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EXPERIMENTAL ENDOLYMPHATIC HYDROPS: ARE COCHLEAR AND VESTIBULAR SYMPTOMS CAUSED BY INCREASED ENDOLYMPHATIC PRESSURE?

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The correlation between inner ear pressure and cochlear function was investigated in guinea pigs with unilaterally obliterated endolymphatic sacs and ducts. In 11 animals that developed endolymphatic hydrops, auditory thresholds as monitored by auditory evoked action potentials had increased with recruitment. Most of these animals also experienced episodes of spontaneous nystagmus. In control ears endolymphatic pressure did not differ more than 0.5 cm H2O from perilymphatic pressure. In six of 11 hydropic ears, endolymphatic pressure was more than 0.5 cm H2O higher than perilympathic pressure; auditory thresholds in all these ears had deteriorated within 2 weeks before pressure recording. No further hearing deterioration within this period was noted in five hydropic ears with endolymphatic pressure equal to or lower than perilymphatic pressure. Endolympathic-perilymphatic pressure gradients may contribute to auditory threshold increase in endolymphatic hydrops, but are not its only cause.

KEY WORDS — guinea pig, inner ear pressure, Meniere's disease, Preyer's reflex, Reissner's membrane rupture.

INTRODUCTION

The cochlear and vestibular symptoms in Meniere's disease are well known.[1-3] The pathogenesis of the disease, however, still remains a matter of speculation. Operative obliteration of the endolymphatic sac and duct in the guinea pig produces a model of this disease in which many of the cochlear alterations but only sporadic vestibular symptoms can be reproduced.[4-9] The only consistent morphologic finding in patients with Meniere's disease and in the animal model is an enlargement of the endolymphatic space, or so-called endolymphatic hydrops. This distended appearance of the membranous labyrinth often has been considered to represent elevated pressure in the endolymphatic space. There is also evidence that elevated inner ear pressure impairs cochlear function.[10-15] Thus, many current theories on the pathogenesis of Meniere's disease[16-18] presume that there is, at least intermittently, an increased endolymphatic pressure (ELP). Increased ELP, however, has never been demonstrated directly in patients with Meniere's disease.

With the servocontrolled micropipet system,[19] reliable hydrostatic pressure recordings in very small fluid compartments such as the scala tympani and scala media of the guinea pig have become possible. In normal guinea pigs, ELP is approximately equal to perilymphatic pressure (PLP), and in all situations in which inner ear pressure has been altered acutely by different manipulations, both ELP and PLP changed concomitantly.[20-22] Even in experimental endolymphatic hydrops, Long and Morizono[23] and Matsubara et al[24] found very similar PLP and ELP. Higher ELP than PLP in individual ears has been reported to date only in one small series of guinea pigs 3 months after obliteration of the endolymphatic sac.[25]

The present study was designed to investigate whether there is a correlation between inner ear pressure and alterations of cochlear and vestibular function in the guinea pig model of endolymphatic hydrops.

METHODS

Thirty-five pigmented guinea pigs weighing 400 to 800 g with normal Preyer's reflex thresholds[26] were used; 15 of them provided reliable data. With anesthesia produced by intramuscular ketamine hydrochloride (Ketalar 40 mg/kg) and xylazine (Rompun 8 mg/kg), silver ball electrodes were implanted on the round window membranes in both ears, and a stainless steel screw electrode was inserted into the skull at the vertex as a reference. Screw electrodes also were placed at the anterior and posterior border of the right orbit for recording horizontal eye movements. All electrodes were attached to a small connector (Amphenol) that was fixed to the skull with dental cement. The endolymphatic sac and duct on one side were obliterated with bone wax by use of an extradural posterior fossa approach.[27]

Regular auditory and vestibular tests were performed in the awake animal at least once every 10 days. In a soundproof room, the guinea pig was placed in a small box with only the head exposed and with the head fixed (similar to Aran and Erre[28]). For cochlear stimulation, clicks and tone bursts of 1, 2, and 4 kHz (four cycles, 4- to 1-millisecond duration) were applied in a closed system with a small earphone placed on the pinna. Compound nerve action potentials (APs) recorded from the round window membrane were amplified (500

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to 5,000 times), filtered (8 Hz to 8 kHz), averaged (64 observations), and plotted by a Medelec digital averager system. To estimate the auditory function independent of technical problems (displacement of electrodes, etc), Preyer's reflex thresholds were tested with eight different sinusoidal tone bursts between 0.25 and 8 kHz at each session.[26] Vestibular function was tested by recording the vestibulo-ocular reflex and spontaneous nystagmus in the dark. The animals were rotated sinusoidally on a simple platform while the horizontal eye movements were recorded with a Beckman Dynograph recorder. No attempts were made to quantify the responses because of the lack of an established method to calibrate corneoretinal potentials in the guinea pig.

