Clinical Neurophysiology 119 (2008) 1028–1041

www.elsevier.com/locate/clinph

Neural and receptor cochlear potentials obtained by transtympanic electrocochleography in auditory neuropathy ☆

Rosamaria Santarelli [a,*], Arnold Starr [b], Henry J. Michalewski [b], Edoardo Arslan [a]

[a] *Department of Medical and Surgical Specialities, Service of Audiology and Phoniatrics, University of Padua, Via Giustiniani 2, I-35128 Padua, Italy*
[b] *Department of Neurology, University of California, Irvine, CA, USA*

Accepted 26 January 2008

Abstract

Objective: Transtympanic electrocochleography (ECochG) was recorded bilaterally in children and adults with auditory neuropathy (AN) to evaluate receptor and neural generators.
Methods: Test stimuli were clicks from 60 to 120 dB p.e. SPL. Measures obtained from eight AN subjects were compared to 16 normally hearing children.
Results: Receptor cochlear microphonics (CMs) in AN were of normal or enhanced amplitude. Neural compound action potentials (CAPs) and receptor summating potentials (SPs) were identified in five AN ears. ECochG potentials in those ears without CAPs were of negative polarity and of normal or prolonged duration. We used adaptation to rapid stimulus rates to distinguish whether the generators of the negative potentials were of neural or receptor origin. Adaptation in controls resulted in amplitude reduction of CAP twice that of SP without affecting the duration of ECochG potentials. In seven AN ears without CAP and with prolonged negative potential, adaptation was accompanied by reduction of both amplitude and duration of the negative potential to control values consistent with neural generation. In four ears without CAP and with normal duration potentials, adaptation was without effect consistent with receptor generation. In five AN ears with CAP, there was reduction in amplitude of CAP and SP as controls but with a significant decrease in response duration.
Conclusions: Three patterns of cochlear potentials were identified in AN: (1) presence of receptor SP without CAP consistent with pre-synaptic disorder of inner hair cells; (2) presence of both SP and CAP consistent with post-synaptic disorder of proximal auditory nerve; (3) presence of prolonged neural potentials without a CAP consistent with post-synaptic disorder of nerve terminals.
Significance: Cochlear potential measures may identify pre- and post-synaptic disorders of inner hair cells and auditory nerves in AN.

Keywords: Pre- and post-synaptic; Auditory nerve synchrony; Adaptation

1. Introduction

Auditory neuropathy (AN) is a disorder of auditory nerve function (Starr et al., 1996) characterized by hearing deficits affecting auditory perceptions dependent on temporal, but not intensity or high frequency spectral cues (Zeng et al., 2005). Adult patients typically complain of difficulty in understanding speech especially in the presence of noise and the extent of their speech comprehension is impaired out-of-proportion to the pure tone hearing loss (Sininger and Oba, 2001, for review). Clinical criteria for diagnosis include absence or marked abnormality of auditory brainstem potentials (ABRs) beyond that expected for the hearing loss, preserved cochlear receptor outer hair cell activities (otoacoustic emissions [OAEs] and/or cochlear microphonics [CMs]), and absent acoustic middle ear muscle reflexes (Starr et al., 1996; Berlin et al., 2005). The disorder has a wide range of etiologies (e.g., hereditary, infectious, toxic–metabolic, immunological, developmen-

☆ The work was done at the University of Padua, Service of Audiology and Phoniatrics.

* Corresponding author. Tel.: +39 0422 328286; fax: +39 0422 322351.
E-mail address: rosamaria.santarelli@unipd.it (R. Santarelli).

1388-2457/$34.00
doi:10.1016/j.clinph.2008.01.018

tal, etc.) and occurs in all age groups (Starr, 2001, for review).

The particulars of the disrupted auditory nerve activity in this disorder are not known. However, it is known that AN accompanies disorders of the auditory nerve (post-synaptic or Type I AN; Starr et al., 2003), and disorders of inner hair cells and their synapses with auditory nerve terminals (pre-synaptic or Type II AN; Starr et al., 2004; Rodriguez-Ballesteros et al., 2003). Temporal bone analyses from patients with Type I AN (Spoendlin, 1974; Hallpike et al., 1980; Starr et al., 2003) reveal loss of auditory ganglion cells and their processes with remaining axons and dendrites showing myelin and axonal abnormalities. The inner and outer hair cells (IHCs, OHCs) appeared normal. On the basis of these findings the expected physiological effects would be absence or marked abnormalities of ABRs due to loss of auditory nerve fiber activity and altered neural synchrony accompanying abnormal conduction in remaining fibers. Activities of hair cells including otoacoustic emissions, the faint sounds emitted by OHCs in response to acoustic stimulation (Probst et al., 1991) as well as cochlear microphonics (CM) generated by both IHCs and OHCs, would likely be preserved.

Temporal bone analyses from patients with AN due to disordered IHC functions (Type II AN) as might accompany mutations of otoferlin gene (Varga et al., 2003; Rodriguez-Ballesteros et al., 2003) have not yet been reported. The gene mutation is thought to adversely affect neurotransmitter release and absence of ABRs in this disorder is consistent with a functional loss of auditory nerve input.

ABRs are limited in providing detailed information of cochlear nerve and hair cell activities since the recording electrodes are placed at a distance from these generators. Details of cochlear potentials including both receptor (SP, CM) and auditory nerve activities (CAP) can be more effectively evaluated by near-field recordings with an electrode placed on the cochlear bony promontory known as transtympanic electrocochleography (ECochG) (Eggermont and Odenthal, 1974a). Indeed the amplitude of the compound action potential (CAP) and summating potentials (SP) reflecting hair cell activation recorded by a needle electrode on the promontory wall can be as much as 30-fold larger than auditory nerve potentials recorded as Wave I of the far-field ABRs. When utilizing click stimulation the neural fibers in the basal turn are activated at short latency and are the major contributors to the recorded CAP (Eggermont, 1976; Kiang et al., 1976). The SP is typically not detected in the ABRs.

Recordings from IHCs and OHCs in experimental animals have identified intracellular potential changes accompanying acoustic stimulation that contribute to the SP and CM receptor potentials. CM is believed to result from the vector sum of the extracellular components of receptor potentials arising almost exclusively in OHCs with minor or no contribution from IHCs (Dallos and Wang, 1974). On the basis of the estimated length constant of this extracellular activity, the CM recorded at the promontory is deemed to arise from basal portions of the cochlea, while apical regions make almost no contribution to its generation (Withnell, 2001). SP is a slow sustained potential whose polarity is highly dependent on the frequency and intensity of the stimulus (Eggermont, 1976; Ferraro et al., 1994). The SP recorded from the round window in experimental animals is believed to be primarily generated by IHCs of the basal portion of the cochlea with a minor contribution arising from OHCs of both the basal and apical turns (Zheng et al., 1997; Durrant et al., 1998).

In this study we evaluated auditory nerve (CAP) and receptor potentials (CM, SP) recorded by transtympanic ECochG in eight children and young adults with AN. We hypothesized that both post-synaptic neural and pre-synaptic receptor abnormalities would be identified reflecting specific cochlear physiological deficits accounting for disrupted auditory nerve activities in AN.

2. Methods

2.1. Subjects

We studied eight subjects with AN ranging in age from 5 to 48 years (mean = 21.1 years). Details of their clinical and neurological findings, diagnoses, and laboratory measures are included in Table 1. All patients had absence or severe abnormalities of the ABRs with preserved OAEs. The etiologies of the auditory nerve disorders were hereditary (3 subjects), immunological (3 subjects), degenerative (1 subject), and congenital (1 subject).

The patients' cochlear functions were evaluated at the University of Padua Service of Audiology and Phoniatrics by bilateral transtympanic recordings methods as part of their audiological evaluation of hearing disorders. These patients were referred for ECochG to define threshold for CAP as their ABR results were inconclusive. There have been approximately 200 patients tested by this method over the past 7 years; typically children with prematurity, hypoxia and hyperbilirubinemia who had been admitted to NICU, children with delayed speech development accompanying autism or mental retardation. In some of the children the transtympanic results did not show objective evidence of a peripheral auditory disorder. Therefore, the ECochG data from 16 subjects with "normal" thresholds and latency of CAP served as "controls" for comparison with the patients with AN. The age of the controls ranged from 1 to 7 years with a mean of 3.8 years. There was only one control subject which was younger than 2 years. While the controls were considerably younger than AN subjects, we do not consider this variable to be a major limitation. First, the latency of ABR wave I evaluated by narrow band noise techniques is comparable to adult values by 1–2 years of life (Eggermont et al., 1991). Also measures of adaptation to rapid stimulus rates show minor interactions of rate and development after 1 year of age (Salamy et al., 1978; Lasky et al., 1992).

