Original Paper

ORL

ORL 2011;73:219–228
DOI: 10.1159/000329791

Received: March 8, 2011
Accepted after revision: May 24, 2011
Published online: July 21, 2011

Protection of Inner Ear Function after Cochlear Implantation: Compound Action Potential Measurements after Local Application of Glucocorticoids in the Guinea Pig Cochlea

Susanne Braun[a, b, e] Qing Ye[f] Andreas Radeloff[c] Jan Kiefer[d]
Wolfgang Gstoettner[a] Jochen Tillein[a, g]

Departments of [a]Sensory Physiology II and [b]ENT, J.W. Goethe University, Frankfurt am Main, [c]Department of ENT, Julius Maximilian University Wuerzburg, Wuerzburg, and [d]Department of ENT, Klinikum rechts der Isar, Technical University Munich, and [e]MED-EL Deutschland GmbH, Munich, Germany; [f]Department of Otolaryngology, Fujian Medical University, Fujian Provincial Hospital, Fuzhou, China; [g]MED-EL Innsbruck, Innsbruck, Austria

Key Words
Glucocorticoids · Cochlear implantation · Compound action potentials · Hearing preservation · Otoprotection

Abstract
Background: Cochlear implant users with residual hearing often benefit greatly from simultaneous electric and acoustic stimulation. However, implantation can cause trauma to the inner ear, resulting in poorer hearing postoperatively. We investigated whether a single local injection of glucocorticoids can reduce hearing loss in long-term implanted guinea pigs. ***Methods:*** Three groups of animals underwent bilateral surgery. One ear was implanted with an electrode, and the contralateral ear received a cochleostomy only. A single dose of the glucocorticoids triamcinolone or dexamethasone, or of artificial perilymph was infused into cochleae via cochleostomy. Compound action potentials were measured before and after application and for 3 months postoperatively. Tissue growth was measured as the percentage of the total area of the scala tympani that was obliterated. ***Results:*** Ears subjected to cochleostomy only and treated with glucocorticoids demonstrated a mild hearing loss. In the implanted ears, both glucocorticoids preserved hearing at least temporarily. The volume of tissue growth within the scala tympani was not reduced, and there was no relation between the amount of tissue and hearing loss. ***Conclusions:*** Both glucocorticoids show a potential benefit for hearing preservation in implanted ears. Glucocorticoid therapy may be useful to protect residual hearing during cochlear implantation.

Introduction

Cochlear implants have developed progressively over the past 30 years and are now a well-established intervention not only for profound hearing loss, but also for partial deafness, in which direct electrical stimulation of the auditory nerve is provided in combination with acoustic amplification of low-frequency residual hearing. This is called electric-acoustic stimulation (EAS) [1–6]. Atraumatic cochlear implantation typically preserves low-frequency hearing [1], thereby yielding improved speech understanding, especially in noise, and potentially improving music appreciation possibly due to enhanced perception of low-frequency speech formants and of the lower harmonic frequencies in music [7, 8]. Several EAS studies have presented clear evidence of substantial patient benefit [1, 2, 9, 10]. However, there is a potential risk

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0301–1569/11/0734–0219$38.00/0

Accessible online at:
www.karger.com/orl

Dr. rer. nat. Susanne Braun
Zentrum für HNO, Physiologie/Audiologische Akustik
Universitätsklinikum der J.W.-Goethe-Universität
Theodor-Stern-Kai 7, DE–60590 Frankfurt am Main (Germany)
Tel. +49 69 6301 6728, E-Mail s.braun@med.uni-frankfurt.de

of losing residual hearing immediately after surgery due to insertion trauma or later as a result of delayed body reactions.

Using thin and flexible electrode arrays with an insertion depth not exceeding 20 mm has been shown to improve hearing preservation by reducing mechanical trauma in the cochlea [1–4, 9, 11, 12]. Recent studies have also shown that hearing can be maintained with deeper insertions of very flexible electrode arrays [13]. When hearing is lost, it may be lost immediately, within days of implantation or over subsequent months. The exact mechanisms of hearing loss are not completely understood. Among others, inflammatory and immunological responses of the body to implantation with subsequent connective and bone tissue growth have been suggested. Therefore, inflammation-suppressing substances, such as glucocorticoids, have been applied locally during implantation [2–4, 14]. The impact of glucocorticoids on hearing was first published in the late seventies [15]. That publication demonstrated a therapeutic effect of chronic administration of cortisone on autoimmune inner ear disease.

In a previous study of ours, intracochlear application of a crystalline suspension of the glucocorticoid triamcinolone (Tria) succeeded in alleviating hearing loss caused by drilling a cochleostomy for 1 month [16]. Other studies showed that the corticosteroid dexamethasone (Dex) applied locally with a micropump [17] or at the round window (RW) [18] reduced hearing loss after insertion trauma [17] and chronic implantation [18] for 1 month [17, 18] and 3 months, respectively [19]. Local drug delivery has several advantages over systemic application, including fewer side effects and the ability to deliver higher doses at the intended site.

We addressed 3 primary questions in our study: (1) Does a locally applied glucocorticoid lead to hearing preservation or threshold recovery after cochlear implantation during a time span of 3 months? (2) What is the pharmacological effect of locally applied glucocorticoids in nonimplanted cochleae? (3) Does a locally applied glucocorticoid influence postsurgical tissue growth within the scala tympani?

Materials and Methods

Electrode Design

We implanted custom-made guinea pig electrodes consisting of 2 platinum wires and 2 flat PT contacts in a medical grade silicone carrier with a total diameter of 0.5 mm (MED-EL GmbH, Innsbruck, Austria). A 5-pole connector was linked to the contacts. The remaining poles were later connected to 2 RW and 1 indifferent gold electrode placed in the neck muscle. The connector was permanently fixed to the skull to allow consecutive compound action potential (CAP) measurements over 90 days.