The cochlear and vestibular functions of the hydropic and control ears were tested over 35 to 100 days. Inner ear pressures were recorded as a final experiment. The animals were anesthetized with intramuscular ketamine and xylazine and with intraperitoneal pentobarbital (Nembutal 20 mg/kg). A tracheostomy was performed, and artificial breathing with room air was provided by a Harvard model 66 animal respirator. Hydrostatic pressures in the inner ear fluids were recorded with a servocontrolled micropipet system.[25,29] By an approach through the posterior bulla, a bevelled micropipet (tip diameter, 10 μm) first was placed with a micromanipulator on the round window membrane, where a calibration and baseline determination was performed in a small drop of Ringer's solution. The pipet then was advanced through the round window membrane into the scala tympani, where PLP was recorded, and then through the basilar membrane into the scala media, where ELP was measured. The DC potentials (relative to a silver–silver chloride electrode in the soft tissue of the neck) were recorded simultaneously with the pressure through the micropipet to monitor the location of the micropipet tip. In some of the ears, pressure recordings were complicated by granulation tissue that had formed along the silver electrodes on the round window membrane.

TABLE 1. PROPORTIONAL SCALA MEDIA AREA (MEAN ± SD)

	Cochlear Turns			
	Basal	*Second*	*Third*	*Fourth*
Controls (n = 11)	27 ± 3	36 ± 5	36 ± 4	35 ± 6
Failed obliterations (n = 4)	25 ± 4	36 ± 4	36 ± 4	37 ± 3
Hydropic ears (n = 11)	63 ± 17*	74 ± 15*	68 ± 15*	73 ± 10*

*Differs significantly from controls ($p < .01$, t test).

After pressure recording in both ears, the animals were killed painlessly and celloidin-embedded serial sections of the temporal bones were prepared for histologic evaluation of the inner ear. The areas of

