Effects of sustained release dexamethasone hydrogels in hearing preservation cochlear implantation

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Abstract

It has been shown that glucocorticoids reduce the hearing threshold shifts associated with cochlear implantation. Previous studies evaluated the administration of glucocorticoids immediately before surgery or the repeated pre- or perioperative systemic application of glucocorticoids. The aim of this study was to evaluate the effects of a sustained release dexamethasone hydrogel in hearing preservation cochlear implantation. To address this issue, a guinea pig model of cochlear implantation was used. 30 normal hearing pigmented guinea pigs were randomized into a group receiving a single dose of a dexamethasone/poloxamer407 hydrogel one day prior to surgery, a second group receiving the hydrogel seven days prior to surgery and a control group. A silicone cochlear implant electrode designed for the use in guinea pigs was inserted to a depth of 5 mm through a cochleostomy. Compound action potentials of the auditory nerve (frequency range 0.5–32 kHz) were measured preoperatively, directly postoperatively and on postoperative days 3, 7, 14, 21 and 28. Following the last audiometry, temporal bones were harvested and histologically evaluated.

Dexamethasone hydrogel application one day prior to surgery resulted in significantly reduced hearing threshold shifts at low, middle and high frequencies measured at postoperative day 28 (p < 0.05). Application of the hydrogel seven days prior to surgery did not show such an effect. Dexamethasone application one day prior to surgery resulted in increased outer hair cell counts in the cochlear apex and in reduced spiral ganglion cell counts in the basal and middle turn of the cochlea, a finding that was associated with a higher rate of electrode translocation in this group.

In this study, we were able to demonstrate functional benefits of a single preoperative intratympanic application of a sustained release dexamethasone hydrogel in a guinea pig model of cochlear implantation.

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1. Introduction

Glucocorticoids (GCs) are used for the treatment of a variety of conditions affecting the inner ear. Amongst others, the indications for GCs in this setting include sudden sensorineural hearing loss, Ménière’s disease, cisplatin ototoxicity and autoimmune-mediated hearing loss (Casani et al., 2012; Marshak et al., 2014; Rauch et al., 2011; Trune and Canlon, 2012). Technical and surgical advances in the field of cochlear implantation (CI) resulted in an extension of the indication criteria. Due to the audiological benefits of electric-acoustic stimulation (EAS), residual hearing preservation has
become a major point of interest for CI surgeons (Arnoldner et al., 2010; Gantz et al., 2016; Gifford et al., 2013; von Ilberg et al., 2011). Various electrode-related histological alterations, including fibrosis, fractures of the osseous spiral lamina or foreign body giant cell infiltration have been described in the literature (O’Leary et al., 2013). In addition to the direct surgical trauma caused by the electrode, inflammation and the induction of apoptosis can result in a further, delayed hearing loss (Eshraghii et al., 2013). Most of these deleterious reactions are directly or indirectly affected by GCs, which have therefore been extensively studied in the setting of hearing preservation CI. In the guinea pig model, preoperative or perioperative application of topical and systemic GCs has been shown to reduce hearing threshold shifts (Chang et al., 2009; Connolly et al., 2011; Eastwood et al., 2010; Kuthubutheen et al., 2015; Lee et al., 2013; Maini et al., 2009; Quesnel et al., 2011). Whilst extended preoperative systemic GCs have been demonstrated to be effective in the prevention of hearing loss after CI (Kuthubutheen et al., 2015), only short-term preoperative topical application protocols have been evaluated so far (James et al., 2008). This is at least partly due to the loss of fluids through the Eustachian tube, which makes prolonged and controlled topical drug delivery to the inner ear challenging. Out of various studies aiming at releasing GCs via the Eustachian tube (Barritat et al., 2012; Borden et al., 2011; Plontke et al., 2009), the use of thermoreversible poloxamer407 (POX407) hydrogels has emerged as a very promising approach (Honeder et al., 2014; Lambert et al., 2012; Piu et al., 2011), which is currently also evaluated in clinical studies. These gels can be injected into the middle ear in a fluid state at room temperature and turn into a hydrogel at body temperature (Engleder et al., 2014). Also, intratympanic (IT) application of POX407 hydrogels does not cause adverse effects except for a transient conductive hearing loss (Honeder et al., 2014; Wang et al., 2009). It has been shown that the IT application of POX407 hydrogels results in therapeutic GC levels in the inner ear for more than ten days (Honeder et al., 2014; Piu et al., 2011), and that the IT application of a dexamethasone/POX407 hydrogel leads to a reduction of cisplatin-induced hearing loss in an animal model (Fernandez et al., 2016). Even though our group failed to show reduced hearing threshold shifts after the intraoperative application of dexamethasone and triamcinolone-acetonide POX407 hydrogels (Honeder et al., 2015b), there is experimental evidence pointing to a potentially higher efficacy of preoperative application protocols (Kuthubutheen et al., 2015). Most GC effects are caused by the regulation of gene transcription via direct interaction of the GC receptor with GC-responsive elements or via transactivation or transrepression of other transcription factors (Kassel and Herrlich, 2007). Hoang et al. showed, that the upregulation of the anti-apoptotic genes Bcl-2 and Bcl-xL in organ of Corti explants required 48 h after exposure to dexamethasone (Hoang et al., 2009). Furthermore, upregulation of Fkbp5, a protein involved in immunosuppression and inhibition of apoptosis, was exclusively described hours after GC application (Maeda et al., 2010, 2012). Advantages of the POX407 hydrogel as compared to other delivery protocols include its release profile, which results in sustained therapeutic GC perilymph levels after a single IT injection, and the potential to translate this approach into clinical practice without any expected major complications (Lambert et al., 2012; Piu et al., 2011). An additional benefit is that long-term release of GCs from the round window niche reduces drug gradients in the perilymph and thus results in higher drug concentrations in the apical parts of the cochlea (Salt et al., 2011), which are of special interest in the setting of hearing preservation CI.

