above since it was not possible to obtain a masked threshold, they almost certainly reflect extensive contiguous IHC damage such that even off-frequency listening cannot occur.

Auditory filter width

The relative auditory filter widths (ERB/center frequency) for the control subjects at 500 Hz, 1 kHz, 2 kHz, and 4 kHz were invariant with frequency (Table

FIG. 2. Variation of auditory filter width (expressed as a proportion of center frequency) with frequency for subjects with the A3243G mutation. The mean and standard error for ten control subjects are shown for comparison. The four subjects with extensive dead regions and auditory filter widths greater than that attributable to the passive cochlear partition (subjects in bottom row of Fig. 1) are not represented.

1, Fig 2). The values between 0.1 and 0.2 are consistent with those previously reported for normal subjects (Moore et al. 1999). Data for some of the subjects with mitochondrial disorder show increased auditory filter widths at all frequencies, and there was a tendency for more subjects to show abnormal widths at higher frequencies (Table 1, Fig 2). Two of the three subjects with normal absolute thresholds demonstrated slightly increased filter widths. Every subject with mild, moderate, or severe hearing loss demonstrated abnormal filter widths, particularly at high frequencies. Certain moderately or severely hearing-impaired subjects showed very high relative filter widths, i.e., > 1 dB. This happens when the signal threshold does not decrease, or it even increases, with increasing notch width. As the frequency selectivity of the passive mechanism in the cochlea (when the OHCs are nonfunctional) leads to filter widths < 1 dB (Moore and Glasberg 1997), widths > 1 dB probably reflect a dead region at the signal frequency. Consistent with this confounding effect of dead regions, very-large-width estimates often occurred for frequencies where the TEN test demonstrated dead regions.

Figure 3 shows the variation of auditory filter widths with hearing loss in the patient group and a systematic relationship similar to that previously demonstrated (Moore et al. 1999). The presence of a clear relationship between auditory filter widths and the degree of hearing loss is consistent with a substantial proportion of the hearing loss having an OHC basis. When filter widths are plotted as a function of the calculated hearing loss attributable to IHC and OHC damage (for

FIG. 3. Variation of auditory filter width with hearing loss for subjects with the A3243G mutation. Auditory filter widths greater than that attributable to the passive cochlear partition are not represented.

subjects without dead regions), a systematic relationship is shown for the OHC component of loss only (Moore et al. 1999). Although estimated filter widths > 1 dB can be attributed to IHC damage, Figure 3 shows a clear relationship between filter widths and degree of hearing loss even when high values of filter width are ignored.

Correlation of mutation load with hearing loss and auditory filter width

Table 1 shows that all of the subjects with hearing impairment had percentage mutation loads greater than 50%. Dead regions were demonstrated in all of these subjects and tended to be more extensive in subjects with greater mutation load. A correlation with the mutation load was demonstrated for the mean hearing loss (Spearman's $\rho = 0.64$, $p < 0.05$, one-tailed) and for the hearing loss at 4 kHz (Spearman's $\rho = 0.60$, $p < 0.05$, one-tailed). There was no correlation with mutation load at the $p < 0.1$ level for the auditory filter width at any of the four frequencies tested.

DISCUSSION

In this study we addressed the mechanism of cochlear damage in a common mitochondrial disorder. Cochlear hearing loss can arise from IHC dysfunctions and OHC dysfunction. IHC dysfunction leads to decreased efficiency of the transduction of the basilar membrane motion into neural activity, while OHC dysfunction produces less basilar membrane motion for a given sound input. In models such as that of Moore and Glasberg (1997), hearing loss can be partitioned

into that caused by IHC damage and that caused by OHC damage. In this study we examined *in vivo* phenomena that are assumed to be specific to the IHCs and OHCs in order to better characterize the cochlear lesion in this mitochondrial disease. Such characterization has implications for the treatment of deafness in mitochondrial disorder. We discuss here the mechanism of damage suggested by our results and its practical implications.