Glucocorticoids and Control Suspension (Dose in Single 3-μl Injection)

(1) 120 μg Tria (triamcinolone acetonide 21-dihydrogenphosphate disodium; Volon A solubile 40 mg/ml; Dermapharm AG, Grünwald, Germany), (2) 24 μg Dex (dexamethasone 21-dihydrogenphosphate dipotassium; Fortecortin inject 8 mg/ml; Merck KGaA, Darmstadt, Germany) and (3) artificial perilymph (custom made; AP) were used. The drug formulae were applied as typically used by surgeons during cochlear implantation surgery in human patients, i.e. as provided by manufacturers. Glucocorticoids were sterile and noncrystalline (i.e. nondepot) preparations and were taken directly from sealed glass ampullae prior to in vivo administration. AP was sterile filtered and frozen until in vivo application.

Antibiotics

Two to 3 drops of enrofloxacin (Baytril; Bayer AG, Leverkusen, Germany) were administered into the bulla after surgery followed by daily subcutaneous injection of the same antibiotic (10 mg/kg) on surgery day and the 3 consecutive days.

Anesthesia

During surgery and for subsequent electrophysiological measurements, the animals received intraperitoneal injections of 85 mg/kg ketamine (Pharmacia & Upjohn GmbH) and 8.5 mg/kg xylazine (Bayer AG). Prior to surgery, a single intraperitoneal dose of 0.25 mg/kg atropine sulfate (B. Braun AG, Melsungen, Germany) was administered to suppress secretion within the respiratory tract and to stabilize blood pressure.

Experimental Animals

Fifteen pigmented guinea pigs (BFA bunt; Charles River Wiga, Sulzfeld, Germany) were used in this study. The experiment complied with the ethical guidelines for the Land Hessen, Regierungspräsidium Darmstadt (approval No. F40/21). Because each animal had 1 implanted and 1 cochleostomized ear treated with the same drug/AP, experimental groups consisted of ears per group instead of animals per group. The 2 glucocorticoids were delivered at different concentrations because Dex has a potency 4–5 times that of Tria when applied systemically [20]. The implanted and cochleostomized ears were divided into 3 experimental groups, Tria, Dex and AP, with each group consisting of 5 ears.

Surgery and Implantation

Before surgery normal hearing was probed roughly with Preyer's reflex followed by more precise measurements of click auditory brainstem response (ABR) thresholds. Guinea pigs were operated on both ears consecutively using a retroauricular approach. First, Teflon-coated gold wires (Goodfellow, Bad Nauheim, Germany) for CAP measurements were placed bilaterally at the RW. This was followed by the first measurement of click CAP thresholds and audiograms that served as reference measurements for all following measurements for each animal. ABR and CAP measurement procedures will be described in more detail in the following section.

A cochleostomy was carefully drilled into the basal turn of the cochlea ventrally from the RW, through which a volume of 3 μl of either Dex, Tria or AP was carefully (approx. 20 s) infused executing a small amount of pressure into the scala tympani by means of a 10-μl Hamilton syringe (Hamilton, 26-gauge needle = 0.405 mm) that was inserted 1 mm into the cochlea. The implant was then inserted so that both contacts were completely inside the scala tympani, i.e. up to 3 mm deep. Insertion depth was therefore very consistent. A small amount of backflow was observed due to the fluid displacement, but because the procedure and the drug infusion were performed in a similar fashion in all guinea pigs the assumed fluid loss and intracochlear distribution of drug were approximately the same for all ears. The contralateral ear was treated similarly but without implantation. Each animal was treated with the same drug in both ears to avoid artifacts from crossover diffusion of the drug via the cochlear aqueduct. Cochleostomies were covered with a small muscle graft.

CAP and ABR Test Parameters and Measurements

All measurements were made in a soundproof chamber (IAC 400-A) with an inversely driven microphone (B&K 4134, 1/2 inch; Bruël & Kjær, Germany) that was inserted in the outer ear canal.

Auditory Brainstem Responses. For measurements thin silver wires were pulled through the skin with a sterile cannula and placed behind the pinnae and on the vertex, respectively. The wires were soldered to plugs allowing the connection to the recording device. Clicks (100 ms duration) were averaged over a rate of 100 repetitions per intensity step (2 dB). The bandpass filter was set between 10 Hz and 10 kHz.

Compound Action Potentials. Settings for click CAP measurement and repetition rate were the same as for ABR recordings except for the bandpass filter that was set between 0.1 and 3 kHz. CAP audiograms were obtained by stimulating with gaussian-curve-shaped tone pips (bandwidth: 2/3 octave) with a frequency range of 0.1–64 kHz (2 steps/octave for a total of 19 frequencies) and at intensities between 10 and 100 dB attenuation (0 dB = 120 dBSPL, 5-dB steps, 30 repetitions/intensity step). Stimuli were generated by a PC system equipped with a multifunction I/O interface card (National Instruments) and Audiolab software (http://otoconsult.de, Germany). The software automatically calculated the thresholds that were then shown color coded. Additionally, each threshold was confirmed visually on prints.

We tested hearing before and after drug/AP application and implantation, followed by consecutive measurements on days 1, 3, 7, 14, 21, 28, 60 and 90. From day 3 on, additional click ABR thresholds were measured to check CAP gold electrodes for proper operation. The impedance of all electrodes was monitored continuously during measurements. Results were given in threshold shift relative to the presurgery thresholds.

