Electrode-nerve interfaces: Long-term stable sensors and electrode corrosion

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Cochlear Implants (CI) have become a well-established method for patients with profound sensory neural hearing loss with increasing technological evolution. One of the main challenges nowadays is reliable current transmission on the electrode-nerve interface. However, clinical results indicate that in some cases corrosion or encapsulation processes lead to high impedance and hinder successful stimulation of the auditory nerve. Furthermore, histological evidence of platinum was found in post mortem analysis in CI carriers. It is unclear whether processes in the cochlea trigger the corrosion of the electrodes, or the corrosion of the electrode causes the physiological reaction. In order to understand the interrelation, it is important to investigate both the chemical changes of the microenvironment by the physiological reaction, the electrode corrosion and nature of the released substances.

Analysis of explanted CI electrodes from humans revealed electrode corrosion correlating with high impedances and poor hearing results. In vitro models were established in order to investigate the electrode surface during acoustic stimulation in standardized conditions, measurement of the pH and laser scanning microscopy to document the changes of the surface. The findings support the general assumption that noble metal electrodes show pitting corrosion in the presence of halide ions at low pH.

Electrochemical microsensors could be used to characterize the microenvironment next to the electrode in vivo. However, they are too large to address the electrode/nerve interface directly and often lack sufficient long-term stability. Therefore, it is proposed to use the stimulation electrodes themselves as part of a microsensor concept. Chronoamperometric protocols with potentiometric phases have been developed providing integral parameters such as oxidizable or reducible species. Such protocols, in comparison to typical stimulation, have negligible impact on the microenvironment itself allowing their application in animal models and ultimately in patients.

The combination of in vitro corrosion analysis and in vivo sensing using the stimulation electrode itself provides the possibility to investigate the interrelation between physiology and corrosion of CI electrodes during stimulation of the auditory nerve. The described methodology has the potential to be translated to other electrode-tissue interfaces such as in the brain, the spinal cord or for cardiac stimulation.

Implanteable pumps for interventional neurorehabilitative drug administration

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Today, the standard method to administer drugs is systemic application. Using this approach, drugs are inevitably diluted, become widespread through the body and can have severe side effects. Moreover, some parts of the body, like ear, eye or brain provide biological barriers. Therefore approaches for a local drug delivery have been developed to enable a direct access of a drug to a desired application site, a minimum dilution of the same and a reduced time delay of the medical effect. Amongst the realized concepts are local drug depots, partially implantable systems as known for the treatment of diabetis, but also fully implantable pumps, all these with or without external control. The latter are currently mainly used for pain or cancer treatment with more applications being under development. This presentation will focus on the most important design goals for realizing systems to be implanted and operated in narrow spaces, as for instance the vicinity of the human ear or the human eye. Here, we find an urgent need for novel, currently not available drug delivery systems. They must (1) dose extremely small, adjustable amounts of highly potent drugs (µl/min to µl/hr) in (2) an externally controlled manner, including an accurate monitoring of the administered amount. To be used in a large variety of applications (3) their performance has to be independent of the physicochemical nature of different conceivable drugs. Also, the drug delivery system (4) must not have negative side effects onto the drugs in use. Finally, (5) such systems have to be built with a minimal volume (a few cm^3) to be implanted in-situ in narrow spaces and with short cathether lengths to the application site. Details of these challenges, potential solution concepts and medical applications will be demonstrated for the therapy of diseases of the middle and inner ear.

In-vitro and *in-vivo* sensors for monitoring neuronal restauration

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Conservation of residual hearing is one of the major challenges in cochlear implantation (CI). Foreign body reactions, inflammatory processes and formation of fibrous scar tissue cannot only destroy functional residual hair cells or neurons but can also deteriorate audiological performance by increasing electrical resistance. So far, limited information is available about these mechanisms and when they exactly occur. The biochemical composition of human perilymph may be correlated to the function and pathophysiology of the inner ear. The goal of the project is to develop a microsensor system applicable for acute as well as chronic monitoring in situ inner ear fluid analysis in order to investigate the reaction of the cochlea to the foreign body.

Pathophysiologically relevant biochemical parameters especially low molecular weight acute indicators of inflammation markers as reactive oxygen species (ROS), O_2, glucose, H_2O_2, and ionic composition (pH, Ca^{2+}, K^+, Na^+, Cl^-) will be investigated. The analysis will be performed during surgery (CI surgery peri- and short term postoperative) or routine audiological testing within minutes. For chronic implantation microdialysis catheters will be inserted and connected to an *ex vivo* microfluidic chip.

From a technological point of view, miniaturized integrated bio- and chemosensors are used to monitor low concentrated biomarkers measuring oxygen, pH, H_2O_2 and glucose and solid state potentiometric ion sensors using neutral carrier membranes will be tested *in vitro* with respect to stability and reliability. As pH sensor preferably an IrOx electrode deposited by an electrochemical deposition protocol can be used. Preliminary investigations show an excellent and reproducible sensitivity and long-term stability up to one week.