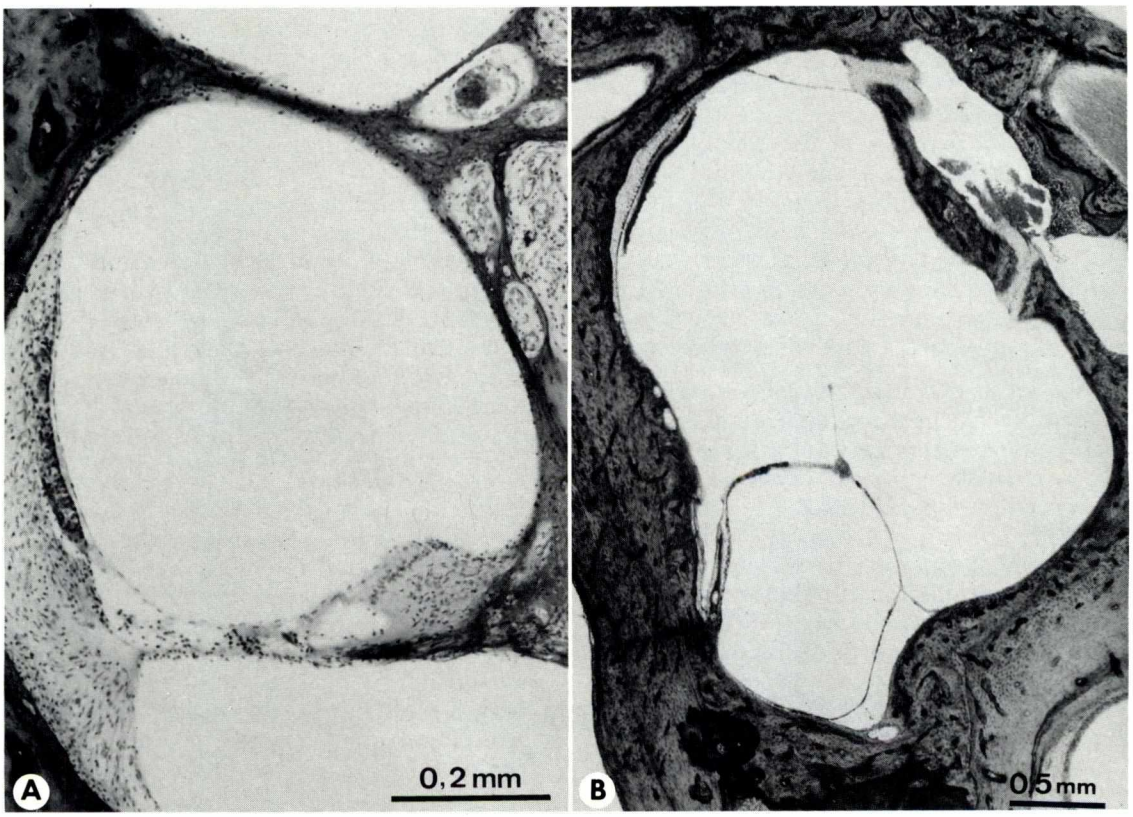

Fig 1. A) Collapsed Reissner's membrane in second turn in guinea pig AX. B) Ruptured saccular membrane in guinea pig AW.

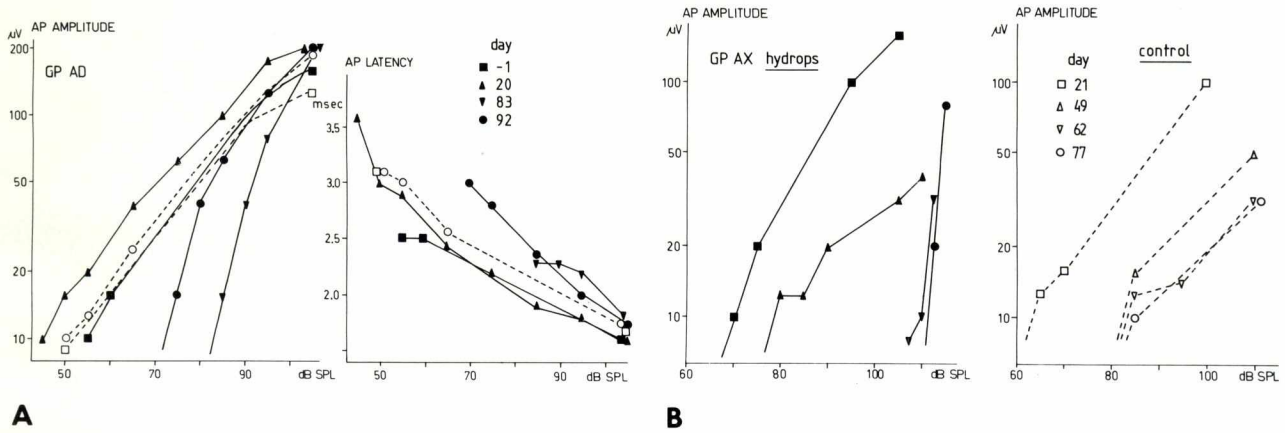

Fig 2. Input-output function of compound action potentials (AP) elicited by 2-kHz tone bursts. Open symbols and broken lines — control ear, solid symbols and solid lines — hydropic ear. A) In guinea pig AD. B) In guinea pig AX, which developed chronic otitis media in both ears. There is shift of input-output curve to right in control ear, and additional inner ear hearing loss with recruitment in hydropic ear.

scala media (SM) and scala vestibuli (SV) of each turn were determined by means of a computerized morphometer (ASBA, Wild and Leitz) and the proportional SM area was calculated as SM/(SM + SV) x 100.

RESULTS

Morphologic Findings. Endolymphatic hydrops was found in 11 of 15 ears (73%) with obliterated endolymphatic sacs (Table 1). Four animals did not develop endolymphatic hydrops; histologic examination of these ears revealed "obliterations" that were not performed deep enough into the endolymphatic duct. These ears will be referred to as failed obliterations. None of the control ears (unoperated ear of the contralateral side) showed hydropic changes. The proportional SM area varied only minimally among control ears and ears with failed obliterations, but was increased significantly in the hydropic ears (Table 1).

