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Abstracts

HEARING PRESERVATION WORKSHOP VII

KANSAS CITY
OCTOBER 16–19, 2008

hearingpreservation.com

Host: Hinrich Staecker, University of Kansas

KU UNIVERSITY of KANSAS
Department of
Otolaryngology
Head & Neck Surgery

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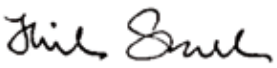
Dear Colleagues,

It gives me great pleasure to welcome you to the VIIth Hearing Preservation Workshop in Kansas City which is taking place in October of this year. We are planning an exciting program which will focus on the clinical and research aspects of hearing preservation and cochlear implantation. The meeting will focus on drug delivery and imaging technology. Historically, Kansas City has been the starting-off point for people travelling to the unexplored western portion of the United States, and I am sure that this meeting will give us the chance to extend our exploration of inner ear functions in implantation. I am looking forward to a meeting of productive dialogue.

Sincerely yours,



Hinrich Staecker MD PhD,
Host of Hearing Preservation Workshop VII

October 16th: Arrival of Participants

6:00–9:00 pm Welcome Reception in the Rooftop Bar of the Intercontinental

October 17th: Hearing Preservation and EAS, Rehabilitation

7:30	*Registration in front of the meeting room Salon 3*		
		Chair: Hinrich Staecker	
8:00	Keynote Lecture: Recent Studies of Psychophysics and Speech Perception in Patients Who Combine Acoustic and Electric Stimulation	Michael Dorman	6
8:30	Cross-Sensory Plasticity and Language Perception In Individuals With Early-Onset Hearing Impairment	Ed Auer	7
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9:15	The Atraumatic Cochleostomy and EAS Insertion	David Friedland	9
9:45	EAS Concept & Surgical Video	Hinrich Staecker	10
10:15	**Coffee Break**		
		Chair: Paul Van de Heyning	
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11:30	Surgical Procedure in EAS and PDCI – Difficult Cases	Robert Podskarbi-Fayette, Henryk Skarzynski	14
11:45	Bilateral EAS and Bimodal Hearing after CI with MED-EL PULSAR$_{CI^{100}}$	Paul Van De Heyning	15
12:00	Vienna Experience of Electric Acoustic Surgery	Wolf-Dieter Baumgartner	16
12:15	Acoustical Low-Frequency Amplification to the Contralateral Acoustic Ear with Ipsilateral Cochlear Implantation – An Extension of the EAS Model	Ross Tonini	17
12:30	Hearing Preservation with Cochlear Implantation: Reflections and Future	Charles M. Luetje, Bradley Thedinger, Robert Cullen	18
12:45	**Lunch Break**		
		Chair: Peter Roland	
1:45	Anatomy of the Basal End of the Basal Turn and the Round Window Niche	Peter Roland	19
2:15	Technology in Hearing Preservation Surgery: Optical Coherence Tomography and Evaluation of Function Post Implantation	Hinrich Staecker	20
2:45	Fluorescence Microendoscopy of the Mammalian Cochlea	Nikolas Blevins	21
3:15	The Ultrasonic Approach to Cochleostomy	Domenico Cuda	22
3:45	*Panel on Insertion Depth and Cochleostomy Site*	Hinrich Staecker, Peter Roland, Patricia Leake, Paul Van De Heyning, Michael Dorman	
4:30	**Coffee Break**		
		Chair: Jean-Pierre Bébéar	
5:00	Spiral Ganglion Cell Population	Mark Chertoff	24
5:15	Fitting of DUET and Audiological Aspects of EAS	Marek Polak	25
5:30	EAS Initiates Research into Better Fine-Structure Coding in Cochlear Implants	Peter Nopp	26

5:45	Audiological Assessment of EAS Patients: Benefits of Binaural Acoustic Hearing	René Gifford	27
6:00	New Flex Optima Electrode for EAS	Jean-Pierre Bébéar	28
6:15	End		
7:30	**Dinner at Nelson Atkins Museum**	*buses depart at 7:00*	

October 18th: Neural Enhancement, Pharmacotherapy

7:00	*MED-EL 5K Run*		
		Chair: Allen Ryan	
8:30	Factors Influencing Auditory Prosthesis Function: Insights from Animal and Human Temporal Bone Studies	Patricia Leake	29
9:00	Pharmacoprotection of the Inner Ear: Strategies Based on Cellular Mechanisms of Damage	Allen Ryan	31
9:30	Current Status of Local Drug Delivery to the Inner Ear	Stefan Plontke	32
10:00	Elution of Dexamethasone from a Cochlear Implant: Release Profiles and Efficacy Evaluation	Carolyn Garnham, Jan Kiefer	34
10:30	**Coffee Break**		
		Chair: Jochen Tillein	
11:00	Protection of Auditory Hair Cells Against Trauma-Induced Apoptosis by Dexamethasone: Cellular & Genetic Mechanisms	Tom Van De Water	35
11:30	The differential Actions of Glucocorticoids and Mineralocorticoids in the Inner Ear	Dennis Trune	36
12:00	Molecular Strategies to Prevent Hearing Loss in a Mouse Model of Cochlear Implantation	Hinrich Staecker	38
12:30	The Effect of Local Corticosteroid Treatment in Implanted Guinea Pigs on Intracochlear Tissue Growth	Jochen Tillein, Susanne Braun	39
1:00	**Lunch**		
		Chair: Alec Salt	
2:00	Microfluidic Pump	William Sewell	40
2:30	Application of Drugs to the Inner Ear: Techniques, Drugs, and Results	Claude Jolly, Carolyn Garnham	41
3:00	Evaluation of Reservoir-Based Dexamethasone Delivery	Alessandro Martini	42
3:30	**Coffee Break**		
		Chair: Philippe Lefebvre	
4:00	Local Drug Delivery to the Inner Ear: Strategies and Potential Patient Groups	Alec Salt	43
4:30	Neurotrophins and the Development and Maintenance of Inner Ear Innervation	Bernd Fritzsch	45
5:00	Hair Cell Regeneration: Identification of Progenitor Cells That Gives Rise to Hair Cells	Philippe Lefebvre	47
5:30	End		
7:30	**Dinner at Fiorella's Jack Stack BBQ**	*buses depart at 7:00*	

October 19th: Working Breakfast, 8:00 am

Recent Studies of Psychophysics and Speech Perception in Patients Who Combine Acoustic and Electric Stimulation

M F Dorman[1], R Gifford[2], A Spahr[1], L Loiselle[1]
[1]Arizona State University, USA
[2]Mayo Clinic Rochester, USA

In this talk we will summarize our recent studies with EAS patients. The issues include:

- the minimum amount of low-frequency acoustic information that is required to achieve speech-perception benefits in listeners with a cochlear implant in one ear and low-frequency hearing in the other ear,
- the overlap in information provided by electric and acoustic stimulation in listeners with a cochlear implant in one ear and low-frequency hearing in the other ear,
- temporal and spectral resolution for both acoustic and electric stimulation in EAS patients,
- speech recognition by EAS (bimodal) patients vs. 10 mm Hybrid patients,
- speech recognition by EAS patients vs. bilateral patienets from all three manufacturers.

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Cross-Sensory Plasticity and Language Perception in Individuals with Early-Onset Hearing Impairment

E Auer

In typically developing human perceivers, inputs from multiple sensory systems are integrated to form unified percepts of the world. For these individuals, spoken language input arrives via both the auditory and visual sensory systems, with the auditory input typically providing the majority of the information. In contrast, for individuals with severe-to-profound hearing impairments, spoken language input arrives via auditory, visual, and somatosensory input, with the auditory system providing only minimal information. Additionally, for these individuals, language input may also take the form of manual signs and gestures in combination with speech or on their own. The cortical substrate for language perception will likely be altered by development under conditions of early-onset hearing impairment. This talk will review the evidence from work in my laboratory and others investigating cross-sensory plasticity for language perception in individuals with early-onset hearing impairment. At present, the results suggest that cortical reorganization in the auditory cortex of perceivers with early-onset hearing impairment is associated with effects of visual input as well as from somatosensory stimulation. Potential functional implications of cross-sensory cortical plasticity for cochlear implantations will be discussed.

