Investigation of the Neuroinflammatory Response to Antioxidant Releasing Mechanically-Adaptive Polymer Implants

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Statement of Purpose: Several classes of medical devices are used within the central nervous system (CNS) with variable clinical success. In the case of intracortical microelectrodes, a decline in performance can be directly linked to the foreign body response to the implanted device.[1, 2] Previously, our lab has shown that the inflammatory response to intracortical microelectrodes has a biphasic response.[3] Therefore, a combinatorial approach may be ideal to adequately address the inflammatory response during both acute and chronic neurodegenerative onsets. We have previously demonstrated the efficacy of two natural antioxidants, resveratrol and curcumin, in reducing neuroinflammation. Specifically, we found that a single systemic administration of resveratrol is able to reduce the neuroinflammatory response at acute time points.[4] Alternatively, local delivery of curcumin was also able to temporarily inhibit neuroinflammation in response to microelectrodes.[5] Additionally, we have demonstrated that mechanically-adaptive polymer implants are able to reduce the chronic neuroinflammatory response by reducing the mechanical mismatch between traditionally stiff microelectrode materials and neural tissue.[6] However, the mechanically-adaptive polymer implants had limited influence on the inflammatory response at acute time points. Therefore, we hypothesize that a synergistic approach utilizing local release of either resveratrol or curcumin from mechanically-adaptive polymers implants could reduce neuroinflammation during both acute and chronic neurodegenerative onsets.

Methods: To test our hypothesis, in vitro assays are performed to test cell toxicity, drug release profiles, and antioxidant activity for various resveratrol and curcumin concentrations, released from the materials used to create mechanically dynamic intracortical microelectrodes. After determining optimal drug release conditions, adult male rats are implanted with antioxidant releasing polymers in the cerebral cortex for acute and chronic time points of inflammation. Tissue is processed and histology performed to evaluate glial scar formation and neural degeneration. Expression of neurodegenerative factors, including oxidative stress markers, activation of microglial/astrocytic cells and neuronal cell death are quantified up to 500 µm away from the interface.

Results: Antioxidant releasing polymers showed no cytotoxicity at various resveratrol and curcumin concentrations after 48 hours. Additionally, release studies in ACSF demonstrated ~50-60% antioxidant release by 72 hours (**Figure 1**). Measurement of free radical scavenging with polymer samples also validated antioxidant activity in vitro. Optimal drug concentration for in vivo implantation was chosen by modeling antioxidant release to be within the therapeutic range of 10-20 µM around the implantation site. In vivo experiments are currently ongoing.

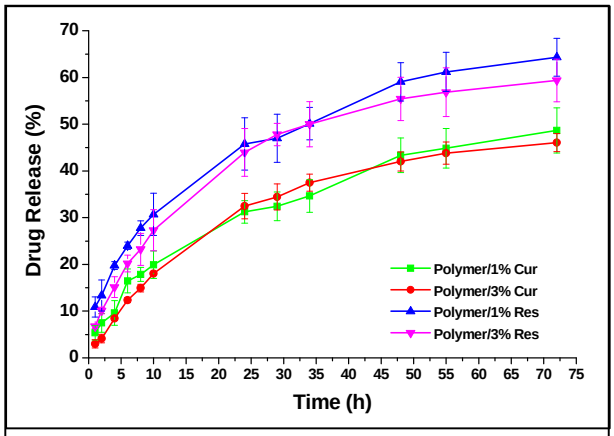

Figure 1. Release profile of various concentrations of two types of antioxidants, resveratrol and curcumin.

Conclusions: There are a variety of factors that contribute to the neuroinflammatory response to intracortical microelectrodes. Therefore, a synergistic approach addressing various aspects of the foreign body response is needed to improve material design and long-term performance for neural implants. Our system utilizes anti-oxidant therapy and material modulus to affect the inflammatory response at acute and chronic time points, respectively. Future studies will utilize functionalized mechanically-adaptive polymer implants to correlate reduction in inflammatory response to improved neuronal recordings.

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