In six of 11 hydropic ears Reissner's membrane was distended in all turns. In guinea pig AX, Reissner's membrane was distended in the apical turn, but severely collapsed in the lower part of the cochlea (Fig 1A), including the saccule, while in guinea pig AW, a rupture of the saccular membrane with thickened ends and a collapse of only the lateral part of the basal turn was observed (Fig 1B). In the three other ears, slightly collapsed or wavy Reissner's membranes were seen in single turns.

Cochlear Symptoms. In all 11 hydropic ears, the compound AP thresholds had increased by at least 20 dB with clear recruitment at suprathreshold stimulation (Fig 2A). Preyer's reflex showed a Metz recruitment as illustrated in Fig 3. In some of the control ears, the AP threshold had increased, too, but always without recruitment (Fig 2B, right). This was interpreted as either conductive hearing loss due to slight infections around the electrode and/or as a deterioration of the recording electrode. In the few hydropic ears in which the threshold increased both with and without recruitment (Fig 2B, left) only threshold increases with recruitment were used for further calculations.

The mean threshold increase for 1-, 2-, and 4-kHz tone bursts in all hydropic ears was 36 ± 13 dB (Table 2). The time course of this increase was progressive with slight fluctuations in five ears. In six ears hearing thresholds increased suddenly, 3 weeks (one animal) or 8 to 11 weeks (five animals) after obliteration of the endolymphatic sac. Figure 3 illustrates the time course of hearing deterioration in three animals, each with its corresponding control ear. Action potential threshold increases during

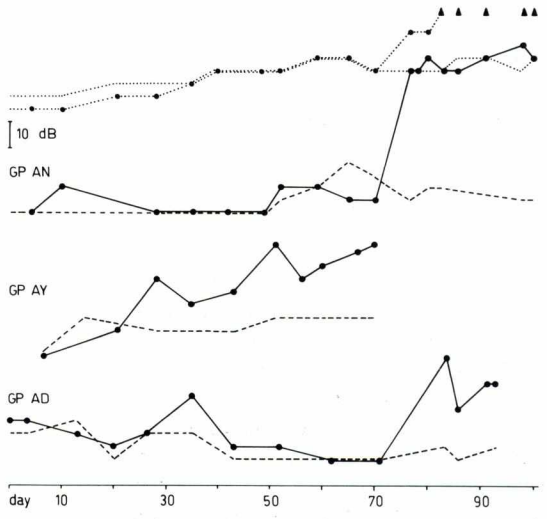

Fig 3. Time course of action potential (AP) threshold increase in three hydropic ears (solid circles and lines) and in corresponding control ears (broken lines). Acoustic stimuli were 2-kHz tone bursts. For guinea pig AN, Preyer's reflex thresholds elicited with 2-kHz tone bursts are also given (dotted lines with solid circles — hydropic ear, dotted line — control ear, triangles — abolished Preyer's reflex). Metz recruitment is seen with Preyer thresholds 40 dB above AP thresholds at beginning, but only 15 to 20 dB higher when AP thresholds increase.

TABLE 2. MEAN ACTION POTENTIAL THRESHOLD INCREASE IN HYDROPIC EARS FOR 1-, 2-, AND 4-KILOHERTZ TONE BURSTS

Guinea Pig	*Survival Time (d)**	*Total Increase (dB)*	*Increase During Last 2 Weeks (dB)*	*Hearing Loss Type*	*Hearing Loss Time Course (d)*
BC	35	21	21	P	4-35
AZ	67	42	27	P	29-67
AY	70	26	9	P	21-70
AW	70	43	5	P/S	48-55
BB	71	53	26	P/S	69-70
AT	78	27	10	S	15-25
AO	84	27	28	S	71-77
AD	92	43	21	S	71-83
AX	99	32	0	S	49-56
AN	100	60	12	S	77
AB	100	20	20	S	88-99
Mean ± SD		36 ± 13	15 ± 10		

P — progressive, S — sudden.

*After obliteration of endolymphatic sac.

the last 2 weeks before pressure recording turned out to be the important parameter for correlating cochlear function with inner ear pressure. Therefore, threshold increase during these 2 weeks is given separately in Table 2.

Vestibular Symptoms. An early period of spontaneous nystagmus related to manipulations at the endolymphatic sac had to be distinguished from late episodes of nystagmus related to endolymphatic hydrops (Fig 4).

