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A strategy to passively reduce neuroinflammation surrounding devices implanted chronically in brain tissue by manipulating device surface permeability

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ABSTRACT

Available evidence indicates that pro-inflammatory cytokines produced by immune cells are likely responsible for the negative sequela associated with the foreign body response (FBR) to chronic indwelling implants in brain tissue. In this study a computational modeling approach was used to design a diffusion sink placed at the device surface that would retain pro-inflammatory cytokines for sufficient time to passively antagonize their impact on the FBR. Using quantitative immunohistochemistry, we examined the FBR to such engineered devices after a 16-week implantation period in the cortex of adult male Sprague–Dawley rats. Our results indicate that thick permeable surface coatings, which served as diffusion sinks, significantly reduced the FBR compared to implants either with no coating or with a thinner coating. The results suggest that increasing surface permeability of solid implanted devices to create a diffusion sink can be used to reduce the FBR and improve biocompatibility of chronic indwelling devices in brain tissue.

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1. Introduction

The foreign body response (FBR) negatively impacts the biocompatibility of a number of devices implanted in brain tissue including hydrocephalic shunts [1], DBS electrodes [2,3], and intracortical microelectrode recording arrays [4]. Irrespective of the type of implant, species studied, or implantation method, a hallmark of the FBR to such devices is a persistent, sterile inflammatory response (i.e. inflammation occurring without infection) signaled by biomarkers for neuroinflammation including activated macrophages and upregulation of pro-inflammatory cytokines [5–7]. Included in the FBR is a region of hypertrophic astrocytes surrounding the implantation site that may also involve infiltrating meningeal cells and fibroblasts. Emerging evidence also indicates that the blood brain barrier (BBB) is compromised surrounding chronically implanted devices [7]. In addition, local nerve fibers and neuronal cell bodies are reduced in density and demyelinated [5–8].

These findings suggest that the chronic FBR to implanted devices likely affects the electrophysiological and neurobiological activity of nearby neurons and neural circuitry by a variety of neuroinflammatory mechanisms including disruption of the BBB, demyelination, and changes in the local ionic milieu. The biology of the FBR shares many features with the sterile inflammatory response that accompanies surgery, trauma, ischemic injury and a variety of neurodegenerative diseases including multiple sclerosis and Alzheimer's disease. Such similarities may explain the relapsing and remitting effect of the FBR on electrophysiological recording performance frequently observed in chronic recording studies when devices are implanted in brain tissue [9,10].

There is increasing evidence indicating that small pro-inflammatory molecules (such as TNF-α, MCP-1, IL-1β, IL-6) that are released by macrophages and other immune cells near the biotic–abiotic interface are responsible for the negative inflammatory sequela associated with device implantation in the brain tissue [5,7,11,12]. Based on this assumption, we hypothesized that implant designs that passively reduce the concentrations of these small molecules surrounding the implant will reduce the severity of the FBR and by definition improve device biocompatibility. While anti-cytokine immunotherapy is being developed to reduce the impact of specific pro-inflammatory cytokines, little effort has been directed at exploring more general device design-based approaches to minimize the impact of these molecules on the surrounding tissue [7].

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To address this need and identify a simple strategy for improving next generation devices, we examined the efficacy of enhancing the clearance of small molecules at the device surface by changing the surface permeability of a chronically implanted device. A surface was designed to serve as a passive diffusion sink, absorbing macrophage and immune cell-released pro-inflammatory cytokines into the device and away from adjacent brain tissue. To facilitate the design process and hypothesis testing, we used a computer aided design (CAD) approach and modeling tools to predict the steady-state distribution of such released soluble factors surrounding virtually built devices with and without permeable surfaces. The computational approach allowed us to explore the relationship between the diffusivity of brain tissue, the biological half-lives of these molecules and the diffusion sink capacity. The modeling showed us that it was possible to retain pro-inflammatory cytokines in the diffusion sink to passively reduce their concentration and their subsequent impact on the biology of the surrounding tissue as long as their residence time in the sink exceeded their biological half-life. Given the appropriate size of the sink, cytokines diffusing into the semi-permeable surface of the device would be unlikely to diffuse out of this region in their active state, and thus would be effectively silenced.

We chose to use solid, silicon intracortical microelectrode recording arrays as the test bed for studying the approach as their FBR is well characterized. Moreover, intracortical microelectrode arrays have shown clinical potential in various brain machine interface (BMI) applications for treating spinal cord injury (SCI), limb amputation and ALS [13,14]. However, perhaps more so than any other CNS device, FBR-related performance issues currently limits the clinical usefulness of such devices [4], necessitating the need to find strategies to reduce the FBR that will continue to work over a clinically relevant time frame.