Histology

The amount of tissue growth was determined in percent of the area of scala tympani in the basal turn and correlated with threshold shift. After hearing testing, animals were deeply anesthetized and perfused transcardially with 4% paraformaldehyde. Cochleae were removed and processed for paraffin embedding. Sagittal sections cut along the midmodiolar plane were stained with hematoxylin-eosin and Azan. At least 5 sections of each cochlea were submitted to quantitative area measurements (NIH Image, Scion Image).

Statistical Analyses

CAP data were analyzed with the nonparametric Wilcoxon-Mann-Whitney U test at $\alpha = 0.05$. Histological data were analyzed with the Spearman correlation analysis (2-tailed, $\alpha = 0.05$).

Results

Frequencies from 0.1 to 64 kHz were classified in groups from 0.125 to 0.7 kHz (low frequencies), 1 to 8 kHz (middle frequencies) and 11.3 to 64 kHz (high frequencies). Mean threshold values were calculated for each frequency group and individual ear, yielding 3 values per ear and date. Threshold shifts immediately following the surgery were observed in all groups with some recovery occurring in some animals, irrespective of treatment.

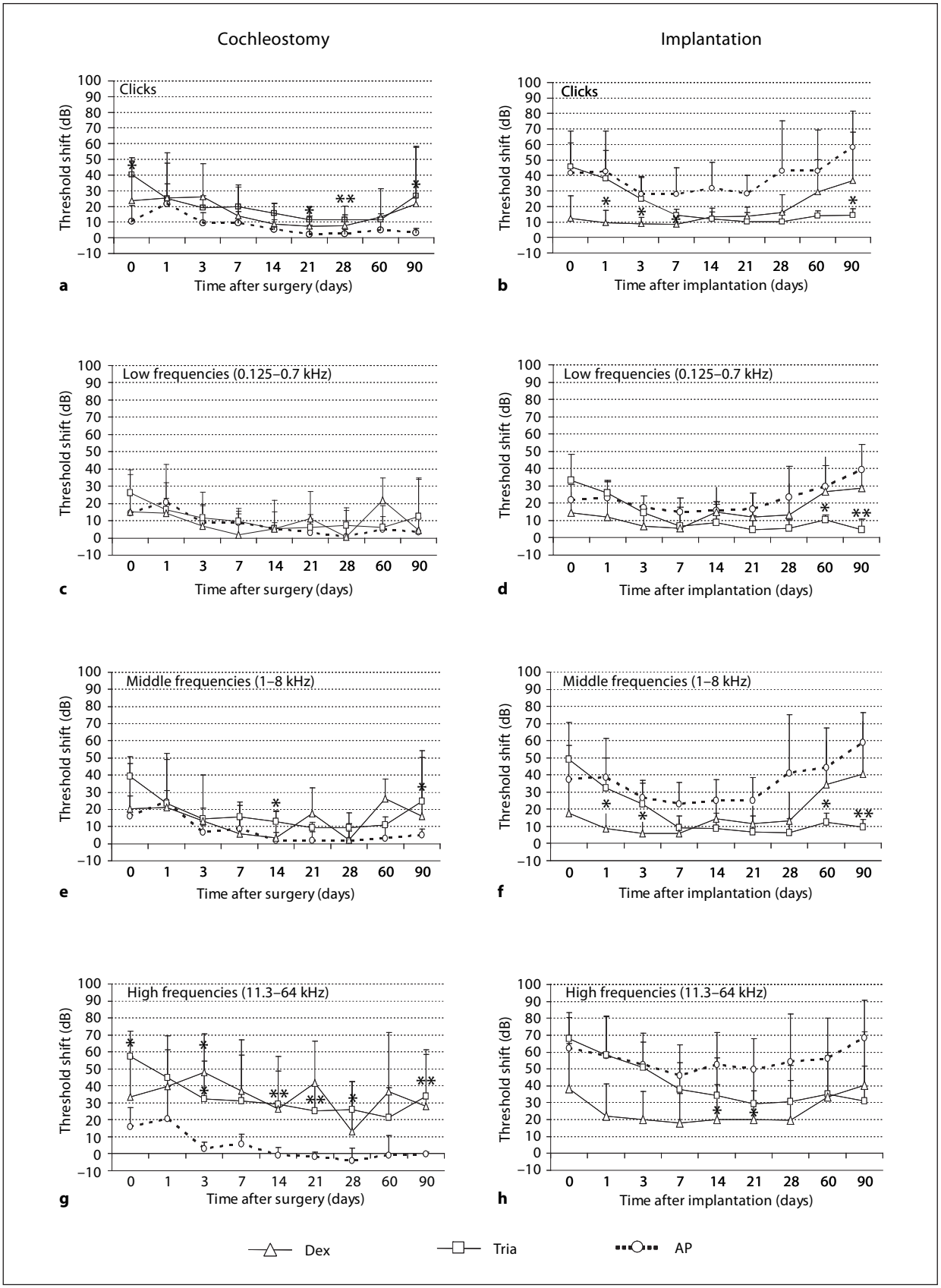
Click CAP Threshold Shifts

For click CAP shifts in glucocorticoid/AP-treated cochleostomized ears (fig. 1a), no differences in threshold shifts were observed between Dex and AP ears over the course of 90 days. On the other hand, Tria-treated ears revealed significantly greater shifts after 21 days (table 1).