Because activity in the auditory nerve arises via the IHCs, severe damage to IHCs can produce regions where no transduction is possible. Such dead regions will not occur with OHC damage alone. Dead regions were found at high-frequency (basal) regions of the cochlea in subjects with mild hearing loss and more extensively in subjects with severe hearing loss. Deficits in transduction at specific frequencies are difficult to explain by stria dysfunction, as an alternative indirect mitochondrial mechanism; the endolymphatic potential generated by the stria is likely to affect all the hair cells in a similar fashion. Moreover, the absence of transduction in certain regions is most likely to reflect the selective *death* of IHCs, which again is difficult to explain on the basis of stria dysfunction. Therefore, these data strongly suggest IHC damage as a primary effect of the mitochondrial mutation. Several subjects also show high thresholds in noise over a wide frequency range without meeting criteria for the presence of dead regions. This suggests decreased "detection efficiency" in regions where the IHCs are dysfunctional but not completely dead.

OHC dysfunction produces deficits in nonlinear processing in the cochlea, in addition to elevation in absolute threshold. Such nonlinear processes include frequency selectivity and compressive input-output functions on the basilar membrane (Moore et al. 1999); these processes depend little if at all on IHC function. In this study, we psychophysically assessed frequency selectivity for use as a measure of OHC function. The increased auditory filter widths demonstrated in the patient groups are consistent with dysfunction of the active motile mechanism in the OHC membrane. That mechanism is thought to be driven by changes in transmembrane charge, independent of ATP or calcium (Nobili et al. 1998). Although the active motile mechanism is not *immediately* dependent on ATP generation, maintenance of the integrity of the OHCs and the motility mechanism in the membrane will be. It is also possible that if death of OHCs were to occur, this could affect not only the active mechanism but also the passive mechanical properties of the cochlear partition. Thus, the most parsimonious explanation for the auditory filter data is OHC dysfunction or damage as a primary consequence of the mitochondrial respiratory chain defect.

These data show that dead region determination

and auditory filter width measurement are sensitive as well as specific measures of cochlear damage in this mitochondrial disorder. We have demonstrated dead regions in cases where there was only a mild hearing loss at the test frequency. This can happen when the test frequency is *just inside* a dead region, and it indicates that the conventional audiometric threshold can underestimate the severity of damage at a particular frequency. In some cases, auditory filter widths were shown to be somewhat abnormal even in subjects defined as having normal absolute thresholds. This may reflect a partial dissociation of frequency selectivity and sensitivity, with the former being a more sensitive indicator of OHC damage (Moore et al. 1999).

Dead regions and auditory filter widening have been shown to occur at different levels of hearing loss and mutation load. Dead regions have been detected in subjects with mean hearing levels greater than 20 dB and mutation loads of greater than 50%. Auditory filter widening has been shown to occur, even in subjects with hearing levels defined as normal and mutation loads of 50% or less. This may reflect the operation of a stochastic process affecting both IHCs and OHCs with equal probability, where the threshold for the demonstration of the psychophysical effects observed is different. We feel it is reasonable to suggest that the threshold for showing IHC death may be higher than that for the demonstration of OHC dysfunction not requiring cell death. Alternatively, it is possible that the mitochondrial dysfunction in this disorder has a greater tendency to affect the OHCs. This might occur if the probability of involvement of any hair cell is fixed, by virtue of the fact that there are four times as many OHCs as IHCs. If structural cell damage is taken to correlate with the degree of metabolic insult, then a pathological study of the cochlea of a single patient with moderate hearing loss is consistent with greater insult to the OHCs (Yamasoba et al., 1999). Light microscopy showed only occasional damage to IHCs and more frequent damage to OHCs.

CONCLUSIONS

This study has provided evidence for both IHC dysfunction and OHC dysfunction in a common mitochondrial disorder. The fact that the deficits occurred selectively over specific frequency ranges is not consistent with a general effect of stria vascularis dysfunction, often emphasized in the mitochondrial literature. Further work on other mitochondrial disorders is required to investigate whether this is a typical pattern of cochlear damage. In view of the large numbers of genetic and acquired mitochondrial disorders that may affect the cochlea, we do not feel there are strong *a priori* grounds for suggesting a universal mechanism.

The methods described here would allow characterization of other mitochondrial disorders affecting the cochlea, allowing demonstration of a dissociation between IHC dysfunction and OHC dysfunction.

This study has practical implications for the investigation and treatment of mitochondrial deafness. We have used a simple practical procedure for the diagnosis of dead regions in the cochlea. Dead regions were common in even mildly hearing impaired subjects, and amplification of frequencies well inside these frequency regions is likely to be ineffective (Moore 1998). We suggest that dead region determination is a useful procedure in subjects with deafness due to mitochondrial disease. The presence of extensive dead regions may be a factor in favor of cochlear implantation in these subjects.

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