During the first 2 days after sac obliteration, spontaneous nystagmus toward the operated side was observed in three animals; four animals also showed transient head tilts. Between day 2 and day 7 after the sac obliteration, five of six animals with nystagmus recordings during this period showed spontaneous nystagmus in the dark, with the fast phase toward the unoperated side. These findings disappeared in all animals during the next 2 weeks. All these animals developed endolymphatic hydrops, while none of the animals with failed obliterations showed spontaneous nystagmus.

After 1 month, nine of the 11 guinea pigs with hydrops showed transient episodes of slight spontaneous nystagmus in the dark. In two animals, this could be related to a hearing deterioration in the control ear (acute otitis, fast phase of nystagmus toward the operated ear). Seven of the 11 episodes of spontaneous nystagmus were related in time with hearing deterioration in the hydropic ear (Fig 4, bottom). In three cases the nystagmus was beating toward the hydropic ear, and in four cases toward the control ear. No other late vestibular symptoms such as head tilt or obvious gait instability were observed.

Inner Ear Pressures and Endocochlear Potentials. Figure 5 gives an example of a pressure recording from both the hydropic and the normal contralateral ears in one animal. In control ears, measurements of PLP, ELP, and endocochlear potential (EP) were successful in only four ears. Therefore, additional data from nine normal ears of another study (A. Böhmer, unpublished observations) are included in Table 3. Absolute values of ELP and PLP varied from 1.4 to 4.0 cm H2O among different

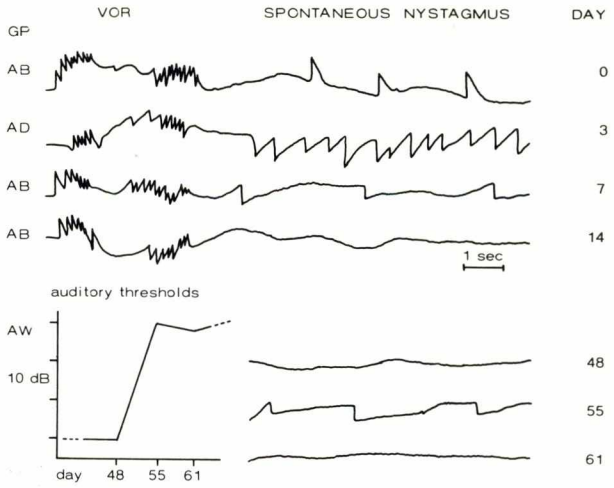

Fig 4. Vestibulo-ocular reflex (VOR) induced by clockwise and counterclockwise horizontal rotation and spontaneous nystagmus in dark related to endolymphatic sac surgery (top four traces) and to auditory threshold increase in hydropic ear (three lower traces). In all traces upward deflections indicate eye movement toward hydropic ear. Topmost recording (day 0) was done 6 hours after obliteration of endolymphatic sac. For guinea pig AW, auditory action potential thresholds (2 kHz) are given at left side. GP — guinea pig.

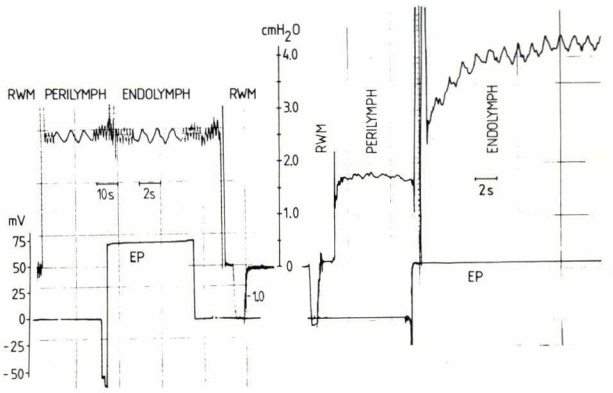

Fig 5. Pressure recording in scala tympani and scala media in control ear (left) and hydropic ear (right) in guinea pig AB 100 days after sac obliteration. Micropipet was guided through round window membrane (RWM) into perilymphatic space (PERILYMPH), and then through basilar membrane into endolymph (ENDOLYMPH). Respiratory pressure oscillations became visible in inner ear fluids, but not on RWM. Direct current potentials recorded simultaneously through micropipet monitored pipet localization: negative potential indicated passing through organ of Corti; positive potential appearing afterward is endocochlear potential (EP), indicating position of micropipet tip in scala media. Before and/or after pressure measurements, calibration (−1.0 cm H2O) was performed on RWM. Note higher endolymphatic than perilymphatic pressure and lowered EP in hydropic ear.

