Chronic Cellular Reactions to Silicon Neural Probe Implant

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Abstract

Chronic use of micromachined silicon neural probes is limited due to the formation of a complex sheath of cells and extracellular proteins that electrically isolates devices from adjacent neurons and neuronal damage. Understanding device-tissue interactions in the brain will provide a basis for developing successful interface strategies for biocompatible microdevices. While the reactive responses to single shank silicon devices inserted into neocortex are well characterized, responses in other regions have not been described. This study was designed to determine if the reactive responses observed in hippocampus and thalamus are similar to those observed in neocortex. This information is necessary to design and implement appropriate intervention strategies to control regional cell and tissue responses. Study of responses in hippocampus and thalamus has important scientific and clinical implications.

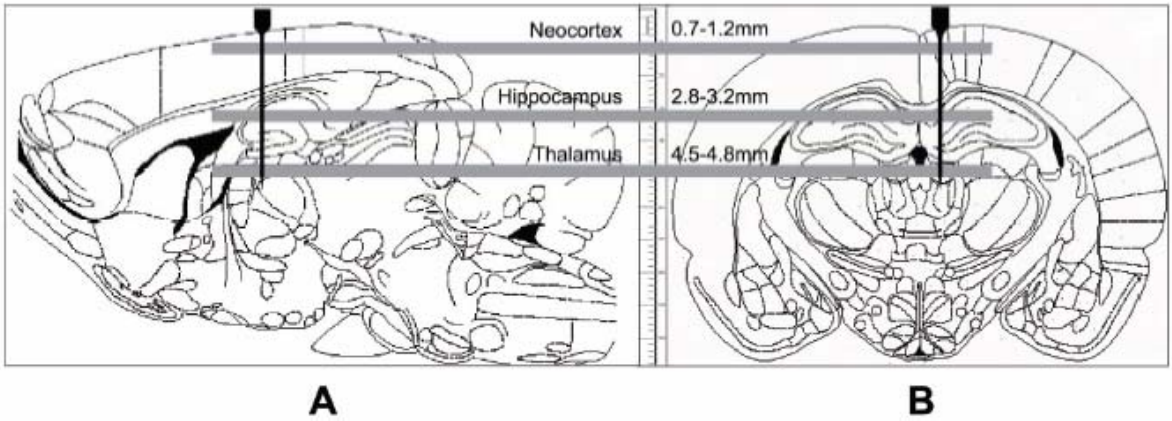

Fig. 1 Schematic diagrams showing probe placement in the brain. Silicon probes were implanted into the right hemisphere of adult Sprague-Dawley rats. (A) Sagittal section (B) Coronal section. Blocks were sectioned into tissue slices 100 μm thick from three different brain levels: neocortex, hippocampus, and thalamus.

1 In vivo implant surgery and in vitro experimental setup

A craniotomy was performed over the right hemisphere near the sensory motor cortex 3-mm distal and 1-mm lateral from Bregma(Fig.1). A hole, with a diameter larger than the tabs of the devices (700 x 700 μm2), was drilled through the skull, and the dura was reflected. Devices used for these experiments had a single 5-mm long shaft. The cross-section of the shaft was 50 μm (thickness) x 128 μm (width). Each silicon device was inserted using a custom made automated inserter at a speed of 2mm/sec. At 1 hr, 24 hr, 1 wk, or 6 wk following device insertion, animals were anesthetized with tribromoethanol and perfusion fixed with 4% paraformaldehyde in phosphate buffer, pH 7.4.

2 Chronic cellular reactions to silicon neural probe

We examined region-specific differences of reactive response in three different brain regions: neocortex, hippocampus, and thalamus. Silicon devices with shafts 5 mm long and 50 x 128 μm in cross-section were used. Immunohistochemistry was performed to identify reactive astrocytes (GFAP), vasculature (laminin), and activated microglia (CD11b) at 1 hr, 24 hrs, 1 wk, and 6 wk. Images were collected as three-dimensional data sets using laser scanning confocal

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microscopy. Though the morphology, distribution, and numbers of reactive cells in the deeper brain regions differed from those observed in neocortex, the reactive responses in all three brain regions followed a similar pattern.