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Electric Acoustic Stimulation (EAS): A Filtered Speech Test to Better Define the Indication Criteria

F Seldran, E Truy, C Berger-Vachon, L Collet, H Thai-Van, S Gallégo

With Electric Acoustic Stimulation, the patient hearing system is stimulated by two different ways. The low frequency part of the signal is processed by an acoustic unit, as it could be processed by a classical BTE hearing aid, which means that the low frequencies are stimulated by an amplified acoustic signal, while the high frequency part of the signal is processed by a cochlear implant unit which will deliver an electrical signal to the implanted electrodes.

The aim of our study is to develop a set of audiometry tests that uses a low-pass filtered speech in order to better define the indication criteria for EAS and to determine if a patient is a good candidate for bimodal stimulation. We believe that classical audiometry tests are not sufficient to evaluate EAS patient candidacy.

We first set up a preliminary study with 20 normal-hearing subjects in order to establish a model of "syllables intelligibility based on speech cut-off frequency". This test is then given to hearing impaired subjects having residual hearing in the low frequencies. We then compared the results of hearing impaired with normal hearing patients in order to assess low frequency contribution in speech intelligibility.

Thus, we can better and quickly evaluate if the subject uses only low frequency information to understand speech. This test allows us to assert if a hearing-impaired subject with low frequency residual hearing is a good indication for an Electric Acoustic implant or if bimodal stimulation may not give him enough benefit. In the second step, we can also anticipate the cut-off frequency between acoustic and electric stimulation. This test may be a useful tool for the evaluation of EAS candidacy.

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The Atraumatic Cochleostomy and EAS Insertion

D R Friedland

Hearing preservation during cochlear implantation has historically been irrelevant as candidacy criterion required profound hearing loss. The past decade has seen both a relaxation in the criterion regarding pre-operative hearing thresholds and the advent of combined electro-acoustic devices. These advances have placed new focus on the surgical implantation procedure and the techniques that may preserve residual hearing. Although large-scale prospective and controlled studies have not been performed, surgical experience has helped to define rationale guidelines for hearing preservation. This "soft" insertion technique relies on reducing disturbance of the inner ear milieu while placing the electrode array. These methods include refined placement of the cochleostomy, avoidance of suction of perilymph, atraumatic opening of the cochlea endosteum, the avoidance of bone dust and blood introduction into the inner ear, and the use of topical lubricant and steroid during implantation. Increasing experience with the soft insertion technique will help define those steps critical to the preservation of pre-operative hearing.

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An Introduction to Electric Acoustic Stimulation

H Staecker

There has been a significant growth of interest in combining cochlear implantation with residual acoustic hearing. Initial studies suggest that benefits include improving hearing in background noise and extension of implant benefit to patients who are not considered traditional implant candidates. Important issues in hearing preservation surgery include the surgical approach, choice of electrode and insertion depth. The advent of implanting ears with significant residual function also raise the opportunity to evaluate and develop new drugs for hearing preservation.

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Clinical Experience with the MED-EL Electric Acoustic Stimulation System

O F Adunka, C A Buchman, M C Adunka, H C Pillsbury

Objective: To assess the safety and effectiveness of the MED-EL electric acoustic stimulation system in one institution as part of the North American clinical trial.
Methods: Each subject underwent thorough preoperative audiometric testing before enrolment. Unilateral cochlear implantation was then performed using surgical techniques established for hearing preservation. About four weeks postoperatively, each subjects was fitted and tested with the cochlear implant alone mode. Six to eight weeks thereafter, the ipsilateral hearing aid was introduced and subjects were tested in various conditions at various intervals thereafter. Overall, a follow-up of 12 months was obtained.
Patients: Eleven subjects with substantial and stable low frequency residual hearing meeting inclusion criteria for the clinical trial.
Results: Some degree of hearing preservation was obtained in 10 of 11 subjects. One subject lost hearing in the first days after surgery. Of the 10 subjects with ipsilateral hearing preservation, 3 had complete preservation of pure tone thresholds, whereas the remaining 8 demonstrated various degrees of partial hearing conservation. Residual hearing remained stable throughout the study period. Also, the combination of electric and acoustic stimuli resulted in improved speech discrimination scores; especially in conditions with background noise.
Conclusion: Hearing preservation during cochlear implantation seems feasible in most patients. Subsequent combined electric acoustic stimulation provides an additional benefit especially for speech perception abilities in background noise.

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Round Window and Cochleostomy Approaches for Electrical-Acoustic Stimulation

D Jiang[1], S Connor[2], A F O'Connor[1]
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[2]Guy's Hospital, London, UK

Background: The round window was the common route for insertion of the early design cochlea implant electrode in 1970s and 1980s. There were concerns raised regarding its close proximity to osseous spiral lamina, hence an osseous cochleostomy approach was favoured. Anatomical reconstructive study and insertion experiments carried out recently with the new breed electrodes suggested that insertion through the round window may offer an alternative with less risk of basal turn trauma
Objectives: To compare the result of the round window with that of conventional cochleostomy insertion in patients who underwent cochlear implant for combined electrical-acoustic stimulation (EAS), and to discuss safety issues in the round window approach.
Methods: MED-EL EAS electrodes were introduced via round window membrane cochleostomy in 3 patients, and conventional osseous cochleostomy in 5 patients. For round window insertion, the round window area was visualised through the posterior tympanotomy, the overhang of the niche was removed with a low velocity burr to display the round window membrane. A partial circumferential incision is made anterior inferior in the membrane. The conventional cochleostomy is made at 1 mm anterior and inferior to the round window. The precautious recommended for EAS surgery were applied to both approaches. The post-operative CT was carried in all patients to assess the location of the electrode.
Result: Insertion of the electrode was achieved without resistance in all round window and cochleostomy patients. Functional hearing preservation achieved in 7 out of 8 patients. One patient lost significant amount of residual hearing. The electrode was inserted, in this case, via cochleostomy. One patient in each group showed worsening of residual hearing at 12 month after initial device fitting. All seven patients benefit from EAS. The post-operative CT scan showed insertion angles ranging from 240 to 370 degree. Round window insertion is associated with a closer modiolar location for the proximal part of the electrode and the electrode is located safely away from basilar membrane.
Conclusion: Round window approach can achieve atraumatic electrode insertion for EAS.

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EAS for Partial Deafness: The Perth Experience

G P Rajan, E Statham, M Atlas, R Marino

Background: EAS for partial deafness is proving to be an emerging alternative for patients who cant be aided conventionally. EAS-Implantation requires different reasoning and alterations to conventional cochlear implantation in order to preserve residual hearing. We want to share our experiences with our first 4 EAS cases

Methods: Case series study

Outcomes: Outcomes of Hearing preservation, SRTs and music perception will presented and factors perceived to influence outcomes

Discussion: The key factors in our experience for hearing preservation (patients selection, preimplantation conditioning, surgical technique) and rehabilitation (rehab time, learning curve) and potential means of improvement will be discussed.

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Surgical Procedure in EAS and PDCI – Difficult Cases

H Skarzynski, R Podskarbi-Fayette

Recently, due in part to great progress in cochlear implant technology, we are expanding the boundaries of candidacy for cochlear implantation. Surgical experience, as well as better hardware and software used in cochlear implants have brought about incremental improvements in speech understanding. New patients demand an optimized solution for their type of hearing impairment. This is especially true for individuals with residual hearing. Preservation of residual hearing during surgical procedures is fundamental for the concept of electro-acoustic stimulation of the cochlea.

In our extensive, since 2000, experience in treatment of patients with residual hearing the round window approach was the preferred, most often used passage to the cochlea. It was proven by the outstanding results achieved in patients, to be the superior solution when it came to preservation of residual hearing and partial deafness cochlear implantation (PDCI). It is the most physiological and least traumatic method of electrode insertion assuring optimal and direct stimulation of the organ of hearing.

In the majority of cases the round window niche can be well visualised through the slightly widened posterior tympanotomy. The round window needs some preparations, but the final result is not difficult to obtain and an intact membrane can be clearly visible.

