The foreign body response to CNS implants is accompanied by decreased neurogenesis in the hippocampus

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Statement of Purpose: Multiple biomedical devices in use or under development to treat diseases or injuries of the central nervous system require chronic indwelling periods. Available evidence indicates that all such implants chronically activate the innate immune system irrespective of implant type, brain location, animal age, or the species implanted[1, 2]. Emerging evidence shows that such inflammatory sequelae reduces hippocampal cell proliferation and depresses the genesis of new neurons in the subgranule zone (sgz) of the dentate gyrus[3]. Therefore, we sought to understand whether the persistent inflammation that accompanies biomaterial implantation in the brain is sufficient to reduce hippocampal proliferation and neurogenesis.

Methods: We implanted adult male Sprague Dawley rats (225-250 g., n=9 per group) with planar or lattice silicon microelectrode arrays (SiMEAs) at -3.2 mm from Bregma, 3 mm lateral, and to a depth of 3 mm, which penetrated CA1. In addition, we implanted a cohort of animals with SiMEAs into the cerebral cortex (n=6; depth = 2 mm), or PAN-PVC hollow fiber membranes (HFMs; n=6; depth = 7.3 mm) at +0.2 mm forward of Bregma, and 3 mm lateral, and investigated the tissue response using similar methods. Twelve weeks after implantation, rats were transcardially perfused with 4% paraformaldehyde in PBS. Indirect IHC was used to identify neuronal and glial biomarkers, while doublecortin (DcX) was used to quantify newborn neurons, and Ki-67 to assess cellular proliferation in the sgz.

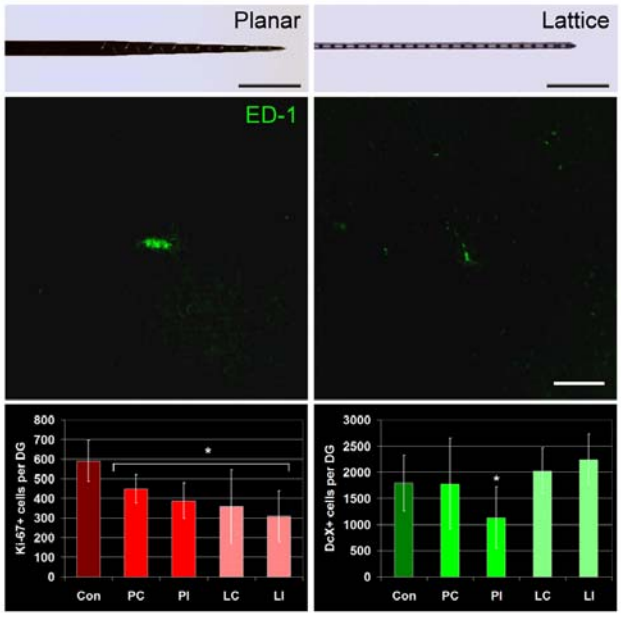

Figure 1. Lattice electrodes resulted in a reduced number of inflammatory cells at the biotic-abiotic interface. Both implants reduced cell proliferation in the sgz. Planar implants with greater surface area also reduced the number of immature neurons in the implanted side compared to control (con). All scalebars = 100 µm.

Results: Implantation of both the planar and lattice SiMEAs resulted in a local inflammatory reaction consisting of activated microglia/macrophages at the biotic-abiotic interface, astrocyte hypertrophy, reduction in neuronal staining and BBB breakdown, with a response that was proportional to the surface area of the implant (Figure 1). We observed a statistically significant reduction in the amount of Ki67 staining in both cohorts, which was greater in the ipsilateral hippocampus. In addition, implantation of SiMEAs restricted to the cerebral cortex resulted in similar inflammation and changes in hippocampal neurogenesis, as did HFMs placed millimeters away from the hippocampus.

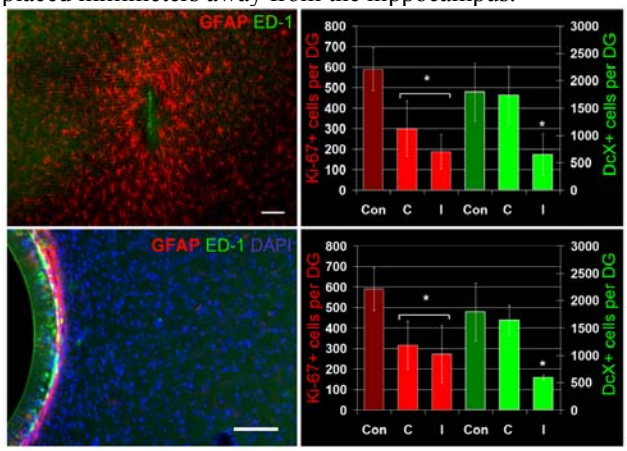

Figure 2. Cortical SiMEA implantation (top) resulted in inflammation and reduced hippocampal proliferation and neurogenesis 12 weeks after implantation. HFM implants showed a similar reactive phenotype (bottom panels).

Conclusions: We found that the implantation of SiMEAs in the hippocampus significantly reduced cellular proliferation and the turnover of new neurons in the sgz. SiMEAs and HFMs implanted in more rostral regions millimeters away from the hippocampus also significantly reduced cellular proliferation in the sgz and the turnover of new neurons, suggesting that CNS implant associated inflammation can reduce neurogenesis. Moreover, it raises the possibility that in patients with such long-term implants as hydrocephalic shunts and DBS electrode chronic inflammation may decrease cognition. The SiMEAs with decreased surface area showed a reduced level of chronic inflammation, which did not cause a reduction of new neurons in the sgz. This suggests that the next generation of CNS implants should be based upon designs that reduce the inflammatory footprint of the device.

Abbreviations: planar contralateral (pc); planar ipsilateral (pi); lattice contralateral (lc); lattice ipsilateral (li).

References:

[1] Biran RB. Exp Neurol 2005; 195:115-126.
[2] Kim YT. Biomaterials 2004; 225:2229-2237
[3] Monje ML. Science 2003; 302:1760-1765