2. Methods

2.1. Modeling

Models of solid 300 μm-wide Michigan (MI)-style microelectrode arrays with and without permeable hydrogel coatings were created using COMSOL multiphysics (COMSOL Group, Stockholm, SE). A concentric, scaled copy of the original construct was added to mimic the $CD68^+$ layer of cells found surrounding these devices implanted in brain tissue [5]. This cell layer served as the source of pro-inflammatory cytokines in the model; with production rates based on values from published studies [5,15,16]. MCP-1 and TNF-α were used to model cytokine distribution, as studies have indicated that macrophages adherent to explanted microelectrode arrays actively produce these molecules. MCP-1 is a chemokine involved in opening the blood brain barrier (BBB) and recruiting monocyte-derived macrophages to sites of injury and inflammation as is TNF-α, which also can have direct effects on neurons and oligodendrocytes [11].

A rectangular block was included to simulate the surrounding brain tissue where diffusion and clearance of macrophage-released factors occurred. The isotropic, apparent tissue diffusivities for such soluble factors in brain tissue and in permeable hydrogel coatings were based on diffusivities of similarly sized dextrans and other molecules in brain tissue [15,17].

The clearance/degradation of macrophage-released soluble factors in brain tissue and the permeable hydrogel coating were based on reported literature values for their half-lives ($t_{1/2}$) [15,16]. A no-flux boundary condition was used for all solid device surfaces as well as the upper surface of the brain tissue block. An open boundary was applied to the five remaining faces of the tissue block with an initial 0 mol/L concentration outside of the block. Fig. 1 shows the different regions and parameters involved in the finite element (FE) model used to predict the steady state distribution of MCP-1 and TNF-α surrounding a planar, 300 μm-wide MI-style microelectrode array.

2.2. Microelectrodes

Solid 300 μm wide silicon microelectrode arrays, identical to those modeled and used previously [7], were supplied by the Professor Ken Wise, Center for Wireless Integrated Microsystems, at the University of Michigan. To facilitate handling, we attached the microelectrode to a 0.25 mm diameter stainless steel wire with a UV-curable, medical-grade adhesive (MD-1187-M, Dymax, Torrington, CT). We cleaned all electrodes by immersion in 70% ethanol followed by several rinses in sterile DI water. Following cleaning, we sterilized the microelectrodes with ethylene oxide. Sterilized samples were allowed to outgas for at least 48 h prior to implantation.

2.3. Diffusion sink construction

We chose to construct our diffusion sink from a sodium alginate hydrogel as it has been shown to be well tolerated in brain tissue. To couple the hydrogel to the surface of the electrode we first functionalized the silicon microelectrode surface with an epoxy-silane (3glycidoxypropyl-trimethoxy-silane) via chemical vapor deposition at 120 °C in a N_2 atmosphere for 18 h. After functionalization we repetitively dipped each electrode with an inverted, fine tooth syringe pump into a sterile 1.5% (w/v) sodium alginate/DI H_2O solution followed by immersion in a sterile 2 mM $CaCl_2$/DI H_2O solution until the desired coating thickness was achieved (either a thin coating obtained with one coating or a thick, approximately 400 μm, diameter coating obtained after roughly 20 cycles). The calcium concentration was matched to the concentration within rat cerebral spinal fluid (CSF) to better ensure that the polyelectrolyte coating would not change volume due to calcium exchange following implantation. The coating scheme is shown in Fig. 2. We confirmed the presence and thickness of the thin hydrogel coating using X-ray photoelectron spectroscopy (XPS), ellipsometry, and light microscopy.

2.4. Animal surgery

All procedures involving animals were approved by the University of Utah Institutional Animal Care and Use Committee (IACUC) and similar to those described previously [5–7]. Briefly, male Sprague–Dawley rats (225–250 g) were anesthetized

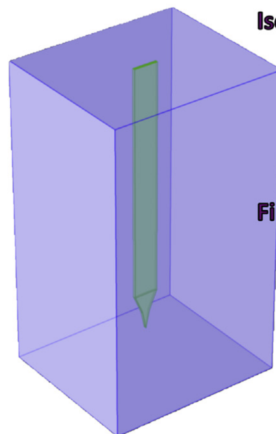

Fig. 1. Example 3-D composite structure created in COMSOL for a 300 μm-wide planar MI-style microelectrode surrounded by a 10 μm thick macrophage layer (green) embedded within a simulated block of brain tissue (purple). The top face of the electrode is flush with the top of the brain tissue block. The electrode is implanted to a depth of 3 mm. The macrophage layer surrounding the electrode acts as a constant source of soluble factor production. Transport of these factors through brain tissue or the hydrogel coating is governed by apparent isotropic diffusion. Subsequent soluble-factor clearance and degradation within the tissue block or hydrogel coating is modeled via first-order elimination. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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