Regarding click CAP shifts in glucocorticoid/AP-treated implanted ears (fig. 1b), a comparison of figure 1a and b reveals a clear increase in the extent and persistence of hearing loss after implantation for the ears treated with AP as compared with cochleostomized AP ears. Dex and Tria ears did not show such an effect. Also, hearing recovery was smallest in AP ears (fig. 1b). Threshold shifts in Dex ears were significantly smaller compared with AP ears during the first 7 days but increased thereafter (table 1). On the other hand, Tria ears started with large shifts, as in the AP ears, that decreased after 1 week but were then significantly smaller in comparison to AP ears by day 90 (table 1).

Frequency-Specific CAP Threshold Shifts

In glucocorticoid/AP-treated cochleostomized ears (fig. 1c, e, g), there was an initial threshold shift after surgery in all frequency ranges. However, only the AP-treated ears exhibited a complete recovery that persisted for 90 days. Limited recovery took place in the 2 glucocorticoid-treated groups but this did not include the middle and high frequencies (fig. 1e, g). In the low frequencies, threshold shifts were generally small in all groups (fig. 1c). No significant differences were seen between glucocorticoid-treated and AP-treated ears over the course of 90 days (table 1). In the middle frequencies, when comparing the Dex and AP ears, the data revealed no differences be-


Cochleostomy
Implantation
Clicks
Low frequencies (0.125–0.7 kHz)
Middle frequencies (1–8 kHz)
High frequencies (11.3–64 kHz)
Threshold shift (dB)
Time after surgery (days)
Time after implantation (days)
a
b
c
d
e
f
g
h
Dex
Tria
AP

1

Table 1. p values for threshold shifts

	Clicks		0.1–0.7 kHz (low)		1–8 kHz (middle)		11.3–64 kHz (high)	
	Dex	Tria	Dex	Tria	Dex	Tria	Dex	Tria
Threshold shift after cochleostomy								
0 days	0.37	0.03*	0.37	0.19	0.8	0.06	0.15	0.016*
1 day	0.55	0.22	0.69	0.84	0.55	0.31	0.31	0.15
3 days	0.1	0.1	0.73	0.84	0.29	0.15	0.016*	0.03*
7 days	0.84	0.42	0.73	0.69	1	0.31	0.29	0.15
14 days	0.69	0.06	1	0.84	0.9	0.02*	0.29	0.008**
21 days	0.69	0.03*	0.9	0.55	0.55	0.06	0.29	0.008**
28 days	0.69	0.008**	0.41	0.84	0.55	0.22	0.41	0.03*
60 days	1	0.15	0.4	0.84	0.07	0.15	0.57	0.06
90 days	0.69	0.02*	0.69	0.55	0.31	0.02*	0.1	0.008**
Threshold shift after implantation								
0 days	0.17	0.69	0.35	0.29	0.17	0.41	0.35	0.55
1 day	0.03*	0.42	0.22	0.55	0.03*	0.69	0.1	1
3 days	0.03*	0.84	0.1	0.55	0.03*	0.55	0.06	0.55
7 days	0.03*	0.15	0.15	0.55	0.1	0.15	0.1	0.84
14 days	0.15	0.1	1	0.55	0.42	0.095	0.03*	0.22
21 days	0.1	0.1	0.55	0.1	0.22	0.06	0.03*	0.22
28 days	0.42	0.15	0.22	0.1	0.42	0.06	0.1	0.31
60 days	0.31	0.11	0.69	0.03*	0.82	0.02*	0.22	0.11
90 days	0.22	0.02*	0.69	0.008*	0.42	0.008*	0.15	0.1

Statistical evaluation of threshold shift data: 2-tailed nonparametric Wilcoxon-Mann-Whitney U test at $\alpha = 0.05$ (significance levels: * $p < 0.05$, ** $p < 0.01$).

Fig. 1. Click-evoked (**a**, **b**) and frequency-specific (**c–f**) CAPs in cochleostomized and implanted ears treated with Dex, Tria or AP. Comparisons are made between treatments with glucocorticoids and ears treated with AP. * $p \leq 0.05$, ** $p \leq 0.01$. **a** Click-evoked CAP shifts after cochleostomy: initially large threshold shifts are evident on days 0 and 1 after all treatments. In Tria ears, shifts on day 0 are significantly larger compared to AP ears. Although a decrease in threshold shift is observed in all groups, recovery is most pronounced in AP ears. The difference is only significant between Tria and AP ears but not between Dex and AP ears. **b** Click-evoked CAP shifts after implantation: threshold shifts after AP administration are large throughout the whole measurement time. This was also the case for Tria-treated ears on the first 3 days; however, the shifts decrease towards the end of the measurements. On day 90, the difference from AP ears is significant. Dex ears, in contrast, reveal significantly smaller threshold shifts compared with AP ears on days 1, 3 and 7. Threshold shifts increased thereafter. **c** CAP shifts of low frequencies (0.125–0.7 kHz) after cochleostomy: no differences among treatments were seen at any time point. Average threshold shifts were between 0 and 20 dB. **d** CAP shifts of low frequencies (0.125–0.7 kHz) after implantation: threshold shifts in Tria-treated ears are significantly smaller on days 60 and 90. There is no difference between Dex and AP ears. **e** CAP shifts of middle frequencies (1–8 kHz) after cochleostomy: no difference was seen between Dex and AP ears. Threshold shifts in Tria ears were significantly greater on days 14 and 90. **f** CAP shifts of middle frequencies (1–8 kHz) after implantation: there is a difference in time course of efficacy between the 2 glucocorticoids; on days 1 and 3, significantly smaller threshold shifts are present in Dex ears, whereas in Tria ears this was the case on days 60 and 90. **g** CAP shifts of high frequencies (11.3–64 kHz) after cochleostomy: in Dex ears, a significantly larger threshold shift was present on day 3 only. Threshold shifts in Tria ears were significantly greater on days 0, 3, 14, 21, 28 and 90. **h** CAP shifts of high frequencies (11.3–64 kHz) after implantation: threshold shifts in Dex-treated ears are smaller over the course of 28 days after implantation. This was significant on days 14 and 21. Shifts increased thereafter. Threshold shifts in Tria ears were similar to those of AP ears during the first week after implantation. They decreased towards the 3rd month compared with the shifts in AP ears that remained large. The difference did not reach significance.

