Studies of the Foreign Body Response to Chronically Implanted Utah Electrode Arrays in Rat Cortex

Nicholas F. Nolta, Michael B. Christensen, Patrick A. Tresco
Department of Bioengineering, University of Utah, Salt Lake City, UT

Statement of Purpose: The Utah Electrode Array (UEA) has allowed humans with tetraplegia to gain volitional control over prosthetic devices, but inconsistent performance at chronic time points remains a critical barrier to clinical use. It is widely believed that the foreign body response (FBR) contributes to inconsistent performance and that reducing the severity of the FBR would improve device performance. However, the FBR to the UEA is poorly characterized; to our knowledge no studies exist in the rat, which has the most well-developed set of biomarkers available. To bridge this gap, we studied the FBR to the UEA implanted in the rat cortex.

Methods: 16-channel Utah Electrode Arrays (Blackrock Microsystems, Salt Lake City, UT) were fitted into custom-fabricated headstages and implanted into 22 adult male Sprague-Dawley rats. The devices were positioned stereotaxically and then gently pushed in using forceps after removal of the dura. 3 additional rats had an array inserted and immediately removed (stab wound). At time points between 2 and 5 weeks, rats were perfused transcardially and their brains postfixed for 24 h in 4% paraformaldehyde. 30 µm horizontal brain sections were obtained using a cryostat and the spatial organization of cell nuclei (DAPI), astrocyte cytoskeleton (GFAP), neuronal nuclei (NeuN), neuronal processes (NF-160), macrophages/microglia (IBA-1), activated macrophages/microglia (CD68), blood-brain-barrier (BBB) leakage (IgG), myelin (RIP), and axons (NF-200) evaluated using immunohistochemical methods.

Results: Representative horizontal sections at 4 wks showed increased BBB leakage, hypercellullarity, macrophage recruitment or proliferation, macrophage activation, astrogliosis, and loss of neuronal nuclei, processes, myelin and axons in superficial sections near the base of the array. The spatial distribution did not conform to the shape of the device, with irregular swaths of inflamed tissue likely the result of infarcts caused by vascular damage during implantation. In non-infarcted areas the FBR was closely confined to individual tines. The infarcts were present in both stab wounded and implanted animals at 4 wks and were characterized by loss of neural tissue, astrocyte hypertrophy at the infarct border, and BBB leakage (Figure 1). Stab-wounded animals showed little evidence of macrophage activation or individual tine tracts as opposed to implant-associated sections.

Conclusions: The increase in markers of the FBR in superficial cortex are likely due to the particular architecture of the UEA, which creates multiple closely spaced penetrating injuries. Since the base of the UEA provides a large area for macrophage attachment and only one direction for inflammatory cytokines released by macrophages to diffuse away, cytokines reach high local concentrations, cause secondary cell death, recruit more macrophages, and continue to remodel tissue; meanwhile, the tips are smaller structures and are located far enough away from the base that cytokines are less concentrated and induce less tissue remodeling. Although it is encouraging that the FBR was reduced near the electrically-active tips, the FBR at the base of the device is still a concern because the FBR at the base may enhance secondary cell loss associated with initial vascular damage and influence cortical circuitry in motor cortex, which has a columnar organization. These changes to the neural architecture in the upper layers of the circuit may interfere with its operation. In addition, the inflammatory burden of an indwelling device may impact neurogenesis in other parts of the CNS leading to unintended functional impairments. Vascular damage of the scale observed in this work was rarely observed in our previous studies using simpler devices that made a single penetrating injury[1][2][3]. Gaining a better understanding of how to avoid and mitigate the effects of vasculature damage will result in more biocompatible recording devices.

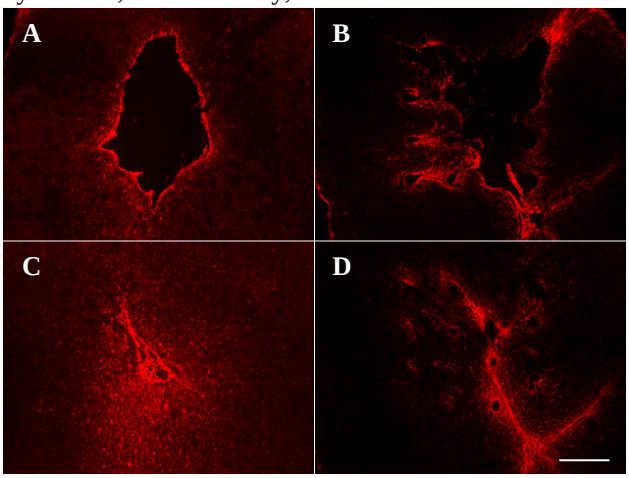

Figure 1: GFAP (red) was upregulated at the border of infarcted areas visible in both stab wounded (A, C) and implanted animals (B, D) at 4 wks. Infarcts were larger in superficial cortex (A, B) compared to near the tine tips (C, D). Scale bar = 500 µm.

References:

[1] Biran R Exp Neurol. 2005 Sep;195(1):115-26
[2] Winslow BD Biomaterials 2010 Mar;31(7):1558-67
[3] Skousen JL Prog Brain Res. 2011;194:167-80