Cases exist in which the round window niche cannot be visualized well enough to ensure proper insertion of the electrode at an optimal angle. It needs to be prepared with a transmeatal approach due to obstruction of the view posed by the posterior tympanotomy approach. In such conditions it is advised to turn the view to the transmeatal perspective and to perform an anterior tympanotomy. The puncture and initial insertion are performed through anterior tympanotomy and final sliding and positioning of the electrode can be performed while holding the electrode array through the posterior tympanotomy approach.

We are presenting basis and modifications of our six-step surgical procedure taking into consideration difficulties in accessing the round window. Modifications of our standard procedure and application of technology available in modern otosurgery assure proper insertion of the electrode array through the round window membrane. In our opinion, the round window approach is an advantageous and technically simple procedure providing good landmarks for the surgeon and thus allowing him to be confident that the electrode is correctly inserted in the scala tympani.

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Bilateral EAS and Bimodal Hearing after CI with MED-EL PULSARCI100

P Van de Heyning[1], K Vermeire[1,2], E Cochet[1], A Hofkens[1], A Kleine Punte[1]
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Background: The aim of this clinical study was to assess speech understanding in noise and hearing-specific-quality-of-life effects of a series of cochlear implant patients with a cochlear implant (for tinnitus reduction) and contralateral functional acoustic hearing and a patient with a bilateral electro-acoustic stimulation.
Methods: Eighteen subjects participated in this study. Nine of these subjects are normal hearing (NH-group) on the contralateral side, 9 use a hearing aid (HA-group). Patients were implanted with a COMBI 40+ M implant or a PULSARCI100 FLEXSOFT implant, with the electrode fully inserted in the scala tympani.
The bilateral EAS patient was implanted unilaterally with a PULSARCI100 EASSOFT electrode advanced up to electrode 10 and contralaterally with PULSARCI100 FLEXSOFT electrode with full insertion. All patients were fitted with the CIS algorithm.
Subjects were tested 12 months after the first fitting of their CI. Speech recognition in noise was tested in two listening conditions, i.e., with their acoustic hearing alone (AH-only), and with adding the CI to the acoustic hearing (bimodal). Subjective improvement in daily situations was evaluated, using the Speech Spatial and Qualities (SSQ) Hearing Scale was used.
Results: All eighteen patients report benefit from bimodal stimulation. Results indicate that there is no significant binaural summation from adding the CI. A significant squelch effect from adding the CI could be seen for the HA-users, but not for the NH subjects. Additionally, in both groups a significant combined head shadow and squelch effect can be seen.
In the bilateral EAS patient, also in the fully inserted 31mm flex electode side, the acoustic hearing coul be kept. Bilateral EAS hearing proved to be superior to all other hearing combination eg CI-CI, CI-EAS, acoustic-CI, acoustic-EAS.
Conclusions: The 12 month results of these eighteen subjects suggest that cochlear implantation is an adequate treatment providing improved hearing in unilateral profound sensorineural hearing loss. However, it has to be taken into account that the primary indication for cochlear implantation in these patients was the tinnitus reduction. The bilateral EAS patient had no tinnitus. His hearing achievements showed the added value of bilateral EAS and the feasibility in preserving acoustic hearing also with full insertion of the Flex Soft electrode, using the EAS surgical methods.

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Vienna Experience of Electric Acoustic Surgery (EAS)

W Baumgartner, A Jappel, S Reiss

In 1999 Christoph v Ilberg introduced the Electro Acoustical Stimulation (EAS) as a combination of conventional hearing aid and cochlear implant on the same ear. Through a very soft and cautious insertion the clear evident residual hearing should be preserved. After successful EAS implantation cochlear implant and hearing aid are combined on the ipsilateral ear.

In Vienna we performed since 1999 20 cochlear implantations in residual hearing patients, concerning the aspects of EAS. In the majority of patients we preserved residual hearing.

Those successfull EAS-patients use hearing aid and cochlear implant on the same ear effectively together. Over the years different electrode arrays from MED EL company have been used. Beginning with standard electrodes in 1999, over different custom made devices onto the recent Med EL Flex soft EAS Electrode array. Consequently the surgical procedure changed, from a cochleostomy procedure, towards a round window insertion nowadays or a special fenestration technique usind stapedotomy instruments. Still today there is no so called standardised EAS surgical technique recognised. We show the development of electrode array and implant technique since 1999 and compare to the outcome of patients.

Additionally to the EAS procedure itself, indication and wording has changed in the pst decade, too. Actually implanted patients considered for an EAS procedure, are audiologically different from thouse implanted in 1999.

We focus on the different "schools of EAS" (Frankfurt, Gstöttner-Kiefer; Warszawa, Skarczynsky; Vienna, Baumgartner) and our results in the short and long run from January 2000 until June 2008.

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Acoustical Low-Frequency Amplification to the Contralateral Acoustic Ear with Ipsilateral Cochlear Implantation – An Extension of the EAS Model

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The electro-acoustical stimulation model is predicated on the concept that there is a synergistic effect of acoustical and electrical stimulation to the implanted ear. We have hypothesized that low-frequency acoustical stimulation to the contralateral ear may also provide the same synergistic gains upon speech discrimination in noise. We will report on our clinical experience in both children and adults who have low-frequency residual hearing in their contralateral ear and who were successful hearing aid users in that ear. Our results provide encouraging evidence that the benefit seen in the ipsilateral ear with electro-acoustical stimulation may also be possible with low-frequency acoustical amplification to the contralateral ear and electrical stimulation in the implanted ear.

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Hearing Preservation with Cochlear Implantation: Reflections and Future

C M Luetje, R D Cullen, B . Thedinger

Study design: Personal historical and current experience and review of literatrue re Hybrid implantation.
Setting: Independent referral center for cochlear implantation.
Patients: Thirteen patients from author's experience and others reported in the literature.
Main outcome measures: Benefits of high-frequency electrical stimulation from the Hybrid cochlear implant as measured by conventional audiometry, consonant-nucleus-sonsonant monosyllabic word and Bamford-Kowal-Bench sentence in noise testing.
Results: Historical, unpublished data indicated short electrode intracochlear electrode insertion with hearing preservation was possible. Follow-up cases reported to date with the Hybrid implant from Cochlear Corporation have indicated preserved hearing immediately postoperatively. However, delayed hearing losses may alter future candidacy with regards to age criteria and length of hearing losses. The comments expressed are limited to the author's experience and published data because of confidentiality issues relating to data submission process to the FDA.

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Anatomy of the Basal End of the Basal Turn and the Round Window Niche

P S Roland, CG Wright, B Issacson

The anatomy of this portion of the labyrinth will be described and an approach to making a cochleostomy will be suggested that has the following features:

1. It is a surgical approach that most surgeons will be comfortable with because it uses a standard mastoidectomy and posterior tympanotomy.
2. The extent of drilling (and therefore the amount of trauma) associated with cochleostomy placement is minimized.
3. The approach uses visible and reliable landmarks that improve the probability that the electrode will enter the middle of the scala tympani below the basilar membrane and spiral ligament.
4. It permits an angle of insertion that minimizes intracochlear trauma.
5. Because the round window membrane is the principal landmark used to locate the cochleostomy, the insertion technique described will permit correct electrode placement even in the face of a fairly wide range of anatomic variations of the cochlea.

Anatomic features of the RW niche relevant to the placement of an FMT will be noted and illustrated.

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Technology in Hearing Preservation Surgery: Optical Coherence Tomography and Evaluation of Function Post Implantation

H Staecker, S Prentiss

An increasing number of patients with significant residual hearing are being referred for cochlear implantation. Those implant recipients who are able to combine both electrical and retained acoustic hearing(EAS) have improved pitch resolution compared to pure implant listeners. The advantages of EAS hearing are made possible when preoperative function in the implanted ear can be preserved. Implant design, technique, and perioperative care are under examination with the focus on hearing preservation. A key surgical component of hearing preservation during cochlear implantation is the correct and a-traumatic placement of the cochleostomy. We examine a novel catheter-based Optical Coherence Tomography (OCT), on the inner ear. We demonstrate the capability of OCT to allow visualization of inner ear structures in live mice through bone. We additionally used OCT to image the inner ear in a human temporal bone. OCT was able to delineate soft tissue structures within the cochlea and may be useful as an adjunct to cochlear implantation. Utilization of hearing preservation strategies have the potential to improve not only hearing but also to allow the preservation of vestibular function. In a series of patients examined with vestibular evoked myogenic potential testing, vestibular function was preserved with hearing preservation approaches but not with standard cochleostomies.