Therefore, the aim of this study was to evaluate the preoperative application of a 6% dexamethasone/POX407 hydrogel one day or seven days before surgery for otoprotective effects in an animal model for CI.

2. Material and methods

All animal experiments were approved by the local animal welfare committee and the Austrian Federal Ministry for Science, Research and Economy (BMWF-66.009/0251-II/3b/2013).

2.1. Experimental groups

30 pigmented guinea pigs weighing between 697 and 970 g were randomized into one of three groups, each consisting of 10 animals. The first group received an IT injection of a thermoreversible dexamethasone hydrogel with extended release characteristics one day prior to surgery (Dex d-1) and the second group received the same hydrogel seven days before CI (Dex d-7). Animals in the control group underwent CI after the application of 50 µl of the control hydrogel (20% w/v POX407) one day or seven days prior to surgery. As a previously published study using the same animal model and delivery device did not show a protective effect of intraoperative glucocorticoid hydrogel application, an intraoperative administration group was not included into this study (Honeder et al., 2015b).

2.2. Auditory testing

All audiometric measurements were performed in a soundproof chamber (mac-2; Industrial Acoustics Company, Niederkrüchten, Germany). A DT-48 loudspeaker (Beyerdynamic, Heilbronn, Germany) was positioned 3 cm from the tested ear and a K2 microphone (Sennheiser, Wedemark, Germany) was placed directly at the level of the pinna for calibration. A wax earplug (Oropax, Werheim, Germany) was used to occlude the contralateral external ear canal during auditory functional testing. A custom-made setup, including a PC system equipped with a multifunction I/O card (National Instruments, Austin, TX, USA) and AudiologLab software (Otoconsult, Frankfurt am Main, Germany), was used for the measurement of auditory potentials. Stimuli for the determination of auditory brainstem response (ABR) and compound action potential (CAP) thresholds included clicks and tone bursts (3 ms duration; 1 ms rise/fall) presented in the frequency range of 0.5–32 kHz. Signals were amplified (80 dB), band-pass filtered (ABR: 10 Hz to 10 kHz; CAP: 200 Hz to 5 kHz) and averaged (512× or 32×) for the measurement of ABRs and CAPs, respectively. The digital sampling rate for ABR and CAP measurements was 50 kHz. Click-ABR measurements were performed approximately one week before CI to guarantee normal hearing of the animals prior to study-inclusion. Frequency-specific CAP thresholds were determined at three frequencies per octave and in 5 dB steps directly before CI-electrode insertion and immediately after surgery, as well as on postoperative days 3, 7, 14, 21 and 28. Threshold shifts were calculated for every single frequency and point in time by subtracting the preoperative baseline CAP thresholds from the respective postoperative results. For statistical analysis CAP threshold shifts were grouped into low (0.5–2 kHz), middle (2.5–8 kHz) and high frequencies (10–32 kHz).

