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Institutionen för klinisk vetenskap, intervention och teknik, enheten för öron-, näs- och halssjukdomar

Regeneration of the auditory nerve – a cell transplantation study

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ABSTRACT

Since in mammals, the hair cells or the spiral ganglion neurons (SGNs) in the inner ear do not regenerate, damage to these cells is an irreversible process. Presently the only aid for patients with severe to profound hearing impairment due to damaged hair cells is a cochlear implant (CI). A CI converts sound to electrical signals that stimulate the SGNs via an electrodes that is implanted into the cochlea. Hence, for a successful outcome the CI is dependant on the activation of the auditory nerve. There are several conditions, diseases or even traumatic events that primarily may impair the function of the SGNs in the auditory nerve. It is also known that in the absence of nerve stimuli due to hair cell damage, the SGNs will eventually degenerate. Lately there has been an increasing interest in regenerative medicine and bioengineering. This thesis presents results from in vivo experiments aiming to replace or repair the injured SGNs with the use of transplanted stem cells or neuronal tissue. All transplanted cells were labeled with a green fluorescent protein facilitating identification in the host animal.

Paper I presents a new animal model of selective auditory nerve injury with preserved hair cells. The lesion was induced in rats by the application of β-bungarotoxin to the round window niche. Immunohistochemical straining confirmed the loss of SGN while the hair cells were kept intact. The induced hearing impairment was verified by auditory brain stem response (ABR).

Paper II presents a surgical approach for the injection of stem cells to the auditory nerve by the internal auditory meatus (IAM). It was shown that this approach does not significantly affect the hearing as verified by ABR. Further, neuronal tract tracing with the enzyme horseradish peroxidase illustrated that injection of selected substances may be distributed by intra-axonal transportation centrally to the brain stem as well as peripherally to the cochlea. Furthermore it was illustrated that statoacoustic ganglions transplanted by the IAM survived for up to five weeks, though in low numbers. No cells had migrated through the Schwann-glia transitional zone into the cochlea. survival and neuronal differentiation of the transplanted cells. It was also demonstrated that supplement of the enzyme chondroitinase ABC in PA gel facilitated migration of transplanted cells through the transitional zone.

Paper IV presents the use of human neural progenitor cells for transplantation to the auditory nerve by the IAM. We further assessed supplement of BDNF in the PA gel. After three weeks, survival and differentiation of the transplanted cells were observed. After six weeks of survival the majority of the surviving cells had differentiated into neurons. The addition of BDNF in PA gel significantly increased both survival and differentiation. The transplanted cells migrated to the brain stem and formed neuronal profiles including extensive arborisation of nerve fibers in the vicinity of the cochlear nucleus.

In conclusion, this thesis presents a new animal model for a selective lesion of the auditory nerve. Further, promising results were demonstrated regarding the possibility of replacing auditory SGNs including increased rates of survival and neuronal differentiation of the transplanted cells in the presences of BDNF. These results suggest for further studies on auditory nerve replacement but also for functional assessment of the transplanted cells.

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