Hearing Research 255 (2009) 67–72

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Research papers

Factors influencing the efficacy of round window dexamethasone protection of residual hearing post-cochlear implant surgery

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ARTICLE INFO

Article history:
Received 12 December 2008
Received in revised form 1 May 2009
Accepted 18 May 2009
Available online 17 June 2009

Keywords:
Cochlear implantation
Round window membrane
Dexamethasone
Pharmacokinetic
Residual hearing

ABSTRACT

Aim: To protect hearing in an experimental model of cochlear implantation by the application of dexamethasone to the round window prior to surgery. The present study examined the dosage and timing relationships required to optimise the hearing protection.
Methods: Dexamethasone or saline (control) was absorbed into a pledget of the carboxymethylcellulose and hyaluronic acid and applied to the round window of the guinea pig prior to cochlear implantation. The treatment groups were 2% w/v dexamethasone for 30, 60 and 120 min; 20% dexamethasone applied for 30 min. Auditory sensitivity was determined pre-operatively, and at 1 week after surgery, with pure-tone auditory brainstem response audiometry (2–32 kHz). Cochlear implantation was performed via a cochleostomy drilled into the basal turn of the cochlea, into which a miniature cochlear implant dummy electrode was inserted using soft-surgery techniques.
Results: ABR thresholds were elevated after cochlear implantation, maximally at 32 kHz and to a lesser extent at lower frequencies. Thresholds were less elevated after dexamethasone treatment, and the hearing protection improved when 2% dexamethasone was applied to the round window for longer periods of time prior to implantation. The time that dexamethasone need be applied to achieve hearing protection could be reduced by increasing the concentration of steroid, with a 20% application for 30 min achieving similar levels of protection to a 60 min application of 2% dexamethasone.
Conclusions: Hearing protection is improved by increasing the time that dexamethasone is applied to the round window prior to cochlear implantation, and the waiting time can be reduced by increasing the steroid concentration. These results suggest that the diffusion dexamethasone through the cochlea is the prime determinant of the extent of hearing protection.

1. Introduction

Cochlear implant patients with residual (acoustic) hearing in the implanted ear can combine both electrical and acoustic stimulation (EAS) to improve speech perception, particularly in the presence of background noise (Gifford et al., 2007; James et al., 2006; Turner et al., 2008). Consequently, the preservation of hearing in the implanted ear has become a goal of cochlear implant surgery. But even with the introduction of minimally-traumatic "soft" surgical techniques (Lehnhardt, 1993) (Rogowski et al., 1995) and electrodes that have been modified to reduce intracochlear trauma during their insertion (Gantz and Turner, 2004; Lenarz et al., 2006), residual hearing is lost or incompletely preserved in a third of cases (Gstoettner et al., 2004, 2008). Some researchers have begun to explore the possibility that better hearing preservation may be achieved by the application of protective pharmacological agents to the inner ear at the time of surgery (Eshraghi et al., 2007; James et al., 2008; Ye et al., 2007), and here we examine the dose-time relations for hearing preservation when the glucocorticosteroid, dexamethasone is applied to the round window in an experimental model of cochlear implantation.

Cochlear protection with steroids is presumably achieved primarily through suppression of the inflammatory response initiated by cochlear implant surgery (Cope and Bova, 2008), and possibly also through direct anti-apoptotic effects (Sasson and Amsterdam, 2003) on cochlear tissues. Clinically, residual hearing may be lost progressively over the first few days after cochlear implant surgery (Adunka et al., 2006). Over this period of time there will be progression of the inflammatory response initiated by the surgical trauma, and there is experimental evidence to suggest that the permanent hearing loss may be due in part to secondary oxidative

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0378-5955/$ - see front matter
doi:10.1016/j.heares.2009.05.010

stress and apoptosis of hair cells (Eshraghi, 2006). In addition, cochlear inflammation has other effects known to be detrimental to hearing, such as disturbance of inner ear fluid homeostasis (Ichimiya et al., 2000; Maeda et al., 2005) and the promotion of fibrosis and/or osteoneogenesis (Li et al., 2007). That suppression of the cochlear inflammatory response, by the intra-operative application of steroids to the inner ear, reduces hearing loss has been demonstrated experimentally in models of cochlear implantation (Eshraghi et al., 2007; James et al., 2008; Ye et al., 2007).

The authors have demonstrated that high frequency hearing can be protected in the guinea pig when a 2% solution of dexamethasone is applied to the round window on a polymeric sponge (Seprapack™, Genzyme) 30 min prior to cochlear implantation. The round window was chosen as the route of delivery because it is accessible during surgery, and locally delivered steroids are known to achieve a higher intracochlear drug concentrations than with systemic administration. Seprapack™ (Genzyme, Cambridge, MA, USA), a carboxymethylcellulose hyaluronic acid polymer was chosen, as it allowed for an extended delivery of the drug. Dexamethasone delivered via a Seprapack sponge was as still detectable within the cochlea 24 h after the initial round window application(James et al., 2008) Local delivery also has the advantage of avoiding the potential risk of systemic complications associated with the parenteral administration of steroids, and there is a clinical precedent for its use in the treatment of sudden sensorineural hearing loss, intractable tinnitus and Meniere's disease (Chandrasekhar, 2001; Dodson et al., 2004; Gouveris et al., 2005; Silverstein et al., 1996).

