Recent advancements toward gapless neural-electrode interface post-cochlear implantation

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Cochlear implants (CI) are widely used to provide auditory rehabilitation to individuals with moderate to severe sensorineural hearing loss (Eshraghi et al., 2012). The scala tympani (ST) of the cochlea is the site of implantation of the intracoil electrode array. In a healthy, normal ear, the cell bodies of the spiral ganglion neurons (SGNs) reside in Rosenthal’s canal, a small cavity adjacent to the ST. SGNs have a perihilar neurite that projects to the hair cells on the basilar membrane of the organ of Corti, and a central axon that projects to the brainstem via the auditory nerve (Landry et al., 2013). From SGN cell bodies, the dendrites extend through the modiolus and the osseous spiral lamina to make synaptic contact with hair cells in the organ of Corti (Rusznik et al., 2009). In severe to profound deafness, the cochlea has few to no hair cells (Shibata et al., 2010). A CI helps overcome the problem of functional hair cells by directly stimulating the SGNs in the inner ear via short biphasic electric pulses (Li et al., 2017).

In the CI field, there is an increased interest in how to improve and restore the functionality and number of SGNs which may contribute to the success of CI for providing auditory rehabilitation (Shibata et al., 2010; Li et al., 2017). An anatomical gap between the electrode array and the auditory neurons in the inner ear impedes optimal electrical stimulation with CI. Hence, current devices are limited by 1) inadequate spatial specificity of inputs, thus suboptimal sound quality; and 2) large stimulation currents, thus high energy consumption (Wilson and Dorman 2008; Senn et al., 2017). Overlapping electrical fields, interference between channels, and spread of excitation from the electrodes lead to low resolution and low specificity of auditory perception. This may be one of the major reasons for suboptimal sound quality as well as variability of speech and music perception. The gap between the electrode array and the auditory neurons leaves insufficient bridging between the perilymph-surrounded electrode contacts in the scala tympani and the SGNs in Rosenthal’s canal of the bony modiolus. The CI must generate electrical stimulation that reaches fibers from the electrode. To cross the gap and reach the SGNs, greater stimulation currents are needed. This structural gap also limits the count of possible non-overlapping stimulation points. SGNs receive inputs from a broad spectrum of frequencies, resulting in poorer frequency discrimination of sounds such as speech and music. Physical contact could potentially minimize current spread and enable the use of smaller currents to reach the stimulation thresholds of the contiguous auditory neurons (Li et al., 2017). In this perspective, we discuss the recent advancements toward gapless neural-electrode interface (Figure 1) post-CI.

Neurotrophins (NTs) are a class of growth factors that induce the survival, development, and function of neurons. Cochlear hair cells are the primary source of endogenous NT peptides. A deficit of neurotrophic factors following the loss of hair cells in the deafened cochlea markedly reduces the number of peripheral fibers and SGNs via apoptosis. One such factor is pleiotrophin (PTN), a NT for different types of neurons expressed in the postnatal mouse cochlea. PTN knockout mice exhibit severe deficits in auditory brainstem responses, which signifies the importance of PTN in inner ear development and function, thus making it a promising candidate to support the viability of SGNs (Bertram et al., 2019). Both spiral ganglion cell explants and dissociated SGNs were cultivated with PTN in vitro at varying dilutions of 1:4, 1:8, and 1:16. While PTN showed a beneficial effect on neurite length and number of dissociated SGNs at dilutions of 1:4 and 1:8, no statistically significant effect was found for SGN neurites in organotypic explants (Bertram et al., 2019).

Brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) are also key NTs that promote the survival, development, and neurotrophic effects of auditory neurons and the CI electrodes (Figure 1). The calcium phosphate hollow nanospheres were coated on CI electrodes and loaded with NTs. Calcium phosphate hollow nanosphere capacity for uptake and release of NTs was determined using RGD-conjugated g1 cell line-derived neurotrophic factor. Neurites from human vestibulocochlear ganglion explants reached and established physical contact with the glial cell line-derived neurotrophic factor-loaded calcium phosphate hollow nanospheres coating the CI electrodes positioned at 0.7 mm away. 3D-reconstruction of the Z-stacked images showed that TuJ1 (a nerve development marker) positive neuronal extensions took root on the coating and grew to reach the electrodes (Li et al., 2017). These axon guidance effects suggest NT delivery with NEPQNTs (Calcium phosphate hollow nanospheres coating may be a key toward a gapless neural-electrode interface.

In addition to targeted sustained release, long-term NT administration is necessary for protective benefits to auditory neurons. Delivery via NT injection is generally short term, and repeated injections are not ideal due to the risk of infection and immune response. However, implantation of mesenchymal stem cells (MSCs) genetically modified to overexpress BDNF may be a feasible drug delivery system. The stem cells encapsulated in alginate protect against host immune response and prevent their uncontrolled migration (Blaurock et al., 2008). A physiologically stable hydrogel that allows bidirectional transfer of small molecules in (nutrients, growth factors, oxygen), and out (waste products, insulin, BDNF) can further facilitate continuous NT release in the setting of auditory preservation and regeneration. Alginate, a polysaccharide isolated from bacteria or the cell wall of brown algae, is one such material which meets the above-mentioned criteria (Schweiger et al., 2020). Ultrahigh viscous alginate is even more suited for medical applications as it fulfills the requirements of high molecular weight, low endotoxin levels, and sterility. There is no alginic-degrading enzyme in humans. Using an in vitro dissociated rat SGN co-culture model, alginate-mesenchymal stem cell samples were electrically stimulated, and alginate stability, as well as MSC survival were monitored. Electrical stimulation of “biphasic 800 μs pulses (400 μs per phase) and 120 μs interpulse gap for 24 hours in an incubator” (Schweiger et al., 2020), was used. After 21 days, 330 μA of this electrical stimulation caused calcium phosphate or survival of MSCs within the investigated time frame compared to unstimulated controls (Schweiger et al., 2020). However, it was not mentioned whether the electrical stimulation was charge balanced or not. Alginate stability was tested using a multiplexing system from the tdTomato marker protein; reduction in fluorescence indicative of damage of the stimulated alginate-embedded cells was not seen.

Does long-term NT delivery (via injection from mesenchymal stem cells (MSCs) compared to short-term NT delivery (via injection) produce a targeted and differentiable difference on the site of implantation and reach the CI electrode. Biodegradable calcium phosphate hollow nanospheres display promise as a potential avenue for sustained, long-term release of growth-promoting NTs when coated on CI electrodes (Li et al., 2017). Using a 3D in vitro culture model, it was shown that the regenerating auditory neuron dendrites were attracted by targeted NT release and were able to grow toward direct physical contact with the auditory neurons and the CI electrodes (Figure 1).
By attracting neurons using neurotrophic stimulation and replacing the perilymph with an extracellular gel matrix, the anatomical gap between the auditory nerve and electrode could be closed. Peripheral dendrites grow from modiolus (*) via osseous spiral lamina (**) and through habenula perforata (***) to scala tympani. Another route is growing directly through canaliculi perforantes (arrow). Reduced distance will result in minimized current spread from the cochlear implant, enabling the use of a higher number of non-overlapping stimulation points (adapted from Rask-Andersen et al., 2012; reprinted from Li et al., 2017 with permission from Elsevier).

Figure 1 An illustration of spiral ganglion neurons guided toward a cochlear implant electrode.

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