Karolinska Institutet

The Department of Neuroscience

Drug-based Therapies for Auditory Trauma

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Lennart Nilsson salen, Nobels väg 15A, Karolinska Institutet, Stockholm

Fredagen den 13 december 2013, kl 10.00

av

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ABSTRACT

Deafness is one of the most common health conditions in the developed countries, and worldwide, an estimated 70 million people are deaf. For people with severe to profound hearing loss**,** a cochlear implant is the only treatment today. The most common forms of severe hearing loss and deafness are related to morphological changes in the cochlea.

Aim: The aim of these studies was to investigate several therapeutic compounds, including nucleosides and nucleotides, two types of neurotrophic factors, and two oxysterols, to determine if they could preserve spiral ganglion neuron (SGN) survival and maintain SGN electrical responsiveness**,** as determined by measuring electrically-evoked auditory brainstem response (eABR) in deafened guinea pigs. It was also important to investigate the compoundsô effectiveness when delivered into the inner ear several weeks after deafening (ñDelayed treatmentò). In some experiments, the animals stayed in the study for several weeks after cessation of treatment to determine if eABR thresholds remained and the extent of SGN survival after treatment cessation.

Methods: All animals in these studies were deafened with the ototoxic compound neomycin sulfate by intracochlear or transtympanic infusion. They received a cochlear implant and an osmotic pump for inner ear drug delivery. To determine any changes in hearing (i.e., SGN electrical responsiveness), eABR was measured weekly. After the last measurement cochleae were collected for morphological analysis.

Results: We found that nucleosides and nucleotides seem to have a trophic effect on spiral ganglion neurons, showing low eABR thresholds and a statistically significant ($p<0.001$) SGN survival compared with the control group. Results from the study with glial cell line-derived neurotrophic factor (GDNF) showed that delayed GDNF treatment helped to prevent loss of electrical responsiveness and auditory nerve cell death up to four weeks after GDNF cessation. Cometin, a new neurotrophic factor, showed low eABR thresholds but with fewer surviving SGNs. The oxysterols study showed a different pattern compared to all our previous studies. In the acute study both oxysterols showed low eABR thresholds compared to the control group, but SGN survival was equal to the control group that did not received any treatment. In the delayed treatment study only one of the oxysterols showed lower eABR thresholds during the whole experiment compared to the control group. Despite that, SGN survival was equally low in the oxysterol groups and the control group.

Of the therapeutic agents tested in this study GDNF was most the promising compound.