In order to determine whether the delivery of steroids to the round window has the potential to be a useful strategy for hearing protection in the clinical setting, its duration of local delivery must be optimised. In our previous study with 2% dexamethasone applied for 30 min, protection was achieved in the lower basal turn of the cochlea, at the site of electrode insertion. However, the residual hearing to be protected in cochlear implant recipients is in the lower frequencies originating in the second and upper cochlear turns. Therefore, for this strategy to be clinically useful, round window delivery of steroids must be shown to protect lower frequency hearing. Better hearing protection might be achieved by either increasing the time that the steroid is applied to the round window prior to implantation, or by increasing the concentration of the drug applied to the round window. Here, we examine these dose-time relations, drawing upon theoretical models of cochlear pharmacokinetics to inform the experimental design (Salt, 2002). Such models are based upon drug diffusion, and predict the most efficient way of increasing the spatial extent over which the drug is distributed, is to increase the application time. Secondly, it is predicted that the duration required to achieve a therapeutic effect may be shortened (off-set) by increasing the concentration of the drug (Salt, 2002; Salt and Plontke, 2005). It is anticipated that the results from this study will assist in the translation of this approach to clinical application.

2. Methods

2.1. Animals

Thirty-four adult, normal hearing guinea pigs (Dunkin–Hartley strain), weighing between 750 and 900 g were used in this project. The project was approved by the Royal Victorian Eye and Ear Hospital Animal Ethics Committee (Ethics Approval #07/140A). Both intramuscular and inhalation anaesthesia were used during auditory brainstem response (ABR) recordings and during surgery. The intramuscular agents were 4 mg/kg ketamine and 60 mg/kg xylazine. The inhalation anaesthesia, ****isoflourane, was administered with oxygen at a concentration of 0.5–1% and at a rate of 500 ml/min. Respiration rate was used to monitor the depth of anaesthesia.

2.2. Materials

Dexamethasone (Dexamethasone 21-Phosphate disodium salt, Sigma–Aldrich, USA) was made into solutions of 2%(w/v) and 20%(w/v) in sterile water and adsorbed into 2 mm discs of the carboxymethylcellulose hyaluronic acid polymer, Seprapack (Genzyme Biosurgery, Framingham), for 1 min prior to round window application.

The non-stimulating electrodes used in these studies consisted of three platinum rings spaced 0.75 mm apart (centre-to-centre) on a Silastic carrier. The rings were used to help gauge the depth of insertion. The diameter at the tip of the electrode was 0.41 mm with a maximum shaft diameter of 0.43 mm. A 25 μm platinum wire was welded to the platinum rings to reinforce the electrode. The electrodes were ultrasonically cleaned and sterilised with ethylene oxide and sealed in a plastic envelope.

2.3. Experimental design

Hearing guinea pigs were implanted with a dummy cochlear implant electrode, following application of the dexamethasone, or controls, to the round window. The main outcome measure was a frequency-specific change in auditory brainstem response (ABR) threshold 1 week after implantation. This timeline was chosen because hearing thresholds were stable after 1 week of observation in our previous study (James et al., 2008). A secondary outcome measure was the histological appearance of the cochlea at the end of the experiment. Animals were randomly allocated into saline control ($n = 7$) and treatment (dexamethasone) groups. Dexamethasone treated animals were further divided into groups receiving different durations of application of drug prior to implantation, [30 min ($n = 4$), 60 min ($n = 6$) and 120 min ($n = 4$) all with a dexamethasone concentration of 2%(w/v)] and animals receiving 20%(w/v) dexamethasone concentration for 30 min ($n = 6$). The prediction of intracochlear dexamethasone concentrations derived from Salt's Cochlear Fluid Model is found in Table 1. Note that this model predicts a similar concentration of dexamethasone at the site of cochlear implantation (32 kHz region) when 2%(w/v) dexamethasone is applied for 60 min and when a 20%(w/v) solution is applied for 30 min. Therefore, similar levels of hearing protection may be predicted from both of these groups.

2.4. Auditory brainstem response recordings

ABR recordings were taken from all guinea pigs to assess hearing across the experiment timeframe. Guinea pig ABR recordings were made immediately pre- and post-surgery and 7 days after surgery, immediately prior to perfusion of the animals and harvesting of cochleae for histology.

Once anesthetised, the animal was placed inside an acoustically shielded room. To isolate the implanted ear acoustically, the contralateral ear was filled with Otoform-K2 (DLT, West Yorkshire), a vulcaning silicone. Computer-generated acoustic stimuli (5 ms tone pips with 1 ms rise/fall times) were delivered via a

Table 1
The predicted concentration of dexamethasone (mM) present in the perilymph at various frequencies along the cochlea at the time of surgery. The concentrations were calculated using the Washington University Cochlear fluid Simulator V1.6 with round window delivery and no middle ear clearance.

	2% Dex 30 min	2% Dex 60 min	2% Dex 120 min	2% Dex 30 min
32 kHz	0.224	2.360	8.125	2.239
24 kHz	0.028	0.803	4.763	0.276
16 kHz	0.001	0.132	1.895	0.009
8 kHz	>.001	0.002	0.251	>.001
2 kHz	>.001	>.001	0.001	>.001