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Fluorescence Microendoscopy of the Mammalian Cochlea

N H Blevins, A Monfared, E L M Cheung, J C Jung, G Popelka, A Ricci, M J Schnitzer

We have developed a technique for examining cellular-level cochlear anatomy in vivo using fluorescence microendoscopy (FME). FME represents an emerging minimally invasive imaging modality that provides micron-scale resolution in tissues inaccessible to light microscopy. Rigid endoscope probes (0.5 – 1mm diameter) with gradient refractive index (GRIN) lenses and tissue-specific fluorescent dyes have been used to image the basal cochlear turn of live guinea pigs. Cochlear capillary blood flow and hair cells have been successfully examined using this technique.

Disruption of cochlear microcirculation may be a significant cause of hearing impairment following cochlear implantation. The inability to image cochlear blood flow in a non-destructive manner has limited investigation of this factor. Using FME with intravenous fluorescein we have been able to map individual erythrocytes within capillaries in the Organ of Corti, and objectively assess blood flow rates in the inner ear.

Similarly, the presence and viability of hair cells and spiral ganglion cell dendrites may also play a role in residual hearing and outcome following cochlear implantation. We have been imaged these structures using styryl dyes in vivo, providing potential evidence for the functional state of these cellular elements. Imaging has correlated with pathologic and electrophysiologic changes expected following aminoglycoside administration.

As we continue to refine our technique, and hope to apply FME to humans undergoing cochlear implantation. We hope to correlate microanatomic findings with clinical outcomes to better understand the anatomic determinants of performance, and help design more effective techniques and prostheses.

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The Ultrasonic Approach to Cochleostomy

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A new way to perform osteoplasty by means of an ultrasonic device has been recently described in oral and maxillofacial surgery. Basically, in this device (Piezosurgery® - PZS) a high frequency electrical current is applied to a handpiece's ceramic rings generating microscillations in the ultrasonic range (25-27 KHz). The micromovements are 20-80 micron wide and are transmitted to different surgical tips. The device allows to remove carefully the bone without any torque or the typical macrovibration of the drill. Another important characteristic of this device is that just mineralized tissue are removed without any effect on soft tissues.

Based on this interesting characteristics the PZS has been applied in the pericochlear bone surgery. In particular it has been used to perform cochleostomy for cochlear implantation (CI) in patients with profound hearing loss. In this case the cochlear endostium has been easily preserved before to open the scala tympani for insertion.

Since the most interesting potential application of the PZS is the hearing preservation in the CI recipients for electroacoustic stimulation the question of possible acoustic trauma produced by the device need to be fully investigated.

An experimental study on safety of piezoelectric surgery for cochleostomy was then planned. Sprague Dawley rats has divided in two groups of 5 animals each (10 total). Each animal in both groups received a cochleostomy in the left ear. The right ear served as control. In group one the PZS system was used to remove the bone to the periosteum of the scala tympani. Group two had the bone drilled in the standard manner, with the 1 mm diamond burr, and the bone was removed to the periosteum of the scala tympani. In day one the animals were Hydrated with 1 cc saline, subcutaneously. In day two aseptic surgery was performed. Animals were anesthetized with isoflurane inhalant, hydrated with 1 cc saline, subcutaneously and finally 0.05mg/kg buprenorphine was injected subcutaneously as prophylactic pain killer and 5.0 mg/kg enrofloxacin as prophylactic antibiotic. The area posterior to external ear canal was shaved, then cleaned and disinfected. Then aseptic surgical prep of the left middle ear and cochleostomy were performed without opening the

periosteum. Cochlear bone temperature was measured before drilling and every 5 minutes. At the end of the operation muscle was closed with absorbable sutures and skin with non-absorbable sutures. Following recovery from anesthesia, the animals were housed in the main facility. In the days 3-8 the animals were monitored daily for signs of distress or wound infection and 0.05 mg/kg buprenorphine was given twice daily for the first 2 days. Any behaviour indicative of a vestibular upset (head tilt, nystagmus, circling) was monitored. Vestibular upsets that didn't resolve within several hours were considered a toxic effect and the animal sacrificed. Preyer's reflex were be used to monitor general audiologic function during the post-surgical period. At day 8 the animals were anesthetized with ketamine and xylazine and sacrificed by decapitation of the sedated animal. The temporal bones were quickly harvested. The bones were opened and the inner ear on the medial half was carefully opened and perfused with fixative. The cochlea was dissected and the organ of Corti was examined for damage in each cochlear turn, base to apex. The examiner was blinded to the condition of the animals by assigning random numbers to the samples before analysis. The identical processing and analyses was performed on the control tissue. The average level of trauma indicated by the results of the behavioral and histological analyses for each condition was compared to determine the relative safety of the piezoelectric surgical system to the standard 1 mm diamond-burr drill in performing "soft" cochleostomy. The main results will be presented and discussed.

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Spiral Ganglion Cell Population

M Chertoff

The long-term goal of the research in my lab is to develop clinical techniques that quantify hair cell transduction and auditory nerve function in order to provide a greater understanding of the pathophysiology associated with hearing loss. Diagnosis based on pathophysiology will lead to new treatment strategies such as improved signal processing algorithms for hearing aids and cochlear implants. Moreover with future developments in hair cell regeneration and genetic therapy, this research will provide tools to target the site for therapeutic agents. In this talk I will present our latest research to determine if the compound action potential (CAP) could be used to estimate the number and health of auditory nerve fibers in impaired ears.

The Mongolian gerbil was used as our animal model. A needle electrode was inserted through the dorsomedial wall of the round window antrum to deliver current or mechanically damage the auditory nerve. Animals recovered for approximately two months after which CAPs were recorded from an electrode placed on the round window. Stimuli ranged from 1000-16000 Hz with levels ranging from 15-100 dBSPL. Animals were euthanized, histologic sections prepared, and auditory nerve fibers counted using stereologic procedures. Dependent measures consisted of the parameters of a convolution model of the CAP. In this initial study the cochlea was spared to avoid confounding effects of cochlear damage.

For normal ears (number of animals = 24), the auditory nerve consisted of approximately 16,879 (± 3001 sd) fibers. Lesioned ears (number of animals = 10) had fewer fibers as compared to normal ears but showed normal CAP thresholds. The N parameter, which in the convolution model represents the number of fibers, decreased proportionately as the percent of damage to the auditory nerve increased. In four animals, the frequency parameter which describes the unit waveform decreased. These changes indicate that the quantities derived from the CAP are sensitive to the number of auditory nerve fibers and may be able to predict auditory nerve status.

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Fitting of DUET and Audiological Aspects of EAS

M Polak

Recently, Partial Deafness Cochlear Implantation subjects were upgraded with the DUET Hearing System (Combined Electric and Acoustic Stimulation device, EAS) from MEDEL.

The goals of the study were to:

- Identify important parameters of the DUET and to find optimized default values
- Identify group of subjects benefiting from EAS
- Evaluate Indication criteria for EAS
- Identify group of subjects benefiting from DUET
- Identify optimized speech performance and subjective opinion w/ DUET
- Optimize EAS programming and to find fitting paradigm

Twenty four EAS subjects with at least 12 months of experiences with their cochlear implants (CI) and minimum of one month of hearing aids (HA) participated. Speech tests and subject's opinions were investigated and evaluated for each parameter change. The detailed results will be discussed during the presentation.

The mean improvement for monosyllables in quiet was 47% (38% for CI Only) in the best aided condition for the implanted ear. Several programming parameters such as low frequency slope, compression, AGC threshold and electric and acoustic frequency ranges play an important role in the fitting of EAS. The parameters are dependent on the amount of residual hearing. Optimized programming has an effect on speech test performance and quality of hearing in EAS. The CI and HA parts may be programmed separately, but several aspects have to be taken into account.