Table 1
Clinical data

Subjects#	#1	#2	#3	#4	#5	#6	#7	#8
Clinical								
Gender	F	F	M	F	M	F	F	M
Age tested	21	48	24	5	6	17	19	19
Deaf onset	9	28	23	5	5	16	14	14
Illness signs	Vision	Vision	Hypotonia	Vision	Skin	ANA	Raynaud	Platelet
Age onset	9	9	<1	4	1	16	14	Birth
Etiology	Genetic	Genetic	Genetic	Unknown	Immune	Immune	Immune	Congenital
Audiology	AD/AS							
Hearing loss	Mild	Mild/Mod	Mild	Mod/Mild	Mod	Mod	Prof/Sev	Prof/Mild
Slope	Rising	Falling	Flat	Rising	Flat	Rising	Falling	Flat
PTA dB HL	35/40	40/50	35/30	50/40	70 FF	50/45	105/80	110/30
Speech %	0/0	0/0	50/50	NT/NT	NT/NT	30/40	0/0	0/0
After CI	80/0						70/0	
OAEs	N/N	N/N	N/N	N/N	ABS/N	N/N	N/N	N/N
Stap. reflexes	ABS/ABS	ABS/ABS	110/110	ABS/ABS	ABS/ABS	ABS/ABS	ABS/ABS	ABS/ABS
ABR	ABS/ABN	ABS/ABN	ABN/ABN	ABS/ABS	ABS/ABS	ABS/ABS	ABS/ABS	ABS/ABS
Gaps[a] (ms)	77	164	48	100	NT	NT	NT	NT
Neurology								
Ankle reflex	N	N	ABS	ABS	ABS	N	N	N
Optic nerve	Atrophy	Atrophy	Atrophy	Atrophy	N	N	N	N
Eye movements	N	N	ABN	N	N	N	N	N
Vibration	N	N	ABS	ABS	NT	N	N	NT
Muscle	N	N	N	Atrophy	NT	N	N	N
Gait	N	N	Ataxia	Ataxia	NT	N	N	N
Procedures								
NCV	N	N	Slow	Slow	NT	NT	NT	NT
ENG	NT	ABN	NT	NT	NT	N	N	NT
MRI	N	N	N	N	N	N	N	N

ANA, anti-nuclear antibody; AD/AS, right ear/left ear; Mod, moderate; Sev, severe; Prof, profound; PTA, pure tone average; FF, free-field; Speech %, percent of speech recognition; NT, not tested; CI, cochlear implant; OAEs, otoacoustic emissions; N, normal; Stap. reflexes, Acoustic reflexes of stapedius muscles; ABS, absent; ABR, auditory brainstem response; ABN, abnormal; Gaps: threshold in ms for detecting brief silent periods in noise; NCV, nerve conduction velocity; ENG, electronystagmography; MRI, magnetic resonance imaging.

[a] Testing was free-field.

2.2. Audiological studies

2.2.1. Pure tone audiometry

We tested air conduction thresholds at octave frequencies from 125 to 8000 Hz and bone conduction thresholds at octave frequencies from 250 to 4000 Hz (Grason-Stadler GSI 61 audiometer) in a sound-attenuated room. The degree of hearing impairment was defined by the pure tone average (PTA) threshold levels at 0.5, 1, 2, and 4 kHz. Hearing loss was classified as mild (PTA 21–40 dB HL), moderate (PTA 41–70 dB HL), severe (PTA 71–95 dB HL) and profound (PTA > 95 dB HL) (European Concerted Action Project on Genetics on Hearing impairment, 1996).

Tympanometry and acoustic reflex thresholds (both ipsilateral and contralateral to the stimulated ear) were measured with an impedance Grason-Stadler GSI 33 audiometer. Acoustic reflexes were considered absent when no response was found at intensities higher than 110 dB HL.

2.2.2. Speech audiometry

Speech tests included the evaluation of the reception threshold and word intelligibility, which were obtained by utilizing an Italian word list for adults (Bocca and Pellegrini, 1950) or children (Rimondini and Rossi Bartolucci, 1982) at increasing stimulus intensities.

2.3. Auditory brainstem responses (ABRs)

Potentials were recorded from scalp electrodes (vertex to mastoid ipsilateral to the stimulated ear) to 2000 trials of alternating polarity clicks presented monaurally using a TDH-50 transducer earphone at a maximum intensity of 125 dB p.e. SPL (corresponding to 90 dB nHL, referred to the psychoacoustical threshold of normally hearing subjects). The filter settings of the amplifier were set between 5 and 4000 Hz.

2.4. Distortion product otoacoustic emissions (DPOAEs)

DPOAEs were obtained by means of the ILO-92 OAE system (Otodynamics). During DPOAEs recordings the primary tones f1 and f2 were presented at 70 dB p.e. SPL and the f2/f1 ratio was kept at 1.21. The frequency was changed in 1/4 octave steps from 708 to 6299 Hz. Four

spectral averages were summed for each stimulus condition.

2.5. Transtympanic recordings: electrocochleography (ECochG)

Six AN subjects were tested under local anesthesia (lidocaine, 10%) and two under general anesthesia (sevoflurane). The control subjects had all been tested under general anesthesia. A sterile stainless steel needle electrode (0.7 mm), insulated except for the tip, was passed through the tympanic membrane to contact the promontory wall with the aid of an operating microscope. Stimuli consisted of rarefaction and condensation 0.1 ms clicks, separately delivered in free-field by means of two high frequency drivers (Electro-Voice DH1A/2MT 16 Ω) mounted on a single polyurethane horn (Electro-Voice HP420) with a maximum intensity of 120 dB p.e. SPL (corresponding to 90 dB nHL, referred to the psychoacoustical threshold of normally hearing subjects). The stimulus was calibrated in a free-field by means of a Brüel and Kjaer 4165 microphone (mounted on an 800 B Larson–Davis sound level meter) placed at 1 m from the base of the polyurethane horn, which corresponded to the distance of the patient's ear from the horn. The procedure of comparing the peak-to-peak amplitude of the click to the peak-to-peak amplitude of a 2 kHz tone was utilized to calibrate the click level (p.e. SPL).

Condensation and rarefaction clicks were delivered separately for seven intensity levels from 60 to 120 p.e. SPL. The stimulus paradigm used in six AN patients (12 ears) and in 16 controls (23 ears) consisted of an initial click, followed 15 ms later by ten clicks with an inter-stimulus interval of 2.9 ms (the click train and responses from a control subject are shown in Fig. 5). This sequence was repeated every 191 ms. This stimulus paradigm was used to help distinguish between CAP and SP potentials by taking advantage of different effects of adaptation induced by high stimulation rates on these responses (Eggermont and Odenthal, 1974b). In the remaining AN subjects (#4, 8) and controls a repetitive click stimulation with an inter-stimulus interval of 91 ms was performed.

The potentials were differentially amplified (50,000 times), filtered (5–8000 Hz) and digitized (25 μs) for averaging (500 trials).

The procedure of averaging the responses evoked separately by condensation and rarefaction clicks was applied to extract the CAP with the superimposed SP. This procedure is illustrated in Fig. 1. The top panel contains superimposed averages to condensation and rarefaction clicks showing phase-reversed CMs intermixed with negative in-phase SPs and CAPs occurring in the first 2 ms. In the second panel, the condensation and rarefaction responses are averaged to attenuate out-of phase CMs revealing the in-phase SP and CAP. Attenuation of CMs was often incomplete when stimulus intensities were higher than 110 dB p.e. SPL. The spectral energy of the CM was maximum between 1500 and 3000 Hz so that a low pass digital filter (2000 Hz, 12 dB/octave) was employed to attenuate the residual CM, if needed. The third panel displays the difference waveform between the condensation response containing CM, SP, and CAP and the derived response in the second panel containing SP and CAP to show out-of-phase CM alone.

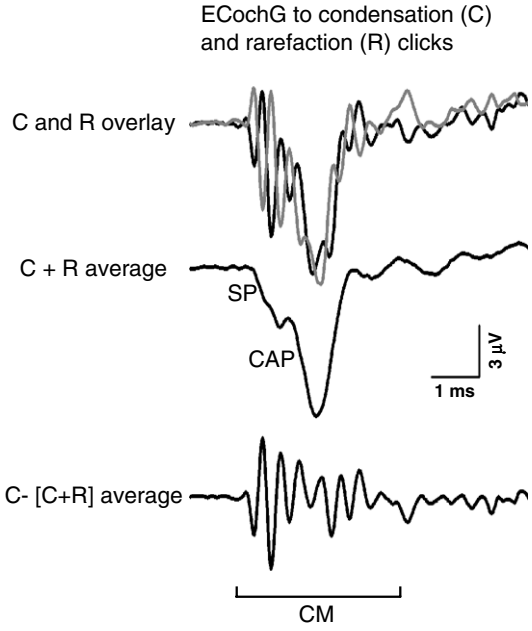

Fig. 1. Procedure utilized to separate the cochlear microphonic (CM) from the compound action potential (CAP) and summating potential (SP). The ECochG responses to condensation (C) and rarefaction (R) clicks recorded from one control ear at 120 dB p.e. SPL are superimposed in the top panel. The CAP together with the superimposed SP was obtained by averaging the recordings to condensation and rarefaction clicks (C+R average) through the attenuation of the out-of phase cochlear microphonics (middle panel). The CM shown in the lower panel results from subtracting the (C+R) average from the ECochG response to condensation clicks.

2.6. ECochG response measures

Latency was defined relative to the onset of the CM in milliseconds (ms). Amplitude was computed relative to the period 1 ms before CM onset in microvolts (μV).

In controls SP appears as a small shoulder preceding the CAP. We defined latency of SP at the initial negative deflection arising from baseline after CM onset, CAP onset at the negative potential arising from the SP, CAP peak at maximum negative potential, CAP end at the return of the CAP to baseline, CAP duration by the difference between CAP onset and CAP end. An identification of a separate SP and CAP was possible in all control ears while they could not often be distinguished from each other in AN patients (see Section 3). We therefore considered SP and CAP as a single event, the SP/CAP, and defined the SP/CAP onset at the initial negative deflection arising from baseline, SP/CAP peak at maximum negative potential

and SP/CAP end at the return to baseline. The values contained in the text and tables indicate means ± standard error.