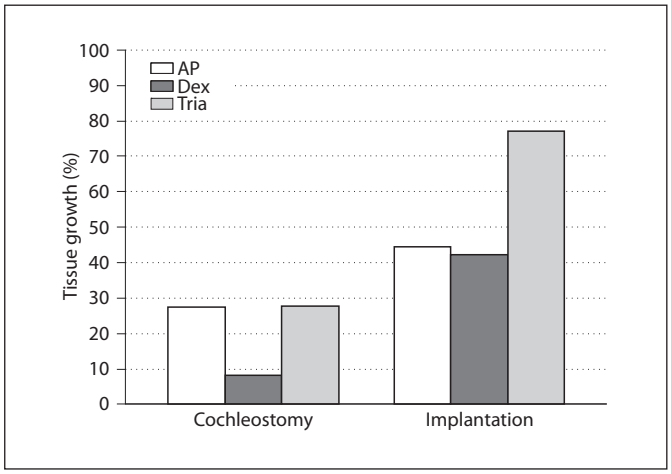


Fig. 2. Tissue growth after surgery (at 3 months): cochleostomy versus implantation. There is a tendency for more tissue growth in scalae tympani in implanted cochleae compared with cochleostomized inner ears. Due to high variability between ears, this was not statistically significant (Spearman correlation test, 2-tailed). There was no difference between the glucocorticoid treatments and nontreated (AP) cochleae, not for glucocorticoid-treated or for nontreated scalae tympani.

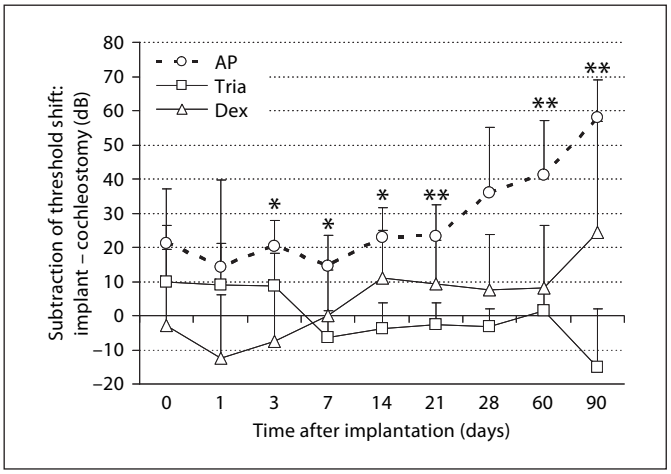


Fig. 3. CAP shifts of middle frequencies (1–8 kHz): efficacy of the pharmacological treatment in implanted ears. This was determined by subtracting the threshold shifts of cochleostomized ears from those of implanted ears. Only the results of middle frequencies are shown here. The values are given in decibels on the y-axis. Statistics: Mann-Whitney U test, 2-tailed, and Bonferroni adjusted $p \leq 0.025$. From day 3 on, threshold shifts were significantly larger in untreated (AP) implanted ears, whereas shifts in implanted ears treated with glucocorticoids did not differ from equally treated cochleostomized ears. * $p \leq 0.05$, ** $p \leq 0.01$.

tween the 2 treatments (fig. 1e). Mean threshold shifts were significantly greater in Tria ears than in AP ears only on days 14 and 90 (table 1). In the high frequencies, threshold shifts after glucocorticoid application were consistently greater than those obtained by treatment with AP (fig. 1g). When comparing Dex and AP ears, threshold shifts were significantly greater only on day 3 in Dex ears (table 1). In contrast, the high-frequency threshold shifts were significantly greater in Tria ears than in AP ears over almost the whole course of the 90 days (table 1).

In glucocorticoid/AP-treated implanted ears (fig. 1b, d, f, h), the audiograms demonstrate that the largest threshold shifts were obtained for the highest frequencies, nearest the site of cochleostomy, drug delivery and electrode insertion. Compared with AP ears, Dex ears revealed smaller threshold shifts during the month succeeding the implantation but deteriorated thereafter. In contrast, after initially large threshold shifts, Tria ears showed clear recovery of low- and mid-frequency hearing by day 28, which was maintained through day 90 (fig. 1d, f). In the low frequencies, when comparing all 3 groups, no difference in threshold shifts was observed in the course of the experimental time span except from days 60 and 90 (fig. 1d) when shifts where significantly smaller in Tria ears than in AP ears (table 1). In the middle and high frequencies, as seen for click threshold shifts, an antidromic time course of threshold shifts was seen in Dex and Tria ears in comparison with AP ears whose shifts were overall greater over the course of the experiment (fig. 1f, h). In comparison with AP ears, shifts in Dex-treated ears were significantly smaller over the course of 28 days (table 1). In contrast, shifts in Tria ears were as large as in AP ears at the beginning but decreased significantly towards day 90 in the middle frequencies (table 1).