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EAS Initiates Research into Better Fine-Structure Coding in Cochlear Implants

P Nopp, P Schleich, A Möltner, D Meister, T Bräcker, E Aschbacher

The coding strategy provides the crucial algorithm in a cochlear implant, by mans of which the stimulation data are derived from the sound signal. Recently, the interest has shifted towards better coding of the temporal fine structure in cochlear implant coding strategies. This shift was initiated by results showing that users of EAS show better speech discrimination and music listening abilities than regular cochlear implant users. Coding strategy research at MED EL therefore heavily concentrates on better coding of the fine structure, and as a result of these efforts, the FSP strategy was released with the OPUS 1 and OPUS 2 speech processors. However, although showing favourable results, research into fine structure coding continues with the aim of making fine structure information clinically available across a wider frequency range, and of making the temporal coding more accurate. In this presentation, the latest results in fine structure coding will be presented and discussed.

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Audiological Assessment of EAS Patients: Benefits of Binaural Acoustic Hearing

R H Gifford

Hearing preservation with cochlear implantation is typically associated with the surgical insertion of a short-electrode array such as that associated with the Med El EAS or Nucleus Hybrid implant systems; however, eleven patients from Mayo Clinic in Rochester have demonstrated significant preservation of low-frequency hearing with conventional, long electrode implantation. The mean degree of postoperative threshold elevation ranged from 22.7 to 28.2 dB in the range of 250 to 750 Hz. Monosyllabic word recognition in quiet was evaluated for ten of the eleven subjects in the electric alone and bimodal (electric plus contralateral aided acoustic) conditions. Mean CNC word recognition performance was 76 and 86 percent in the electric only and bimodal conditions, respectively. The degree of hearing preservation, however, was not found to be correlated with higher speech perception performance using CNC monosyllabic word recognition lists—though the small sample size may not have sufficient power to allow for such an analysis. A subset of these hearing preservation patients have also been evaluated on measures of music and speech perception in complex listening environments. The hearing preservation patients demonstrate consistently higher levels of performance on all measures. These data—while preliminary in nature—support soft surgical techniques with a goal of hearing preservation for all cochlear implant recipients.

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New Flex Optima Electrode for Electric Acoustic Stimulation

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Atraumatic soft surgery in cochlear implantation of patients with severe hearing losses is of upmost importance in order to preserve the low frequency hearing allowing a good Electric Acoustic Stimulation (EAS).
The opening of the cochlea without drilling and through the round window is the first parameter for a good EAS surgery, and the 2nd important factor is the atraumaticity of the electrode array which should be very thin and flexible as the FLEXeas electrode proposed by MED-EL since 2006.
One question or problem remains the insertion depth into the cochlea: if too short, the electrode could be not efficient enough, and if too long, it could damage the residual hearing in the low frequencies.
Together with MED-EL we propose a new electrode design: the FlexOptima electrode from 16,5 to 19,5 mm long. This electrode should be inserted with an average insertion depth of 16,5 mm for the stimulation part (electrodes contacts). The total length of the electrode from the tip to the base (marked by a silicone overhang at the base to close the round window opening) is 19,5 mm. We expect from this new electrode design a soft and atraumatic insertion and high preservation chances of low frequency residual hearing.

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Factors Influencing Auditory Prosthesis Function: Insights from Animal and Human Temporal Bone Studies

P A Leake

Our previous research in cats has demonstrated significant neurotrophic effects of electrical stimulation (ES) delivered by a cochlear implant, in ameliorating degenerative changes after early deafness. In animals deafened either at birth (to model congenital hearing loss) or at 30 days of age (to model early acquired deafness) several months of ES can elicit ≈20% higher spiral ganglion (SG) density as compared to the contralateral side; but SG survival is still far from normal in these stimulated ears. Exogenous administration of neurotrophins can further improve SG survival, but it is unclear whether initial benefits will lead to long-term efficacy when combined with subsequent prolonged ES.

Anatomical changes in the cochlear nucleus (CN) also have been examined in these animal models and related to functional consequences of ES assessed in electrophysiological experiments recording in the auditory midbrain or inferior colliculus. The fundamental cochleotopic organization of the SG-to-CN pathways are intact even in animals deafened at birth, but due to the reduced size of the CN, the topographic specificity (inferred frequency resolution) may be significantly poorer than normal after congenital deafness. Further, several months of unilateral ES from a cochlear implant introduced at <8 weeks of age shows little effect in reversing (or exacerbating) the degenerative CN changes in neonatally deafened animals. In contrast, pathological alterations in the CN are significantly less severe in animals deafened at 30 days as compared to subjects deafened as neonates. Together, findings suggest that there is an important critical or sensitive period early in development, during which the CN changes induced by deafness may be largely irreversible and electrical stimulation from a cohlear implant may not be an adequate substitute for normal auditory experience.

Electrophysiological studies also indicate that the fundamental cochleotopic organization of the central auditory system, at least to the level of the inferior colliculus, develops normally even after neonatal deafening. Following severe SG degeneration, ES can improve degraded temporal resolution but does not reverse the markedly

poorer spatial selectivity and dynamic range associated with severe pathology. These findings suggest that early profound deafness causes significant central pathology, and synchronized neural activity elicited by ES exerts a powerful influence that may profoundly alter central auditory processing in the deafened developing auditory system.

Another important finding in animal studies is that electrode insertion trauma leads to local neural degeneration in damaged cochlear sectors. Further, SG survival in the region near the stimulating electrodes is correlated with electrophysiological thresholds (electrically-evoked auditory brainstem responses, minimum neural thresholds in the inferior colliculus). These findings demonstrate the functional importance of SG survival when other factors (e.g., electrode position) can be controlled and have led to our human temporal bone studies of how mechanical attributes and positioning of CI electrodes are related to insertion trauma. Recent studies have defined a cochlear neural frequency map, i.e., a frequency-position function for the SG, inferred from the Greenwood function for the organ of Corti and by mapping the trajectories of the radial nerve fibers in normal human temporal bones. These studies also demonstrated that basal coil diameter (mean of 2 orthogonal measurments estimated from organ of Corti reconstructions) is correlated to organ of Corti length. This suggests that if one could measure basal coil diameters in individual human subjects in pre-opertive images, the frequency map as a function of mm distance around the cochlear spiral and thus optimum depth of electrode insertion might be predictable from pre-operative assessment, thus allowing the surgeon to optimize the implantation procedure for individual subjects.

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Pharmacoprotection of the Inner Ear: Strategies Based on Cellular Mechanisms of Damage

A F Ryan, K Pak, Y H Choung

Recent research in many laboratories has identified intracellular processes and pathways that participate in damage to inner ear hair cells (HCs). These include the generation of reactive oxygen species (ROS), the activation of signaling pathways that lead to cell death, and the counteracting influence of pathways that promote cell survival. We primarily study processes involved in HC loss due to ototoxic drugs.

ROS have been suggested to play a major role in HC loss due to a variety of pathways, but they are difficult to detect. Moreover, many forms of ROS occur normally in cells, where they have roles in metabolism, cell signaling and other processes. It is the highly-reactive forms of ROS (hROS) that are associated with cellular damage. Aminophenyl fluorescein (APF) and hydroxyphenyl fluorescein (HPF) are vital dyes that selectively detect hROS in cells. We assessed the presence of hROS in the neonatal rat organ of Corti (OC) during chronic exposure to 50 μM gentamicin (GM) in vitro, to examine the relationship between cell damage and hROS across HC types and across the three cochlear turns. hROS were observed in HCs prior to any visible damage, and closely matched the pattern of vulnerability of these cells. This suggests that hROS formation is an important initial step in GM-induced HC damage. Moreover, the differential sensitivity of HCs in the OC appears to be closely related to differences in the presence of hROS.

Downstream events were studied using inhibitors and activators of cell signaling and effector pathways. Signaling through the small G protein kRas, mixed lineage kinases and the JNK MAP kinase appears to play a significant role in HC death, leading to the activation of apoptosis. Cell death signaling is opposed by survival signaling mediated by hRas/MEK/Erk MAP kinase, as well as by PI3 kinase/Akt/PKB/PKC signaling. HC apoptosis is opposed by inhibitor of apoptosis (IAP) proteins.