2.7. Adaptation of ECochG potentials

Adaptation for both control and AN subjects with distinct SP and CAP was examined at the latency of each individual's peak amplitude of SP and CAP, respectively. Adaptation for AN subjects without distinct SP and CAP was evaluated at the average peak latencies of control SP (0.7 ms) and control CAP (1.4 ms). This method allowed us to test (a) whether adaptation in AN with SP and CAPs were similar to controls and (b) whether adaptation of ECochG potentials in AN without distinct SP and CAP was consistent with neural and/or receptor generation. Adaptation was defined as the difference in durations and amplitudes to the first (#1) and last click (#11) in the stimulus train: the former expressed as absolute difference in ms; the latter expressed as a percentage change relative to the initial click.

2.8. Statistical evaluation

Analysis of variance procedures (ANOVA) for repeated measures were used to analyze the measures of SP/CAP onset, peak latency, duration, amplitude, and CM amplitude. Separate three-factor ANOVAs with factors of group (AN vs. controls), ear stimulated (right vs. left), and stimulus intensity (seven levels between 60 and 120 dB) were used to evaluate latency, amplitude, and duration measures. Post hoc tests involving multiple comparisons (e.g., differences among intensity levels) were conducted with the Tukey–Kramer procedure. The effects of adaptation used *t*-tests to examine separately latency, amplitude, and duration changes of the response to the initial (#1) and last click (#11) of the stimulus train in controls. The level of significance was set at $p < 0.05$ for all tests.

3. Results

3.1. Clinical features

Table 1 contains clinical, audiological, and neurological data from the eight AN patients ordered according to etiology which is diverse in AN (Starr et al., 2000). The disorder was genetic in three (#1–3), degenerative in one (#4), immunological in three (#5–7), and congenital in one (#8). There was a neuropathy of optic nerves in four (#1–4), of peripheral nerves in three, (#3–5), and both optic and peripheral nerves in two (#3,4). A hearing impairment was the presenting manifestation of the illness in two (#6,7), and an associated finding in the other six.

Subjects #1 and 2 were mother and daughter. Both developed visual problems while in elementary school. Speech comprehension impairment was recognized in the mother when she was 28 and in the daughter shortly after the onset of the visual problems. Subject #3 had hypotonia at birth and developed visual impairments as an infant and a hearing loss as an adult (age 24). Subject #4 had both auditory and visual problems at the age of 4 while peripheral neuropathy appeared 2 years later. The three subjects (#5–7) with an autoimmune etiology had diverse syndromes including scleroderma (#7), an unspecified immune disorder (#6) with abnormal anti-nuclear antibody (ANA) (>1:160, normal < 1:40) identified at onset of deafness (age 17) while subject #5 with immunological disorder had hearing loss developing at age 5 during a subacute illness marked by pancytopenia and dermatitis. He had absence of deep tendon reflexes and urinary incontinence. He died at age seven. Subject #8 had a congenital disorder (Kasabach Merritt syndrome) manifested by thrombocytopenic purpura that improved at 10 years of age. Four years later there was the gradual onset of hearing impairment.

3.2. Audiological and neurological measures

Audiological evaluations were made within 4 years of the onset of their hearing problems in all but the two patients (#2,8) who were tested 10–20 years after the onset of the hearing impairment. Hearing loss varied widely ranging from mild to profound. Speech comprehension was affected more than would be expected in subjects with mild to moderate threshold elevation. All but one subject (#3) had absent middle ear muscle acoustic reflexes and that subject had reflexes only at high intensity at one of the four tests. OAEs were present bilaterally in seven and unilaterally in one (#5). ABRs were absent bilaterally in five, showed a low amplitude and delayed Wave V in two (#1, 2), and a normal latency Wave I with a delayed Wave V in one subject (#3).

Thresholds for gap detection tested in free-field at "comfortable" loudness levels were abnormally elevated in the four tested subjects (48–164 ms, the upper limit of naïve normal listeners is 7 ms, Zeng et al., 2005).

Neurological examination showed optic atrophy bilaterally in four (#1–4), clinical peripheral nerve involvement in three (#3–5) with at least one of the following nerve abnormalities (loss of tendon reflexes, loss of vibration sense in toes, slowed nerve conduction), gait ataxia in two (#3,4), and nystagmus in one (#3). Brain MRIs were normal in all.

3.3. Auditory nerve and receptor potentials

All patients showed CMs of normal or enhanced amplitude. CAPs could be separately identified from the SP in 5/16 ears. In 7 out of the remaining 11 ears the ECochG response consisted of a broad negative deflection which was significantly reduced in amplitude, increased in peak latency, and prolonged in duration compared to controls.

ECochG recordings from a control and AN subject #6 are shown in Fig. 2 as a function of signal intensity. The cochlear microphonics (top panels), displayed at the same gain are not significantly different between AN and control. The lower panels display the SP and CAP as a function of

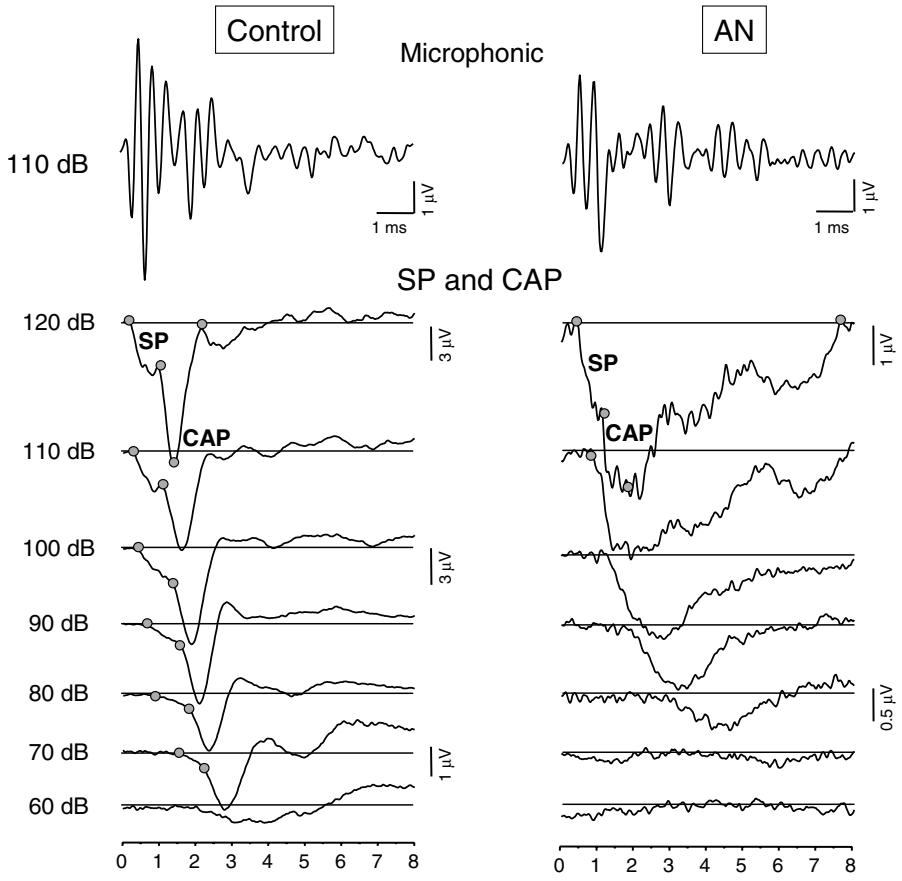

Fig. 2. Receptor potentials (CM, SP) and compound action potential (CAP) obtained from both control and AN patient (#6, left ear). The upper panel reports the cochlear microphonics recorded at 110 dB p.e. SPL at the same gain in control and AN subject. The lower panel reports the CAP with the superimposed SP at decreasing stimulation intensities from 120 to 60 dB p.e. SPL. Note the decrease in amplitude and the broadening in duration of the neural response obtained from AN subject compared to control. At threshold, the ECochG potentials from both AN and control have similar form.

signal intensity at different gains. In the control, the negative SP begins shortly after CM (left panels in Fig. 2). The SP onset latency lengthens and the SP peak amplitude diminishes as stimulus intensity is reduced. A separate SP and CAP cannot be defined at threshold intensity (60 dB). The latency of CAP onset, the subsequent CAP peak, and the return of CAP to baseline becomes progressively delayed as signal intensity decreases. CAP duration is relatively constant at suprathreshold intensities (2.01 ± 0.06 ms at 120 dB p.e. SPL) but broadens at low stimulus intensities to 2.97 ± 0.13 ms at threshold (60 dB p.e. SPL). There are several differences of the ECochG responses in AN (right panels in Fig. 2). The amplitude of the potentials is reduced and the CAP can only be distinguished from SP at 120 dB and at that intensity the response appears as a broad plateau slowly returning to baseline by 8 ms. A separate SP and CAP cannot be identified at lower stimulus intensities.

Fig. 3 reports the responses to 110 dB p.e. SPL clicks from eight controls and eight AN subjects, using the ear of each subject having the highest amplitude response. The traces begin 1 ms prior to the onset of the CM indicated by the arrows on the time base below. Note the presence of a broad potential in several AN subjects. In 5 cases (Table 4) this potential persisted as long as 7–12 ms compared to control durations (mean 2.22 ± 0.07 ms, range 1.53–3.40 ms at 110 dB p.e. SPL). A separate CAP (circle) could be distinguished from SP only in two AN ears.