Histological Evaluation

Cochleae showed great variability in terms of tissue growth (fig. 2). A loose mesh of fibrous tissue could be seen only in the first half of the basal turn of the scala tympani in both implanted and cochleostomized cochleae. In some cases ossification of various degrees was apparent. Implants were always enclosed in a solid sheath of connective tissue. Implanted cochleae tended to exhibit more pronounced tissue growth than cochleostomized cochleae (fig. 2). Cochleostomized ears showed less growth than implanted ears but this difference was not

significant. There was also no correlation between hearing loss and tissue growth in cochleostomized (r = 0.145) and implanted cochleae (r = –0.107) 90 days after surgery or implantation, respectively.

Discussion

This study is the first to reveal a protective effect for hearing after cochlear implantation from a single application of 2 different glucocorticoids measured over a 90-day follow-up period. Moreover, the results suggest a possible difference in the time-dependent behavior of the effects of the 2 drugs Tria and Dex with the dosing regimen used. Although glucocorticoids have already been applied locally in EAS surgery [4] because of their assumed benefit for hearing preservation, it has not yet been part of the surgical routine. The results of our study and others [17–19] strongly suggest their use as routine in cochlear implantation in combination with atraumatic surgery and the use of suitable EAS electrodes, especially in EAS surgery to counteract or prevent mechanisms that otherwise might lead to loss of residual hearing.

Study Design

This study aimed at investigating the efficacy of 2 glucocorticoids that are commonly used in hospitals under routine operating conditions. This included drugs in their ready-to-use formula because surgeons rarely prepare drugs especially for use in implantation. The comparison of 2 different glucocorticoids provided additional information whether glucocorticoids perform equally well or whether differences in efficacy between glucocorticoids should be considered. We measured CAPs rather than ABRs because of their more accurate frequency specificity. In addition, we chose frequencies between 0.125 and 64 kHz in 2 steps/octave for a total of 19 frequencies. The experimental time of 90 days allowed investigation of long-term efficacy, which is important in hearing preservation implantation. The additional investigation of a pure pharmacological effect in cochleostomized cochleae further enhanced the scope of our study.

Our electrode design suggested implantation through a cochleostomy rather than through the RW. RW insertion of the wired and thus relatively stiff electrode requires heavy bending with an obtuse angle, which enhances the risk of damaging the modiolus. The RW approach has however an advantage over cochleostomy inasmuch as it makes drilling redundant and might therefore abate noise trauma [21]. But as threshold shifts in cochleostomized cochleae treated with AP (fig. 1) demonstrate, there is only a mild if any hearing loss, which rather rules out a distinct influence of the drilling on hearing. By the same token, it has been shown that making a cochleostomy by means of a diamond drill caused only minimal hearing loss in guinea pigs, even less than using a laser [22].

Although we achieved significant results with only 5 ears/group, a lot of variability was seen. Some visible trends did not reach significance that might have been achieved with a larger number of ears. This is apparent for instance in middle and high frequencies of implanted ears. The beneficial effect of Dex treatment actually lasts until day 28 (fig. 1f, h). Likewise, hearing improvement in Tria-treated ears already starts on day 21 (fig. 1f) and day 14, respectively (fig. 1h).

The use of commercially available steroid preparations might have implied a risk of uncontrolled effects on hearing. Therefore, we chose alcohol-free formulas to avoid potential neurotoxic effects. Nonetheless, a possible toxic effect was seen for both preparations after direct injection into cochleostomized ears, possibly filling a large portion of the basal turn. In implanted ears the benefit of the 2 glucocorticoids for hearing preservation prevailed over those potentially detrimental effects. It is also possible that a simple cochleostomy does not cause enough trauma for glucocorticoids to act against. James et al. [18] demonstrated a greater hearing benefit after Dex treatment in a group of guinea pigs implanted forcefully compared with a group implanted less forcefully. Therefore, had the ears in the present study suffered more trauma, we might have seen larger effects.

Efficacy of Glucocorticoid Treatment

The crucial question is whether there is a benefit for hearing when implanted ears are treated with glucocorticoids or if they would do just as well without treatment. To address this question, we further analyzed our data by subtracting threshold shifts of cochleostomized ears from those of implanted ears treated with the same substances, i.e. cochleostomized ears served as a control group for implantation. The reason for this analysis was that we wanted to see the net effect of glucocorticoid treatment on implantation by also taking into account their slightly deteriorative effect in cochleostomized ears.

Although cochleostomized ears might have received a slightly higher dose than implanted ears because of a possible displacement of drugs by the insertion of the electrode, a benefit for local glucocorticoid treatment in implanted ears was seen primarily in the region most af-

fected by implantation, i.e. in the middle (fig. 3) and high frequencies (not shown here). In contrast, hearing in implanted ears treated only with AP further deteriorated towards the end of the 90-day experimental observation time.

Comparison with Previous Research

Hearing loss after cochlear implantation occurred to varying degrees in guinea pigs in all our experimental groups. However, local application of the 2 glucocorticoids in a single injection succeeded in substantially decreasing threshold shifts in implanted ears, albeit for different time intervals. These results are supported by Eshraghi et al. [17], in which local application of a cumulative dose of 20 μl Dex over 8 days after brief electrode insertion resulted in a decrease in ABR threshold shifts after 1 month and a prevention of their further progression. However, this method is not entirely comparable to ours because the electrode was inserted and removed immediately to investigate surgical trauma rather than chronic implantation effects. Two studies using a model more comparable to ours found similar results 1 month [18] and 3 months [19] after implantation by acute RW application of Dex before surgery in cochlea-implanted guinea pigs.

Apart from our study, only 1 other animal study demonstrated an effect of locally applied glucocorticoids on chronically implanted ears for more than 1 month. In agreement with our results, the study showed the benefit of an RW application of Dex for hearing preservation in a guinea pig model of cochlear implantation 3 months after surgery [19]. However, in clinical use, the clinician should take into account that human RW membranes are thicker and maybe less permeable to drugs than those of guinea pigs [23]. In addition, the transmitted amount has been shown to vary significantly in humans [24].