To assess the potential for synergy between these pathways, we evaluated combinations of damage pathway inhibitors and survival pathway activators for the protection of HCs from GM-induced damage and hROS production. Some combinations proved to be more effective than single inhibitors.

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Current Status of Local Drug Delivery to the Inner Ear

S K Plontke

During the last decade there has been a rapidly increasing interest in the treatment of human inner ear disorders by local drug application to the inner ear. Local drug delivery to the inner ear exhibits obvious advantages over systemic therapy by avoiding the blood-brain-barrier, resulting in higher perilymphatic drug levels and thus a lower rate of systemic side effects because of lower systemic drug doses.

Although in humans the substances used most frequently are the aminoglycoside gentamicin and the glucocorticosteroids dexamethasone and methylprednisolone, to date a large variety of drugs have been used for local inner ear treatments. These drugs include anaesthetics (cocaine, tetracaine, novocaine, lidocaine), neurotransmitters and neurotransmitter antagonists (glutamate, glutamic acid, caroverine), prostaglandins (latanoprost), the TNF alpha blocker Infliximab, the cytokinin Kinetin and the apoptosis inhibitor AM111. Candidate treatments include calcium channel blockers, growth factors such as GDNF and NT3 and antioxidants such as methionine, thiosulfate, vitamins (ACE), magnesium, inorganic or organic selenium compounds, delivery of specific genes via viral or non-viral gene transfer to the inner ear and stem cell transplantation.

Current clinical evidence, however, is mostly based on case series and only very few controlled and even fewer randomized controlled studies exist. In an own randomized, double blind, placebo controlled trial on the safety and efficacy of continuous intratympanic dexamethasone delivered via a temporarily implanted round-window catheter for severe to profound sudden idiopathic sensorineural hearing loss after failure of systemic therapy in 23 patients, we observed an average hearing improvement in the treatment group of 13.9 dB (SD: 21.3) and in the placebo group of 5.4 dB (SD: 10.4). This difference was statistically not significant, However, the tendency for better hearing improvement in the dexamethasone group together with the rather conservative inclusion criteria, the limited placebo-controlled observation period and the absence of serious adverse events, supports further investigation of this treatment option, with an earlier start of this second line or salvage therapy after ISSHL or even as a primary therapeutic option.

As more candidate substances for the treatment of inner ear disorders are being discovered, it is equally important to develop appropriate drug delivery strategies for extra- or intra-cochlear delivery of drugs. For local drug delivery to the inner ear, a variety of drug delivery systems exist. They range from intratympanic injections of fluids with and without volume stabilization and with an without inspection of the round window niche prior to drug application to the use of controlled release drug delivery systems including different biodegradable biopolymers and external and internal pumps. Although simple intratympanic injections for drug application the round window niche are most commonly used to date, various pharmacokinetic aspects prove disadvantageous for this easy and feasible application method (as detailed in another talk at this conference).
For future strategies it will be important to address aspects of safety, feasibility and effectiveness of local inner ear drug delivery systems.

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Elution of Dexamethasone from a Cochlear Implant – Release Profiles and Efficacy Evaluation

J Kiefer, Y Liu, C Fauser, C Jolly, H Schneider, J Steinhof, H Ebenhoch, J Muller, A Lohner, K Hauber, W Arnold
Presented by C W Garnham

Objectives: Pharmacological treatment of the cochlea may be a keystone of future approaches in cochlear implantation. Among a variety of possible drugs, corticosteroids are well established and previous studies suggest that they have protective properties in relation to surgical trauma. The objective of this study was to evaluate a novel drug release system that delivers pure dexamethsone to the cochlea after implantation.
Methods: 1: In vitro: Rods of dexamethsone-eluting silicone were created with drug loading of a few percent. Release profiles of the novel cochlear implant electrode were evaluated in small and large volumes of artificial perilymph. Samples were taken at regular intervals and the concentration of dexamethasone was measured using HPLC.
2: In vivo: In a guinea pig animal model, we performed cochlear implant electrode insertion of dexamethsone-eluting electrodes and control electrodes (n=18/group). Auditory thresholds were established using BERA in response to tone-bursts and by Distortion Product Otoacoustic Emissions (DPOAE).
Results: 1: The release profiles show an initial peak of drug release, followed by release at a constant rate over 4 months and longer. Whereas the rate of release was primarily determined by the surface area in contact with the fluid, its duration was determined by the total load of substance.
2. In vivo results demonstrated at 1 month a significantly lower threshold shift, at mid to high frequencies, after implantation with dexamethasone-eluting electrodes than in animals implanted with control electrodes. This difference was maintained for 24 weeks in 9 animals evaluated for this period.
Conclusions: We have developed a novel cochlear implant electrode, capable of dexamethsone delivery with rate and duration highly reproducible and controlled by design. Animal model results suggest that the novel electrode concept may be effective in reducing the risk of significant hearing loss after cochlear implantation in selected patient groups.

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Protection of Auditory Hair Cells Against Trauma-Induced Apoptosis by Dexamethasone: Cellular & Genetic Mechanisms

T R Van De Water, C Dinh, S Haake, K Hoang, G Hoosien, S Chen, A A Eshraghi, T J Balkany

Hypothesis: Dexamethasone (DXM) protects auditory hair cells (HCs) against tumor necrosis factor alpha (TNFa)-induced loss by the activation of NFkB signaling and with the down regulation of pro-apoptotic genes and up regulation of anti-apoptotic genes.

Background: Elevated expression of TNFa and its receptor, TNFR1, is associated with trauma-induced hearing loss. DXM treatment protects the cochlea and hearing thresholds against several types of trauma-induced hearing losses, e.g. sound trauma. Electrode insertion trauma-induced hearing and HC losses are prevented in an animal model by the direct treatment of the cochlea with DXM immediately following insertion trauma.

Methods: P-3 rat organ of Corti explants challenged with an ototoxic level of TNFa was the experimental system and treatment of explants with dexamethasone was the otoprotection drug treatment system accessed. The efficacy of DXM otoprotection against TNFa and the action of a peptide inhibitor of NFkB on the observed DXM otoprotection was determined by counts of FITC-phalloidin stained HCs and qRT2-PCR was used to detected changes in the expression levels of apoptosis-related genes (i.e. Bax, Bcl-2, Bcl-xl, and TNFR1).

Results: The HC counts showed: 1) exposure to toxic levels of TNFa directly kills auditory HCs by initiating apoptosis; 2) treatment of TNFa-exposed explants with DXM protects HCs against TNFa-induced apoptosis; 3) application of an NFkB specific peptide inhibitor blocks the otoprotective action of DXM whereas treatment with the control peptide had no effect on the otoprotective effect of DXM. The results obtained from the gene expression studies show that DXM treatment of TNFa-exposed explants: 1) up regulate the transcription of anti-apoptotic genes (i.e. Bcl-2, Bcl-xl); 2) down regulate a pro-apoptotic gene (i.e. Bax); and 3) down regulate a gene associated with trauma-induced hearing loss, i.e. TNFR1.

Conclusions: Treatment of the organ of Corti with DXM protects against the ototoxic effects of the inflammation associated cytokine TNFa by initiating NFkB signaling and altering the expression pattern of apoptosis-related genes which then favor the survival of the TNFa-exposed auditory HCs. These results support the incorporation of DXM into a drug-based therapy for the conservation of residual hearing of cochlear implantation patients that will receive bimodal stimulation, i.e. EAS.

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The Differential Actions of Glucocorticoids and Mineralocorticoids in the Inner Ear

D R Trune

In spite of glucocorticoids being the major therapy for hearing loss, little is known of their direct impact on inner ear cellular functions besides immune suppression and anti-inflammation. The major role of mineralocorticoids in the ear is control of ion homeostasis, primarily via the transport of Na+ and K+. However, most natural and synthetic glucocorticoids also bind to the mineralocorticoid receptor, implying a potential role in cochlear ion homeostatic functions as well. Recent studies have begun to differentiate the cellular processes in the ear controlled by these steroid classes, as well as provide some insight into their potential therapeutic uses.

