Hippocampal Neurogenesis is Down-Regulated in Animals with Small-Scale Nervous System Implants

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Statement of Purpose: It has been well documented that the implantation of microelectrode devices and anchoring devices, such as peripheral nerve cuffs, lead to a persistent inflammatory response around the device, including the recruitment of activated macrophages. Previous research in other labs has demonstrated that administration of LPS into either the central nervous system (CNS)[1] or peripheral nervous system (PNS)[2] is sufficient to up-regulate the number of activated macrophages in the hippocampus of the dentate gyrus, leading to a down-regulation of newborn neurons in that area. Here, we investigated whether the chronic implantation of microelectrodes in the CNS, either in or away from the hippocampus, as well as the implantation of peripheral nerve cuffs around the sciatic nerve, was sufficient to reduce hippocampal neurogenesis.

Methods: Single-shank microelectrode arrays provided by the Center for Neural Communication Technology (CNCT) at the University of Michigan were implanted to either a depth of 3mm into the hippocampus, or to a depth of 2mm, 1mm away from the hippocampus. In a separate cohort of animals, silicone peripheral nerve cuffs were implanted around the main trunk of the right sciatic nerve. All experiments were performed in adult male rats. Following a 12 week (CNS electrodes), or 60 day (PNS cuffs) implantation period, animals were transcardially perfused and their brains were processed for immunohistochemical analysis. Antiserum against doublecortin (DcX), a marker for immature neurons, was applied to every 10th horizontal brain section, following which the entire dentate gyrus from each of these sections was imaged and the number of DcX+ cells counted. Non-implanted age-matched animals for each experiment were used as controls.

Results: Quantification of DcX+ cells showed a significant reduction in neurogenesis associated with CNS microelectrode implantation ipsilateral to the implant, regardless of implantation location (Figure 1). Further, results showed that the implantation of silicone PNS cuffs also sufficiently reduced hippocampal neurogenesis (Figure 2). Considering that previous research has shown a link between inflammation and a decrease in neurogenesis, these data suggest that even a minimal inflammatory footprint, such as those found around microelectrodes or peripheral nerve cuffs, has systemic effects which negatively impact the generation of new neurons, which may lead to cognitive impairment. Of great importance is the fact this inflammatory footprint can be far removed from the CNS, as suggested by the results from the nerve cuff implantations.

Conclusions: This study shows that the chronic inflammatory environment present around small scale devices, regardless of their implantation site in the nervous system, is sufficient to negatively impact hippocampal neurogenesis. Although we have not yet tested the affect of devices located outside of the nervous system on neurogenesis, other research has documented inflammatory environments surrounding myriad biomedical devices, which are very similar to the FBR we observed. This study suggests that such inflammation, although it may be minimal, may reduce the birth of new neurons which could, in turn, lead to cognitive deficits in the patient. Further research investigating the influence of devices located outside of the nervous system on neurogenesis, as well as correlative studies between neurogenesis levels and cognition, need to be conducted.

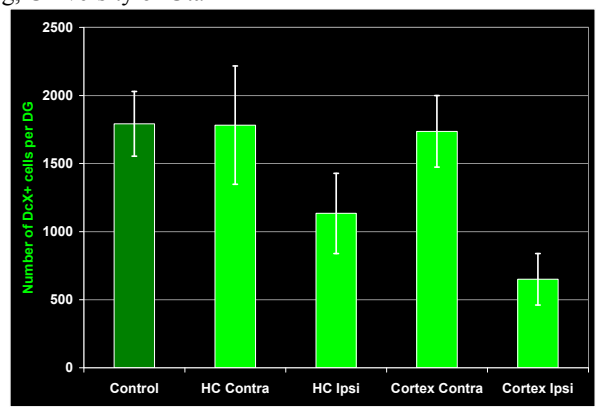

Figure 1: Microelectrode implants located in the hippocampus or the cortex were both sufficient to decrease ipsilateral hippocampal neurogenesis.

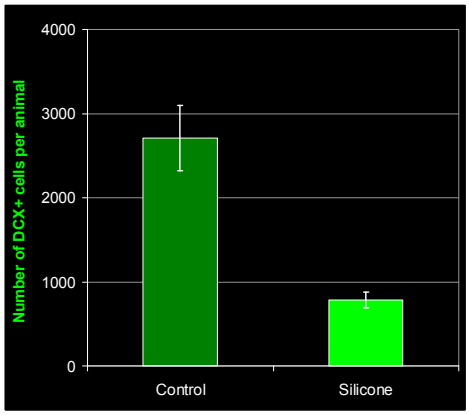

Figure 2: Silicone peripheral nerve cuff implants, despite their remote location to the brain, were also sufficient to reduce hippocampal neurogenesis.

References:

1. (Ekdahl CT. Proc Natl Acad Sci USA. 2003;100:13632-13637)
2. (Monje ML. Science. 2003;302:1760-1765)