2.3. Anesthesia

Hydrogel application as well as CI surgery was performed under general anesthesia, using medetomidine (0.3 mg/kg), midazolam (1 mg/kg), fentanyl (0.03 mg/kg) and ketamine (10 mg/kg). For CI surgery, lidocaine (4 mg/kg) was used for local anesthesia. At the end of the procedures, anesthesia was partially antagonized using atipamezole (1 mg/kg) and flumazenil (0.1 mg/kg). All guinea pigs received carprofen (4 mg/kg) and enrofloxacin (7 mg/kg) before surgery and once per day on the following 2 days. During CI surgery,
heart rate and vascular pO2 were measured using a pulse oximeter to monitor physical condition. To maintain body temperature at 38 °C, a heating plate was used when performing surgery or hearing measurements.

2.4. Hydrogel preparation and application procedure

The 20% w/v POX407 hydrogel (BASF SE, Ludwigshafen, Germany) was prepared using the cold technique (Engleder et al., 2014). POX407 was slowly added to 10 mM PBS pH 7.4. After the addition of 6% microcrystalline dexamethasone (Gatt-Koller, Absam, Austria), the solution was stored at 4 °C and resuspended directly before use. Under visualization with an operating microscope, the tympanic membrane was perforated in the superior posterior quadrant and 50 μl of the hydrogel were applied to the area of the round window niche using a YOU-1 micromanipulator (Narishige, Tokyo, Japan) and Hamilton syringes (Hamilton, Badduz, Switzerland) with blunt 29G needles (Honeder et al., 2015a).

2.5. Cochlear implant surgery

A custom-made, conically shaped silicone electrode with one contact (MED-EL GmbH, Innsbruck, Austria) was used. The diameter was 0.3 mm at the tip of the electrode and increased to a diameter of 0.5 mm 4 mm from the tip. In general anesthesia, the right postauricular area was shaved and prepared with povidone iodine (“Betadona”, Mundipharma, Limburg, Germany). Following the postauricular skin incision, the bulla was exposed and opened using a number 15 scalpel. As the next step, a teflon-insulated gold wire (Goodfellow, Bad Nauheim, Germany) was attached to the bony ridge of the round window niche using histocryl glue (Braun Melsungen, Melsungen, Germany) and preoperative CAP thresholds were determined before drilling a 0.8 mm cochleostomy approximately 1 mm from the round window niche. Then, the electrode was inserted 5 mm and the cochleostomy was sealed with a muscle graft. The transcutaneous pins of the electrode were placed at the vertex of the animal using two 4 mm stainless steel screws and denture resin (Paludur, Heraeus Kulzer, Hanau, Germany), which was also used to close the bulla. Finally, the gold wire was soldered to an additional pin to allow for future CAP measurements and wounds were closed in two layers using 4-0 Vicryl sutures (Ethicon, Norderstedt, Germany).