TABLE 3. PERILYMPHATIC AND ENDOLYMPHATIC PRESSURE AND ENDOCOCHLEAR POTENTIALS

	PLP (cm H2O)	*ELP (cm H2O)*	*ELP-PLP Gradient (cm H2O)*	*EP (mV)*
Controls (n = 4)	2.8±0.5	2.8±0.7	0.0±0.1	75± 4
Other normal ears (n = 9)	2.1±0.8	2.2±0.9	0.0±0.2	76± 4
Failed obliterations (n = 4)	2.8±0.5	2.9±0.8	0.1±0.3	75± 4
Hydrops (n = 11)	2.0±1.2	3.2±2.1	1.2±2.4	50±12
Guinea pig				
BC	0.6	1.2	0.6	47
AZ	1.2	1.9	0.7	42
AY	4.4	3.6	−0.8	20
AW	1.8	2.0	0.2	45
BB	2.3	4.0	1.7	55
AT	3.2	3.4	0.2	60
AO	1.0	8.5	7.5	60
AD	1.8	3.8	2.0	63
AX	0.7	1.0	0.3	60
AN	3.5	1.5	−2.0	50
AB	1.5	4.0	2.5	50

PLP — perilymphatic pressure, ELP — endolymphatic pressure, EP — endocochlear potential.

control and normal ears, but the pressure difference between endolymph and perilymph (ELP-PLP gradient) in individual ears was minimal, ranging from −0.3 to +0.4 cm H2O. The ears with failed obliterations did not differ from these control ears. The EP measured 70 to 80 mV in all of the control, normal and failed obliteration ears, but was less than 65 mV in all of the hydropic ears.

The mean ELP and PLP in the hydropic ears were in the same range as in the normal ears. Individual hydropic ears, however, showed much larger variations of the ELP-PLP gradient (Table 3).

Correlation Among Hearing Loss, Inner Ear Pressure, and Morphology. Three groups of ears could be distinguished according to the time course of hearing threshold increase. These groups also differed distinctly in the ELP-PLP gradients (Fig 6).

Group 1 showed no significant hearing threshold increase. It included the four control ears and the four failed obliterations. The ELP-PLP gradients were in the same range, −0.4 to +0.5 cm H2O, as in the other normal ears. Temporal bone histology showed normally positioned Reissner's membranes in all these ears.

Group 2 had a hearing threshold increase of more than 20 dB during the last 2 weeks before pressure recording. This group consisted of six hydropic ears in which ELP was higher than PLP (ELP-PLP gradient higher than 0.5 cm H2O). Reissner's membrane was distended in four ears at the pressure-recording site in the basal turn, but partially collapsed in the other two ears.

Group 3 showed a hearing threshold increase of more than 20 dB during the whole observation time

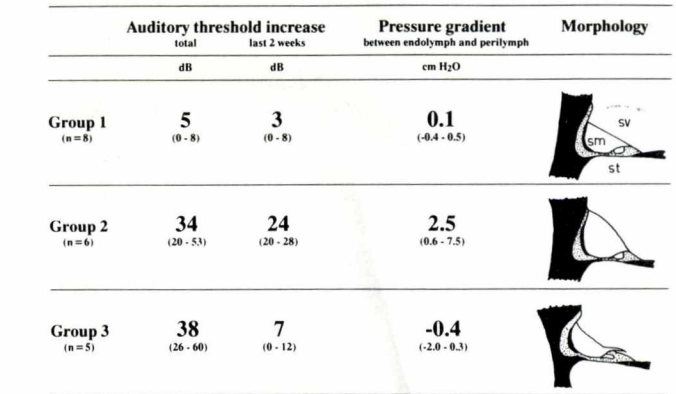

Fig 6. Endolymphatic-perilymphatic pressure gradients and shape of Reissner's membrane at site of pressure recording in three groups of ears with different patterns of auditory threshold increase. For threshold increases and pressure gradients, mean and (in parenthesis) range are indicated. Sketches of scala media (sm) at pressure-recording site illustrate one typical ear of group. sv — scala vestibuli, st — scala tympani.