The same principle can be used to produce ion sensors using a pH sensor as internal reference and a liquid membrane electrode as selective sensor. Long-term stability can be achieved by using an appropriate sealing technology of the ion sensor membranes with the substrate. Liquid membranes are available for K^+, Na^+, Ca^{2+} and Cl^- and as reference electrode, an external Ag/AgCl electrode will be used.

For glucose, oxygen and ROS measurement, a well-established amperometric principle will be used to obtain measuring times in the day range with good long-term stability. For higher molecular weight biomarkers as heat shock proteins, cytokines or oxidized proteins, a microfluidic multiplexed Micro-ELISA combined with microdialysis for the simultaneous analysis of various interleukins will be implemented. Preliminary results show feasibility and reproducibility of the cytokine detection in perilymph samples of CI patients. For visual long-term monitoring and to compare pathological tissue response, glass-fibre based micro-OCT will be used.

Identifying functional biomarkers for responsive control of cochlear implants

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Abstract

Current cochlear implants (CIs) employ stimulation strategies founded on large cohorts of psychophysical experiments with little attention to the individual patient's history, situation, and anatomy. The CI restores a sense of hearing and promotes speech comprehension and production but fails to fully replace a healthy ear's ability to support speech comprehension in noise or sound localization. In particular, speech comprehension changes over time, as the implants surrounding adapts to the foreign body. In order to make the most out of a specific CI-auditory nerve interface and thus to improve the maximum benefit for CI patients, it is proposed to introduce an individualized and permanently optimized stimulation paradigm, based on neuronal activation markers originating along the patient's auditory system. We used two different animal models, congenitally deaf cats and neonatally deafened rats, to characterize prominent differences in activation of the experienced and deaf auditory systems. Both groups were bilaterally electrically stimulated with CIs. By multi-electrode recording from the inferior colliculus (IC) and/or the primary auditory cortex (A1) of the CI-implanted animals, we recorded single-/multi-units, and LFPs. Under bilateral CI stimulation with varying interaural time and level differences (ITDs/ILDs), we identified a high number of multi-units with sharp and reproducible tuning curves in the IC of deaf rats. The ITD/ILD responsiveness was comparable with hearing rats. ITD and ILD tuning curves were identified also in A1 of deaf cats. Their tuning and responsiveness were, however, reduced in comparison to the hearing cats. In addition, activation of A1 in deaf cats were biased to superficial cortical layers and the induced cortical activation, reflecting integration of incoming sensory information with ongoing cortical activation, was dramatically reduced both in LFP as well as in multiunit activity.

This distinct and robust activation of auditory pathways identified by invasive recordings can be supplemented by noninvasive recordings. Evoked auditory brainstem and cortical responses were measured from the activated auditory system via surface electrodes. These signals provide information on the strength and temporal sequence of activation from the different subcortical and cortical auditory regions, including superior olive, IC, and A1. This information can be used to infer functional states of auditory pathways in CI individuals.

Complementing the experimental approach a computational network model will help us to characterize the interplay between relevant brain structures of the auditory pathway including IC and A1, similar to our ongoing work on the primary visual system. This model will allow us to address fundamental questions of binaural auditory processing and rehabilitation via computer simulation, and it will support the development of the closed-loop approach described above.

In the present study we identify and discuss the possible neuronal signals and their characteristics, which can serve as feedback signals for optimal adaptation of recording positions and stimulating protocols for CIs. By continuous online measurement and processing of these functional markers in CI users we can monitor and assess rehabilitation progress in CI patients following cochlear implantation. Based on this knowledge, we want to develop a permanently optimized stimulation paradigm to improve the benefit for individual CI patients.

Cellularized chitosan-based hydrogel compartments for potential application in the therapy of inner ear neuronal structures

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Hollow cylindrical physical hydrogels of chitosan (hydrogel tubes) were produced for cell culture in “confined” environment, i.e. without flushing the cell medium in contact with the cells. To produce the hydrogel tubes, a viscous weakly acidic solution of 5 %wt chitosan was extruded, under controlled air pressure through a 3 mm syringe tip of a fluid dispenser (Performus I, Nordson EFD), into a 7 M NaOH coagulation bath. After partial coagulation of chitosan for a few minutes in the basic bath, the tube lumen of the produced cylindrical hydrogel was washed under distilled water flow (200 mL/min), allowing the removal of the inner remaining solution of chitosan and thereby the production of hollow macrofibers.

The inner compartment of the hydrogel tubes was seeded with skin human fibroblast cells and the tubes were closed by ligature. Diffusion of oxygen and nutrients was allowed through the hydrogel membrane. The hydrogel compartment allowed cell proliferation. Hydrogel tube microstructure was characterized by atomic force microscopy (AFM) and cryo-scanning electron microscopy (cryo-SEM), as well as hydrogel mechanical properties by AFM and tensile test. It was investigated the impact of the hydrogel morphology and cell culture conditions on cell viability, as determined by life/dead cell viability assays. Such cell culturing conditions in confined compartments, in relation with the microstructure and morphology of the hydrogel, set the basis for the processing of more complex 3D hydrogel micro-architectures by additive bioprinting for applications in cell-assisted pharmacological therapy of inner ear neuronal structures.