Multiple ion transport functions are required for regulating endolymph and the critical endolymphatic potential. The natural mineralocorticoid aldosterone controls Na+,K+-ATPase and the endothelial sodium channel, both prevalent in the stria vascularis and vestibular epithelia. Because maintenance of endothelial cell tight junctions (blood labyrinth barrier) is necessary for these ion homeostatic functions, any disorder that interferes with endothelial cell integrity can cause hearing loss. Interestingly, the endothelial cell is an active participant in the innate immune response, producing inflammatory cytokines and suppressing genes for tight junction and gap junction proteins. Thus, immunologic attacks (antibodies, immune complexes) can directly compromise cochlear ion transport by disrupting tight junctions and gap junctions.

Recovery of hearing loss or vestibular dysfunction can occur by a variety of mechanisms with these steroids. Glucocorticoids can directly suppress inflammation and other immune functions. However, they also upregulate genes for tight junction proteins to potentially restore the blood labyrinth barrier. In addition, they can bind to the mineralocorticoid receptor and directly upregulate genes for ion transport (Na+,K+-ATPase and the endothelial sodium channel). Water movement into the endolymph through aquaporin channels also appears to be regulated in part by glucocorticoids. Furthermore, recent animal and human clinical treatments with the mineralocorticoid aldosterone show dramatic recovery of ear disorders, suggesting disrupted ion homeostasis is an underlying factor.

These multiple functions of glucocorticoids on the ear may explain their effectiveness in some forms of hearing loss when there is no apparent immune problem. This might include sudden hearing loss or even Meniere's disease, a known disorder of ion homeostasis. Thus, a response to glucocorticoid therapy does not necessarily prove an immune-mediated hearing loss has occurred. Future therapy development must take these ion transport functions into account as a potential underlying cause.

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Molecular Strategies to Prevent Hearing Loss in a Mouse Model of Cochlear Implantation

S Pfannenstiel, H Staecker

Currently significant effort is being expended on examining the acute effects of implantation. The two best developed strategies involve the delivery of steroids to the inner ear or the delivery of anti apoptotic peptides to guinea pig implantation models. These models have used normal hearing guinea pigs and acute implantation and demonstrated that these rodents can be implanted without loss of hearing with the utilization of molecular interventions. Several lines of evidence demonstrate that it may be easier to damage an already impaired auditory system and no studies exist to elucidate whether implantation serves as a source of low grade inflammation in the cochlea, potentially damaging an already impaired system. Current animal implantation models have been chosen based on ease of surgical access not as models of hearing degeneration. A number of mouse strains exist that have hearing losses that mirror human progressive hearing loss. The C57Bl/6 mouse develops loss of high frequency hearing at 3-4 months of age and by 9 months of age has a severe to profound sensorineural hearing loss. A variety of studies have demonstrated that oxidative stress accelerates hearing loss in these mice. We have used this mouse as a model for cochlear implantation in animals with progressive hearing loss. We will review the relevant anatomy and our initial outcomes in implantation in this mouse.

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The Effect of Local Corticosteroid Treatment in Implanted Guinea Pigs on Intracochlear Tissue Growth – Histological Findings 3 Months After Implantation

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Electric acoustic stimulation (EAS) has recently become a widely accepted intervention for subjects suffering from hearing loss in the mid and high frequency range who gain no benefit from hearing aids alone. The insertion of an intracochlear electrode in a partially intact cochlea is still prone to risk, and usable residual hearing can not currently be preserved in all patients. Mechanical damage of cochlear tissue may lead to hearing loss immediately after insertion. Also secondary processes (inflammation, foreign body reaction, apoptosis) occurring days to months after the implantation may subsequently result in further, even total loss of hearing. A reduction of mechanical trauma has successfully been achieved through the development of softer electrodes and improved surgical techniques (e.g. round window insertion). A range of Pharmacological approaches to suppress secondary processes have been evaluated in animal studies – for example using a specific inhibitor of substances involved in apoptotic pathways (DJNKI-1), and long-term delivery of antioxidants and anti-inflammatory agents.

In the present animal study we used a local, single-shot treatment of the glucocorticoids dexamethasone and triamcinolone due to their broad spectrum of activity covering e.g. anti-apoptotic, antioxidant and anti-inflammatory effects. We focused on the question whether these steroids are able to preserve hearing after electrode implantation of normal hearing guinea pigs over a time span of 3 months. At the last HP workshop, physiological measurements (compound action potentials) were presented which demonstrated a clear benefit for steroid treated implanted animals versus a control group implanted and infused with artificial perilymph. The present talk is focussed on the amount of tissue growth within the scala tympani with respect to implantation and pharmacological treatment. For the histological analysis animals were perfused three months after surgery, and cochleae were removed and stored in Paraformaldehyde. Before sectioning the cochleae were decalcified and embedded in paraffin. Mid-modiolar sections (7µm) were stained with Azan and HE. For each section the area of tissue filling the Scala tympani at the implantation/cochleostomic site was measured in relation to the area left free. Inflammation is generally known to result in increased tissue growth. The following comparisons were therefore made: 1) a comparison of the extent of increased tissue growth between implanted and non implanted but cochleostomized ears. 2) The correlation between hearing loss and the amount of tissue growth and 3) the relative effects of the two steroid treatments.

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Microfluidic Pump

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A pharmacological approach to orchestrate regeneration of inner ear components will likely require the timed, sequenced delivery of relatively unstable agents directly into the inner ear. The presentation will review approaches to inner ear drug delivery from animal models to development of systems for use in patients. Emphasis will be placed on recent developments with pumps based on Microfluidic and Microelectromechanical Systems (MEMS) technology.

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Application of Drugs to the Inner Ear: Techniques, Drugs, and Results

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Experimental results demonstrate that a thin cochlea implant electrode can deliver, reliably, between .1 and 1 µg of pure dexamethasone per day over a period of several months to several years. Release curve with loading of .25% to 2% per weight of electrode were tested over several months using HPLC. Relative standard deviation varies between 1% and 6% depending on loading(n=12, each conditions).

The main technical problem to solve is confining the release between 2 weeks and 2 months. In vivo experiment show better preservation in guinea pig implanted with steroid eluting silicone than those implanted with non eluting silicone.

Another way to deliver drugs into the cochlea is through passive diffusion from an intra operatively loaded reservoir within the electrode. This is preferred for limited stability, protein rich, solutions (nerve growth factors). Release curves from the drug delivery reservoir are being documented with a marker solution.

A third way for inner ear drug delivery is through a bolus of drug injected prior to electrode insertion. A soft and low trauma catheter and technique can perform this operation, while a drop of drug at the cochleostomy does not penetrate into the scala. CT scan of temporal bones show that a contrast agent after injection 15 mm into the scala tymapani remains in the scala. Histology is being performed to assess damage.

Finally, a biodegradable coating on the electrode has been investigated. A burst release followed by a shorter release is possible. Electrode mechanical properties are affected by the coating and localized PH changes need quantification.

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Evaluation of Reservoir-Based Dexamethasone Delivery

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This study is an evaluation of the feasibility of delivering a drug passively from a reservoir in a cochlear implant electrode. The concept for the full-sized (human) implant involves the passive diffusion of a drug from a 10µl reservoir built within the electrode itself. The reservoir would allow the drug to diffuse through a slit or through micro channels built within the silicone of the electrode carrier. Openings would be limited to the intra cochlear portion of the array - the reservoir however could in principle extend several cm within the middle ear portion of the array to increase the therapeutic period. Loading of the drug into the reservoir would take place intra operatively through the same port and septum that has been designed and tested for long term drug delivery. The potential advantages of this system include tight control of dosage, uniformity of delivery along the array, burst release followed by continued delivery, a generic delivery device loadable by the surgeon, and little change in electrode properties. The same principle might also be developed for drugs in gel form. Evaluation of the concept was taken further through in-vitro and in-vivo evaluations of a simplified device scaled down to the dimensions of a guinea pig cochlea - a tube filled with 4.5 microlitres of Fortecortin (an injectable preparation of dexamethasone), open at one end. The release of drug over time into saline, and its reproducibility, was evaluated with high performance liquid chromatography (HPLC) analysis at 37 degrees. The practicalities of device filling and implantation were evaluated in a guinea pig model, and resulted in design modifications to improve the ease of filling and to retain the drug within the reservoir. The efficacy of the first prototype device in combination with Fortecortin was evaluated in two separate studies against a saline-filled control reservoir. The results of these studies appeared contradictory and possible reasons for the inconsistent efficacy data will be considered. Finally, six tubes implanted for 90 days were explanted, and examined for the presence of tissue growth and invasion by common infective species of bacteria. None were found in these devices.
In conclusion, a system to evaluate the reservoir concept has been developed. It shows that the device is feasible, however further development work and assessment is needed to take the concept further.