2.6. Histology

In deep general anesthesia, animals were perfused transcardially with buffered paraformaldehyde (PFA 4%; Sigma Aldrich, Seelze, Germany) before temporal bones were harvested. Tympanic bullae were opened carefully and postfixed in buffered PFA for at least 48 h. Subsequently, samples were randomly assigned to the preparation of organ of Corti whole mounts or embedding, sectioning and hematoxylin-eosin (H&E) staining. As one cochlea per group was lost due to damage during harvesting or processing, only 4 samples per group were available for the preparation of organ of Corti whole mounts. In these cases, the bony capsule of the cochlea was carefully removed from the fixed specimens for the preparation of organ of Corti whole mounts. Samples were stained using phalloidin-tetramethylrhodamine B isothiocyanate (0.3 μg/ml PBS; Phalloidin-TRITC; Sigma-Aldrich, Vienna, Austria) and Hoechst 33342 trihexylcholride tribhydrate (0.05 mg/ml PBS; Molecular Probes, Invitrogen Corp., Carlsbad, CA) for 30 min at room temperature. After staining, each turn of the cochlea was separately embedded in FluorSave reagent (Calbiochem, Darmstadt, Germany) and at least five 200 μm sections per turn were evaluated for inner hair cell (IHC) and outer hair cell (OHC) numbers by means of confocal microscopy (Honeder et al., 2015a). To allow for H&E staining, 5 bullae per group were decalciﬁed in 8% ethylenediaminetetraacetic acid until bony structures allowed trimming. The demineralization facilitated the faultless removal of the histoacryl glue and the electrode, without any secondary damage to the samples. After embedding in parafﬁn, the preparation was cut at a thickness of 4 μm and every fifth section was stained with H&E for morphologic evaluation. About thirty sections were evaluated per specimen and representative sections were photographed under a light microscope (Polyvar, Reichert-Jung, Vienna, Austria). To describe the location and to allow a semi-quantitative evaluation of the fibrosis, scala tympani was divided into four quadrants, with Q1 = upper inner quadrant, Q2 = upper outer quadrant, Q3 = medio-inferior and Q4 = latero-inferior quadrant according to O’Leary et al. (Fig. 1A). Also osteoneogenesis was rated according to O’Leary et al. as absent, minimal, and occupying less or more than one quarter of the tissue response (O’Leary et al., 2013). Ellipse 3D software (ViDiTo, Kosice, Slovakia) was used to count all nucleated spiral ganglion cells (SGC) in three mid-modiolar sections - each separated by 25 μm - and to calculate the density by dividing the number of SGC by the area of Rosenthal’s canal (Fig. 1B and C). All histopathological examinations were performed blinded to the assigned treatment.

2.7. Calculations (Greenwood function)

According to the Greenwood function for guinea pigs: 
\[
F = 0.35(10^{2.118.5x} - 0.85)
\]
(Greenwood, 1990), the analyzed frequency-groups tested for different effects of the electrode insertion trauma (EIT). Taking into account the cochleosteoty site 1 mm from the round window membrane and the insertion depth of 5 mm, frequencies from 10 to 32 kHz represent the area directly affected by the electrode insertion. Frequencies from 2 to 8 kHz represent the area in proximity to, but not directly affected by the CI-electrode, whereas the lowest frequencies from 0.5 to 2 kHz represent the cochlear apex.

2.8. Statistics

Data points represent mean values. Error bars represent SD or SEM as indicated below the respective ﬁgure. Data analysis was performed using IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY). Statistical analysis was performed using one-way ANOVA and Tukey’s HSD for post-hoc analysis.

Fig. 1. Micrographs of mid-modiolar cross-sections through guinea pig cochleae. Hematoxylin-eosin staining. (A) Illustration of the quadrants of the scala tympani for the semiquantitative evaluation of apparent tissue response according to O’Leary et al., 2013. The scala tympani (ST) was divided into 4 quadrants (Q1, Q2, Q3 and Q4). The scala vestibuli (SV), ductus cochlearis (DC), basilar membrane (BM) and Rosenthal’s canal (RC) were labelled for better orientation. (B, C) Micrographs of Rosenthal’s canal in the lower turn of the cochlea of control (B) and Dex d-1 (C) animals. Density of spiral ganglion cells (SGC) per area of Rosenthal’s canal (RC) was reduced in Dex d-1 animals compared to control animals. Scale bar (A) 100 μm and (B, C) 50 μm.
3. Results