Table 2 reports the CM amplitudes measured at 120 dB p.e. SPL together with the presence/absence of CAP (CAP threshold) and ABR Wave V in each AN ear. CM amplitudes were within control values except for two AN patients (#3, 4) who showed abnormally elevated amplitudes in their right ear. CAP could be distinguished from SP only in five AN ears and this was at high stimulation intensities in subjects #4 and 6 and from 120 to 60 dB p.e. SPL in subject #3. In the remaining ears the ECochG response took the appearance of a negative deflection (SP/CAP) without distinction between SP and CAP. The presence of the ABR Wave V was independent of CAP identification.

Since the distinction between SP and CAP could only be made for some AN ears, we considered the whole response as a single event (SP/CAP) to compare onset, duration, peak latency and amplitude measures between AN and controls. Ears showing severe-to-profound hearing loss (both ears of subject #7, right ear of subject #8) were not included in the SP/CAP analyses due to the expected absence of the neural response at very low sensation levels (Aran et al., 1971;

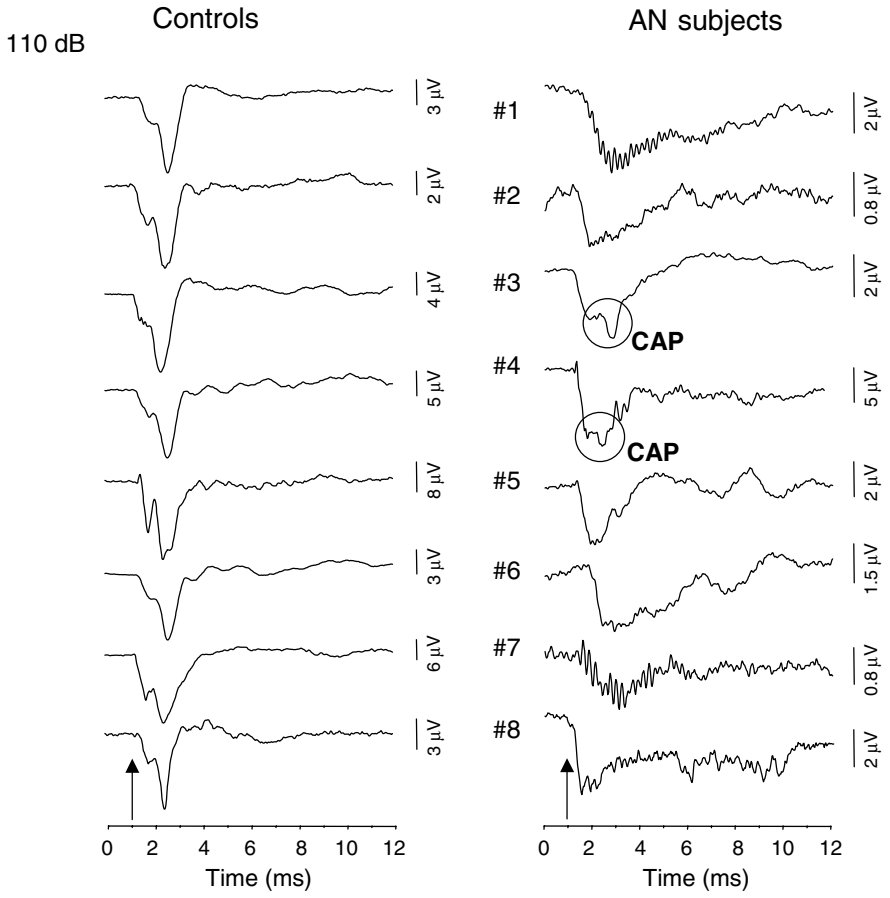

Fig. 3. Summating potential (SP) and compound action potential (CAP) recorded from eight controls (left panel) and AN subjects (right panel) to 110 dB p.e. SPL clicks. The ears with the highest response amplitude are reported for each AN patient. CAP is clearly distinguishable from the SP in controls while it can be identified only in two AN ears (circle). In the remaining AN ears the response took the appearance of a broad negative deflection where CAP and SP cannot be separately identified. Arrows at the bottom indicate CM onset.

Schoonhoven et al., 1999). Thirty-two control and 13 AN ears were included in the SP/CAP analyses.

The means and standard error of CM amplitude (16 AN ears) and SP/CAP onset latency, peak latency, duration, and peak amplitude are plotted as a function of signal intensity in Fig. 4 for both control and AN subjects. Table 3 summarizes ANOVA results including *F*-values and significance levels for SP/CAP and CM measures.

SP/CAP onset latency was delayed as stimulus intensity decreased for both control and AN groups. While no overall group effects were indicated, there was a significant group by intensity interaction (Fig. 4A). Post-tests indicated that onset latencies were significantly delayed in the AN group compared to controls at 100, 90, and 80 dB.

SP/CAP peak latency lengthened significantly as stimulus intensity decreased for both control and AN groups with a significant main effect for group (AN > controls). A significant group by intensity interaction was indicated for peak latencies (Fig. 4B). Latencies were prolonged for AN subjects between 60 and 100 dB compared to controls; no latency differences at 110 and 120 dB were found between the two groups.

SP/CAP duration was longer for AN subjects than controls between 60 and 120 dB (Fig. 4C). The differences were significant for group and intensity by group while no significant effect was found for intensity. SP/CAP durations lengthened as stimulus levels decreased only for controls ($F = 10.92$, $P < 0.001$, df = 6).

SP/CAP peak amplitude increased with stimulus intensity for both groups but the changes with intensity were larger for the controls than AN subjects. The differences were significant for group, intensity, and a significant group by intensity interaction was found (Fig. 4D). Peak amplitudes were significantly larger for controls than AN subjects between 80 and 120 dB.

No significant main effects or interactions between the stimulated ears in any of the reported measures were found.

CM potential amplitudes increased with intensity for both AN and controls. No overall group differences or interactions with intensity were indicated (Fig. 4E).

3.4. Adaptation of ECochG potentials in controls

Adaptation in controls was accompanied by a significantly greater attenuation of CAP that was approximately double that of SP. The ECochG potentials recorded from a control subject at 110 dB p.e. SPL are shown in Fig. 5A.

Table 2
Detection of CM, CAP and ABR Wave V

	Controls	Subjects # (AD/AS)							
	Mean ± Std. Err. (min–max)	1	2	3	4	5	6	7	8
ABR wave V	+	–/+	–/+	+/+	–/–	–/–	–/–	–/–	–/–
CM amplitude at 120 dB (μV)	13.94 ± 10.69 (1.56–37.60)	10.04/9.83	7.60/4.49	53.13/11.21	145.90/8.12	5.48/4.98	2.69/14.2	6.60/14.55	3.32/5.86
CAP threshold (dB SPL)	47.00 ± 1.60 (30.00–60.00)	–/–	–/–	60/60	100/–	–/–	100/120	–/–	–/–
SP/CAP threshold (dB SPL)	47.00 ± 1.60 (30.00–60.00)	50/70	100/100	60/60	70/80	80/90	80/80	110/110	120/100
SP amplitude at 110 dB (μV)	4.11 ± 0.57 (0.69–14.98)	–/–	–/–	1.65/4.84	12.07/–	3.69/2.31	1.14/–	1.02/1.32	–/–
CAP amplitude at 110 dB (μV)	6.50 ± 0.93 (1.34–19.97)	–/–	–/–	3.12/2.40	2.02/–	–/–	0.18/–	–/–	–/–
CAP latency at 110 dB (ms)	1.53 ± 0.03 (1.35–1.72)	–/–	–/–	1.90/1.82	1.43/–	–/–	3.07/–	–/–	–/–
SP/CAP onset at 110 dB (ms)	0.28 ± 0.03 (0.07–0.50)	0.37/0.42	0.32/0.30	0.17/0.20	0.35/0.61	0.32/0.30	0.57/0.80	0.40/0.55	0.17/0.30

Std. Err., standard error; AD/AS, right ear/left ear; min–max, minimum–maximum value.

The stimulus sequence consisted of an initial click, followed after 15 ms by a train of ten clicks with an inter-stimulus interval of 2.9 ms that was repeated approximately 5/s. Details of the SP and CAP to the last (#11) and first click (#1) in the sequence are shown in Fig. 5B. This individual SP is only slightly attenuated (8%) whereas CAP is markedly attenuated (61%). Fig. 5C plots the mean attenuation and standard error of SP and CAP from 23 control ears as a function of click position in the train. There is rapid decrease of amplitude during the first 3–4 clicks for both SP and CAP. The amplitude of SP then asymptotes while that of CAP continues to have a gradual decline. By the end of the train, CAP peak amplitude showed $68.3 \pm 2.3\%$ reduction compared to $27.2 \pm 3.6\%$ reduction of SP amplitude (Table 4 and Fig. 5D). The difference was significant (*t*-test for independent samples, $t = 9.527$, $p < 0.001$). Adaptation in controls was also accompanied by a small but significant delay of latency of CAP peak (0.13 ± 0.02 ms, paired *t*-test, $t = 7.688$, $p < 0.001$) without any significant change in CAP duration (paired *t*-test, $t = 0.843$, $p = 0.409$, ns) (Fig. 5D).

3.5. Adaptation of ECochG potentials in AN

Adaptation was accompanied by changes of both amplitude and duration of the ECochG responses (Table 4 and Fig. 6). According to these changes and to the identification of a distinct CAP, three patterns of ECochG responses were identified.

