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Mechanically Adaptive Materials for Intracortical Implants*

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Cortical microelectrodes allow electrical contacts with neural cells and show promise as electrical interfaces to the brain, which allow for the treatment of several neurological deficits. However, the functionality of current electrodes decreases over time, in part due to neuron degeneration and foreign body encapsulation. One hypothesis is that the mismatch of the mechanical properties of the electrode and the brain tissue is a significant contributor to these events. We recently developed a new approach to chemically responsive, mechanically adaptive polymer nanocomposites, which are initially highly rigid, but soften considerably upon exposure to physiological conditions and aqueous environments in general. Initial in-vivo experiments suggest that the materials promise to be a useful platform for the design of next-generation intracortical devices.

I. Introduction

Many factors contribute to neuroinflammation in response to the implantation of intracortical devices, including the mechanical mismatch between the implant and the brain tissue, and oxidative stresses caused by acute inflammation. Based on the hypothesis that each of these pathways plays a unique role in different time regimes, we have studied such effects on the basis of implants based on physiologically responsive, mechanically adaptive polymer nanocomposites, which optionally release anti-inflammatory drugs.

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II. Results and Discussion

A. Design and Properties of Mechanically Adaptive Polymer Nanocomposites

We demonstrated in a series of studies that the stiffness of polymer nanocomposites that contain rod-like cellulose nanocrystals (CNCs) can be reversibly changed by controlling the degree of interactions between the rigid filler particles. Above the percolation concentration, the CNCs form a percolating network within the polymer, which is primarily held together by hydrogen bonds among the CNCs' surface hydroxyl groups. This causes a significant mechanical reinforcement of the polymer. Upon exposure to chemicals that can also form hydrogen bonds with the CNCs, in particular water, the interactions between individual CNCs are reduced and the materials soften considerably. This mechanically adaptive behavior can be well-described by mechanical models. A first generation of such mechanically-adaptive nanocomposites was prepared based on a rubbery ethylene oxide-epichlorohydrin copolymer (EO-EPI) CNCs isolated from tunicates (t-CNCs). The incorporation of 19% v/v t-CNCs into the EO-EPI resulted in a 200-fold increase of the room-temperature storage modulus, E', from 3.7 MPa to 800 MPa. The material displays a significant modulus reduction from 800 to 20 MPa upon exposure to water. The use of a glassy polymer matrix, which can be additionally plasticized upon aqueous swelling, has been shown to reinforce the effect. Thus, in nanocomposites based on poly(vinyl acetate) (PVAc) and t-CNCs E' changes from 5.2 GPa to 12 MPa upon exposure to water. Virtually the same switching was observed upon exposure to emulated physiological conditions.

The realization of intracortical electrodes, and other medical devices based on such materials might require mechanically adaptive materials with even higher stiffness and we therefore explored stimuli-responsive nanocomposites based on poly(vinyl alcohol) (PVOH) as the matrix and CNCs derived from tunicates (t-CNCs) or cotton (c-CNCs) as the filler. This design was based on the fact that PVOH features many hydroxyl groups that can interact with the surface hydroxyls of the CNCs and the hypothesis that strong matrix-filler interactions could further increase the stiffness in the dry state. Indeed, this approach afforded materials, which, upon exposure to simulated physiological conditions displayed a softening from 9.0 GPa to 1 MPa for c-CNCs and from 13.7 GPa to 160 MPa for t-CNCs. It was shown that the swelling characteristics of the materials and the extent of mechanical switching could be influenced via the amount and type of CNCs and also the processing conditions, in particular a thermal annealing step, which served to cross-link the material and reduce the extent of aqueous swelling.

B. Drug-Releasing Mechanically Adaptive Nanocomposites

To minimize acute and chronic responses, the mechanically adaptive nanocomposites were further modified to also release anti-inflammatory drugs. This was achieved by incorporating either curcumin or resveratrol into PVOH/CNC nanocomposites. The two drugs employed are well-known to reduce oxidative stress and enhance the stability of the blood-brain barrier. Similar to the drug-free PVOH/CNC nanocomposites discussed above, these materials display a dry-state modulus of several GPa (depending on the composition), but soften by a factor of up to 1000 upon exposure to emulated physiological conditions. The release of the antioxidant drugs was studied *in vitro*, using artificial cerebrospinal fluid at body temperature. Both drugs are eluded with burst-release profiles; most of the release occurs within ca. 10 hours.

C. In-Vivo Studies

Several studies were conducted to explore the neuroinflammatory response of implants based on the above-discussed physiologically responsive mechanically adaptive materials *in-vivo*. Overall, it appears that, similar to traditional, rigid silicon implants, the response is multiphasic and that benefits arise from the use of softening materials.

In an initial study that involved PVAc/CNC nanocomposites, the histological evaluations revealed that at four weeks post-implantation in the rat cortex, compliant implants stabilized neural cell populations at the device interface better than rigid reference systems. However, no significant difference between the mechanically-dynamic and the much stiffer reference implants with respect to local neuron density was observed after 8 weeks. In a recent, separate study, it was shown that 16 weeks post-implantation, the adaptive implants demonstrated significantly reduced neuroinflammatory and neurodegenerative responses in comparison to rigid reference materials with matched surface chemistry. We observed a pronounced reduction of reactive microglia and astrocytes at the implant-tissue interface for the adaptive material, and such implants also offered a better stability of the blood-brain barrier than the rigid reference materials.

We also probed the *in-vivo* response of physiologically responsive, mechanically adaptive curcumin-releasing PVOH/CNC implants, with the goal to investigate if the combination of two independently effective mechanisms – softening of the implant and anti-oxidant release – could lead to synergistic effects. Interestingly, four weeks after implantation, the curcumin-releasing, mechanically adaptive implants showed a higher neuron survival and a more stable blood-brain barrier at the implant-tissue interface than the (also adaptive) PVOH reference materials. Twelve weeks post implantation, however, the curcumin release showed no benefits; no statistically significant difference in neuronal density around the implant was seen in the comparison between the two materials (with and without curcumin).

III. Conclusion

Our research has afforded a large palette of physiologically responsive, mechanically adaptive nanocomposites based on cellulose nanocrystals and a variety of polymer matrices. The mechanical characteristics of these materials and the "contrast" between initial dry and post-implantation state can be controlled over a wide range via the composition and processing conditions. Initial *in-vivo* experiments support the hypothesis that implants based on such mechanically adaptive materials cause a significantly reduced neuroinflammatory response. While further studies are required to pinpoint the exact mechanisms and relationships between mechanical, chemical, and inflammatory events, as well as the role of the brain blood barrier stability, it appears that under chronic conditions, mechanically adaptive materials present a significant advantage in stabilizing the neural interface. It will be important to transfer these findings to actual devices and explore if functional neural electrodes derived from these adaptive substrates can indeed offer an improved stability of neural recordings.

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