3.1. Compound action potentials

The insertion of the CI-electrodes resulted in pronounced CAP threshold shifts in all frequency groups (Fig. 2). In the low frequencies (0.5–2 kHz), which represent the most apical part of the cochlea, postoperative threshold shifts in the Dex d-7 group (35.2 dB) were significantly higher than in the Dex d-1 (26.1 dB) and the control group (28.8 dB). Threshold shifts in the Dex d-1 group showed a higher rate of recovery and were significantly lower than in the other groups at days 21 and 28. Low-frequency threshold shifts on day 28 were 14.2 dB, 23.1 dB, and 23.3 dB in the Dex d-1, the Dex d-7, and the control group, respectively (Fig. 2A). In the middle frequencies (2.5–8 kHz), which represent the area apical to the tip of the electrode, threshold shifts in the Dex d-1 group were significantly lower than in the other groups at all points in time. Additionally, a significant difference between the Dex d-7 group and the control group was found immediately after surgery, but resolved by day 3. In this frequency range, mean threshold shifts on day 28 were 24.8 dB, 36.6 dB, and 35.9 dB, for the Dex d-1, the Dex d-7, and the control group, respectively (Fig. 2B). CAP threshold shifts were most pronounced in the high frequency range (10–32 kHz), which represents the basal part of the cochlea (Fig. 2C). This portion of the inner ear is implanted with, and thereby directly affected by the CI-electrode. In these frequencies, postoperative threshold shifts were also significantly smaller in the Dex d-1 group (30.3 dB) as compared to the Dex d-7 group (53.7 dB), and the control group (51.4 dB). Over the time course of 4 weeks, threshold shifts decreased slightly to 20.2 dB, 42.6 dB, and 41.0 dB, in the Dex d-1, the Dex d-7, and the control group, respectively. Compared to the Dex d-7 group and the control group, animals in the Dex d-1 group showed significantly lower threshold shifts at all points in time (Fig. 2C).

3.2. Organ of Corti whole mounts

Hair cell counts were evaluated in the middle and apical part of the cochlea and are presented as the average number of IHCs and OHCs per 200 μm section of the organ of Corti. Due to the EIT and the associated fibrosis we were unable to perform meaningful hair cell counts in the basal turn of the cochlea. In the middle turn of the cochlea, IHCs were almost completely preserved and OHCs were partially lost, but no statistically significant difference between the experimental groups was found (Fig. 3A and B). IHCs were intact in the apical area of the cochlea in all treatment groups. In this area, a significantly higher number of OHCs was found in the Dex d-1 group as compared to the control group (Fig. 3A and B).

3.3. H&E stainings

The histopathological examination revealed a relatively traumatic electrode insertion and showed a fracture of the osseous spiral lamina as well as an electrode dislocation into scala vestibuli in 80% of Dex d-1, 40% of Dex d-7 and 20% of control animals (Table 1). Fibrosis and osteoneogenesis were evaluated on the section with the largest cochleostomy diameter, as well as on mid-modiolar sections. Both, fibrosis and osteoneogenesis were present in all cochleostomy sections and were associated with the EIT. Histopathological findings in the scala tympani of the basal turn, which were evaluated in the mid-modiolar sections are summarized in Tables 1 and 2. In these sections, the amount of fibrosis and osteoneogenesis appeared to correlate with the EIT and electrode translocation. SGC quantification revealed a significantly lower SGC-density in the lower turn of the cochlea of Dex d-1 animals, a slightly, but significantly reduced number of SGCs in the middle turn and no significant differences in the apical turn of the cochlea (Table 3).

4. Discussion

Despite the evaluation of different GC delivery protocols, it remains unclear until today which mode (systemic or topical) and timing of application yields the most favorable outcomes (Eastwood et al., 2010; James et al., 2008; Kuthubutheen et al., 2015; Lee et al., 2013). The aim of this study was to shed light on these important questions.

Preoperative GC administration is a promising strategy to improve outcomes in hearing preservation CI because it allows the ear to prepare for the upcoming insult of electrode insertion.
and results in a long-term release of GCs to the inner ear with peak concentrations during the first day after application (Honeder et al., 2014; Piu et al., 2011).