The first group (subjects #5, 7) did not have an identifiable CAP and their ECochG potentials' duration were within or slightly above the control range. Adaptation had little or no effect on the amplitude or duration of the potentials (Table 4 and Fig. 6A).

The second group (subjects #3, 4, 6) did have identifiable SP and CAP that in the two subjects tested with rapid stimulus rates (#3, 6) became attenuated during adaptation similar to SP and CAP in controls. The duration of the cochlear potentials in this group was prolonged compared to controls and was reduced to control levels in the adapted state (Table 4 and Fig. 6B).

The third group (subjects #1, 2) did not have identifiable SP and CAP. Adaptation for these AN subjects was evaluated at the average peak latencies of control SP (0.7 ms) and control CAP (1.4 ms) (see Section 2). ECochG potentials during adaptation showed a decrease in both amplitude and duration. Individual adaptation values for both amplitude and duration are reported in Table 4 while mean amplitude and duration changes are shown in Fig. 6C. It was found that the amount of amplitude decrease at CAP control latency was consistent with that obtained for CAP in controls. Moreover, the duration of the responses was remarkably decreased in the adapted state and the amount of the decrease was even higher than that calculated for the group 2. Adaptation of amplitude measured at the peak latency of the control SP was of control values.

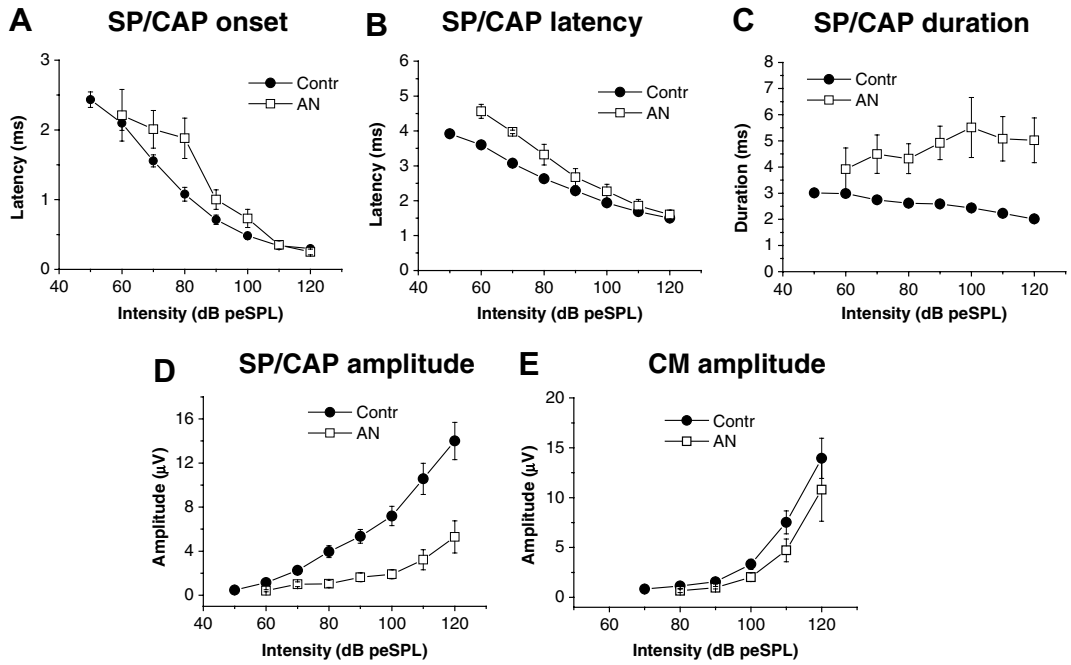

Fig. 4. Means and standard errors of SP/CAP onset (A), peak latency (B), duration (C), peak amplitude (D), and CM amplitude (E) are reported for controls (filled circles) and AN subjects (open squares). There are significant differences between the two groups for SP/CAP peak latency, duration and peak amplitude.

4. Discussion

The major conclusions we have drawn from this study of cochlear potentials in eight children and adults with AN is that the disorder reflects abnormalities of both pre-synaptic (e.g., IHCs) and post-synaptic (e.g., auditory nerve) functions. We found that cochlear receptor functions as reflected by CMs, OAEs, and SPs, were normal. In contrast, auditory nerve CAPs were either absent or of abnormal amplitude and latency. In the majority of subjects cochlear potentials consisted of a long lasting negative deflection that was attenuated in amplitude and prolonged in duration without a clear distinction between a SP and CAP.

In order to clarify whether these abnormally attenuated and prolonged potentials resulted from neural or receptor activations, we used an adaptation procedure that preferentially attenuates neural responses with minor changes in SP amplitude (Eggermont and Odenthal, 1974b).

Table 3
ANOVA summary of SP/CAP and CM measures

	Group		Intensity		Interaction of group by intensity	
	F	*P*	*F*	*P*	*F*	*P*
SP/CAP onset	3.25	ns	251.40	***	13.11	***
SP/CAP peak latency	5.57	*	6362.90	***	243.10	***
SP/CAP duration	13.89	**	<1	ns	2.34	*
SP/CAP peak amplitude	6.25	*	24.15	***	4.83	***
CM amplitude	<1	ns	13.03	***	<1	ns

ns, not significant.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

4.1. Adaptation of ECochG potentials in controls

Neural adaptation to fast stimulus rates reflects decreased responsiveness of both synaptic and spike generating processes (Eggermont and Odenthal, 1974b; Charlet de Sauvage and Aran, 1976). In the present study in control children, adaptation of the amplitude of the CAP was profound (68% reduction) whereas the decrease of the SP amplitude was significantly less averaging 27%.

The effects of high stimulus rate on the CAP have been extensively investigated in normal hearing adults and consist of CAP attenuation to approximately the same extent as that found in the present study (Eggermont and Odenthal, 1974b; Charlet de Sauvage and Aran, 1976; Wilson and Bowker, 2002; Ohashi et al., 2005). In contrast, few papers have addressed the issue of the effects of high stimulus rates on the SP amplitude. Prior studies in normal hearing adults reported almost no reduction of the SP amplitude (Eggermont and Odenthal, 1974b; Charlet de Sauvage and Aran, 1976). However, when we inspected one of the figures of Eggermont and Odenthal (1974b) we saw SP amplitude to decrease by approximately 40% by the fourth stimulus at 100/s rate, close to the upper limits of SP attenuation we found in the present study. We suggest that both SP and CAP can be attenuated during adaptation to rapid stimulus rates and that the extent of the attenuation, on average, is double for CAP than SP. We do not think that the SP attenuation observed at high rate

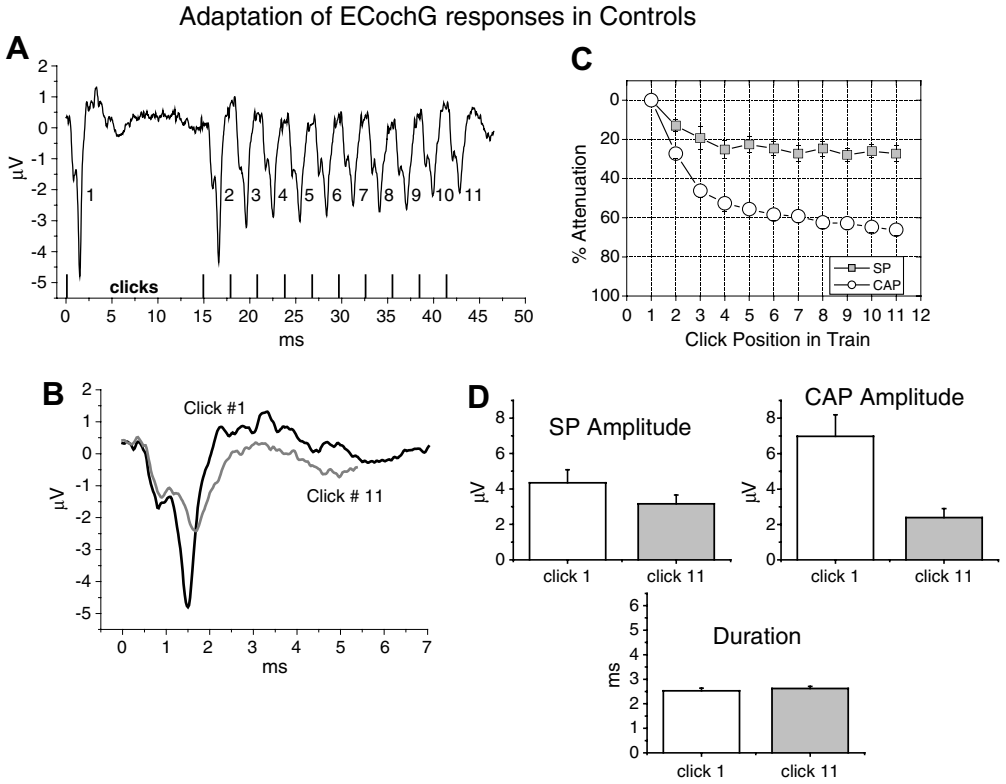

Fig. 5. Adaptation of ECochG potentials in controls. The upper panel (A) shows the ECochG response obtained from one control ear to clicks (110 dB p.e. SPL) in the stimulus sequence. The timing of each click is indicated by an upward line along the abscissa and the accompanying potentials to each click are indicated by the numbers along the responses to individual stimuli. The potentials to the first (#1) and last stimulus (#11) are superimposed in the lower panel (B). On the right side (C) the mean and standard error of attenuation (100 – [amplitude to click #11/click #1 × 100]) of controls for SP (squares) and CAP (circles) is shown as a function of click position in the stimulus sequence. There is rapid decrease of amplitude during the first 3–4 clicks for both SP and CAP, but the amplitude of SP then asymptotes while that of CAP continues to have a gradual decline. Mean amplitudes of both SP and CAP together with mean SP/CAP duration calculated for the first (#1) and last click (#11) of the stimulus sequence are also reported on the right (D). The response attenuation was significantly larger for CAP than for SP ($t = 9.527$, $p < 0.001$) while the duration of the whole SP/CAP response was not significantly changed ($t = 0.843$, $p = 0.409$, ns).

is due to attenuation of acoustic input by acoustic reflex activation of the middle ear muscles since amplitudes of CM did not change throughout the rapid stimulus sequence.