The protective effects of the glucocorticoids we used in our study differ in their time pattern with Dex being more effective at the beginning and Tria more towards the end of the experimental time. This might also apply to other corticoids, even more so for those with a stronger impact not only on glucocorticoid, but also on mineralocorticoid receptors, as is the case with prednisolone, which should, therefore, be taken into consideration in clinical use. The results suggest that a treatment regimen should include either a different dosage or mode of delivery of Dex or the sole use of Tria because of its longer-term beneficial effects.

Because the preservation of low (0.12–1 kHz) and middle (1–8 kHz) frequencies is most important for speech recognition [25] and listening [7] in noisy environments, drug administration in the more apical, i.e. the low-frequency, region is an important goal. This could be achieved with deeply inserted drug-delivering electrodes [26]. However, as our study demonstrated, even a single injection of both Dex and Tria was most effective in the high and middle frequencies because those are the regions with the greatest drug concentration.

Tissue growth was observed to various degrees in both implanted and cochleostomized cochleae with a tendency for more pronounced growth in implanted ears. There was no significant difference among treatments for the doses used here. A recent study [27] revealed less fibrosis in implanted ears treated with higher systemic doses of Dex than in those with lower doses or controls. However, as found in our study, the difference was not statistically significant. We observed no correlation between hearing loss and the amount of tissue within the cochlea.

Despite this finding, we cannot rule out that very pronounced tissue growth, especially with bone tissue, might lead to a worsening of residual hearing in patients due to an alteration in the impedance across the cochlear partition. An increase in electrode impedance would additionally necessitate higher electrical currents for stimulation, which consequently might diminish frequency selectivity. A higher electrical current could also cause unwanted nonauditory side effects such as costimulation of the facial nerve.

Implications for Future Research

A single treatment with glucocorticoids was adequate for a longer-term effect of 28 days with Dex and 90 days with Tria, respectively. For clinical use, this benefit should be strengthened or achieved more reliably, possibly to the extent of even a permanent hearing improvement by repeated or sustained applications, as was shown by Eshraghi et al. [17] who applied Dex for 8 days using an osmotic micropump system and achieved improved hearing thresholds for 2 months.

Another method of prolonged application would be to place a degradable substance at the RW membrane loaded with the drug and releasing it for a prolonged period. Recent studies showed that using alginate beads as a vector for acute Dex delivery [18, 19] was successful for the protection of high frequencies after chronic (1- and 3-month) cochlear implantation. However, the presence of high concentrations of a steroid in the vicinity of the entry point to the cochlea may have the potential to increase healing time around the entry point of the electrode array. This would increase the time frame in which

bacteria that reside in the middle ear could enter the inner ear, thus causing infections or even increase the risk for meningitis. Ideally, the electrode itself could release drugs inside the cochlea by coating or by being embedded in the material [28]. This could make additional steroid application superfluous, thus eliminating the need for high concentrations outside the cochlea.

Conclusions

Both Dex and Tria show a potential to protect hearing after chronic cochlear implantation. Different time courses were observed for the 2 drugs after a single injection, with Dex showing only a temporary benefit and Tria showing maximum efficacy after 3 months. This difference warrants further investigation. Hearing preservation was seen in all frequency ranges but was most apparent in the high and middle frequencies. Neither Tria nor Dex suppressed tissue growth significantly, nor was there a significant correlation between the amount of tissue within the cochlea and hearing loss. The possible slight toxic effect of injecting the drug preparations directly into the cochlea suggests that caution should be exercised before using this delivery method. Optimization of dosage and delivery regimen is needed to extend this approach to cochlear implantation in humans.

Acknowledgments

The study was supported by the German Research Foundation, grant Gs 161/1 + 2. The authors wish to thank MED-EL Innsbruck, Austria, for providing the guinea pig electrodes. The authors also wish to thank PD Dr. Markus Mueller for providing the computer software support for CAP/ABR measurements and Dr. Rainer Hartmann for technical and scientific support. We would also like to thank Mrs. Anne Schubert for excellent technical assistance. Special thanks go to Dr. Carolyn Garnham for helpful discussions and Dr. Jane Opie for medical writing assistance. We would also like to thank Dr. Martina Deibl for help with the statistical analyses.

References

1 Von Ilberg C, Kiefer J, Tillein J, Pfenningdorff T, Hartmann R, Sturzebecher E, Klinke R: Electric-acoustic stimulation of the auditory system: new technology for severe hearing loss. ORL J Otorhinolaryngol Relat Spec 1999;61:334–340.

2 Kiefer J, Pok M, Adunka O, Sturzebecher E, Baumgartner W, Schmidt M, Tillein J, Ye Q, Gstoettner W: Combined electric and acoustic stimulation of the auditory system: results of a clinical study. Audiol Neurootol 2005; 10:134–144.

3 Gstoettner W, Kiefer J, Baumgartner WD, Pok S, Peters S, Adunka O: Hearing preservation in cochlear implantation for electric acoustic stimulation. Acta Otolaryngol 2004;124:348–352.

4 Gstoettner WK, Helbig S, Maier N, Kiefer J, Radeloff A, Adunka OF: Ipsilateral electric acoustic stimulation of the auditory system: results of long-term hearing preservation. Audiol Neurootol 2006;11(suppl 1):49–56.

5 Gantz BJ, Turner C, Gfeller KE: Acoustic plus electric speech processing: preliminary results of a multicenter clinical trial of the Iowa/Nucleus Hybrid implant. Audiol Neurootol 2006;11(suppl 1):63–68.