(total increase) but no significant further increase during the last 2 weeks before pressure recording. This group included the other five hydropic ears. In none of these ears was ELP significantly increased. The cochlear and vestibular findings of a sudden hearing loss with spontaneous nystagmus 7 weeks after sac obliteration in two of these ears (AX and AW) were in agreement with the histologic findings of ruptures in the membranous labyrinth (Fig 1). Reissner's membrane at the pressure-recording site was wavy in two other ears (AN and AY) of this group and distended in the fifth ear (AT).

DISCUSSION

Our experiments demonstrate equal endolymphatic and perilymphatic hydrostatic pressure in normal guinea pig ears, but important ELP-PLP gradients in ears with experimental endolymphatic hydrops. These pressure gradients were as variable as are auditory threshold alterations in this animal model,[6-8] but were correlated to auditory function: ELP was higher than PLP only in ears with an auditory threshold increase of at least 20 dB during the last 2 weeks prior to pressure recording.

Mean inner ear pressures in three different small series of normal guinea pigs ranged between 2.3 and 6.5 cm H2O, with the higher values obtained when the approach was through the bony cochlea/spiral ligament/stria vascularis instead of the round window membrane/basilar membrane.[20,21,30] Mean PLP and ELP were almost equal in all those series, but none showed ELP-PLP differences for individual ears. Only a few such data are available. Long and Morizono[23] found pressure gradients between −2.2 and +2.7 cm H2O in 25 normal ears, while Ito et al[25] had no gradients larger than 0.3 cm H2O in five ears. The latter finding agrees well with the normal range of ELP-PLP gradients of −0.3 to +0.5 cm H2O found in our animals.

Again, there are only two studies[23,25] that reported ELP-PLP gradients in experimental endolymphatic hydrops. In the latter study, significantly elevated ELP-PLP gradients were measured in five animals with histologically confirmed hydrops 2 to 3 months after obliteration of the endolymphatic sac. Long and Morizono,[23] on the other hand, claimed no difference between ELP and PLP 1 to 25 days after sac obliteration (only two animals were followed longer, and at least one of them had no hydrops).

Direct and indirect experimental evidence reported in the literature suggests a correlation between cochlear function and inner ear pressure.[10-15] However, all the manipulations to change either the PLP or the ELP described in these studies probably did not induce an ELP-PLP gradient, but affected PLP and ELP by the same amount. Reissner's membrane is able to maintain pressure gradients between endolymph and perilymph only when it has lost its high compliance after long-standing distension.[31] Our study demonstrates cochlear dysfunction in relation to a pressure difference between endolymph and perilymph, a condition that has been suspected as a possible cause of hearing impairment in Meniere's disease. However, not all of the different kinds of functional inner ear disturbances that occur in the guinea pig model can be attributed to such ELP-PLP gradients.

In the first weeks after sac obliteration, compound AP thresholds in the low frequency range start to increase and show important fluctuations.[9] In our study these alterations might have been partially missed because of suboptimal recording electrodes resulting in relatively high preoperative hearing thresholds. Important ELP-PLP gradients were never seen within the first 5 weeks after obliteration of the endolymphatic sac.[23,31] These early reversible hearing threshold fluctuations therefore have to be due to another cause.

Also, 2 to 3 months after obliteration of the endolymphatic sac, a positive ELP-PLP gradient occurs in many ears, and this pressure gradient is strictly correlated to mainly irreversible AP threshold increase. Spontaneous nystagmus in this condition is not exactly correlated in time with the hearing loss.

Moreover, in at least two of 11 ears, ruptures of Reissner's membrane or the saccular membrane had occurred, resulting in a sudden hearing loss with recruitment strictly correlated in time with spontaneous nystagmus and in a collapsed Reissner's membrane in the lower cochlea. Endolymphatic pressure was equal to PLP in these two ears. Similar ruptures of the membranous labyrinth together with sudden drops in compound APs also were seen after direct experimental increase of the ELP.[13]

In conclusion, guinea pigs with operatively obliterated endolymphatic ducts develop distension of the endolymphatic space (endolymphatic hydrops) similar to that found in patients with Meniere's disease, and show cochlear and vestibular dysfunction. Endolymphatic pressure is higher than PLP in more than half of the hydropic ears, but not in normal ears. These pressure gradients are correlated to both morphologic and functional changes. Endolymphatic-perilymphatic pressure gradients may contribute to hearing threshold increase, but are not its only cause.

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