4.2. Adaptation of ECochG potentials in AN

The utilization of rapid stimulus rate induced changes in both amplitude and duration of cochlear potentials in AN subjects. According to these changes and the identification of the CAP as a separate response from SP we recognized three patterns of adaptation of cochlear potentials.

Group 1 includes two patients (#5, 7) without a CAP showing no amplitude or duration changes of the cochlear potentials to rapid stimulus rate (Fig. 6 and Table 4). The result is consistent with the negative potential originating from receptor rather than neural sources (Sheykholeslami et al., 2001; McMahon et al., 2005; El-Badry and McFad-

Table 4
Adaptation results

Subjects#	Controls	#1	#2	#3	#4	#5	#6	#7	#8
	Mean ± St Err (min–max)	AD/AS							
SP/CAP duration (ms) – click #1	2.53 ± 0.11	4.58	6.98	3.07	2.55	3.12	8.94	1.37	9.17
	(1.90–3.45)	*12.40*	*4.45*	*3.98*	*7.33*	*3.30*	*7.64*	3.83	*10.33*
SP/CAP duration (ms) – click #11	2.62 ± 0.09	2.40	3.31	3.07	NT	2.97	3.20	Absent	NT
	(2.02–3.30)	*3.03*	*1.80*	*2.20*		3.07	*1.85*	*3.28*	
SP amplitude % reduction	27.19 ± 3.64	2.20	25.95	24.10	NT	2.43	17.65	Absent	NT
	(0.43–56.25)	*55.08*	*21.78*	*23.91*		*21.21*	*44.40*	25.42	
CAP amplitude % reduction	68.27 ± 2.31	57.65	47.97	82.04	NT	0.00	60.00	Absent	NT
	(50.74–87.61)	*50.41*	*59.30*	*75.00*		*25.62*	*53.81*	*23.80*	

St Err = standard error; min–max = minimum–maximum value; AD = right ear; AS = left ear; NT = not tested.

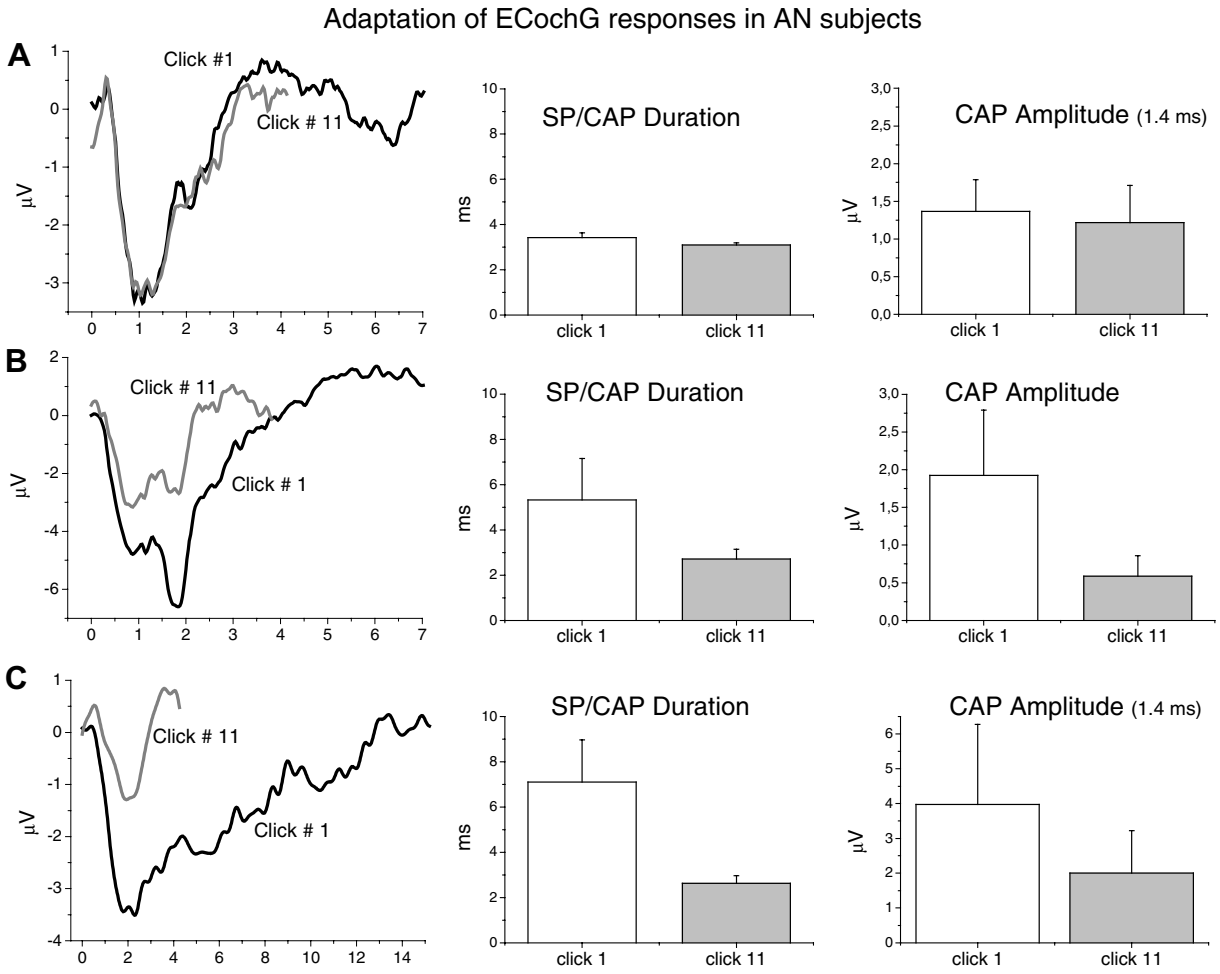

Fig. 6. Adaptation of ECochG potentials in AN subjects. The ECochG responses to the first (#1) and last (#11) click in the stimulus sequence are superimposed for 3 AN ears in the left side. Each AN subject was selected from one of the three patterns of ECochG response found for AN subjects based on (1) whether or not a CAP was present and (2) whether or not the ECochG potentials were prolonged in duration. Mean values of CAP amplitude and SP/CAP duration calculated for the first (#1) and last click (#11) of the stimulus sequence are reported on the right side. Mean latency of control SP and CAP values was used to define CAP or SP amplitude, respectively, when SP and CAP could not be separately identified. Note that no change in amplitude or duration was found in the first group during adaptation (A). The amplitude decrease calculated for both CAP and SP in the second group was consistent with that found in controls; however, the adapted response also showed a decreased duration (B). A striking decrease in both duration and amplitudes was obtained for the third group during adaptation (C).

den, 2007). That the lesion is likely localized in the inner hair cells and/or distal portion of auditory nerve fibers (AN type II) is also supported by the excellent outcome of (subsequent) cochlear implantation in one patient in this group (subject #7) (Santarelli et al., 2006).

The etiology of AN was likely to be immunological in both patients #5 and 7 based on their accompanying medical disorders (scleroderma in #7, and pancytopenia and dermatitis in #5). The finding of absent ankle deep tendon reflexes in #5 is a clinical sign suggestive but not diagnostic of a peripheral neuropathy. Without additional evidence such as sensory or motor changes and without conduction velocities studies, we can only speculate about the possibility of an accompanying peripheral neuropathy.

Group 2 includes three patients (#3, 4, 6) with a CAP. Duration of cochlear potentials were prolonged bilaterally in #6 and unilaterally in #3 and 4. Adaptation was tested in #3 and 6 and showed both SP and CAP amplitudes to be reduced similarly to controls and duration of the prolonged ECochG potential to decrease to control values.

Two of the patients (#3, 4) had hearing impairment as a phenotypic feature of the hereditary neurological disorder that also affected both peripheral and optic nerves. The CAP recorded from subject #3 was of normal amplitude but delayed in latency consistent with a slowed conduction due to demyelination. The slight increase in CAP threshold together with the increase in CAP latency and duration in this subject is similar to the findings obtained in an experimental model of auditory nerve damage due to myelin changes (El-Badry et al., 2007). In contrast, the CAP latency in subject #4 was normal suggesting that the site of the nerve involvement was central to the site of generation of the CAP. Thus, in both subjects #3 and 4, ECochG results suggest a post-synaptic disorder affecting auditory nerve.