6 James CJ, Fraysse B, Deguine O, Lenarz T, Mawman D, Ramos A, Ramsden R, Sterkers O: Combined electroacoustic stimulation in conventional candidates for cochlear implantation. Audiol Neurootol 2006;11(suppl 1):57–62.

7 Kong YY, Stickney GS, Zeng FG: Speech and melody recognition in binaurally combined acoustic and electric hearing. J Acoust Soc Am 2005;117:1351–1361.

8 Zeng FG, Nie K, Stickney GS, Kong YY, Vongphoe M, Bhargave A, Wei C, Cao K: Speech recognition with amplitude and frequency modulations. Proc Natl Acad Sci USA 2005;102:2293–2298.

9 Kiefer J, Tillein J, von Ilberg C, Pfennigdorf T, Stürzebecher E, Klinke R, Gstoettner W: Fundamental aspects and first clinical results of the clinical application of combined electric and acoustic stimulation of the auditory system; in Kubo T, Takagashi Y, Iwaki T (eds): Advances in Cochlear Implants – An Update. The Hague, Kugler Publications, 2002, pp 569–576.

10 Gantz BJ, Turner CW: Combining acoustic and electrical hearing. Laryngoscope 2003; 113:1726–1730.

11 Dorman MF, Spahr AJ, Loizou PC, Dana CJ, Schmidt JS: Acoustic simulations of combined electric and acoustic hearing (EAS). Ear Hear 2005;26:371–380.

12 Gantz BJ, Turner C, Gfeller KE, Lowder MW: Preservation of hearing in cochlear implant surgery: advantages of combined electrical and acoustical speech processing. Laryngoscope 2005;115:796–802.

13 Kleine Punte A, Vermeire, K, van de Heyning P: Bilateral electric acoustic stimulation: a comparison of partial and deep cochlear electrode insertion. A longitudinal case study; in van de Heyning P, Kleine Punte A (eds): Cochlear Implants and Hearing Preservation. Acta Otolaryngol. Basel, Karger, 2010, vol 67, pp 144–152.

14 Huang CQ, Tykocinski M, Stathopoulos D, Cowan R: Effects of steroids and lubricants on electrical impedance and tissue response following cochlear implantation. Cochlear Implants Int 2007;8:123–147.

15 McCabe BF: Autoimmune sensorineural hearing loss. Ann Otol Rhinol Laryngol 1979;88:585–589.

16 Ye Q, Tillein J, Hartmann R, Gstoettner W, Kiefer J: Application of a corticosteroid (triamcinolone) protects inner ear function after surgical intervention. Ear Hear 2007;28: 361–369.

17 Eshraghi AA, Adil E, He J, Graves R, Balkany TJ, van de Water TR: Local dexamethasone therapy conserves hearing in an animal model of electrode insertion trauma-induced hearing loss. Otol Neurotol 2007;28: 842–849.

18 James DP, Eastwood H, Richardson RT, O'Leary SJ: Effects of round window dexamethasone on residual hearing in a guinea pig model of cochlear implantation. Audiol Neurootol 2008;13:86–96.

19 Maini S, Lisnichuk H, Eastwood H, Pinder D, James D, Richardson RT, Chang A, Connolly T, Sly D, Kel G, O'Leary SJ: Targeted therapy of the inner ear. Audiol Neurootol 2009;14:402–410.
20 Derendorf H, Hochhaus G, Mollmann H, Barth J, Krieg M, Tunn S, Mollmann C: Receptor-based pharmacokinetic-pharmacodynamic analysis of corticosteroids. J Clin Pharmacol 1993;33:115–123.
21 Carvalho GJ, Lalwani AK: The effect of cochleostomy and intracochlear infusion on auditory brain stem response threshold in the guinea pig. Am J Otol 1999;20:87–90.
22 Kiefer J, Tillein J, Ye Q, Klinke R, Gstoettner W: Application of carbon dioxide and erbium:yttrium-aluminium-garnet lasers in inner ear surgery: an experimental study. Otol Neurotol 2004;25:400–409.
23 Goycoolea MV: Clinical aspects of round window membrane permeability under normal and pathological conditions. Acta Otolaryngol 2001;121:437–447.
24 Bird PA, Begg EJ, Zhang M, Keast AT, Murray DP, Balkany TJ: Intratympanic versus intravenous delivery of methylprednisolone to cochlear perilymph. Otol Neurotol 2007;28:1124–1130.
25 Turner CW, Gantz BJ, Vidal C, Behrens A, Henry BA: Speech recognition in noise for cochlear implant listeners: benefits of residual acoustic hearing. J Acoust Soc Am 2004;115:1729–1735.
26 Jolly C, Garnham C, Mirzadeh H, Truy E, Martini A, Kiefer J, Braun S: Electrode features for hearing preservation and drug delivery strategies; in van de Heyning P, Kleine Punte A (eds): Cochlear Implants and Hearing Preservation. Acta Otolaryngol. Basel, Karger, 2010, vol 67, pp 28–42.
27 Connolly TM, Eastwood H, Kel G, Lisnichuck H, Richardson R, O'Leary S: Pre-operative intravenous dexamethasone prevents auditory threshold shift in a guinea pig model of cochlear implantation. Audiol Neurootol 2010;2011:137–144.
28 Ghavi FF, Mirzadeh H, Imani M, Jolly C, Farhadi M: Corticosteroid-releasing cochlear implant: a novel hybrid of biomaterial and drug delivery system. J Biomed Mater Res B Appl Biomater 2010;94:388–398.