Interestingly, in our study we found a protective effect of the dexamethasone hydrogel only if it was applied one day prior to CI, which makes us speculate that high perilymph concentrations during electrode insertion are important to achieve otoprotection. In contrast to many previous studies, we were able to show a protection of low frequency hearing after 28 days (Connolly et al., 2011; James et al., 2008; Kuthubutheen et al., 2015). The significantly reduced hearing threshold shifts in the low frequencies after one month, without a significant difference immediately after surgery and the higher number of OHCs in the apical part of the cochlea hint at potential long-term effects of a single preoperative GC dose. Similar effects have also been described for a single perioperative administration of triamcinolone-acetonide directly into the inner ear (Braun et al., 2011). Even though this result is very promising, it has to be interpreted with caution because the volume of the guinea pig cochlea differs considerably from the human inner ear, and in contrast to the human cochlea, the bone of the guinea pig cochlear wall is relatively thin, which allows drugs to enter through the cochlear apex (Mikulec et al., 2009). This could result in significantly different apical GC-concentrations in humans and potentially cause a reduction of the otoprotective effects. In an attempt to overcome this flaw of the guinea pig model, the POX407 solution was applied directly to the round window region, where it quickly solidified into a hydrogel. Therefore, unwanted apical resorption of the GC was minimized. Dexamethasone application one day prior to surgery resulted in reduced postoperative CAP threshold shifts in the middle and high frequencies, which are directly affected by the electrode insertion. Surprisingly, we found a reduced number of SGCs in basal and middle turn of the Dex d-1 animals, which is in contrast to the improved hearing outcomes. The loss of SGCs - especially in the basal turn – could be associated with the greater amount of EIT, particularly electrode translocation into the scala vestibuli, which was more frequent in the Dex d-1 (80%) than in the control group (20%). This relatively high insertion trauma is a minor drawback of the study, as it makes the comparison of the obtained results to clinical EAS cases, which are

Table 1
Histopathology I: Electrode translocation and osteoneogenesis.

| Electrode translocation | Osteoneogenesis absent | Osteoneogenesis minimal | Osteoneogenesis <25% | Osteoneogenesis >25% |
|-------------------------|------------------------|-------------------------|----------------------|----------------------|
| Control                 | 20% (1/5)              | 60% (3/5)               | 20% (1/5)            | 0% (0/5)            |
| Dex d-1                 | 80% (4/5)              | 0% (0/5)                | 0% (0/5)             | 80% (4/5)           |
| Dex d-7                 | 40% (2/5)              | 0% (0/5)                | 80% (4/5)            | 20% (1/5)           |

Table 2
Histopathology II: Fibrosis.

| Fibrosis absent         | Fibrosis in one quadrant | Fibrosis in two quadrants | Fibrosis in three quadrants | Fibrosis in all quadrants |
|-------------------------|--------------------------|---------------------------|-----------------------------|--------------------------|
| Control                 | 20% (1/5)                | 40% (2/5)                 | 20% (1/5)                   | 0% (0/5)                 |
| Dex d-1                 | 0% (0/5)                 | 0% (0/5)                  | 40% (2/5)                   | 20% (1/5)                |
| Dex d-7                 | 0% (0/5)                 | 20% (1/5)                 | 40% (2/5)                   | 0% (0/5)                 |

Fig. 3. Number of A) IHCs and B) OHCs per 200 µm section of the organ of Corti. The 2nd turn and the apical turn of the cochlea were analyzed separately. A significantly higher number of OHCs was found in the cochlear apex after application of dexamethasone 1 day prior to CI. * p < 0.05. Error bars represent SD.
implanted using the “soft surgery” technique, and also to other guinea pig studies, which usually reported lower hearing threshold shifts and electrode translocation rates, more difficult (Chang et al., 2009; Kuthubutheen et al., 2015; O’Leary et al., 2013). As only half of the samples were randomized to histopathology, it is possible that an analysis of all samples would have had a leveling effect on the differing electrode translocation rates. A neurotoxic effect of the hydrogel is unlikely, as no SGC loss was found in the Dex d-7 group. The differing electrode translocation rates. A neurotoxic effect of the hydrogel is unlikely, as no SGC loss was found in the Dex d-7 group.

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Conclusions

Preoperative IT dexamethasone hydrogels can reduce EIT-induced hearing threshold shifts at low, middle and high frequencies. As this application protocol preserved the clinically relevant low-frequency hearing after CI, the findings described herein might have an important impact in the clinical practice. As POX407 hydrogels will most likely be available for physicians in the near future, this strategy should be evaluated in clinical studies.

Conflicts of interest and source of funding

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