Patient #6 had an immune disorder without symptoms of a peripheral neuropathy. Objective tests for conduction velocities were not performed. Differently from the two other subjects included in this group, subject #6 showed delayed SPs and a low amplitude CAP (Fig. 2) followed by a sustained negative potential of approximately 5 ms. The finding of prolonged potentials is a feature of group 3 patients suggesting that there may be several abnormal physiological processes occurring together in AN. For instance, we have also defined that the clinical manifestations of AN in some patients can evolve over time to involve both auditory nerve and OHCs functions (Starr et al., 2004).

The results from Group 2 patients bear on the relationship between the appearance of a CAP and wave I of the ABR. Subject #3 has a CAP of normal amplitude and almost normal duration that peaked at the same latency as Wave I of the ABR consistent with the common generation by similar neural processes (Fig. 7B). In contrast, subject #6 has a CAP but no Wave I in the ABR (Fig. 7C). The CAP "peak" in this subject is very prolonged (more than 1 ms in duration) and half the amplitude of the CAP found in subject #3. The mechanisms interfering with the ability to detect a broad Wave I by means of far-field recordings is beyond the scope of this paper and may be related to limitations of ABR far-field methods to define potentials that are of low amplitude.

Group 3 includes two patients (#1, 2) without identifiable CAP and prolonged duration of ECochG response. Adaptation was accompanied by attenuation of amplitude of ECochG response consistent with that found for CAP in controls. Moreover, the duration of the broad negative potential was reduced to control values during adaptation. These findings are consistent with neural origins of the prolonged negative potential recorded by ECochG.

Similar ECochG abnormalities in AN have also been described by McMahon and colleagues (2005) in young children using different stimulus conditions. They recorded delayed positive sustained SPs in response to 4 kHz tonebursts that at offset were followed by a short duration negative potential they proposed was generated by post-synaptic "dendritic potential" without accompanying nerve action potentials.

Etiology of AN in patients included in group 3 was most likely genetic since mother and daughter were both affected. The involvement of optic nerves as well as the post-lingual onset is inconsistent with mutations of both otoferlin (Rodriguez-Ballesteros et al., 2003) and pejvakin genes (Delmaghani et al., 2006). Mutations affecting mitochondrial functions of both optic and auditory nerves are candidate etiologies in these patients (Ceranić and Luxon, 2004; Amati-Bonneau et al., 2005).

4.3. CM amplitude

An increase in CM amplitude compared to normal subjects has been reported in both AN patients (Starr et al., 2001; Santarelli and Arslan, 2002) and experimental models of AN (El-Badry et al., 2007; El-Badry and McFadden, 2007). Starr and colleagues (2001) found a higher proportion of CM enhancement in infants and toddlers than in teens and adults with AN compared to the present study in adults and children. The etiologies of AN in infants are typically metabolic (e.g., hypoxia, hyperbilirubinemia) whereas genetic and immune disorders are prominent in

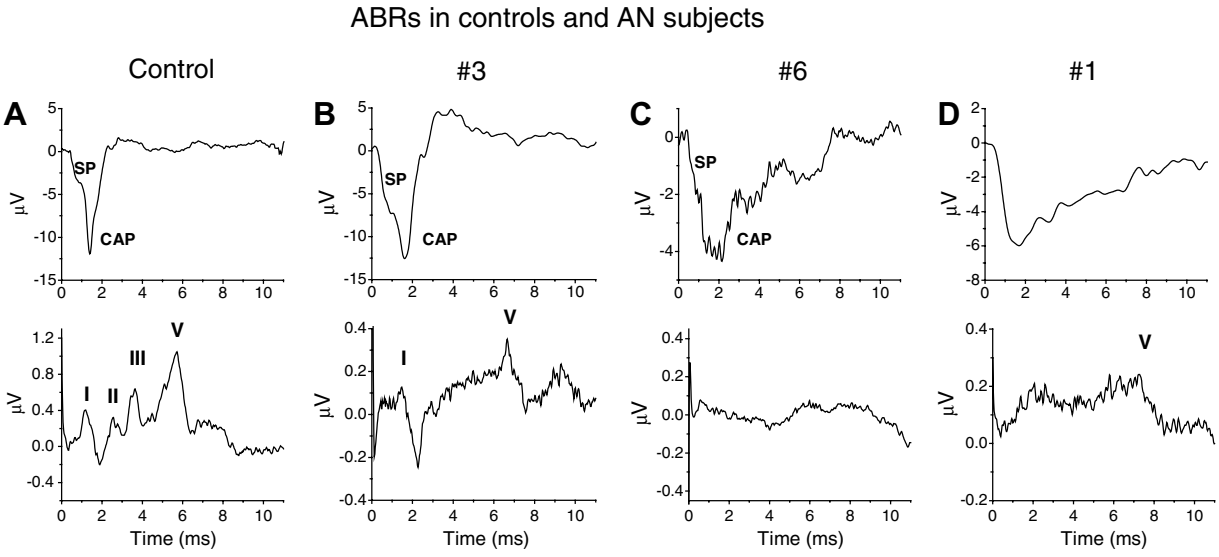

Fig. 7. ABR and ECochG recordings from control and AN ears. The upper panel shows the averaged ECochG potentials to condensation and rarefaction 120 dB p.e. SPL clicks obtained from one control (A) and 3 AN ears (B #3, C #6, D #1). The corresponding averaged ABR potentials to condensation and rarefaction 125 dB p.e. SPL clicks are shown in the lower panel. The onset of the traces corresponds to the CM onset for ECochG and to the click presentation time for ABR, respectively. Note that ECochG recordings are displayed on different *Y*-axes. The identification of the ABR Wave V in AN subjects is not strictly related to the identification of the CAP in the ECochG recordings for subjects #6 and 1 showing broad or absent CAPs, respectively.

teen years and adults. We suggest that an enhancement of CM may be specific to certain forms of AN.

4.4. Prolonged ECochG potentials in AN

AN ears included in Groups 2 and 3 showed prolongation of ECochG responses up to 12 ms compared to the measures obtained from controls (2.53 ± 0.11 ms at 110 dB p.e. SPL, Table 4). A similar prolongation of the ECochG responses has been previously described in acoustic neuromas (Eggermont et al., 1980; Ohashi et al., 2001). The generators of prolonged potentials in acoustic neuromas appear to be of neural origin since their amplitude is attenuated and their duration reduced using fast stimulus rates (Charlet de Sauvage and Aran, 1976). Eggermont et al. (1980) employed narrow band masking noise to derive the response contributions of neural elements along the cochlear partition in a patient with prolonged potentials due to acoustic neuroma. The derived CAP field potentials were identified as arising from different regions along the basilar membrane and were monophasic rather than having the normal biphasic appearance. They suggested that the transition from the biphasic to monophasic CAP resulted from the "desynchronization of auditory nerve fiber discharge" due to differences in neural conduction times. A similar mechanism could contribute to desynchronization of auditory nerve fiber discharge in subjects of Group 2.

We suggest an alternative mechanism to explain the origin of the broad negative potentials recorded from AN subjects included in Group 3, as reflecting depolarization of nerve terminals that have limited capacity to generate all or none nerve discharges. Fuchs (2005) has shown that the synaptic potentials obtained by intracellular recordings in auditory nerve terminals are of brief duration (1–2 ms) and can occur in rapid succession reflecting packaging and release of transmitter at the IHCs ribbon synapse. If the disorder in these AN patients affected the unmyelinated auditory nerve terminals to limit transmission of dendritic potentials to proximal sites of nerve spike generation, a sustained depolarization would develop and be reflected as an extracellular sustained negative field without clear action potentials.

The normalization of duration of the ECochG potentials that accompanies adaptation to fast stimulus rate is evidence of the prolongation as being neural rather than receptor in origin. We suggest two physiological processes that could account for these prolonged negative potentials. First, in those subjects with a CAP (Group 2), the prolonged duration of the ECochG potentials may result from variable slowing of nerve conduction with overlap of their extracellular fields. Stimulation at high rate would remove these slow components and result in improved synchrony of nerve fiber discharge. Second in those individuals without a CAP (Group 3) the prolonged potentials result from the summation of depolarizations of nerve terminals that have limited ability to generate action potentials. Rapid stimulation rate will result in reduction of neural activity with preservation of receptor components.

4.5. Clinical implications

In the eight AN patients reported in this study we found CM receptor potentials to be of normal or enhanced amplitude while SP receptor potentials were of normal amplitude. In contrast, the auditory nerve CAP varied from being normal, attenuated, or absent.

The prolonged ECochG found in many of the patients is consistent with temporal dispersion of neural activities evoked by acoustic stimulation. Caution should be exercised as to the conclusions of this study as the numbers of patients included are few. However, the results are consistent with the concept that AN can accompany abnormalities of both pre-synaptic (e.g., IHCs) and post-synaptic (e.g., auditory nerve) functions. We suggest that ECochG recordings may help to elucidate and quantify some of the physiological alterations underlying the disruption of auditory nerve activity accompanying AN.

Further studies of AN by ECochG recordings would provide additional quantitative details of underlying cochlear and neural physiological abnormalities. Recordings using both intracellular and extracellular methods in animal models of auditory nerve disorders due to specific gene mutations (Delmaghani et al., 2006; Moser et al., 2006) would identify the physiological consequences of disorders of receptors, synapses, auditory nerve terminals, and auditory nerve fibers. These animal and human studies are likely to lead to the recognition of specific pre- and post-synaptic mechanisms for the clinical disorder known as auditory neuropathy (AN).

