The foreign body response to nerve cuffs is associated with persistent inflammation and changes in nerve fiber composition.

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Statement of Purpose: Nerve cuffs are used directly as sensing and stimulating arrays, and are used to anchor sieve and penetrating electrodes for a variety of basic science and therapeutic applications. Previous biocompatibility studies have reported alterations in nerve composition including a shift in fiber diameter distributions toward smaller diameter fibers. At present it is unclear how the cuff contributes to such changes in the absence of electrode penetration or direct nerve trauma. Toward this end, we studied the foreign body response to a variety of nerve cuff materials including silicone and a variety of metal meshes using the rat sciatic nerve as a model system with a long indwelling period.

Methods: Solid silicone cuffs, open mesh gold cuffs, or gold mesh cuffs coated with Parylene-C were implanted around the sciatic nerve of Fischer344 rats. After 60 days, animals were transcardially perfused with 4% paraformaldehyde. Both nerves were removed, embedded in plastic, thin sectioned, stained, and quantitatively analyzed. Morphometric parameters, including fiber diameter and g-ratio distributions, were collected. Mean g-ratios from each nerve section were compared across experimental groups at the same location as well as to the same experimental group across locations, using a one-way ANOVA with a Tukey's post-hoc t-test. We used Wilicoxon signed rank or rank sum tests to compare fiber diameter distributions. Retrieved cuffs were examined using IHC and antisera against ED-1.

Results: All retrieved cuffs were covered with ED1 immunoreactivity 60 days after implantation (Figure 1). Quantitative results for g-ratio distributions show that there is no significant difference between groups at the same location or between locations within the same group for any of the cuff types implanted. In general, implanted groups trend toward thinner myelination around the implant, but this trend is not significant. Fiber diameter distributions in general suggest that, regardless of material, there is a loss of larger diameter fibers and an increase in the amount of small diameter fibers both at and distal to the implant site (Figure 2), while changes proximal to the implant are less pronounced. In general, Parylene-C coated mesh cuffs exhibited less of a shift towards smaller diameter fibers than did non-coated mesh cuffs (Figure 2).

Conclusions: Our data suggests that nerve cuffs, irrespective of material composition, show a foreign body response that is accompanied by low level chronic inflammation involving the innate arm of the immune system. In that absence of an accompanying penetrating injury, the reaction is sufficient to cause changes in certain morphometric parameters in the underlying nerve. This could be due to the inflammatory response elicited by these materials, including the recruitment of macrophages to the material interface and the subsequent secretion of pro-inflammatory cytokines. Our data does suggest that the coating of material with a low-protein binding layer (Parylene-C) may help mitigate some of these changes, possibly by reducing the number of activated macrophages at the biotic-abiotic interface. The study of other morphometric parameters, such as fiber density, packing, and fascicle area, to support this observation are ongoing.

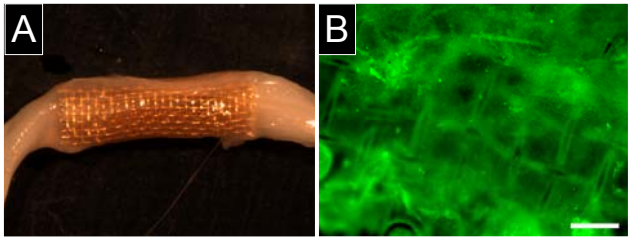

Figure 1. Example of the tissue reaction at the material interface. All retrieved cuffs, such as this gold mesh cuff, were covered with ED1 immunoreactivity, indicative of an ongoing inflammatory reaction. Scale bar = 500µm

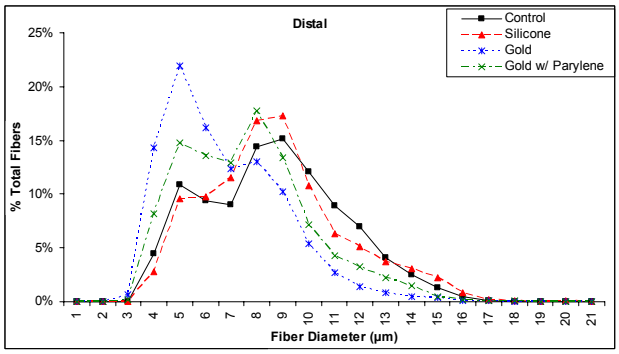

Figure 2. Fiber diameter distributions distal to the implant site. Distributions from the open mesh cuffs show a loss of larger diameter fibers and a shift toward smaller fibers which is less for the Parylene-C coated than the non-coated cuffs. Silicone cuffs did not show a significant shift in distribution distal to the implant, although there was a shift at the implant site.

References:

1. (Jellema T. Brain Res Bull. 1995;37(5):551-554)
2. (Grill WM. J Biomed Mater Res. 2000;50(2):215-226)