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Local Drug Delivery to the Inner Ear – Strategies and Patient Groups

A N Salt

Many disorders of the inner ear could potentially be treated by local drug applications, but use of this approach is limited by our inability to apply drugs quantitatively. Drug delivery must balance patient safety, related to the degree of invasiveness of the procedure, with the reliability and efficacy of the applied drug dose. At one extreme, intratympanic injections are relatively noninvasive and have proven to be safe in clinical practice, but animal studies show that the drug levels achieved in the inner ear are highly variable and primarily localized in the basal cochlear turn. Intralabyrinthine injections provide far better control of the applied drug level, probably improving the efficacy of the applied treatment, but improved efficacy is presently offset by the additional risk of inducing trauma to the ear by the drug application. Advancing the field requires that efficacy and safety of intralabyrinthine drug injections must be demonstrated. Currently-performed invasive surgical procedures, such as stapedectomies and cochlear implants in patients with residual low frequency hearing represent patient groups that could potentially benefit from intralabyrinthine drug applications at the time of surgery, with minimal additional risk. Once safety and efficacy is demonstrated in these groups, other serious problems of the ear, such as sudden sensorineural hearing loss, peripheral tinnitus and acute noise exposure could be considered for intralabyrinthine rather than intratympanic injections. However, appropriate safe and effective intralabyrinthine drug delivery procedures still need to be developed. Drug injections into the basal turn of scala tympani of guinea pigs produce large gradients along the cochlea and a rapidly-declining basal turn concentration with time, due to the combined influences of clearance and redistribution of drug into other parts of the ear. In contrast, experiments in which the entire perilymph space was filled with the marker TMPA by injection from a pipette sealed into the lateral canal produced almost uniform concentrations throughout the entire inner ear. With this protocol, concentration remained considerably more stable with time, because redistribution was almost eliminated. In addition, scala vestibuli provided a substantial "pool" to

replenish losses from scala tympani, as clearance from scala vestibuli and the vestibule was slower than that from scala tympani. For all delivery methods in animals, even small fluid leaks during or after drug injection result in a rapid washout of drug from the ear. Filling the human ear with drugs to a comparable extent to that in animals must take into account interspecies differences, such as the size and patency of the cochlear aqueduct. A lower rate of communication between perilymph and CSF in humans may reduce the risk of drugs influencing the brainstem, but may mechanically limit drug injections into the sealed cochlea. The relatively large cochleostomies performed in cochlear implantation and stapedectomy would provide a suitable outlet if drug was injected via a very small fenestration in the opposing scala. Widespread acceptance of such procedures will depend on whether the benefits of drug application outweigh the additional risks (mechanical and chemical) associated with the application.

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Neurotrophins and the development and maintenance of inner ear innervation

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The history of neurotrophins in the ear goes back to the seminal paper of Rita Levi-Montalcini (1949) showing that the ear exerts a neurotrophic influence on brainstem auditory nucleus development. While Levi-Montalcini became famous for the discovery of nerve growth factor (NGF), this factor appears to be the only neurotrophin with little to no effect on ear development.

During the 1990, single and double null mutations for the neurotrophin brain derived neurotrophic factor (Bdnf) and neurotrophin 3 (NT3, now Ntf3) showed that those two factors and their specific receptors, trkB and trkC (now Ntrk2 and Ntrk3), are essential for the maintenance of embryonic inner ear innervation (Ernfors et al., 1995; Fritzsch et al., 1995). Intriguing and somewhat difficult to resolve were issues related to the specific function of individual neurotrophins and their receptors. The consensus reached is that Bdnf supports all canal cristae innervation, a large part of the saccule and utricle innervations and a small part of the cochlea innervations, somewhat biased toward type II neurons. In contrast, Ntf3 has no importance in canal cristae innervations, has limited importance in utricle and saccule innervations and plays a major role in the innervations of the cochlea. Knockin mice where one neurotrophin was replaced by another one showed that both are functionally equivalent but that spatio-temproal expression profiles result in what appears to beunique actions of each neurotrophin.

While much has been learned about the developmental role of neurotrophins in the inner ear, their roles in the mature inner ear remain unclear because knockouts of neurotrophins or their cognate Trk receptors results in neonatal lethality. Because NT-3 is expressed in the inner hair cells and because exogenous neurotrophins support SGN survival and promote SGN neurite outgrowth in vivo after hair cell loss, it seems likely that the developmental role of NT-3 persists into the mature cochlea. (Also, there is evidence for a role of endogenous NT-3 in the organ of Corti in reinnervation of inner hair cells by SGNs following excitotoxic damage in vitro.)

However, until NT-3 can be selectively knocked out in the postnatal cochlea, the precise roles of NT-3 can't be firmly established.

Given that neurotrophins clearly can exert a beneficial effect on neuronal survival in adult ears it seems logical to pursue this effect further for the ultimate benefit of rescuing all sensory neurons even if no hair cells exist at all, thus allowing long term use of cochlear implants. Such an approach requires resolution of a number of treatment issues that secure regulatable expression levels of neurotrophins in the vicinity of the implanted electrode.

We are using transgenic approaches to induce expression of modified Ntf3 (with signal capacity of both Ntf3 and Bdnf) in stably transfected scala media cells to drive expression levels through the use of clinically insignificant amounts of Erythromicine to activate a bacterial promoter element conjugated to the modified Ntf3 gene. In vitro data already demonstrated the effectiveness of this approach and mouse models are approaching completion for ultimate tests of this approach (Pettingill et al., 2008). If successful, such treatment can be used in early hearing loss to provide long term rescue of sensory neurons before and after cochlear implants. It also could rescue sensory neurons to ultimately reconnect them to newly grown hair cells, should attempts to regenerate hair cells become successful.

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Hair Cell Regeneration: Identification of Progenitor Cells that Gives Rise to Hair Cells

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Hair cell (HC) and supporting cell (SC) productions are completed during early embryonic development of the mammalian cochlea. However, increasing evidence suggests that new HCs can be generated in mammalian sensory epithelium. To produce new HCs in a neonatal sensory epithelium, immature cells must be present, eventually proliferate and differentiate HCs.

We have first search for the presence of progenitors in the organ of Corti. Cultured immature nestin positve cells present in the newborn rat organ of Corti at the level of the great epithelial ridge can proliferate and subsequently differentiate into HCs and SCs together with the detection of nestin (+) cells in vivo at the spiral limbus in the P15 mature organ of Corti.

As a second approach, we have looked for the possibility of existing epithelial cells of the organ of Corti to differentiate into HCs. When fetal rat organ of Corti explants are cultured, supernumerary OHCs and supernumerary Deiters' cells are produced, without any additional cell proliferation. Supernumerary OHCs are produced at the distal edge of the organ of Corti. When the number of OHCs increases, while the total number of cells remains constant, the number of Hensen's cells decrease. In addition to existing OHCs, supernumerary OHCs, tectal cells and Hensen's cells expresse specific HC markers, i.e. jagged2 (Jag2) and Math1 in E19 organ of Corti explants after 5 days in vitro, suggesting that Hensen's cells retain the capacity to differentiate into OHCs . Roscovitine, a chemical inhibitor of cyclin-dependent kinases (CDKs), significantly increased the number of hair cells (HCs) and corresponding supporting cells (SCs) by triggering differentiation of precursor cells without interacting with cell proliferation.

In conclusion, new hairs cells can be generated presumably from the Hensen's cell progenitors and/or from progenitors located in the greater epithelial ridge area or in the inner sulcus area.

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