Acknowledgments

We thank Drs. Pietro Scimemi and Erica Dal Monte for their invaluable help in data collection. We are grateful to engineers Fabio Saccomandi and Marco Okolicsanyi who developed the software for data acquisition and analysis, and Antonio Selmo who set up the equipment for recording. This research was supported in part by a grant to AS from the National Institute for Deafness and Communication Disorders (DC-02618).

References

Aran JM, Charlet de Sauvage R, Pèlerin J. Comparison of electrocochleographic and audiographic thresholds. Statistical study. Rev Laryngol Otol Rhinol (Bord) 1971;92:477–91.

Amati-Bonneau P, Guichet A, Olichon A, Chevrollier A, Viala F, Miot S, et al. OPA1 R445H mutation in optic atrophy associated with sensorineural deafness. Ann Neurol 2005;58:958–63.

Berlin CI, Hood LJ, Morlet T, Wilensky D, St John P, Montgomery E, et al. Absent or elevated middle ear muscle reflexes in the presence of normal otoacoustic emissions: a universal finding in 136 cases of auditory neuropathy/dys-synchrony. J Am Acad Audiol 2005;16:546–53.

Bocca E, Pellegrini A. Studio statistico sulla composizione della fonetica della lingua italiana e sua applicazione pratica all'audiometria con la parola. Arch Ital Otol 1950;5:116–41.

Ceranić B, Luxon LM. Progressive auditory neuropathy in patients with Leber's hereditary optic neuropathy. J Neurol Neurosurg Psychiatry 2004;75:626–30.

Charlet de Sauvage R, Aran JM. Clinical value of adaptation measurements in electrocochleography. In: Ruben RJ, Elberling C, Solomon G, editors. Electrocochleography. New York: University Park Press; 1976. p. 169–81.

Dallos P, Wang CY. Bioelectric correlates of kanamycin intoxication. Audiology 1974;13:277–89.

Delmaghani S, del Castillo FJ, Michel V, Leibovici M, Aghaie A, Ron U, et al. Mutations in the gene encoding pejvakin, a newly identified protein of the afferent auditory pathway, cause DFNB59 auditory neuropathy. Nat Genet 2006;38:770–8.

Durrant JD, Wang J, Ding DL, Salvi RJ. Are inner or outer hair cells the source of summating potentials recorded from the round window? J Acoust Soc Am 1998;104:370–7.

Eggermont JJ, Odenthal DW. Methods in electrocochleography. Acta Otolaryngol Suppl 1974a;316:17–24.

Eggermont JJ, Odenthal DW. Action potentials and summating potentials in the normal human cochlea. Acta Otolaryngol Suppl 1974b;316:39–61.

Eggermont JJ. Electrocochleography. In: Keidel WD, Neff WD, editors. Handbook of sensory physiology. Auditory system. New York: Springer Verlag; 1976. p. 625–705.

Eggermont JJ, Don M, Brackmann DE. Electrocochleography and auditory brainstem electric responses in patients with pontine angle tumors. Ann Otol Rhinol Laryngol Suppl 1980;89:1–19.

Eggermont JJ, Ponton CW, Coupland SG, Winkelaar R. Maturation of the traveling-wave delay in the human cochlea. J Acoust Soc Am 1991;90:288–98.

El-Badry MM, Ding DL, McFadden SL, Eddins AC. Physiological effects of auditory nerve myelinopathy in chinchillas. Eur J Neurosci 2007;25:1437–46.

El-Badry MM, McFadden SL. Electrophysiological correlates of progressive sensorineural pathology in carboplatin-treated chinchillas. Brain Res 2007;1134:122–30.

European Concerted Action Project on Genetics od Hearing impairment. Study group on terminology, definition and hearing assessment. Newsletter 1996. Available from: www.gendeaf.org.

Ferraro JA, Blackwell WL, Mediavilla SJ, Thedinger BS. Normal summating potential to tone bursts recorded from the tympanic membrane in humans. J Am Acad Audiol 1994;5:17–23.

Fuchs PA. Time and intensity coding at the hair cell's ribbon synapse. J Physiol 2005;566:7–12.

Hallpike CS, Harriman DG, Wells CE. A case of afferent neuropathy and deafness. J Laryngol Otol 1980;94:945–64.

Kiang NYS, Moxon EC, Kahn AR. The relationship of gross potentials recorded from the cochlea to single unit activity in the auditory nerve. In: Ruben RJ, Elberling C, Solomon G, editors. Electrocochleography. New York: University Park Press; 1976. p. 95–116.

Lasky RE, Perlman J, Hecox K. Maximum length sequence auditory evoked brainstem responses in human newborns and adults. J Am Acad Audiol 1992;3:383–9.

McMahon CM, Patuzzi RB, Gibson WP, Sanli H. Frequency specific round-window ECoG suggest two possible mechanisms of auditory neuropathy. XIX Symposium of the international evoked response audiometry group, Havana: Cuba; 2005.

Moser T, Neef A, Khimich D. Mechanisms underlying the temporal precision of sound coding at the inner hair cell ribbon synapse. J Physiol 2006;576:55–62.

Ohashi T, Ochi K, Kinoshita H, Kenmochi M, Kikuchi H, Nishino H, et al. Electrocochleogram after transection of vestibulo-cochlear nerve in a patient with a large acoustic neurinoma. Hear Res 2001;154:26–31.

Ohashi T, Ochi K, Nishino H, Kenmochi M, Yoshida K. Recovery of human compound action potential using a paired-click stimulation paradigm. Hear Res 2005;203:192–200.

Probst R, Lonsbury-Martin BL, Martin GK. A review of otoacoustic emissions. J Acoust Soc Am 1991;89:2027–67.

Rimondini P, Rossi Bartolucci R. Approccio alla calibrazione di un reattivo verbale per lo screening in età prescolare. Boll Ital Audiol Foniat 1982;5:98–113.

Rodriguez-Ballesteros M, del Castillo FJ, Martin Y, Moreno-Pelayo MA, Morera C, Prieto F, et al. Auditory neuropathy in patients carrying mutations in the otoferlin gene (OTOF). Hum Mutat 2003;22:451–6.

Salamy A, McKean CM, Pettett G, Mendelson T. Auditory brainstem recovery processes from birth to adulthood. Psychophysiology 1978;15:214–20.

Santarelli R, Arslan E. Electrocochleography in auditory neuropathy. Hear Res 2002;170:32–47.

Santarelli R, Scimemi P, Dal Monte E, Genovese E, Arslan E. Auditory neuropathy in systemic sclerosis: a speech perception and evoked potential study before and after cochlear implantation. Eur Arch Otorhinolaryngol 2006;263:809–15.

Schoonhoven R, Lamoré PJ, de Laat JA, Grote JJ. The prognostic value of electrocochleography in severely hearing-impaired infants. Audiology 1999;38:141–54.

Sheykholeslami K, Kaga K, Kaga M. An isolated and sporadic auditory neuropathy (auditory nerve disease): report of five patients. J Laryngol Otol 2001;115:530–4.

Sininger Y, Oba S. Patients with auditory neuropathy: who are they and what can they hear. In: Sininger Y, Starr A, editors. Auditory Neuropathy: A new perspective on hearing disorders. San Diego: Singular Publishing; 2001. p. 15–36.

Spoendlin H. Optic cochleovestibular degenerations in hereditary ataxias. II. Temporal bone pathology in two cases of Friedreich's ataxia with vestibulo-cochlear disorders. Brain 1974;97:41–8.

Starr A, Picton TW, Sininger Y, Hood LJ, Berlin CI. Auditory neuropathy. Brain 1996;119:741–53.

Starr A, Sininger YS, Pratt H. The varieties of auditory neuropathy. J Basic Clin Physiol Pharmacol 2000;11:215–30.

Starr A. The neurology of auditory neuropathy. In: Sininger Y, Starr A, editors. Auditory neuropathy: A new perspective on hearing disorders. San Diego: Singular Publishing; 2001. p. 37–51.

Starr A, Sininger Y, Nguyen T, Michalewski HJ, Oba S, Abdala C. Cochlear receptor (microphonic and summating potentials, otoacoustic emissions) and auditory pathway (auditory brain stem potentials) activity in auditory neuropathy. Ear Hear 2001;22:91–9.

Starr A, Michalewski HJ, Zeng FG, Fujikawa-Brooks S, Linthicum F, Kim CS, et al. Pathology and physiology of auditory neuropathy with a novel mutation in the MPZ gene (Tyr145 → Ser). Brain 2003;126:1604–19.

Starr A, Isaacson B, Michalewski HJ, Zeng FG, Kong YY, Beale P, et al. A dominantly inherited progressive deafness affecting distal auditory nerve and hair cells. J Assoc Res Otolaryngol 2004;5:411–26.

Varga R, Kelley PM, Keats BJ, Starr A, Leal SM, Cohn E, et al. Nonsyndromic recessive auditory neuropathy is the result of mutations in the otoferlin (OTOF) gene. J Med Genet 2003;40:45–50.

Wilson WJ, Bowker CA. The effects of high stimulus rate on the electrocochleogram in normal-hearing subjects. Int J Audiol 2002;41:509–17.

Withnell RH. Brief report: the cochlear microphonic as an indication of outer hair cell function. Ear Hear 2001;22:75–7.

Zeng FG, Kong YY, Michalewski HJ, Starr A. Perceptual consequences of disrupted auditory nerve activity. J Neurophysiol 2005;93:3050–63.

Zheng XY, Ding DL, McFadden SL, Henderson D. Evidence that inner hair cells are the major source of cochlear summating potentials. Hear Res 1997;113:76–88.