GFAP immunoreactivity was greatest in the hippocampus. CD11b was comparable in neocortex and hippocampus. Laminin expression in all regions extended considerable distances from insertion sites at 1 hr, and decreased at later times. Regional differences in glial cell activation may be caused by differences in microglia and astrocyte density or inflammation-related factors produced by these cells(Fig. 2).

3 Summary

In this paper, we successfully showed that regional differences of reactive responses may result from differences in vascular properties, differences in receptors or amounts of protein products responsible for the response, or sub-types of cells present in different brain regions. These data support our hypothesis that multi-shank devices produce overlapping reactive zones of influence. These results indicate that understanding cell and tissue reactive responses to micro-machined devices in deep brain regions is necessary for developing new generations of deep-brain prostheses.

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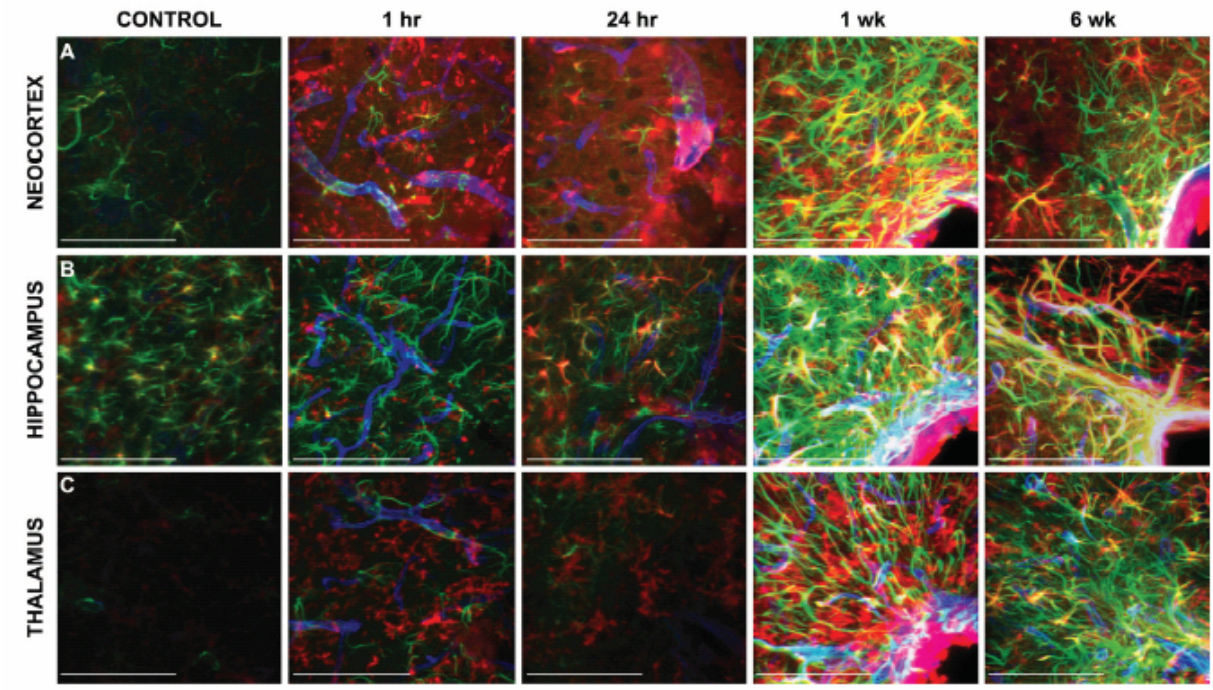

Fig. 2 Triple-labeled images were obtained using a 40X objective lens. GFAP (green), laminin (blue), and CD11b (red) are markers for astrocytes, laminin, and microglia, respectively. Scale bars represent 100 μm. The integration of astroglial, microglial, and vascular responses provides a clearer representation of the reactive responses around inserted devices. The increase in CD11b signal and the delayed increase in GFAP signal clearly demonstrated that ultimately similar numbers of microglia and astrocytes are participating. In hippocampus there was a clear transient decrease followed by a large increase in GFAP signal (row B). The overall increase in CD11b signal/contribution appeared to be less than in neocortex at earlier times, but by six weeks the CD11b and GFAP signals appeared to be similar in both the numbers of cells described and their relative intensities. Clear differences in thalamus responses were observed (row C).