Introduction

The outcome of a cochlear implant (CI) can possibly be improved by a treatment with neurotrophic factors (NTF), e.g. brain-derived neurotrophic factor (BDNF), to support the survival of the stimulated spiral ganglion neurons (SGN). For a longer lasting effect, a chronic application of the NTF is required. This could be achieved by an implantation of drug-producing cells into the inner ear. To improve biosafety, cells can be encapsulated into a bio inert alginate-matrix to avoid their uncontrolled migration and release. Additionally this can protect the cells against shear stress during implantation and shield them against the host immune system. The hydrophilic alginate can also cover the hydrophobic silicon surface of the electrode array. An application of alginate encapsulated NTF-producing cells as a viscous solution or electrode coating are possible delivery methods but may influence the implantability of the CI-electrode array.

Methods

Cell encapsulation:

Bone marrow derived human mesenchymal stem cells were lentivirally modified to produce human BDNF. Cells were expanded, concentrated by centrifugation and mixed with ultra high viscous (UHV-)alginate. The UHV-alginate encapsulated cells were applied as viscous solution (= lubricant) or applied by dip coating as gelled layers on the electrodes surface (Fig. 1).

Fig. 1: Electrode array coating: Tip of a coated human-sized custom-made electrode array. Electrodes (blue) were precoated with a layer of poly-L-lysine (yellow line) to allow the adhesion of alginate to the silicone surface. Following 4 layers of cell-including alginate (enclosed by red line) were applied, covered by 3 layers of cell-free alginate (enclosed by green line). Scale bar: 1000µm

Electrode insertion:

Electrodes were inserted three times into an artificial human cochlea model (aCM) (Fig. 2) using an automated insertion test bench. The aCM was filled with saline and fixed on a force sensor to measure forces occurring during insertion. Forces of three different experimental groups were detected and compared (Fig. 3). Coated electrodes were microscopically documented before and after the first and third insertion and the coated electrodes were classified in different grades of abrasion.

Fig. 2: Electrode array insertion: During insertion, a first contact of the array (blue) with the aCM was detectable at the outer wall (a). A second contact occurred at the inner wall of the model (b). Subsequently the array bent to follow the curved path of the aCM. (c) shows the final array position for a complete insertion into the aCM. Ending of the first (-), the second (--) and the last two (--) embedded copper wires are marked.

Results

Effect of alginate-cell based drug-delivery systems on the insertion forces of CI-electrodes

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Fig. 4: Reduction of insertion forces by array coating: (A) depicts the insertion forces as function of insertion depth, (B) shows the maximal insertion forces. The tested alginate coating significantly reduced the insertion forces by 75% when compared to the reference and the lubricant group. In the lubricant group, the injected alginate-cell solution seems to have a tendency to increase the insertion forces compared to the reference. This difference was not significant. Marked points (a, b, c) in (A) correspond to the images of Fig. 2 and show the position of the array in the aCM during force measurement. Only complete insertions were included in the analysis. Statistics: Mann-Whitney-U-Test, n = 0.001

Discussion and Conclusion

With regard to insertion forces for CI-implantation, both tested application strategies are promising options for a cell-based drug-delivery to the inner ear. The injection of an alginate-cell solution with a subsequent electrode insertion could bridge the anatomical gap between SGNS and electrode with a potential growth matrix for regenerating neurites. But the detected tendency for higher insertion forces would exclude this strategy for patients with residual hearing. In contrast, the alginate-cell coating offers the great advantage of combining a cell-based drug-delivery with a tremendous reduction of insertion forces and therefore ares a huge potential for patients with residual hearing undergoing a CI-implantation.