Cell-based neurotrophin treatment for auditory neuron survival in deafness

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AIM

To promote auditory neuron survival in deafness using cell-based delivery of neurotrophins.

INTRODUCTION

The cochlear implant provides auditory cues to patients with profound hearing loss by electrically stimulating the auditory neurons within the cochlea, but the ongoing degeneration of auditory neurons that occurs in sensorineural hearing loss may be a limiting factor in cochlear implant efficacy. The exogenous application of neurotrophins such as BDNF can rescue auditory neurons from this deafness-induced degeneration[1-4]; however, these survival effects are not maintained[1,5].

A safe and efficient means of delivering neurotrophins to the cochlea, which can be used in conjunction with a cochlear implant for long-term survival of auditory neurons, is required for this therapy to be clinically transferable.

We investigated the survival-promoting effects of cell-based neurotrophin treatment and electrical stimulation, using fibroblasts genetically modified to express BDNF and encapsulated in a biocompatible matrix, on auditory neurons in the deaf guinea pig.

METHODS

Preparation of encapsulated BDNF-expressing fibroblasts

Fibroblasts from adult rat sciatic nerve were genetically modified to express BDNF using Nucleofection, and were subsequently encapsulated in a biocompatible alginate matrix (Living Cell Technologies, Limited).

Implantation of encapsulated BDNF-fibroblasts *in vivo*

Normal hearing guinea pigs were deafened under gaseous anaesthesia using a combination of the ototoxic aminoglycoside kanamycin (130 mg/kg, s.c.) and the loop diuretic frusemide (520 mg/kg, i.v.). Five days post-deafening the animals were implanted bilaterally with encapsulated BDNF-fibroblasts (left cochlea) and control (empty) capsules (right cochlea), or unilaterally with encapsulated BDNF-fibroblasts and a stimulating cochlear implant electrode array. Auditory neuron survival was quantified one, three or six months post-implantation.

RESULTS

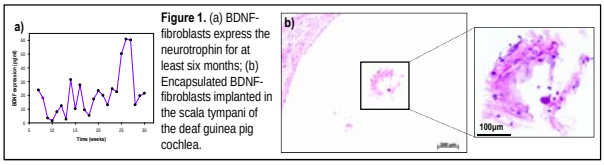

Figure 1. (a) BDNF-fibroblasts express the neurotrophin for at least six months; (b) Encapsulated BDNF-fibroblasts implanted in the scala tympani of the deaf guinea pig cochlea.

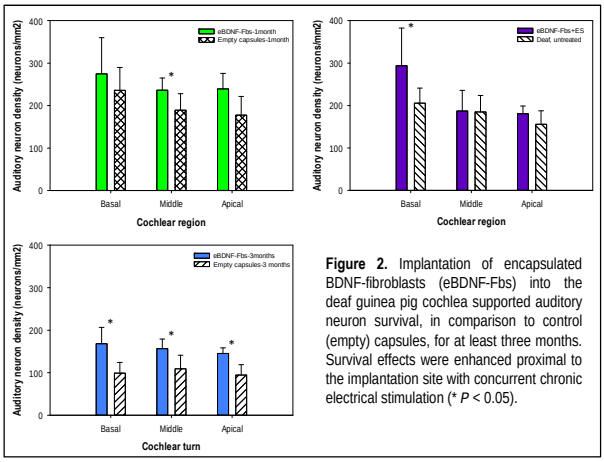

Figure 2. Implantation of encapsulated BDNF-fibroblasts (eBDNF-Fbs) into the deaf guinea pig cochlea supported auditory neuron survival, in comparison to control (empty) capsules, for at least three months. Survival effects were enhanced proximal to the implantation site with concurrent chronic electrical stimulation (* $P < 0.05$).

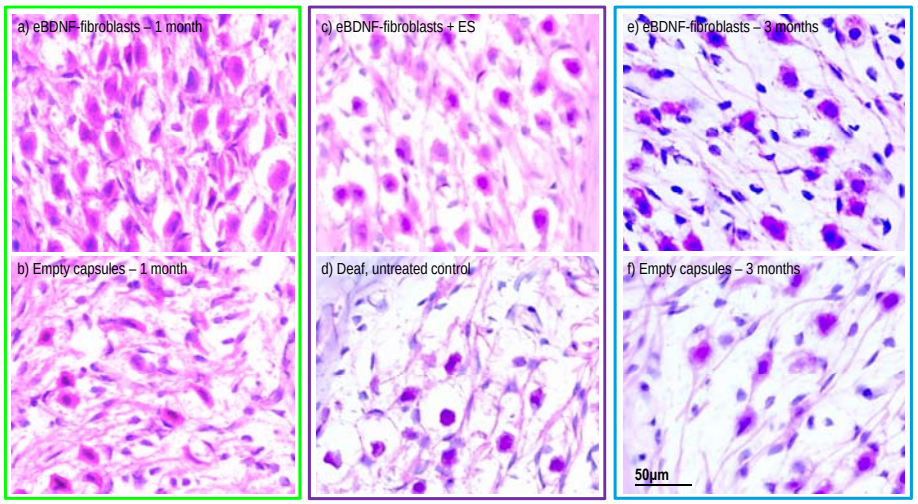

Figure 3. Auditory neurons in the basal turn of the deaf guinea pig cochlea, one month following treatment with encapsulated BDNF-fibroblasts, (b) empty capsules, (c) encapsulated BDNF-fibroblasts and chronic electrical stimulation (ES), or (d) untreated; or three months following implantation of (e) encapsulated BDNF-fibroblasts or (f) empty control capsules. There are more surviving neurons following cell-based neurotrophin treatment and/or chronic electrical stimulation, in comparison to the respective contralateral control, for up to three months.

SUMMARY OF FINDINGS

- Fibroblasts can be genetically modified using Nucleofection to express BDNF for at least six months, with an average rate of expression of ~20±3 pg BDNF/mL/day (mean±SEM).
- Implantation of encapsulated BDNF-fibroblasts into the deaf guinea pig cochlea elicits minimal tissue response.
- Implantation of encapsulated BDNF-fibroblasts into the deaf guinea pig cochlea supports auditory neuron survival for at least three months.
- The survival effects induced by encapsulated BDNF-fibroblasts are enhanced with concurrent electrical stimulation from a cochlear implant.

CONCLUSIONS

The findings observed in this study suggest that cell-based neurotrophin treatment, combined with chronic electrical stimulation from a cochlear implant, may be a clinically relevant method to support long-term auditory neuron survival in deafness, which in turn may improve the efficacy of the cochlear implant and lead to improved speech perception and language outcomes for cochlear implant patients.

Acknowledgements

Funding for this project was provided by the Garnett Passe and Rodney Williams Memorial Foundation, the National Health and Medical Research Council of Australia, Living Cell Technologies Limited and the Bionics Institute. The Bionics Institute acknowledges the support it receives from the Victorian Government through its Operational Infrastructure Support Program.

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